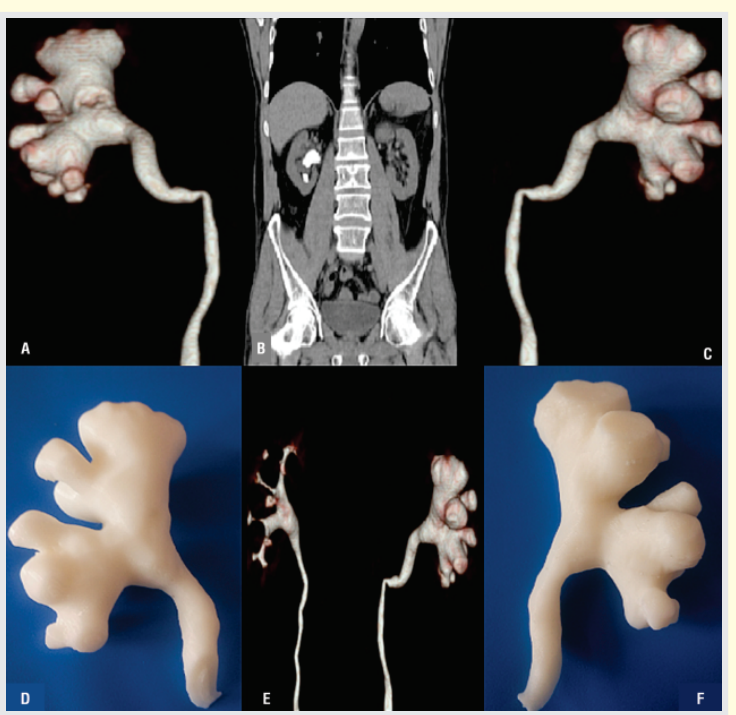
ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 43, NUMBER 3, MAY - JUNE, 2017



Patient 2 A) Posterior view of collecting system, B) Coronal view of collecting system, C) Anterior view of collecting system, D) Posterior view of 3D printed model, E) Posterior-lateral view of 3D printed model, F) Anterior view of 3D printed model. (Page 473)

XXXV Brazilian Congress of Urology
August 26-29, 2017 - Fortaleza - CE - Brazil

INTERNATIONAL

BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

INTERNATIONAL
BRAZ J UROL

INTERNATIONAL
BRAZ J UROL

Eletronic Version: Full text with fully searchable articles on-line:

http://www.intbrazjurol.com.br/

Correspondence and Editorial Address:

Rua Bambina, 153 – 22251-050 – Rio de Janeiro – RJ – Brazil
Tel.: + 55 21 2539-6787; Fax: + 55 21 2246-4088; E-mail: brazjurol@brazjurol.com.br

The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.

The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development.
Editorial and Graphic Composition

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology–SBU, has a circulation of 6,000 copies per issue and is published 6 times a year (bimonthly, starting in January - February).
The issue date is up to 2 weeks after the month of issuefor the hard copy and up to 1 week after the month of issue for the electronic version.

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

ONLINE manuscript submission: **www.intbrazjurol.com.br**

DISCLAIMER

CONTENTS

Volume 43 | number 3 | May . June, 2017 | INT BRAZ J UROL

EDITORIAL
IN THIS ISSUE

Volume 43 | number 3 | May . June, 2017 | INT BRAZ J UROL

doi: 10.1590/S1677-5538.IBJU.2017.03.01

Kidney anatomy: three dimensional (3D) printed pelvicalyceal system models of the collector system improve the diagnosis and treatment of stone disease

The May-June 2017 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Erectile Dysfunction, Renal Stones, Prostate Cancer, Renal Cell Carcinoma, Prostate Biopsy, Ureteroscopy, Hemorragic Cystitis, Retrograde Ejaculation, Intermittent Urethral Catheterization, Ureteropelvic Junction Obstruction, Laparoscopy, Vaginal Prolapse, BPH, Vesicoureteral and Renal Anomalies. Papers came from many different countries such as Brazil, USA, UK, Turkey, Korea, France, Taiwan, Greece, China, Italy, Germany, Israel and India, and as usual the editor's comment highlights some papers. We decided to comment the paper about a very interesting topic: The use of pelvicalyceal system models in percutaneous nephrolithotripsy surgery.

Atalay et al. from Turkey reported on page 470 an interesting study about three dimensional (3D) printed pelvicalyceal system models on patient information before percutaneous nephrolithotripsy surgery. The authors studied patients with unilateral complex renal stones with indication of percutaneous nephrolithotripsy surgery. Usable data of patients were obtained from CT scans as Digital Imaging and Communications in Medicine (DICOM) format. Mimics software version 16.0 (Materialise, Belgium) was used for segmentation and extraction of pelvicalyceal systems. DICOM format were converted to stereolithography format. Finally, fused deposition modeling was used to create plasticine 3D models of pelvicalyceal systems. A questionnaire was designed for patients to assess personalized 3D models effect on patient's understanding their conditions before percutaneous nephrolithotripsy surgery (PCNL). The day before surgery, each patient was seen by a urologist to deliver information about surgery. Questionnaire were answered by patients before and after presentation of 3D models and the results of the questions were compared. Results: Five patients' anatomically accurate models of the human renal collecting system were successfully generated. After the 3D printed model presentation, patients demonstrated an improvement on their understanding of basic kidney anatomy by 60% (p=0.017), kidney stone position by 50% (p=0.02), the planned surgical procedure by 60% (p=0.017), and the complications related to the surgery by 64% (p=0.015). In addition, overall satisfaction of conservation improvement was 50% (p=0.02). They concluded that generating kidney models of PCSs using 3D printing technology is feasible, and understandings of the disease and the surgical procedure from patients were well appreciated with this novel technology.

The 3D printed technology is a new technology and had many applications in kidney surgery. Previous studies demonstrated the importance of 3D printing in the presurgical planning for laparoscopic and robotic partial nephrectomy (1, 2). In the present paper the authors showed a new application for this technique that will be very impor-

Volume 43 | number 3 | May . June, 2017 | INT BRAZ J UROL

tant in the relationship between the doctor and the patient.

Recently interesting studies demonstrated the importance of the kidney anatomy applied to training and execution of the flexible ureteroscopy (3, 4). Ureteroscopy surgical training programs use virtual reality simulators. In a recent paper we standardized the building of a three-dimensional silicone mold (cavity) of the collecting system, on the basis of polyester resin endocasts, which can be used in surgical training programs (5).

The two-part silicone mold is feasible, cheap and allows its use for exible ureteroscopy surgical training (5). The 3D printing technology is very precise to show the anatomy of the collector system. In the future this technology could be used to make 3D endocasts of the collector system and improve the surgical training programs of the flexible ureteroscopy and others endo urological kidney procedures.

REFERENCES

1. Wake N, Rude T, Kang SK, Stifelman MD, Borin JF, Sodickson DK, et al. 3D printed renal cancer models derived from MRI data: application in pre-surgical planning. Abdom Radiol (NY). 2017; Jan 7. [Epub ahead of print]
2. von Rundstedt FC, Scovell JM, Agrawal S, Zaneveld J, Link RE. Utility of patient-specific silicone renal models for planning and rehearsal of complex tumour resections prior to robot-assisted laparoscopic partial nephrectomy. BJU Int. 2017;119:598-604.
3. Marroig B, Fortes MA, Pereira-Sampaio M, Sampaio FJ, Favorito LA. Two-part silicone mold. A new tool for flexible ureteroscopy surgical training. Int Braz J Urol. 2016;42:850-1.
4. Marroig B, Frota R, Fortes MA, Sampaio FJ, Favorito LA. Influence of the renal lower pole anatomy and mid-renal-zone classification in successful approach to the calices during flexible ureteroscopy. Surg Radiol Anat. 2016;38:293-7.
5. Marroig B, Favorito LA, Fortes MA, Sampaio FJ. Lower pole anatomy and mid-renal-zone classification applied to flexible ureteroscopy: experimental study using human three-dimensional endocasts. Surg Radiol Anat. 2015;37:1243-9.

Luciano A. Favorito, MD, PhD

Professor Associado da Unidade de Pesquisa Urogenital da
Universidade do Estado de Rio de Janeiro
Urologista do Hospital da Lagoa Federal, Rio de Janeiro
Editor Associado da International Braz J Urol

EDITORIAL

Volume 43 | number 3 | May . June, 2017 | INT BRAZ J UROL

doi: 10.1590/S1677-5538.IBJU.2017.03.02

PRISMA statement and PROSPERO

Independent of who made the first Review in health literature, it is possible to state that the development of the fundamental concepts on Systematic Review and Meta-analysis is attributable to the Cochrane initiative, that signalized the need to gather scientific evidence based on the opinion of medical specialists (1). It is necessary to periodically organize a synthesis, by specialty, of all relevant randomized clinical trials, which stimulated, in 1993, the creation of collaboration, which has been at the forefront of the methodology and in the rigorous systematic review.

Key elements of the model are transparency and reproducibility search methods, which include registration of the title, publication of the protocol and periodic updating in subsequent systematic reviews. At same time at the UK Cochrane Center in Oxford, it was initiated the development of statistical methods for data synthesis, which great influenced on the specifications of the software, especially in relation to meta-analysis (2). Throughout these years, the methodology has been actively improved, including the development of risk assessment instruments for bias in no randomized studies (1).

The items involved in the development of the systematic review, specifically for interventions based on randomized assays, also had their initial definition by the Cochrane Handbook (1994), inserted in its software (RevMan). But in the same way as systematic revisions, it has become a universal process, as well as initiatives have emerged to disseminate these fundamental elements, such as the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) (3), which has its origins in QUOROM (Quality of Reporting of Meta-Analyses) (4), which was a specific instrument for meta--analyzes of Randomized Clinical Trials (1996).

Some major phenomena justified the improvement, the democratization and the expansion of the checklist for systematic reviews, through the creation of PRISMA (2005): the knowledge of driving and publication of systematic reviews has expanded, the concepts of risk of bias were extended, including observational studies, and the synthesis of the evidence used by the authors has become increasingly focused on to address practical issues, making the eligibility criteria of the increasingly inclusive evidence. The PRISMA consists of a "checklist" of 27 items and a 4-stage flow diagram essential for the dissemination and publication, transparent and rigorous, of the methods and results of the systematic review (3).

In the same way, to broaden the global Systematic Reviews of quality, the Center for Reviews and Dissemination (CRD), at York University, which is part of the National Institute of Health Research (NIHR) in the UK, and produces systematic reviews and evaluations of health technology, has developed a record of systematic reviews, the international prospective register of systematic reviews (PROSPERO) (5).

Volume 43 | number 3 | May . June, 2017 | INT BRAZ J UROL

PROSPERO provides the first base to register systematic reviews in health, and through a broad consultation promotes best practice around the World, in order to reduce redundancy, and wasting time and resources.

So Int Braz J Urol is adopting the PRISMA checklist, including the PROSPERO's register, within the rules needed to submitted any systematic review with or without meta-analysis. The authors can access the checklist and flow diagram at Prisma--Statement and the registration at Prospero electronic address, that need to be sent with the whole submission.

Certainly, with this initiative, the level of the Systematic Review and Meta--analysis available in the Int Braz J Urol will be with highest level, consistence and credibility.

REFERENCES

1. Chandler J, Hopewell S. Cochrane methods--twenty years experience in developing systematic review methods. Syst Rev. 2013;2:76.
2. McKenzie JE, Salanti G, Lewis SC, Altman DG. Meta-analysis and The Cochrane Collaboration: 20 years of the Cochrane Statistical Methods Group. Syst Rev. 2013;2:80.
3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
4. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354(9193):1896-900.
5. Davies S. The importance of PROSPERO to the National Institute for Health Research. Syst Rev. 2012;1:5.

Wanderley Marques Bernardo

Faculdade de Medicina da Universidade de São Paulo (FMUSP),
Projeto Diretrizes - Associação Médica Brasileira (AMB),
São Paulo, SP, Brasil

DIFFERENCE OF OPINION

Vol. 43 (3): 385-389, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2017.03.03

PDE-5 inhibitors should be used post radical prostatectomy as erection function rehabilitation?

Opinion: Yes

Laith M. Alzweri [1], Arthur L. Burnett [1]

[1] *The James Buchanan Brady Urological Institute and Department of Urology, The Johns Hopkins School of Medicine, Baltimore, MD, USA*

Keywords: Phosphodiesterase 5 Inhibitors; Erectile Dysfunction; Penile Erection; Prostatectomy

INTRODUCTION

Despite significant improvement in surgical techniques of radical prostatectomy (RP) since the nerve-sparing approach was introduced in 1982 (1), erectile dysfunction (ED) post RP remains a challenge for patients and urologists (2). Although most patients experience some degree of ED post RP, erectile function recovery rates vary according to age, baseline erectile function, comorbidities, and extent of nerve-sparing techniques (3, 4). The concept of penile rehabilitation has been evolving over the last two decades, in parallel with a better understanding of the basic scientific basis for ED post RP. In a recent systematic review of 11 randomized, controlled clinical trials (RCTs) on erection rehabilitation post RP in general, there was no significant improvement in spontaneous erectile function (unassisted by erection aids) rate of 20-25%. This rate was obtained from data in the control arm of trials after nerve sparing radical prostatectomy (NSRP) over the last two decades (5).

Phosphodiesterase phosphate-5 inhibitors (PDE5I) are the first line therapeutic option for organic ED, including ED post RP. In some studies, unassisted erectile function preoperatively was associated with preserved potency post RP in 94% of cases, but self--reported return to baseline erectile function status was shown in less than 40% and 23% of patients with and without the use of PDE5I, respectively (6).

The plausible hypothesis for the use of PDE5I in erection rehabilitation after RP has been investigated in multiple randomized, controlled trials. Although there is no consensus on the definition or algorithm for erection rehabilitation, a multidisciplinary approach addressing general and psychological well-being of patients and their partners, in addition to medical therapeutic options, would facilitate sexual function recovery post RP, including erectile function.

ED post RP

ED post RP is mainly due to surgical trauma resulting in neurapraxia and/or injury of the cavernous nerve, which triggers a penile remodeling process. This process includes endothelial dysfunction and ischemic changes in the penile tissue with fibrosis of cavernosal smooth muscle. Different surgical approaches have been described to mitigate the risk of cavernous nerve injury (7).

Definition of Erection Rehabilitation

Erection rehabilitation was introduced more than a decade ago, in response to an increasing understanding of the anatomical, pathophysiological and biochemical basis of ED post RP. It involves the use of any intervention or combination of interventions (i.e., medications and devices) with the goal of restoring erectile function to pretreatment levels, according to the fourth International Consultation of Sexual Medicine (ICSM 2015) (8).

Evidence supporting PDE5I in ED post RP

PDE5I operate via a well-established mechanism of action for eliciting an improved erection response, through potentiating the NO-mediated relaxation of cavernosal smooth muscle by inhibiting the degradation of its downstream effector cyclic GMP (9). This mechanism of action pertains mainly to its therapeutic use in ED.

Evidence from animal models of cavernous nerve injury resembling the effects of ED post RP has supported the potential positive effect of PDE5I on erectile function recovery. PDE5I help alleviate penile remodeling in terms of promoting cavernous nerve regeneration, reducing inflammation and fibrosis of erectile tissues (10,11).

Erection Rehabilitation RCTs

Multiple RCTs have attempted to study the use of PDE5I for erection rehabilitation post RP. Erectile function recovery in most RCTs was defined by (IIEF-Erectile function (EF) >21 or >22, and Sexual Encounter Profile question 3 [SEP3, successful intercourse rate]). The described "PDE5I-assissted erectile function recovery" during treatment period of the study, reflects ED post NSRP responsiveness to treatment with PDE5I.Erectile function recovery is reflected more accurately ,when IIEF-EF and SEP3 scores are reported based on spontaneous erections during the drug free washout period.

The first study which spearheaded this approach was done by Padma-Nathan et al. (12) in 2008: a randomized, double-blind and placebo-controlled trial for men with normal preoperative erectile function (combined score >7 in response to questions 3 and 4 of the International Index of Erectile Function questionnaire [IIEF]) treated with open NSRP. Nightly sildenafil administration for 36 weeks after surgery significantly increased the frequency of PDE5I-assissted erectile function (P=0.0156), with higher mean scores in response to questions 3 and 4 of the IIEF questionnaire. Four weeks after surgery all 125 men were randomized to double-blind sildenafil (50-100mg) or placebo nightly for 36 weeks, followed by a drug-free washout period for 8 weeks prior to erectile function assessment. Enrollment was stopped prematurely and only 76 men completed the trial, due to a suggested lack of treatment effect at an interim blinded analysis. In a post-termination analysis using Fisher exact test of men who completed the trial, spontaneous erectile function was reported by 27% and 4% of men who received sildenafil (50-100mg) and placebo, respectively. A longer duration of nocturnal erections was also reported in men who responded to sildenafil than non-responders (12).

In two double-blind RCTs [REINVENT (13) and REACTT (14)] Montorsi et al. assessed the effect of PDE5Is nightly versus on-demand on erection rehabilitation post NSRP. REINVENT (Recovery of Erections: Intervention with Vardenafil Early Nightly Therapy) in 2008 assessed the effect of nightly vardenafil (5 or 10mg) versus on-demand (5mg, 10mg or 20mg) taken beginning 4 weeks after NSRP and for 9 months, followed by a 2-month washout period. There was no significant improvement in terms of erectile function recovery (IIEF-EF >21, and [SEP3, successful intercourse rate]) after the washout period. On the other hand, there was a significant improvement of IIEF-EF scores in the on-demand users

of vardenafil when compared with the placebo group (P=0.0001), 48.2% and 24.8%, respectively. SEP3 scores also improved significantly in on-demand users, when compared with nightly dosing or placebo. On-demand dosing of PDE5I is effective treatment in potentiating assisted erections post RP, with no clear positive effect on erection rehabilitation in the same setting (13).

In a large RCT (REACTT), Montorsi et al. (14) in 2014 assessed the effect of daily tadalafil (5mg) versus on-demand (20mg) on erection rehabilitation taken beginning 4 weeks after NSRP and taken for 9 months, followed by a 6 week washout period, and subsequent 3 months open-label treatment with tadalafil 5mg once daily. Men with low and intermediate-risk prostate cancer, with good baseline erectile function preoperatively (IIEF-EF >22), and no medical conditions associated with ED underwent NSRP. ED was defined as [(patient-reported Residual Erection Function score ≤3: "penis is hard enough for penetration but not completely hard")]. Outcomes measured were the rate of IIEF-EF score of >22, SEP3 score and stretched penile length.

The rate of achieving IIEF-EF score >22 was significantly higher (P=0.016) in the once-daily tadalafil (5mg) group, when compared to placebo (25.2% versus 14.2%) during the 9 months' treatment period. There was no statistical significant difference between different groups in achieving IIEF-EF >22 after the washout period and open-label treatment. In a recent analysis, Mulhall et al (15) confirmed that changing the definition for erectile function recovery from IIEF-EF score ≥22 to the more strict definition of "returning back-to-baseline IIEF-EF" had no major impact. Tadalafil (5mg) used once-daily had no effect on erectile function recovery post NSRP, but it improved PDE5I-assisted erectile function after 9 months (15).

Although the change in stretched penile length was significantly less (P=0.032) in the on-demand group when compared to placebo, the difference of penile length loss was only 4.1mm. The suggested potential protective effect of early once-daily tadalafil (5mg) on cavernosal tissues after NSRP and prevention of penile length loss, was echoed in a 2015 analysis of the on-demand tadalafil use by Brock et al. (16).

A post open-label period analysis of the (REACTT) data (14) showed a significantly higher positive SEP3 response rate in the once-daily tadalafil (5mg) group than the placebo group during the double blinded treatment period (55.3% versus 37.8%, P=0.010). It was not significant when compared with the on-demand tadalafil (20mg) group. In a further analysis of the (REACTT) data (14) performed by Moncada et al. (17) in 2015, during the 9 months double-blind treatment , a statistically significant shorter time to PDE5I-assisted erectile function was associated with the once daily tadalafil (5.8 months = 0.03), and on-demand groups (9 months = 0.01), when compared to placebo (9.3 months).

Predictors for erectile function recovery post NSRP were investigated in a recent analysis of the (REACTT) (18). IIEF related predictors included: high preoperative sexual desire, satisfaction with sexual performance and confidence. Pertinently, once-daily tadalafil (5mg) was among the additional non-IIEF related predictors, including use of robotic surgery versus other approaches and quality of nerve sparing (18).

Evidence synthesis

Although there is a rationale supporting erection rehabilitation post RP based on an increasing understanding of the postoperative changes in the physiology of erection and anatomical structures of the penis, there is no consensus to establish an algorithm for management of erection rehabilitation.

A clear distinction should be made between two endpoints, the recovery of erectile function post RP in terms of a patient's ability to obtain an unassisted erection, and response to PDE5I treatment when used for organic ED post RP to obtain PDE5I-assisted erections. Erectile function recovery in most RCTs was based on self-reported functional parameters(IIEF-EF and SEP3),which reflects ED post NSRP responsiveness to PDE5I during treatment period of the study. Erectile function recovery is reflected more accurately, when IIEF-EF and SEP3 scores are reported based on spontaneous erections during the drug free washout period.

Evidence from animal models of cavernous nerve injury resembling the effects of ED post RP has supported the potential positive effect of PDE5I on erectile function recovery. PDE5I help alleviate penile

remodeling in terms of promoting cavernous nerve regeneration and reducing inflammation and fibrosis of erectile tissues (10, 11). Nevertheless, multiple RCTs (12-14) did not show clear evidence of a sustained positive effect on spontaneous erectile function after using PDE5I for erection rehabilitation. The use of PDE5I whether on-demand or daily, was not shown to enhance patients' ability to obtain an unassisted erection (i.e. erectile function recovery), at a statistically significant level after the washout period. There is also a potentially significant added health care cost with the daily use of PDE5I. Although tadalafil use was associated with a statistically significant effect in preserving stretched penile length after NSRP in two analyses, the difference in length was only 4.1mm (15, 16). It is unclear whether this improvement is clinically relevant.

CONCLUSIONS

Our recent literature review supports the use of an on-demand approach of PDE5I to treat ED post NSRP by facilitating PDE5I-assisted erections. Despite evidence of positive effects of PDE5I on erectile tissue after cavernous nerve injury from animal models, in addition to penile length preserving effect in humans, there is no clear evidence to support a sustained positive effect of PDE5I use as erection rehabilitation post NSRP, in terms of a patients' ability to obtain unassisted erections. It is possible that in the foreseeable future and with advancement at the basic science level, a better understanding would culminate in a rigorous and evidence based approach for erection rehabilitation post RP.

REFERENCES

1. Walsh PC, Donker PJ. Impotence Following Radical Prostatectomy: Insight into Etiology and Prevention. J Urol. 2017;197(2S):S165-S170.
2. Mulhall JP, Bivalacqua TJ, Becher EF. Standard operating procedure for the preservation of erectile function outcomes after radical prostatectomy. J Sex Med. 2013;10:195-203.
3. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2009;6:2538-46.
4. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62:418-30.
5. Schauer I, Keller E, Müller A, Madersbacher S. Have rates of erectile dysfunction improved within the past 17 years after radical prostatectomy? A systematic analysis of the control arms of prospective randomized trials on penile rehabilitation. Andrology. 2015;3:661-5.
6. Sopko NA, Burnett AL. Erection rehabilitation following prostatectomy—current strategies and future directions. Nat Rev Urol. 2016;13:216-25.
7. Salonia A, Burnett AL, Graefen M, Hatzimouratidis K, Montorsi F, Mulhall JP, et al. Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. Eur Urol. 2012;62:273-86.
8. Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, Hatzimouratidis K, et al. Sexual Rehabilitation After Treatment For Prostate Cancer-Part 2: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2017;14:297-315.
9. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int. 2005;96:257-80.
10. Sirad F, Hlaing S, Kovanecz I, Artaza JN, Garcia LA, Rajfer J, et al. Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. J Sex Med. 2011;8:1048-60.
11. Martínez-Salamanca JI, Zurita M, Costa C, Martínez-Salamanca E, Fernández A, Castela A, et al. Dual Strategy With Oral Phosphodiesterase Type 5 Inhibition and Intracavernosal Implantation of Mesenchymal Stem Cells Is Superior to Individual Approaches in the Recovery of Erectile and Cavernosal Functions After Cavernous Nerve Injury in Rats. J Sex Med. 2016;13:1-11.
12. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, Montorsi F, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20:479-86.
13. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54:924-31.
14. Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65:587-96.

15. Mulhall JP, Brock G, Oelke M, Fode M, Probst KA, Henneges C, et al. Effects of Tadalafil Once-Daily or On-Demand vs Placebo on Return to Baseline Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy--Results from a Randomized Controlled Trial (REACTT). J Sex Med. 2016;13:679-83.
16. Brock G, Montorsi F, Costa P, Shah N, Martinez-Jabaloyas JM, Hammerer P, et al. Effect of Tadalafil Once Daily on Penile Length Loss and Morning Erections in Patients After Bilateral Nerve-sparing Radical Prostatectomy: Results From a Randomized Controlled Trial. Urology. 2015;85:1090-6.
17. Moncada I, de Bethencourt FR, Lledó-García E, Romero-Otero J, Turbi C, Büttner H, et al. Effects of tadalafil once daily or on demand versus placebo on time to recovery of erectile function in patients after bilateral nerve-sparing radical prostatectomy. World J Urol. 2015;33:1031-8.
18. Montorsi F, Oelke M, Henneges C, Brock G, Salonia A, d'Anzeo G, et al. Exploratory Decision-Tree Modeling of Data from the Randomized REACTT Trial of Tadalafil Versus Placebo to Predict Recovery of Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy. Eur Urol. 2016;70:529-37.

.

Arthur L. Burnett, MD, PhD

The James Buchanan Brady Urological Institute and
Department of Urology,
The Johns Hopkins School of Medicine, Baltimore, MD, USA
JHH-407 Marburg
Maryland, 21287, USA
Fax: +1 410 614-3695
E-mail: aburnett@jhmi.edu

DIFFERENCE OF OPINION

Vol. 43 (3): 390-393, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2017.03.04

PDE-5 inhibitors should be used post radical prostatectomy as erection function rehabilitation?

Opinion: No

Jonathan Clavell-Hernández [1], Run Wang [1,2]

[1] Division of Urology, Department of Surgery, University of Texas Medical School at Houston, Houston, Texas, USA; [2] University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

Keywords: Phosphodiesterase 5 Inhibitors; Erectile Dysfunction; Penile Erection; Prostatectomy

INTRODUCTION

The advancement and refinement in prostate cancer detection and treatment modalities have contributed to a younger patient population undergoing radical prostatectomy (RP) (1). Although it is effective in treating prostate cancer, radical prostatectomy has also been shown to compromise erectile function (EF), and therefore the patient's quality of life and general well being (2). Alemozaffar et al. (3) attempted to predict erectile function after prostate cancer patients undergoing RP, external radiotherapy and brachytherapy. Pretreatment sexual health related quality of life score, age, serum prostate-specific antigen level, race/ethnicity, body mass index and intended treatment details were associated with functional erections 2 years after treatment. They found that 48% of patients (n=1027) with functional erections prior to treatment reported erectile dysfunction 2 years after treatment. In the prostatectomy cohort, 60% of patients with prior functional erections reported erectile dysfunction, along with 42% and 37% of the external radiotherapy and brachytherapy cohorts, respectively. The Prostate Cancer Outcomes study revealed 60% of men experienced self-reported erectile dysfunction 18 months after radical prostatectomy, and only 28% of men reported erections firm enough for intercourse at a 5-year follow-up (4). Many urologists believe more patients would be willing to undergo surgical treatment if it were not for the possibility of developing postoperative ED (2).

The discovery of the neurovascular bundle sparing technique by Dr. Patrick Walsh enabled urologists to provide hope of regaining erectile function after radical prostatectomy (5). However, despite meticulous dissection to preserve the neurovascular bundle, there is evidence that neuropraxia, ischemic and hypoxic nerve insults, fibrotic remodeling, and apoptosis of cavernous smooth muscle contribute to post-surgery erectile dysfunction (6).

After understanding the mechanisms that promote ED after radical prostatectomy, multiple studies have been focused on evaluating ways to increase oxygenation to the cavernosal bodies, decrease tissue fibrosis and apoptosis, and consequentially improve erectile function. In theory, the role of penile rehabilitation is to maintain tissue oxygenation and prevent tissue fibrosis until the cavernosal nerves recover from neuropraxia with the return of spontaneous nocturnal tumescence. However, evidence from our daily clinical practice demonstrates that penile rehabilitation does not necessarily guarantee the return of unassisted spontaneous erections.

By preventing the breakdown of cGMP, PDE-5 inhibitors may exert a protective effect on cavernosal smooth muscle after prostatectomy (7). However, despite their effectiveness in other forms of erectile dysfunction, their success in penile rehabilitation has not been proven to be as transparent. Padma-Nathan et al. (8) performed the first multicenter, double-blind, randomized, placebo-controlled trial to our knowledge investigating the effects of PDE5is on EF after RP. They randomized 125 patients into three treatment groups: placebo, Sildenafil citrate 50mg and Sildenafil citrate 100mg. Out of the 125 patients, only 76 completed the post-8-week washout evaluation period. After the post-washout period, only one of 25 patients (4%)in the placebo arm had adequate EF, versus 14 of 51 patients (27%) in the sildenafil 50mg and 100 mg groups combined (p=0.016). Although they suggested that nightly sildenafil has a benefit for patients with post-prostatectomy ED, there was a significant dropout rate which could call into question the statistical power of the study.

In 2008, Montorsi et al. (9) published a trial that investigated the effect of vardenafil in postoperative penile rehabilitation. This multicenter, double-blind placebo-controlled trial randomized 628 patients with a baseline International Index of Erectile Function (IIEF) score of >26 into taking nightly vardenafil, on-demand vardenafil, or placebo for 9 months. After 9-month treatment period, on-demand vardenafil was associated with more patients obtaining ≥22 on the EF domain of IIEF (IIEF-EF) score. However, after the 2 month washout period, there was no statistically significant difference in erectile function between groups. Similarly, dropout rates were substantial, ranging between 31%-35% in the study arms and there was no defined limit in the drug usage in the on-demand arm. Moreover, the data argued against the use of nightly PDE5i in the treatment of ED after radical prostatectomy.

Pavlovich et al. (10) pursued to investigate whether nightly sildenafil had an advantage over on--demand sildenafil. They randomized 100 men with good EF who had undergone nerve-sparing RP into two groups. The nightly sildenafil group consisted of patients taking nightly sildenafil and on-demand placebo; and the on-demand group consisted of on-demand sildenafil (with a maximum on-demand dose of 6 tablets per month) and nightly placebo starting the day after surgery for 12 months. All men had previously completed an IIEF-EF survey before surgery and had a score of ≥26 before undergoing nerve-sparing RP. Surgeons prospectively recorded the quality of NVB preservation, and this was quantified using a nerve sparing score (NSS) of one to four, with higher scores representing better preservation. The double-blind study period included quality of life assessments every 3 months for 12 months after RP, and a final assessment at 13 months after a washout period of 1 month. Compliance in returning questionnaires ranged from 60%-96% per time-point but was balanced between groups. After adjusting for potential confounding factors, no significant differences were found in EF between treatments at any single time-point after RP. NSS was the only factor that was consistently found to have a significant association with EF outcomes in all longitudinal multivariable models. This study did show some limitations. First, fearing that patients would not want to be randomized to a placebo-only group, a pure placebo arm was not part of the trial. Moreover, 90% of subjects were Caucasian which is not generalizable to all populations.

The REACTT study conducted by Montorsi et al. (11) aimed to compare the efficacy of tadalafil daily and on demand versus placebo in improving unassisted EF and reducing loss of penile length following nerve-sparing RP. Four hundred twenty-three patients were randomized into 9 months of treatment with tadalafil 5mg once daily, tadalafil 20mg on demand, or placebo followed by a 6-week washout period and 3 months open-label tadalafil once daily (to all patients). At 9 months, they found a significant difference in reaching target IIEF-EF ≥22 in the tadalafil once daily group compared to

placebo. However, after the drug free washout period, there was no significant difference in EF between groups. After the open-label tadalafil once daily period, IIEF-EF scores increased in all treatment groups. Regarding penile length, there was significant protection from penile length loss in the daily tadalafil group (2.2mm) compared to other groups (7.9 mm on demand, 6.3mm placebo) at 9 months of treatment. Mulhall et al. reported a descriptive post-hoc analysis using a more strict definition for EF-recovery of returning back to the pre-surgery IIEF-EF level ("back-to-baseline analysis"). However, this had no major impact on results and showed no effect on unassisted EF following treatment cessation after 9 months (12).

All these studies evaluated the use of PDE5is by relying on self-reported outcomes to determine efficacy of therapy which could lead to response bias. Kim et al. (13) conducted a study to evaluate the effects of nightly sildenafil therapy using a more objective approach with nocturnal penile rigidity (RigiScan TM, Gotop Medical, Inc., St Paul, MN, USA) in addition to the IIEF-EF score. They randomized 97 patients of which 74 completed the study into taking daily sildenafil with on-demand sildenafil or daily placebo with on-demand sildenafil. Outcomes were evaluated every 3 months for 12 months and at 13 months after 1 month wash-out period. They noted no significant difference in EF between treatment groups based on IIEF-EF domain or RigiScan, suggesting that nightly sildenafil has no benefit over on--demand sildenafil.

CONCLUSIONS

Although there is not enough evidence to create an algorithm for penile rehabilitation, the use of PDE5-inhibitors has been well-tolerated and no significant harm of rehabilitation has been demonstrated provided the patients understand the side-effects and costs. This has driven urologists to include penile rehabilitation programs in their practices (14). Most have adopted the use of PDE5-inhibitors, either as monotherapy or in combination with other modalities. However, if we base our practice according to current data, the possibility exists that many urologists have integrated penile rehabilitation with PDE5--inhibitors into their practices based more on theoretical hope than concrete evidence. We have noted that research in penile rehabilitation is leading towards the use of combination therapies (15). The ideal rehabilitation modality should consist of one that is effective, convenient, not too expensive and exerts minimal side effects on the patient. Current research lacks convincing data that PDE5 inhibitors contribute to the complete restoration of spontaneous erectile function.

REFERENCES

1. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol. 2011;29:235-41.
2. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008;358:1250-61.
3. Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, et al. Prediction of erectile function following treatment for prostate cancer. JAMA. 2011;306:1205-14.
4. Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD, et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. J Urol. 2008;179(5 Suppl):S40-4.
5. Walsh PC, Partin AW, Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. J Urol. 1994;152(5 Pt 2):1831-6.
6. Wang R. Penile rehabilitation after radical prostatectomy: where do we stand and where are we going? J Sex Med. 2007;4(4 Pt 2):1085-97.
7. Kovanecz I, Rambhatla A, Ferrini M, Vernet D, Sanchez S, Rajfer J, et al. Long-term continuous sildenafil treatment ameliorates corporal veno-occlusive dysfunction (CVOD) induced by cavernosal nerve resection in rats. Int J Impot Res. 2008;20:202-12.
8. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, Montorsi F, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20:479-86.

9. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54:924-31.
10. Pavlovich CP, Levinson AW, Su LM, Mettee LZ, Feng Z, Bivalacqua TJ, et al. Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int. 2013;112:844-51.
11. Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65:587-96.
12. Mulhall JP, Brock G, Oelke M, Fode M, Probst KA, Henneges C, et al. Effects of Tadalafil Once-Daily or On-Demand vs Placebo on Return to Baseline Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy--Results from a Randomized Controlled Trial (REACTT). J Sex Med. 2016;13:679-83.
13. Kim DJ, Hawksworth DJ, Hurwitz LM, Cullen J, Rosner IL, Lue TF, et al. A prospective, randomized, placebo-controlled trial of on-Demand vs. Nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function. Andrology. 2016;4:27-32.
14. Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med. 2011;8:2370-6.
15. Clavell-Hernández J, Wang R. The controversy surrounding penile rehabilitation after radical prostatectomy. Transl Androl Urol. 2017;6:2-11.

Run Wang, MD, PhD

Division of Urology, Department of Surgery
University of Texas Medical School at Houston
6410 Fannin Street
Suite 420 Houston, TX 77030, USA
Telephone: + 1 832 325-7280
E-mail: run.wang@uth.tmc.edu

REVIEW ARTICLE

Vol. 43 (3): 394-406, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0078

Analgesia for patients undergoing shockwave lithotripsy for urinary stones – a systematic review and meta-analysis

Omar M. Aboumarzouk [1], Rami Hasan [2], Ali Tasleem [2], Martin Mariappan [2], Rachael Hutton [3], John Fitzpatrick [3], Laura Beatty [3], Gareth E. Jones [2], Tarik Amer [2]

[1] North Bristol NHS Trust, United Kingdom; [2] NHS Greater Glasgow and Clyde, United Kingdom; [3] Ayr University Hospital, United Kingdom

ABSTRACT

Background: Shock wave lithotripsy (SWL) is the first line treatment modality for a significant proportion of patients with upper urinary tracts stones. Simple analgesics, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are all suitable agents but the relative efficacy and tolerability of these agents is uncertain.

Objectives: To determine the efficacy of the different types of analgesics used for the control of pain during SWL for urinary stones.

Materials and Methods: We searched the Cochrane Renal Group's Specialised Register, MEDLINE, EMBASE and also hand-searched reference lists of relevant articles (Figure-1). Randomised controlled trials (RCT's) comparing the use of any opioid, simple analgesic or NSAID during SWL were included. These were compared with themselves, each-other or placebo. We included any route or form of administration (bolus, PCA). We excluded agents that were used for their sedative qualities. Data were extracted and assessed for quality independently by three reviewers. Meta-analyses have been performed where possible. When not possible, descriptive analyses of variables were performed. Dichotomous outcomes are reported as relative risk (RR) and measurements on continuous scales are reported as weighted mean differences (WMD) with 95% confidence intervals.

Results: Overall, we included 9 RCTs (539 participants from 6 countries). Trial agents included 7 types of NSAIDs, 1 simple analgesic and 4 types of opioids. There were no significant differences in clinical efficacy or tolerability between a simple analgesic (paracetamol) and an NSAID (lornoxicam). When comparing the same simple analgesic with an opioid (tramadol), both agents provided safe and effective analgesia for the purpose of SWL with no significant differences. There were no significant differences in pain scores between NSAIDs or opioids in three studies. Adequate analgesia could be achieved more often for opioids than for NSAIDs (RR 0.358; 95% CI 043 to 0.77, P=0.0002) but consumed doses of rescue analgesia were similar between NSAIDs and opioids in two studies (P=0.58, >0.05). In terms of tolerability, there is no difference in post-operative nausea and vomiting (PONV) between the groups (RR 0.72, 95% CI 0.24 to 2.17, P=0.55). One study compared outcomes between two types of NSAIDs (diclofenac versus dexketoprofen). There were no significant differences in any of our pre-defined outcomes measures.

Conclusion: Simple analgesics, NSAIDs and opioids can all reduce the pain associated with shock wave lithotripsy to a level where the procedure is tolerated. Whilst there are no compelling differences in safety or efficacy of simple analgesics and NSAIDs, analgesia is described as adequate more often for opioids than NSAIDs.

ARTICLE INFO

Keywords:
Calculi; Lithotripsy; Urinary Tract

Int Braz J Urol. 2017; 43: 394-406

Submitted for publication:
February 16, 2016

Accepted after revision:
November 19, 2016

Published as Ahead of Print:
March 24, 2017

INTRODUCTION

Urolithiasis (formation of urinary tract calculi) is common and the incidence is increasing worldwide (1). The lifetime risk is around 13% in men and 7% in women with the peak incidence in the third-to-fourth decades of life (2). Although most individuals will experience only a single episode throughout their lifetime, approximately 25% will have recurrent stone (calculi) formation (1). The process of urolithiasis occurs when urine becomes a supersaturated solution; urinary substances that are normally present in stable levels exceed the level at which they are soluble. This subsequently leads to the formation of crystals through the process of nucleation which then aggregate to form stones (3). Most commonly, stones contain calcium (calcium oxalate and calcium phosphate) with a prevalence of around 84% (1). Other types of stones include: uric acid stones (7-12%), infection (struvite) stones, (4-11%), cystine stones (<1%) and rare stone types (xanthine, 2, 8-dihydroxyadenine, indinavir) (1, 4, 5).

The aim of shock wave lithotripsy (SWL) is to cause fragmentation of a kidney stone thereby facilitating its removal or expulsion. This is achieved by targeting the stone with an externally generated shock wave that is able to propagate through the body (5). Since its introduction in the early 1980s, SWL has revolutionised the management of urinary tract stones (6). Although more than 90% of stones may be considered suitable for treatment with SWL (7, 8) success is dependent on a combination of the following factors:

- size, location and composition of stones
- patient body habitus
- performance of SWL (4)

Success rates of SWL are reported to be 50-80% but this is dependent on the factors above (5). It is important to consider that residual or larger non-fragmented stones can remain that may require either further SWL sessions or an alternative procedure, such as ureteroscopy (URS). The European Association of Urology (4) and the American Urological Association (AUA) (9) consider both SWL and URS as reasonable options for any stone that requires intervention. SWL is regarded as first line management for stones <20mm within the renal pelvis and upper or middle calices (4). It is considered the second line treatment for stones >20mm or for lower pole stones which are <20mm but have unfavourable characteristics for SWL success (shockwave-resistant stones, steep infundibular-pelvic angle, lower pole calyx >10mm, infundibulum <5mm) (4). Although SWL is less favoured for the treatment of ureteric stones, several studies have demonstrated a higher stone-free rate for proximal ureteric stones <10mm when compared to URS (4).

The energy generated by shock waves from SWL produces and influences pain in a number of ways (10).

Direct effect of shock waves on cutaneous pain receptors

Tension within the renal capsule

Movement of stone fragments

Shock wave impact to bones (11th/12th rib, transverse processes, vertebrae) and other skeletal structures

Instrumentation factors (type of lithotriptor, frequency, voltage)

Patient factors (sex, age, pain tolerance) (5, 10)

Pain relief during SWL is important, not only in providing patient comfort, but also in facilitating the success of treatment; stone targeting is improved by reducing pain-induced movements and excessive respiratory excursions (4, 10, 11). A substantial body of evidence exists that compares pain relief modalities during SWL. These include topical preparations, transcutaneous electrical nerve stimulation, anaesthetic injections (local, epidural, extradural), intravenous sedation (propofol), inhaled agents (nitrous oxide) and non-traditional methods (music, acupuncture) (10-17). Although a consensus has yet to be reached regarding the optimal pain management for patients undergoing SWL, the development of newer lithotripters that require lower energy levels and less skin surface contact has led to improvements in pain levels and consequently the need for peri-procedural analgesia (6, 10, 18).

SWL is commonly performed and is recommended as the first line treatment for a significant proportion of kidney stones (4). Given that the level of patient comfort can directly influence treatment outcome, it is essential that adequate analgesia is provided during SWL. As primarily an outpatient

procedure, the use of anaesthetics and sedatives are actively discouraged (18, 19) and therefore an effective analgesic arsenal is important. A number of studies have reported the use of paracetamol (para-acetyl aminophenol), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids in SWL with varying degrees of analgesic success (18, 20, 21). Therefore, debate surrounding the most effective analgesic class still remains. The current EAU guidelines recommend the use of NSAIDs for acute renal colic but do not offer advice on specific analgesics to manage pain during SWL (4). Given the lack of current consensus in the face of a relative abundance of studies on this topic, it would seem logical that a systematic review should be carried out to establish the efficacy of different analgesics for SWL.

OBJECTIVES

The primary objective of this review was to determine the relative efficacy of the different types of analgesics used for the control of pain during SWL for urinary stones (NSAIDs, opioids, simple analgesics). The secondary objective was to evaluate the safety of the various analgesics used, the need for adjuvant analgesia and SWL parameters such as shock wave energy and duration, stone size and location. We also planned to investigate complications related to the drug therapy (such as nausea, vomiting, diarrhoea, constipation, respiratory depression and desaturation.

MATERIALS AND METHODS

Inclusion criteria

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs assessing analgesia for patients undergoing SWL were included. Comparisons included simple analgesics, NSAIDs or opioids. These trials could compare the drug classes above to themselves or to a placebo.

Types of participants

Any adult patient undergoing shock wave lithotripsy treatment for kidney or ureteric stones.

Types of interventions

The interventions of interest are the analgesic efficacy and safety of the above drug classes for the purpose of SWL. We excluded a trial involving rofecoxib which was removed from the market (22). Analgesics include para-acetyl aminophenol (paracetamol); non-steroidal anti-inflammatory drugs (NSAIDs); and opioids.

We excluded agents which were used for their sedative qualities (dexmedetomidine, propofol and midazolam infusions) as these require anaesthetic input and thus would not be relevant to modern ambulatory lithotripsy services such as those in the UK.

Outcome measures

Studies reporting any of the following primary outcome measures were eligible for inclusion:

1. Patient reported pain assessments (visual analogue scales, verbal rating scale, simple descriptive scales) AND/OR requirement for rescue analgesia, frequency of uncontrolled pain.
2. Patient factors: age, sex, weight, height, stone burden and location.
3. Analgesic consumption (frequency and or doses).
4. Procedure variables: duration, energy, number of shocks.
5. Complications: major (renal injury, steinstrasse, bleeding and respiratory depression) and minor complications (nausea, vomiting, pain and dizziness).

Search methods

Electronic searches

We searched the Cochrane Renal Group's Specialised Register [up to 31st April 2014]. The Cochrane Renal Group's Specialised Register contains studies identified from:

- Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
- Weekly searches of MEDLINE OVID SP
- Hand-searching of renal-related journals and the proceedings of major renal conferences

- Searching of the current year of EMBASE OVID SP
- Weekly current awareness alerts for selected renal journals
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Data collection and analysis

Selection of studies

Medline, EMBASE and Cochrane renal databases were searched until January 2014. A combination of the following MeSH terms and keywords was used:

'analgeisa' or 'shockwave lithotripsy' or 'NSAIDs' or 'opiates', 'simple anlagesics' or 'calculi' and 'stones', 'nephrolithiasis', 'randomised control trial'. DARE (Database of Abstracts of Reviews of Effectiveness) databases were also checked for any systematic reviews. The only language restrictions were that at least the abstract had to be in English, thus permitting extraction of relevant data. References from selected articles and reviews were also evaluated to minimise the risk of missing relevant articles.

Three authors (O.A, L.B and T.A.) followed the above inclusion criteria to select potentially relevant articles through abstract screening. Full texts of relevant articles were retrieved and screened for inclusion. Where differences of opinion emerged between the researchers regarding article eligibility, correspondence was conducted until a consensus was reached.

Data extraction and management

Data extraction was carried out independently by three authors (T.A, O.A, R.H) and findings tabulated into MS Excel. Where more than one publication of one study existed, reports were be grouped together and only the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions, these data was used. Any discrepancy between published versions was highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by the three authors using the risk of bias assessment tool (23).

Factors influencing bias to be assessed in the review include:

Sequence generation: Was the allocation sequence adequately generated (selection bias)?

Allocation sequence concealment: Was allocation adequately concealed (selection bias)?

Blinding: Was knowledge of the allocated intervention adequately prevented during the study (detection bias)?

Incomplete outcome data: Were incomplete outcome data adequately addressed (attrition bias)?

Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?

Other potential sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

For dichotomous outcomes, such as pain relief assessment, patient or operator satisfaction, and duration of treatment, results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment, such as number of treatments required, shock waves needed, and size and location of the stones in the renal system, the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (24). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (23).

Data synthesis

Data will be pooled using the random--effects model but the fixed-effect model will also

be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, study quality, that is, analyses of the impact of studies with poor methodology on the final result, or intervention such as different lithotripters). Heterogeneity among participants could be related to age and renal pathology (stone size, location, or composition of stone). Heterogeneity in treatments could be related to prior agents used and the agent, dose and duration of therapy (different dosages of the same medication or different route of administration; or patients were on analgesics for the management of other sources of pain; or the SWL session was considered to be complicated or uncomplicated and required higher dosages of analgesia; lithotripsy differences including type and power setting used). Adverse effects will be tabulated and assessed with descriptive techniques, because they are likely to be different for various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared with no treatment or to another agent.

RESULTS

Description of studies

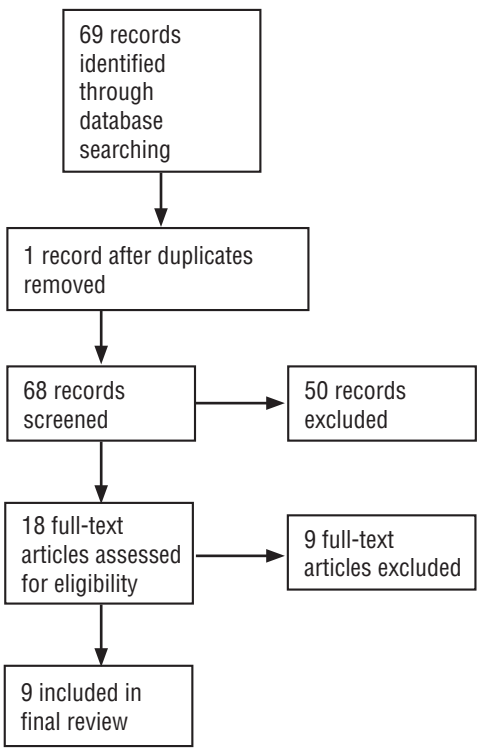
Results of the search

The search strategy identified 68 potentially relevant citations. Of these, 50 trials were excluded on abstract review because they did not meet the inclusion criteria above. Exclusion reasons included studies not being randomized or not comparing simple analgesics, NSAIDs or opioids with themselves or placebo. We assessed 18 full text articles. 10 of these articles were excluded as described below (Figure-1).

Included studies

Our assessment identified 9 studies that involved 539 participants (from 6 countries) which were available for inclusion dating from years 1992 to 2010 (25-33). One of these studies had multiple treatment arms (25). Trial agents included seven types of NSAIDs (lornoxicam, piroxicam, diclofeanc, keterolac, parecoxib, indomethacin and dexketoprofen), one simple analgesic (paracetamol) and five types of opioids (tramadol, remifentanil, fentanyl and morphine and pethidine). NSAIDs were compared against placebo in three studies (26, 29, 32). There were no studies comparing opioids to placebo. Two of the 9 included studies did not report variance data in a form appropriate for meta-analysis. We contacted one of the authors who replied saying that they no longer had their original data (31). We did not hear back from the second author (30). All agents were given parenterally (IM/IV) with one given orally. No studies reported major complications. Owing to the heterogeneous methods of measuring and reporting outcomes between papers, we have been unable to aggregate all outcomes in a form suitable for meta-analysis. In such instances where this occurs, we have systematically reviewed the findings and present them accordingly.

Figure 1 - Search method for suitable studies.



Excluded studies

Four studies were excluded as they did not meet our inclusion criteria (epidural analgesia (14), intrathecal Sufentanil (34), accupuncutre (17, 35). Seven studies were excluded due to crossover between experimental and control arms (21, 36-40). It was possible to include one study where cross-over was present by using first phase data in this review (28). One study (22) was excluded as the trial agent, rofecoxib was excluded from the market. Another study was excluded because on close inspection of its methodology it was apparent that it was not a controlled trial (41).

We excluded 7 studies owing to the challenge of comparing analgesic efficacy in the presence of pre-medication with different agents to the study agents. As the time between pre-medicating and study drug administration was short in all studies, it was not permissive of drug washout. We therefore excluded studies where pre--medication was used in the interests of genuinely testing the clinical efficacy of trial agents. Although this was not a defined exclusion criterion, this was felt nevertheless to be a necessary step. As a result, the following seven studies were excluded (18, 20, 42-46). In the same vain, we also excluded a study where background patient controlled analgesia (PCA) in addition to the study agent was used therefore hindering direct comparisons between two agents. The manuscripts of two potentially relevant studies by Chia (43) and Yang (46) were not available. However, a recent meta-analysis by Mezentev and colleagues (6) utilising these papers enabled some degree of inspection; Yang (46) included multiple agents in research arms making it ineligible for inclusion. The full manuscript for Chia (43) was requested but was not available. A paper by Parkin (21) was also used in the same meta-analysis. We have already excluded this paper for the reasons of crossover of diclofenac in both NSAID and opioid arms.

Risk of bias in included studies

Assessment for risk of bias is described below. Overall, the quality of included studies is low primarily due to non-robust randomisation methods and double-blinding occurring in less than half of studies. Blinding of outcome assessment is clearly defined in only three of nine studies.

Allocation (selection bias)

There is a high risk of selection bias as only two studies (25, 27) mention a robust method of random sequence generation with the remainder not mentioning in sufficient detail to assess methodological quality in this domain. Regarding allocation, only one trial (30) described a method of randomisation which gave sufficient allocation concealment where central allocation was used. The remaining studies gave insufficient information to determine if allocation concealment was sufficient.

Blinding (performance bias and detection bias)

In four studies (25, 30, 32, 33), participants and personnel were blinded to reduce performance bias. In three studies (26, 27, 29), participants alone were blinded. In the remaining two studies, there was no mention of blinding whatsoever (28, 31).

Incomplete outcome data (attrition bias)

Incomplete outcomes were noted in one only study (28). However, the authors acknowledge this, enabling some data extraction.

Selective reporting (reporting bias)

There are no cases of selective reporting in any of the included studies.

Other potential sources of bias

In three trials (27, 30, 33), blinding of outcome assessment is clearly defined. In one study (29), blinding definitely did not occur and in five others there is insufficient information to determine if blinding of outcome assessment did occur (25, 26, 28, 31, 32). Sources of funding were noted in only one study (32).

Simple analgesics versus NSAIDs

Only one of the included trials compared simple analgesics with NSAIDs. Demographic parameters (age, sex, weight and height) were similar between the simple analgesic group (paracetamol 1g

IV) versus the NSAID group (8mg IV lornoxicam) (25). The mean stone size was 13±2.2mm and an overall stone free rate was 64.8%. Unfortunately, the authors have not divided these elements across study groups and therefore subgroup analysis in these domains cannot be performed. Pain was measured with a visual analogue scale (VAS) in this single study at enrolment and at intervals up to 30 minutes. At enrolment, pain scores were similar. Pain scores were similar between paracetamol and lornoxicam at 1, 5, 10, 15 and 25 minutes. At 20 minutes however, pain scores were significantly lower in patients taking paracetamol than those on lornoxicam (P=0.003). The post-operative pain assessment was also similar between study groups (P=0.31). There was no difference observed in the amount of supplementary analgesia required between the groups (P=0.86). Procedure duration was similar between the groups (P=0.75).

Pain control achieved and requirement for rescue analgesia

Supplemental analgesia was administered in 21/30 and 22/30 patients in the paracetamol and lornoxicam groups respectively. This figure can be used to calculate a surrogate for "adequate analgesia" as it implies the study agents alone were not enough to achieve adequate analgesia in those participants. Therefore, 9/30 paracetamol patients and 8/30 Lornoxicam patients achieved adequate analgesia (P=0.77). There was no statistically significant difference in the total dose of supplementary Alfentanil between the two study populations (P=0.86). In two paracetamol patients and three lornoxicam patients the pain was not controlled despite PCA Alfentanil but this difference is not significant (P=0.64). The authors document that overall satisfaction about the efficacy of applied analgesia reported separately by the urologist and the patient was similar in these three groups (P>0.05).

Adverse effects

There was no statistically significant difference in post-operative nausea and vomiting (PONV) between the groups, with 2/30 in the paracetamol arm and 3/30 in the lornoxicam arm (P=64). The mean voltage achieved was similar between the groups (P=0.30).

Simple analgesics versus opioids

This comparison is based on the only included paper to compare the above analgesic classes. The trial by Akcali et al. (25) had three arms, the first two discussed above. Here we assess the comparison between IV paracetamol and IV tramadol. There were no significant differences in demographic variables between study groups. Once again, one cannot perform subgroup analysis regarding stone free rates or stone burdens as the authors have provided overall figures for the whole study population.

Both agents provided effective analgesia for the purpose of SWL with no significant differences apart from pain being lower in the paracetamol arm at 1 minute (P=0.03) and at 20 minutes (P=0.05). There was no difference between the two in terms of procedure duration (P=0.37).

There was more rescue analgesia required in the opioid group versus simple analgesic group but this was not statistically significant (P=0.40). The number of people who still had uncontrolled pain despite said rescue analgesia, was 3 in the simple analgesic group and 7 in opioid group but this is not statistically different (P=0.19). There was no statistically significant difference between groups in terms of mean voltage achieved (P=0.95).

Adverse effects

There was no statistically significant difference between the two groups in terms of PONV (P=0.56) and there were no major complications reported in either group.

NSAIDs versus opioids

Four studies including 221 patients were included in this comparison (25, 28, 30, 31).

Groups were matched for age, sex and height but not weight; with there being lighter patients in the opioid group (MD 4.87; 95% CI 1.77 to 7.97; P=0.002).

Pre procedure baseline score

There was no difference in pre-procedure baseline VAS in the study by Ackal, the only team to assess this in this comparison (25).

Patient rated pain scores

There was no statistically significant difference in pain scores at 1, 5, 10 or 15 minutes in two studies (25, 30). This was also the case post-operatively at 30 minutes (P=0.80) (Figure-3). At 10 minutes, lower VAS scores were recorded in the opioid groups (25, 31) but on meta-analysis this is not significant (Figure-2: MD: 0.81, 95%CI-1.59 to 3.22; P=0.51). Mitsogiannis did not provide variance data and, as such for purposes of meta-analysis this was extrapolated from the provided P value in a method described by the Cochrane handbook (P<0.001). The author was contacted in order to obtain the original data. Unfortunately, this data is no longer available. In the same study, the mean pain score in patients in the NSAID group, after the first dose of analgesia, was significantly higher than patients in the opioid group (3.57 versus 1.76, respectively (P<0.001). However, in patients who responded to the first dose of analgesia, the mean pain scores were similar (P=0.20). After administration of supplementary analgesia, the mean pain scores reported by the patients in both groups did not differ significantly (mean 1.56 versus 1.82, respectively, P=0.21) (31).

Supplementary analgesia

The total dose of rescue analgesia (PCA) in the one included study that reported this was lower for NSAIDs but was not statistically significant (P=0.58) (25). Issa reports no statistically significant difference between NSAIDs and opioids in terms of supplemental analgesia (P>0.05). Due to an absence of provided variance data this data cannot be pooled for meta-analysis (30).

Adequate analgesia

This was calculated by assessing those patients who did not require additional analgesia (either a second dose of study agent or an alternative agent for breakthrough pain). On meta-anaylsis, analgesia could be defined 'adequate' more often for opioids than for NSAIDs (Figure-4: RR 0.358; 95% CI 043 to 0.77, P=0.0002) (25, 28, 31).

Uncontrolled pain despite additional analgesia

This measure was recorded in one study (25), despite there being more cases of uncontrolled pain in the opioid group this is not significant (P=0.09).

Procedure duration

There was no difference in procedure duration between NSAIDs and opioids in terms of procedure duration (MD 0.67, 95% CI from -0.24 to 1.58, P=0.15) (25).

Figure 2 - Comparison between NSAIDs and opioids, visual analogue score at 10 minutes.

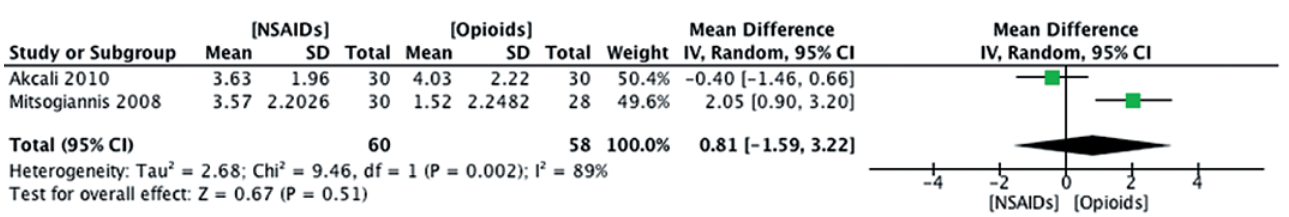


Figure 3 - Comparison between NSAIDS and opioids, post-op visual analogue score.

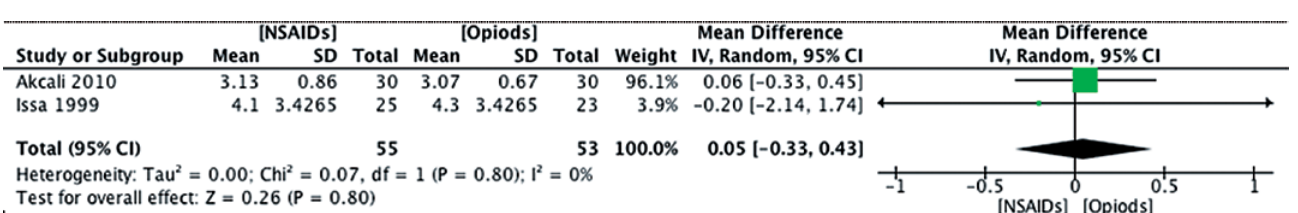
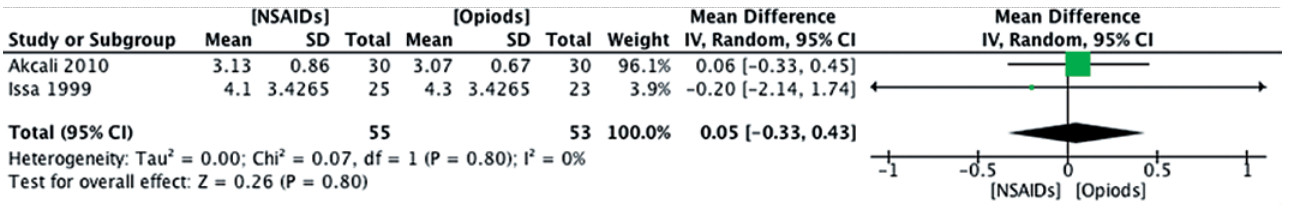


Figure 4 - Comparison between NSAIDs and opioids, adequate analgesia achieved.



Complications

There was no statistically significant difference between three of the four studies (25, 30, 31).

Voltage

There was no statistically significant difference in mean voltage achieved between NSAIDs and opioids (MD 0.80, 95% CI from -0.45 to 2.05, P=0.21) (25), or the percentage mean maximum shock wave level achieved between the groups (MD-0.40, 95% CI from -1.22 to 0.42, P=0.34) (31). Another study found no difference in the number of patients reaching a maximum energy level of 26kv, (RR 0.19, 95% CI from 0.01 to 4.05; P=0.28) (28).

Number of shocks

There were no differences in the number of shock waves between NSAIDs and opioids (MD -15.00, 95% CI from -34.13 to 4.13, P=0.51) (31). Issa et al. (30) provided no variance data and as such their data regarding this outcome cannot be included for comparison.

Number not completing SWL

One patient in the NSAID group (parecoxib) did not complete SWL and this was not statistically significant (RR 3.21, 95% CI from 0.14 to 75.61, P=0.47) (31).

Respiratory depression

This was reported in two studies and there was no difference between groups (30).

NSAIDs versus NSAIDs

One study suitable for inclusion compared outcomes between two types of NSAIDs (diclofenac versus dexketoprofen). There were no statistically significant differences with regards to age, height or weight but only males were included in this study (33). There was no statistically significant difference in proportion of renal versus ureteric stones between study groups. There were no differences in tolerable pain (RR 0.98, 95% CI from 0.81 to 1.19, P=0.84), intolerable pain (RR 2.25, 95% CI from 0.49 to 10.38, P=0.29) or stone burden (MD -1.43, 95% CI from -34.30 to 31.44, P=0.89). However, when pain was reported as intolerable the mean VAS was significantly higher in the diclofenac group versus dexketroprofen (MD 0.97, 95% CI from 0.16 to 1.78, P=0.02).

Opioids versus Opioids

Cortinez and colleagues compared remifentanil and Fentanyl (27). There were no differences between the groups in terms of demographics or stone location. There were no differences between the groups in terms of mean shock wave energy achieved (P=1.00) or mean opioid infusion rate (MD 0.01, 95% CI from -0.03 to 0.05, P=0.59). The procedure was longer in the fentanyl group but this was not significant (MD -8.00 mins, 95% CI from -19.82 to 3.82, P=0.18). There were more cases of PONV in the fentanyl group 18 versus 3 (RR 0.17, 95% CI from 0.06 to 0.49, P=0.001) and this was significant. There was more intra-operative nausea in the fentanyl group (RR 0.05, 95% CI from 0.00 to 0.85, P=0.04). There were significantly fewer cases of intra-op (RR 0.46, 95% CI from 0.21 to 0.99, P=0.04) and post-op desaturation in the remifentanyl group than the fentanyl group (RR 0.13, 95% CI from 0.02 to 0.92, P=0.04). More patients in the Fentanyl group required supplementary analgesia during SWL but this was not significant (RR 0.11, 95% CI from 0.01 to 1.95,

P=0.13). Post procedure, more patients in the remifentanyl group required additional analgesia but this is not significant (RR 7.00, 95% CI from 0.38 to 128.02, P=0.19). Patients in the remifentanyl group had a higher sedation score and this is significant (RR 0.52, 95% CI from 0.34 to 0.80, P=0.003). There were more cases of persisting pain post procedure in the remifentanyl group but this is not significant (RR 3.50, 05% CI from 0.82 to 15.01, P=0.09).

NSAIDs versus Placebo

Three studies compared NSAIDs versus placebo. Aybek and colleagues compared 40mg IM piroxicam (26), Fredman et al. diclofenac sodium 75mg IM29 and Ou et al. indomethacin capsules 50mg commencing shortly after the procedure (32). There were no significant demographic differences between the groups (26, 29, 32) or differences in stone fragmentation rates (RR 1.62, 95% CI from 0.59 to 4.46, P=0.35) (29). The attained shock wave voltage was similar in the single study which recorded this (P=1) (26). There was no difference in procedure duration (MD-3.41; 95% CI from -8.25 to 1.43; P=0.17) (26, 29).

The verbal rating score was lower in the NSAID group (piroxicam) at all intra-operative points with P<0.05 in the one study measuring intra-op pain (26). Post operatively, pain was also lower in two studies; VRS at 6 hours was significantly less in the NSAID group (P<0.00001, MD=-0.95, 95% CI -1.07, -0.83) (26, 29) and at both 12 hours (P<0.0001) and 24 hours (P=0.0004) (26).

On meta-anaylsis, a greater number of shocks were tolerated by NSAIDs (P=0.001; MD 404.18; 95% CI 98.68 to 709.68) (26, 29). Procedure duration was shorter for NSAIDs but not significantly so (MD -3.41, 95% CI from -8.25 to 1.43, P=0.17) (26, 29).

There were more cases of intractable pain in the placebo group (RR 0.24; CI: 0.10 to 0.59; P=0.002) (26, 29). There was no increase in cases of ureteric colic after SWL between NSAID and placebo (RR 0.44, 95% CI from 0.15 to 1.29, P=0.13 (32). There was no significant difference in NSAID patients requiring pethidine for breakthrough pain (RR 0.64, 95% CI from 0.31 to 1.31, P=0.22) (26, 32). The number of patients needing additional analgesia as well as trial agents was significantly less in the one study measuring this, RR 0.25, CI from 0.08 to 0.80, P=0.02 (32). Fredman et al. found the total opioid dose for breakthrough pain was less in the NSAID group versus placebo but not significant (MD -30.00, 95% CI from -98.04 to 38.04, P=0.39). The same authors found no difference in midazolam consumption (MD -0.10, 95% CI from -1.10 to 0.90, P=0.84) or mean voltage (P=1) (29).

DISCUSSION

This review aimed to assess the relative clinical efficacy of simple analgesics, NSAIDs or opioids during shock wave lithotripsy for renal calculi. Based on the one study comparing a simple analgesic (paracetamol) versus an NSAID (lornoxicam), there were no overall significant differences in clinical efficacy or tolerability between these agents. Only one study is included in this subgroup and therefore generalisable conclusions are limited. In summary, both paracetamol and lornoxicam are tolerated by patients to provide adequate analgesia during SWL (25). The same study (of three arms) also compared paracetamol versus tramadol during SWL (25). Once again, overall there was no significant difference in pain scores between the agents at various fixed time points over 30 minutes. No major complications were reported and there was no difference in the number of patients with PONV (P=0.56). Once again, both agents provide safe and effective analgesia for the purpose of SWL.

Overall, there was no significant difference in pain scores between NSAIDs or opioids in the three studies comparing these drug classes. At 10 minutes however, lower VAS scores were recorded in the opioid groups but on meta-analysis this was not significant (MD 0.73; 95% from -0.05 to 1.51, P=0.07) (25, 31). One limitation was that one of the included studies did not provide variance data and as such for purposes of meta-analysis this was extrapolated from the provided P value (P<0.001) using previously reported techniques. In the same study (31), the mean pain score in patients in the NSAID group, after the first dose of analgesia, was significantly higher than patients

in the opioid group (3.57 versus 1.76, respectively (P<0.001). However, in patients who responded to the first dose of analgesia, the mean pain scores were similar (P=0.20). After administration of supplementary analgesia, the mean pain scores reported by the patients in both groups did not differ significantly (mean 1.56 versus 1.82, respectively, P=0.21). In terms of achieving adequate analgesia, this was calculated by assessing those patients who did not require additional analgesia (either a second dose of study agent or an alternative agent for breakthrough pain). On meta-anaylsis, analgesia could be defined as adequate more often for opioids than for NSAIDs (P=0.0001) (25, 31). However, this figure is limited by the considerable heterogeneity (I^2=93%) between studies thus limiting generalisability. In terms of actual doses of consumed rescue analgesia, two studies found similar doses between NSAIDs and opioids (P=0.58, >0.05) (25, 30). The absence of variance data meant that data could not be pooled from one paper (30). In terms of tolerability, there is no difference in PONV between the groups (RR 0.72; 95% CI 0.24 to 2.17; P=0.55) and only one patient in the NSAID group (parecoxib) did not complete SWL (P=0.47) (31). There was no difference in number of cases of respiratory depression (P=0.26) (31). There is no statistically significant difference in mean voltage achieved (P=0.21) (25) or the percentage of maximum shock wave energy achieved (P=0.34) (25, 31).

One study suitable for inclusion compared outcomes between two types of NSAIDs (diclofenac versus dexketoprofen). There were no significant differences in any of our pre-defined outcomes measures. However, when pain was reported as 'intolerable' the mean VAS was higher in the diclofenac group versus dexketroprofen (P=0.02). This study builds on the meta-analysis of three studies by Mezentsev which found that there were no significant difference in efficacy between NSAIDs and opiods for SWL (6).This study builds on this by including more studies and not limiting to type of lithotripter as well as comparing more analgesic classes.

Limitations of this study include the small number of studies suitable for inclusion and the heterogeneity in the reporting of outcome measures. This hinders precise inter-article comparison. The lack of variance data in some studies meant that pooled analysis was done by extrapolating from a provided P value which has implications in terms of pooled analysis. There are numerous sources of bias as described above; notably most studies having non-robust randomisation methods and double-blinding occurring in less than half of studies. Blinding of outcome assessment was clearly defined in only one third of studies.

CONCLUSIONS

This systematic review and meta-analysis distils the literature in this area to show that simple analgesics, opioids and NSAIDs all provide adequate analgesia for the purpose of SWL. In one paper (25), clinical efficacy and tolerability was similar between all three classes. However, against some criteria, meta-anaylsis has shown opioids to offer superior efficacy than NSAIDs. Indeed, pooled data from two studies shows that analgesia could be defined as adequate more often for opioids than for NSAIDs (P=0.0001) (25, 31). On meta-analysis of other outcomes however, there were no significant differences between groups across a range of markers of efficacy; these include consumed doses of rescue analgesia (25, 30), and the percentage of maximum shock wave energy achieved (25, 31). When comparing two opioids (fentanyl versus alfentanil) whilst there were no differences in efficacy, alfentanil was better tolerated.

Overall, NSAIDs, opioids and simple analgesics all provide adequate analgesia for the purposes of SWL. NSAIDs are of more value for SWL than placebo. One would anticipate more side effects with opioids than simple analgesics or NSAIDs. However, this study has not demonstrated this. It would be sensible on the back of this research to address analgesic requirements for SWL with a simple analgesic such as paracetamol. Breakthrough pain could be addressed with NSAIDs initially then opioids. There are an array of lithotripers used in the included studies which may impact on efficacy, pain and tolerability of the procedure. Further research is required in this area to compare the pain associated with different lithotripsy devices. Success rates for ESWL treatment have been reported to be machine-de-

pendant with one study showing a higher stone--free rate and lower re-treatment rate with the HM3 lithotriptor (47). Economic evaluation was not reported as an outcome in any of the studies. This will become increasingly relevant to Urology departments in the future.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. J Urol. 2011;185:1304-11.
2. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. J Nephrol. 2000;13:S45-50.
3. Johri N, Cooper B, Robertson W, Choong S, Rickards D, Unwin R. An update and practical guide to renal stone management. Nephron Clin Pract. 2010;116:c159-71.
4. EAU 2014. European Association of Urologists Extended Guidlines 2014 2014. availablw at. <http://uroweb.org/wp-content/uploads/EAU-Extended-Guidelines-2015-Edn..pdf>
5. Reynard J, Brewster S BS. Oxford Handbook of Urology. 2006.
6. Mezentsev VA. Meta-analysis of the efficacy of non-steroidal anti-inflammatory drugs vs. opioids for SWL using modern electromagnetic lithotripters. Int Braz J Urol. 2009;35:293-7.
7. Miller NL, Lingeman JE. Management of kidney stones. BMJ. 2007;334:468-72.
8. Wen CC, Nakada SY. Treatment selection and outcomes: renal calculi. Urol Clin North Am. 2007;34:409-19.
9. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck C, Gallucci M, et al. EAU/AUA Nephrolithiasis Guideline Panel.. 2007 guideline for the management of ureteral calculi. J Urol. 2007;178:2418-34.
10. Yilmaz E, Batislam E, Basar M, Tuglu D, Yuvanc E. Can prilocaine infiltration alone be the most minimally invasive approach in terms of anesthesia during extracorporeal shock wave lithotripsy? Urology. 2006;68:24-7.
11. Kararmaz A, Kaya S, Karaman H, Turhanoglu S. Effect of the frequency of transcutaneous electrical nerve stimulation on analgesia during extracorporeal shock wave lithotripsy. Urol Res. 2004;32:411-5.
12. Alhashemi JA, Kaki AM. Anesthesiologist-controlled versus patient-controlled propofol sedation for shockwave lithotripsy. Can J Anaesth. 2006;53:449-55.
13. Cepeda MS, Diaz JE, Hernandez V, Daza E, Carr DB. Music does not reduce alfentanil requirement during patient-controlled analgesia (PCA) use in extracorporeal shock wave lithotripsy for renal stones. J Pain Symptom Manage. 1998;16:382-7.
14. Cook RJ, Neerhut R, Thomas DG. Does combined epidural lignocaine and fentanyl provide better anaesthesia for ESWL than lignocaine alone? Anaesth Intensive Care. 1991;19:357-64.
15. Kahnoski RJ, Lingeman JE, Woods JR, Eckley R, Brooks-Brunn J, Coury TA. Efficacy of glucagon in the relief of ureteral colic following treatment by extracorporeal shock wave lithotripsy: a randomized double-blind trial. J Urol. 1987;137:1124-5.
16. Tritrakarn T, Lertakyamanee J, Koompong P, Soontrapa S, Somprakit P, Tantiwong A, et al. Both EMLA and placebo cream reduced pain during extracorporeal piezoelectric shock wave lithotripsy with the Piezolith 2300. Anesthesiology. 2000;92:1049-54.
17. Wang SM, Punjala M, Weiss D, Anderson K, Kain ZN. Acupuncture as an adjunct for sedation during lithotripsy. J Altern Complement Med. 2007;13:241-6.
18. Takmaz SA, Inan N, Goktug A, Erdogan I, Sunay M, Ceyhan A. The analgesic effect of 8 and 16 mg lornoxicam administered before shock wave lithotripsy: a randomized, double-blind, controlled study. Urology. 2008;72:282-5.
19. Bilir A, Gulec S, Turgut M, Cetinkaya D, Erkan A, Kurt I. Lornoxicam in extracorporeal shock-wave lithotripsy; comparison with tenoxicam and placebo in terms of analgesic consumption. Scand J Urol Nephrol. 2008;42:143-7.
20. Basar H, Yilmaz E, Ozcan S, Buyukkocak U, Sari F, Apan A, et al. Four analgesic techniques for shockwave lithotripsy: eutectic mixture local anesthetic is a good alternative. J Endourol. 2003;17:3-6.
21. Parkin J, Keeley FX FX, Timoney AG. Analgesia for shock wave lithotripsy. J Urol. 2002;167:1613-5.
22. Greene TD, Joseph JV, Erturk E. Evaluation and management of post-shock wave lithotripsy pain with third-generation lithotriptors using rofecoxib. J Endourol. 2009;23:395-8.
23. Higgins J. Cochrane Handbook for systematic reviews of interventions version. 2011.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
25. Akcali GE, Iskender A, Demiraran Y, Kayikci A, Yalcin GS, Cam K, et al. Randomized comparison of efficacy of paracetamol, lornoxicam, and tramadol representing three different groups of analgesics for pain control in extracorporeal shockwave lithotripsy. J Endourol. 2010;24:615-20.

26. Aybek Z, Turan T, Yonguç T, Bozbay C, Atahan O, Tuncay OL. Requirement of analgesia for extracorporeal shock wave lithotripsy and efficacy of a nonsteroidal antiinflammatory drug: piroxicam. Eur Urol. 1998;34:207-9.
27. Cortínez LI, Muñoz HR, De la Fuente R, Acuña D, Dagnino JA. Target-controlled infusion of remifentanil or fentanyl during extra-corporeal shock-wave lithotripsy. Eur J Anaesthesiol. 2005;22:56-61.
28. Dawson C, Vale JA, Corry DA, Cohen NP, Gallagher J, Nockler IB, et al. Choosing the correct pain relief for extracorporeal lithotripsy. Br J Urol. 1994;74:302-7.
29. Fredman B, Jedeikin R, Olsfanger D, Aronheim M. The opioid-sparing effect of diclofenac sodium in outpatient extracorporeal shock wave lithotripsy (ESWL). J Clin Anesth. 1993;5:141-4.
30. Issa MM, El-Galley R, McNamara DE, Segall S. Analgesia during extracorporeal shock wave lithotripsy using the Medstone STS lithotriptor: a randomized prospective study. Urology. 1999;54:625-8.
31. Mitsogiannis IC, Anagnostou T, Tzortzis V, Karatzas A, Gravas S, Poulakis V, et al. Analgesia during extracorporeal shockwave lithotripsy: fentanyl citrate versus parecoxib sodium. J Endourol. 2008;22:623-6.
32. Ou YC, Hwang TI, Yang CR, Chang CL, Chang CH, Wu HC. Use of indomethacin in the prophylaxis of ureteral colic following extracorporeal shock wave lithotripsy. Scand J Urol Nephrol. 1992;26:351-5.
33. Tokgoz H, Yurtlu S, Hanci V, Turksoy O, Erol B, Akduman B, et al. Comparison of the analgesic effects of dexketoprofen and diclofenac during shockwave lithotripsy: a randomized, double-blind clinical trial. J Endourol. 2010;24:1031-5.
34. Lau WC, Green CR, Faerber GJ, Tait AR, Golembiewski JA. Determination of the effective therapeutic dose of intrathecal sufentanil for extracorporeal shock wave lithotripsy. Anesth Analg. 1999;89:889-92.
35. Resim S, Gumusalan Y, Ekerbicer HC, Sahin MA, Sahinkanat T. Effectiveness of electro-acupuncture compared to sedo-analgesics in relieving pain during shockwave lithotripsy. Urol Res. 2005;33:285-90.
36. Alhashemi JA, Kaki AM. Dexmedetomidine in combination with morphine PCA provides superior analgesia for shockwave lithotripsy. Can J Anaesth. 2004;51:342-7.
37. Chen TP, Hwang TI, Yu CT, Yang CR, Chang CL, Change CH, et al. Analgesic effect of tramadol HCL in ESWL. Zhonghua Yi Xue Za Zhi (Taipei). 1993;51:134-7.
38. Han YY, Lu HC, Tsai HJ, Hseu SS, Chan KH, Tsai SK. The analgesic effect of oral morphine or pentazocine for extracorporeal shock wave lithotripsy. Acta Anaesthesiol Sin. 2003;41:27-32.
39. Medina HJ, Galvin EM, Dirckx M, Banwarie P, Ubben JF, Zijlstra FJ, et al. Remifentanil as a single drug for extracorporeal shock wave lithotripsy: a comparison of infusion doses in terms of analgesic potency and side effects. Anesth Analg. 2005;101:365-70.
40. Sopidou V, Papaventsis D, Papacharalambous G, Damigos D, Eftychidou E, Petridis A, et al. Comparison of three analgesics medicines during extracorporeal shock wave lithotripsy of ureteral calculli. Ep Klin Farmakol Kai Farmakokinet 2006;24:139–47.
41. Chin CM, Tay KP, NG FC, Lim PH, Chng HC. Use of patient-controlled analgesia in extracorporeal shockwave lithotripsy. Br J Urol. 1997;79:848-51.
42. Beloeil H, Corsia G, Coriat P, Riou B. Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study. Br J Anaesth. 2002;89:567-70.
43. Chia YY, Liu K. Prospective and randomized trial of intravenous tenoxicam versus fentanyl and tramadol for analgesia in outpatient extracorporeal lithotripsy. Acta Anaesthesiol Sin. 1998;36:17-22.
44. Ozcan S, Yilmaz E, Buyukkocak U, Basar H, Apan A. Comparison of three analgesics for extracorporeal shock wave lithotripsy. Scand J Urol Nephrol. 2002;36:281-5.
45. Tauzin-Fin P, Delort-Laval S, Krol-Houdek MC, Maurette P, Bannwarth B. Effect of balanced analgesia with buprenorphine on pain response and general anaesthesia requirement during lithotripsy procedures. Eur J Anaesthesiol. 1998;15:147-52.
46. Yang CP, Cherng CH, Wong CS, Ho ST. Effects of intravenous ketorolac and fentanyl combined with midazolam on analgesia and side effects during extracorporeal shock wave lithotripsy. Acta Anaesthesiol Sin. 2002;40:9-12.
47. Gerber R, Studer UE, Danuser H. Is newer always better? A comparative study of 3 lithotriptor generations. J Urol. 2005;173:2013-6.

Correspondence address:
Tarik Amer, MD
Urology SpR
NHS Greater Glasgow and Clyde
Glasgow, 84 Castle St, Glasgow G4 0ET, UK
E-mail: tarik.amer@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 407-415, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0490

First brazilian consensus of advanced prostate cancer: recommendations for clinical practice

Andre Deeke Sasse [1], Evanius Garcia Wiermann [2], Daniel Herchenhorn [3], Diogo Assed Bastos [4, 5,] Fabio A. Schutz [6], Fernando Cotait Maluf [6, 7,] George Coura Filho [8], Igor Alexandre Protzner Morbeck [9], Juliano J. Cerci [10], Oren Smaletz [7], Volney Soares Lima [11], Ari Adamy Jr. [12], Franz Santos de Campos [3], Gustavo Franco Carvalhal [13], Leandro Casemiro Cezar [14], Marcos Francisco Dall´Oglio [15], Marcus Vinicius Sadi [16], Rodolfo Borges dos Reis [17], Lucas Nogueira [18]

[1] Clínica Médica, Unicamp, Campinas, SP, Brasil; [2] Sociedade Brasileira de Oncologia Clinica, Belo Horizonte, MG, Brasil; [3] Instituto Nacional do Câncer, INCA, Rio de Janeiro, RJ, Brasil; [4] Departamento de Oncologia, Instituto do Câncer do Estado de São Paulo, São Paulo, SP, Brasil; [5] Departamento de Oncologia, Hospital Sirio-Libanes, São Paulo, SP, Brasil; [6] Beneficiência Portuguesa de São Paulo, São Paulo, SP, Brasil; [7] Departamento de Oncologia, Hospital Israelita Albert Einstein, São Paulo, SP, Brasil; [8] Instituto do Câncer, Hospital das Clinicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brasil; [9] Universidade Católica de Brasilia, Taguatinga, DF, Brasil; [10] Universidade de São Paulo, USP, São Paulo, SP, Brasil; [11] Oncocentro, Belo Horizonte, MG, Brasil; [12] Departamento de Urologia, Hospital Santa Casa, Curitiba, PR, Brasil; [13] Departamento de Cirurgia e Departamento de Urologia, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brasil; [14] Hospital Federal Cardoso Fontes, Rio de Janeiro, RJ, Brasil; [15] Departamento de Urologia, Universidade de São Paulo, USP, São Paulo, SP, Brasil; [16] Universidade Federal de São Paulo, São Paulo, SP, Brasil; [17] Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil; [18] Departamento de Urologia, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte. MG, Brasil

ABSTRACT

Introduction: Prostate cancer still represents a major cause of morbidity, and still about 20% of men with the disease are diagnosed or will progress to the advanced stage without the possibility of curative treatment. Despite the recent advances in scientific and technological knowledge and the availability of new therapies, there is still considerable heterogeneity in the therapeutic approaches for metastatic prostate cancer.

Objectives: This article presents a summary of the I Brazilian Consensus on Advanced Prostate Cancer, conducted by the Brazilian Society of Urology and Brazilian Society of Clinical Oncology.

Materials and Methods: Experts were selected by the medical societies involved. Forty issues regarding controversial issues in advanced disease were previously elaborated. The panel met for consensus, with a threshold established for 2/3 of the participants.

Results and Conclusions: The treatment of advanced prostate cancer is complex, due to the existence of a large number of therapies, with different response profiles and toxicities. The panel addressed recommendations on preferred choice of therapies, indicators that would justify their change, and indicated some strategies for better sequencing of treatment in order to maximize the potential for disease control with the available therapeutic arsenal. The lack of consensus on some topics clearly indicates the absence of strong evidence for some decisions.

ARTICLE INFO

Keywords:
Prostatic Neoplasms; Practice Guideline [Publication Type]; Diagnosis

Int Braz J Urol. 2017; 43: 407-15

Submitted for publication:
August 25, 2016

Accepted after revision:
November 21, 2016

Published as Ahead of Print:
February 10, 2017

INTRODUCTION

Except for skin cancer, prostate cancer is the most prevalent malignant neoplasm in men around the World. In Brazil, the number of estimated new patients diagnosed with prostate cancer in 2016 was 61,200, with an estimated risk of 61.82 new patients for every 100,000 men. Every year 13,000 deaths due to prostate cancer are estimated in Brazil (1).

Although associated with a pattern of indolent disease, mainly when diagnosed during population screening, metastatic prostate cancer is an important public health issue, with high mortality rate and complex treatment. Even when initial androgen deprivation is efficient, the disease may inevitably progress to a resistant form. In that case, disease-related death is high. Also, quality of life of patients with prostate cancer resistant to castration (PCRC) is frequently altered due to symptoms associated to fatigue, bone metastasis pain, etc.

After a long period of limited therapeutic options (secondary hormonal treatments), over the last years several clinical studies introduced new treatments that increased free-progression survival, global survival and quality of life (2-7). The better understanding of the role of androgenic pathway (including intracellular synthesis of androgens and the role of androgenic receptors (AR) in prostate cancer, and the knowledge that disease progression remains associated to the activation of that pathway) was fundamental for the development of new drugs that are able to improve clinical outcomes. Due to that fact, the term "prostate cancer refractory to hormonal therapy" was replaced by a more adequate – prostate cancer resistant to castration (PCRC). Also, nowadays there are two available active cytotoxic drugs that may have a positive impact on survival of patients, that would not have had benefits with traditional chemotherapy (6,8).

In spite of the discussed recent advances, there is still great heterogeneity of therapeutic approaches for metastatic prostate cancer. In Brazil, it must be stressed the delayed inclusion of new technologies and regional differences related to access to new drugs and specialists. It is important to evaluate the possibility to include new therapeutic developments in public and private health services in Brazil. With that in mind, a panel of Brazilian specialists discussed and proposed a document with therapeutic recommendations for the treatment of advanced prostate cancer.

Objective

The present consensus is a co-joint initiative of the Brazilian Society of Clinical Oncology (BSCO) and Brazilian Society of Urology (SBU). The objective is to provide guidelines to help clinical decisions by physicians that treat patients with advanced prostate cancer (mainly urologists, clinical oncologists and radio-oncologists).

Methodology

Experts were indicated by BSU and BSCO. Apart from the moderator,18 leading professionals in the field, from different regions of Brazil, were selected. The panel was composed by 8 clinical oncologists, 8 urologists and 2 nuclear medicine physicians.

The consensus format was adapted by the model of the *St. Gallen Advanced Prostate Cancer Consensus Conference* (APCCC) 2015 (9).The items of that consensus were previously turned into clinically relevant questions and posteriorly distributed to participants, in order to systematic review and critically analyze the information. Questions focused on treatment and follow up of patients with metastatic prostate cancer sensible or resistant to castration. Epidemiologic data, treatment of localized disease or screening were not addressed by the consensus. Initially, 60 questions were distributed to a subgroup of 8 selected specialists. A preliminary meeting took place to select the relevant questions, to discuss the best format of questions and to validate the final draft. Also, it was defined which specialists would be responsible for writing the answers to each of the questions. Next, 40 selected questions were formulated to participants, who had a 2-month period of time to critically analyze the studies on the theme, according to pre-defined levels of evidences (10) (See Appendix).

The panel of the Brazilian Consensus of Advanced Prostate Cancer took place in November 4th, 2015, at Rio de Janeiro, Brazil. It was used the Delphi modified method to obtain the consensus (11). Participants agreed to stablish a consensus limit of 2/3 of participants. To each question, it was presented the existing options followed by panelists vote. In case the participant thought that he/she did not have enough experience to vote, or felt unable to pick up an answer, or presented conflicting interests, it was chosen the option "does not apply to my practice/I rather not vote". Under the guidance of the moderator, the panel debated all conflicting data, or when there was no consensus, it was proposed a second vote. In case of maintenance of lack of consensus, it was made clear in the manuscript the lack of agreement on the subject. It was opted to expose in the manuscript all questions and answers, with the votes and respective percentages. The manuscript was written based on the records and meeting minutes, being subsequently approved by all participants.

RESULTS

Development of the consensus and panel discussion

The results of voting with or without consensus are available in the Addendum. Next, we present the main conclusions of the Brazilian Consensus of Advanced Prostate Cancer:

Initial hormonal treatment of advanced prostate cancer sensitive to castration

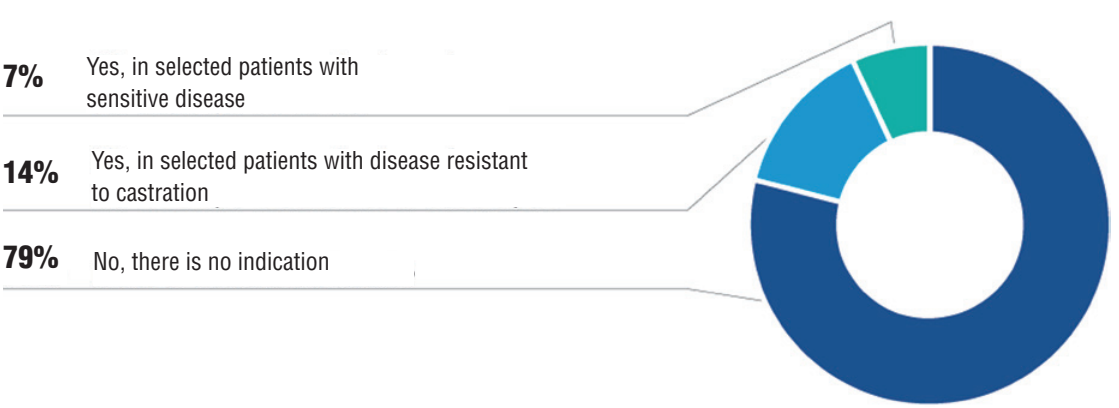
The development and progression of prostate cancer is highly influenced by the androgenic pathway. The main objective of hormonal treatment is to lower androgen action in the organism, avoiding cellular multiplication through signaling pathways present in sensitive cells. GnRH analogues (monotherapy) are the most used drugs with that objective as first line of treatment. However, the existence of other valid modalities of treatment, such as the use of Gn-Rh antagonists, sub-capsular orchiectomy or even the association of testosterone suppression and peripheral anti-androgens were reminded by the panel.

The use of ciproterone acetate was not indicated by the panel, with 79% of concordance (Figure-1). Although still widely used, literature data show worsening of survival of patients taking ciproterone, alone or combined to androgen suppression (12).

There was consensus on the recommendation of serum concentration of testosterone below 50 ng/dL for the definition of castration. However, it was stressed the fact that literature shows a potential clinical benefit to maintain patients with lower levels (such as 20 ng/dL).

Although with benefits on survival, some studies suggest that testosterone suppression in the long follow-up has been associated to important side effects, along with worsening

Figure 1 - Is there any indication for the use of ciproterone in the treatment of metastatic prostate cancer?



of quality of life (13). Patients with well controlled disease may have some benefit with temporary withdrawal of hormonal blockage, adopting an intermittent treatment regimen. However, randomized studies are controversial in relation to efficacy and safety of intermittent hormonal blockage. Based on recent data, 71% of panelists agreed that intermittent hormonal blockage may be recommended to asymptomatic patients, with radiologically confirmed metastasis and with correct lowering of PSA levels (usually above 90% and PSA < 4 ng/mL) (Figure-2).

Chemotherapy of prostate cancer sensitive to castration

Two prospective and randomized trials support the inclusion of docetaxel chemotherapy in the initial treatment using androgen suppression in patients with metastatic prostate cancer in a phase still sensitive to castration: CHAARTED (14) and STAMPEDE (15).

However, a randomized study failed to demonstrate the benefit of early chemotherapy, GETUG-AFU 15 (16). In the CHAARTED study, the inclusion of docetaxel in the group of patients with low volume disease did not demonstrate increase of median global survival. However, it is important to remind that in this group the number of patients was reduced, and the statistical analysis was inadequate due to the low number of deaths observed in that group. Based on the existent studies, 73% of the members of the panel agreed that for patients with metastatic prostatic cancer, with high volume disease, it is recommended the use of docetaxel associated to androgenic suppression. The panel considered the criteria adopted by the CHAARTED study the most adequate to consider the definition of high volume disease: presence of visceral disease and/or four or more bone metastasis, at least one outside the pelvic ring and vertebral column.

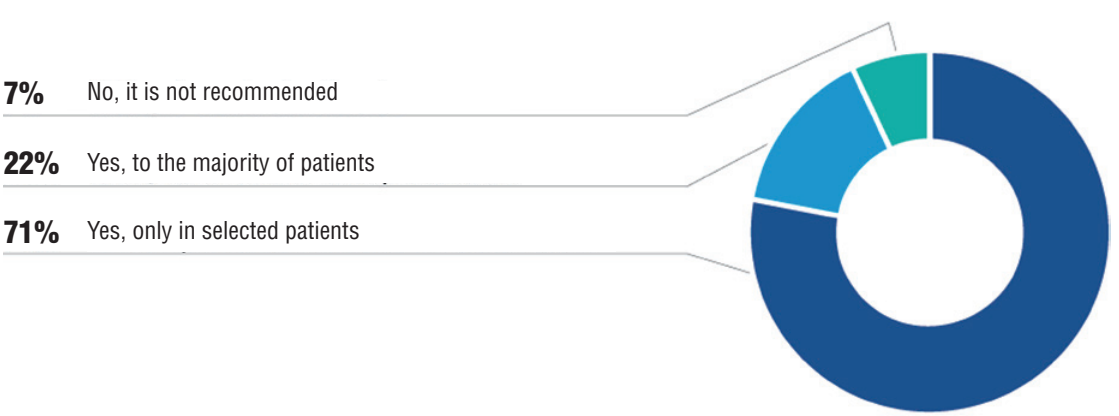
Local therapy in patients with oligo-metastatic disease

Local treatment of oligo-metastatic or metastatic disease, using radiotherapy, cryotherapy, HIFU or radical prostatectomy, in addition to systemic treatment did not show any benefit in relation to single systemic treatment in controlled prospective or randomized studies, with good levels of evidence; however, recent studies have demonstrated benefit on survival and quality of life in a subgroup of patients with minimum metastatic disease submitted to radical prostatectomy or radiotherapy. However, there was consensus on the fact that, at the moment, it is not recommended local treatment of the primary tumor in patients newly diagnosed with oligo-metastatic disease.

Prostate cancer resistant to castration - MO

The panel agreed unanimously that confirmed PSA progression and/or radiologic

Figure 2 - Is it recommended to use intermittent androgen deprivation instead of continous androgen suppression in patients with radiologically documented metastasis that reach adequate PSA lowering?



progression of patients under androgenic suppression define disease resistant to castration, while patients present serum testosterone in castration levels. In the absence of detectable metastasis by image exams, there was a 69% consensus of panelists that there is no indication of additional treatment, due to absence of studies that have shown any relevant benefit.

There was also 81% of agreement that in patients with biochemical progression and negative computerized scan of thorax/abdomen + bone scintigraphy, no other diagnostic method is indicated (Figure-3).

In asymptomatic patients, 69% of panelists agreed to realize periodically image exams in order to screen for metastasis, and not to wait the appearance of symptoms. However, it is not possible to stablish the periodicity of those exams.

Prostate cancer resistant to castration with metastasis (PCRCm)

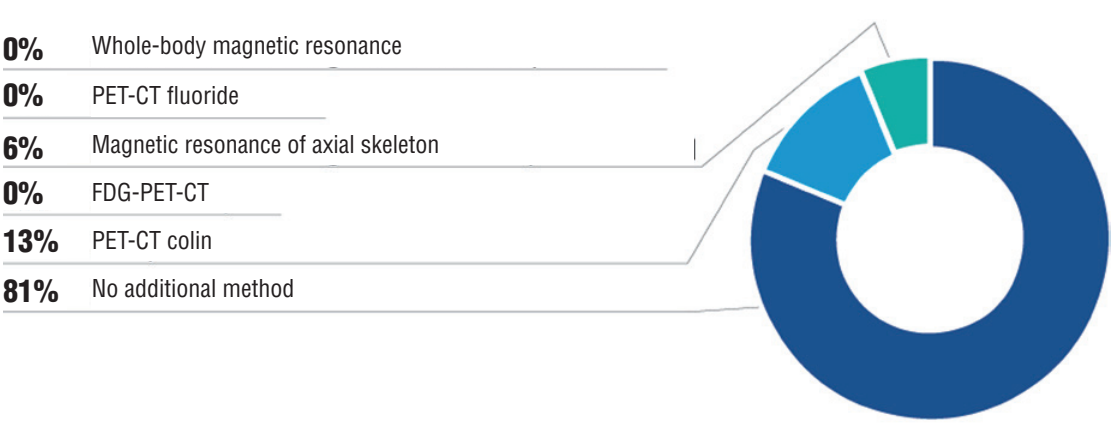
There is a significant heterogeneity of prostate cancer among individuals and also in the same patient. In spite of that, there are no reliable biomarkers at present to define an individual therapy. In most occasions a new biopsy of metastatic lesion for histological exam does not alter the therapeutic decision and there are no studiesthat have shown any efficacy with this strategy. With that in mind, 72% of panelists agreed that it is not necessary to perform routine biopsy at the site of metastasis for patients with progressing PCRCm and with accessible lesions. An exception may be made for patients with suspicion of evolution to neuro-endocrine tumor lines, such as those with very low PSA and development of visceral metastasis.

For control of progression and therapy response, 94% of panelists agreed on re-staging of patients with PCRCm before starting a new line of treatment. PSA progression only, without clinical worsening or radiological progression, does not justify change of treatment, what is supported by 88% of panelists.

All members of the panel agreed on the control using PSA for treatment response to new hormonal agents, associated to regular image exams and clinical evaluation (including analysis of patients symptoms).

In relation to the best initial treatment of PCRCm, there are many aspects regarding the different profiles of patients that potentially are candidate to chemotherapy or the use of new hormonal agents. Gleason score is not recommended as parameter for evaluation of choice between chemotherapy or abiraterone/enzulatamide, according to 88% of panelists. Also, the duration of the response to androgen suppression, the presence of visceral metastasis and the presence or not of symptoms were not considered adequate criteria for the choice between chemotherapy or abiraterone/enzalutamide.

Figure 3 - In patients with biochemical progression and negative scintigraphy and computorized tomography, which other diagnostic method should be used?



In asymptomatic or slightly symptomatic patients, the panel remained divided without consensus when asked if they would recommend the use of docetaxel as first line of treatment in cases where abiraterone/enzalutamide was available. However, when asked if they would recommend the use of abiraterone/enzalutamide in that same population, the consensus reached 88% to indicate the drugs if all options were available, including the drug docetaxel.

In symptomatic patients, there was consensus of 88% of panelists that, if available, it would be recommended the use of abiraterone/enzalutamide as first line of treatment for that population of patients associated to androgenic suppression. In addition, there was an 88% agreement forthe eventual recommendation of the use of chemotherapy with docetaxel as first line of treatment for patients with symptomatic PCRCm associated to androgenic suppression with GnRH analogues.

For new agents that act on the hormonal axis, there was 94% of agreement of panelists that the order of use (initially abiraterone or enzalutamide) doesn't matter in the treatment of patients with PCRCm.

Initially, the panel was divided but after discussion reached 85% of agreement with the possibility of re-treatment with docetaxel of selected patients, even in scenarios without restrict access to other options of treatments. Patients with good initial response to docetaxel, with good tolerability and delayed progression, would be better candidates to re-treatment (Figure-4).

Bone therapy in metastatic prostate cancer

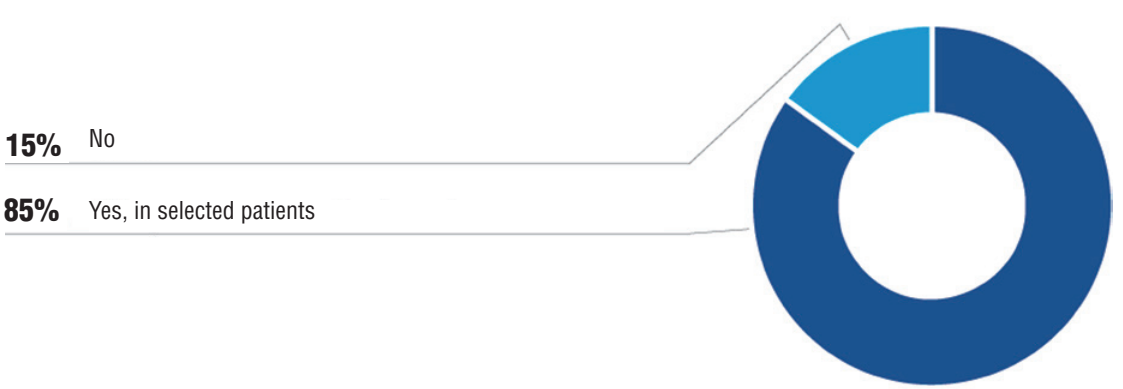
Zoledronic acid and more recently denosumabe are usually used to reduce the risk of bone fractures in patients with PCRCm. Although denosumabe had shown superior reduction of severe bone accidents in relation to zolendronate, it was not observed increase of survival (17); both medications are adequate and may be used. The panel agreed 100% in recommend the use of osteolysis inhibitors in patients with PCRCm and bone metastasis. And also agreed 100%to not recommend the use of osteolysis inhibitors to prevent bone fractures in patients with disease sensitive to castration with bone metastasis.

Ninety-three percent of panelists agreed that Radium-223 may be used, when available, in patients with PCRCm and symptomatic bone metastasis without visceral metastasis, in patients already treated with docetaxel or not. In asymptomatic patients, the panel does not recommend (94%) the use of Radium-223. In exceptional situations, it may be used radio-pharmaceutics such as those that emit beta particles (samarium/strontium) when the objective is to lower bone pain. These therapies are associated to pain improvement in 40-95% of patients (18). A consensus of 82% was reached that samarium and strontium may also be used as palliatives to treat bone pain in selected patients.

Sequencing of therapies in metastatic prostate cancer resistant to castration (PCRCm)

According to randomized studies using abiraterone (COU-AA-301 and COU-AA-302) (4,

Figure 4 - In an environment without any restrict access to other therapeutic options, is there indication of re-treatment with docetaxel?



5) or enzalutamide (AFFIRM and PREVAIL) (2, 3), 10 to 30% of patients show progression of radiological or clinical disease at first evaluation of response. These patients are considered primarily refractory to these new hormonal agents and should be spared of an inadequate treatment if there was any biomarker that could predict response. AR-V7 is an androgen-receptor variant that lost the site of attachment to androgen and remains active regardless stimulation by androgens. In consequence, the new hormonal agents abiraterone and enzalutamide would fail to control those patients' disease (19). However, the methodology to detect AR-V7 in circulating tumor cells is very difficult and not commercially available. Due to the difficulty of methodology to detect this kind of biomarker described in the studies, 93% of panelists agreed that currently there is no indication for the use of biomarkers like AR-V7 for decision between abiraterone/enzalutamide or chemotherapy.

In relation to sequencing of treatments, it was agreed that the time to response to docetaxel should not be considered when choosing subsequent treatments. The panel also recommended the use of cabazitaxel for patients with PCRCm after sequence of treatment with abiraterone/enzalutaide and docetaxel.

Unanimously, the panel considered that abiraterone, enzalutamide, cabazitaxel and Radium-223 may be used in patients with response to docetaxel and with progression of disease in less than three months following suspension of docetaxel.

CONCLUSIONS

This consensus was proposed to provide valuable information for treatment guidance and use of current knowledge of scientific literature in Brazilian reality.

The treatment of patients with advanced prostate cancer is complex, due the existence of several different therapies, with different response and toxicity profiles. It should be pointed out that not always there are enough evidence to compare them. The choice of therapies may be individualized depending on specific clinical characteristics of each patient and some may be preferable.

The panel indicated recommendations regarding preferential choice of therapies, guidelines to justify their change and some strategies for sequencing of treatments, in order to maximize the control of the disease with the available drugs.

The lack of consensus in some topics clearly indicates the lack of strong evidences for some decision making.

In the proposal of recommendations, it was considered the potential benefits, the availability of drugs in Brazil, the costs and the side effects and involved risks.

These guidelines must be regarded as orientations. It is important to have in mind that the use of these recommendations does not warrant an adequate clinical disclosure for all patients. Final judgement on which clinical procedure or treatment plan of a specific patient must be made by the physician according to discussion of options with the patient, to the diagnosis and available therapeutic options. However, it is recommended that significant different approaches during clinical practice in relation to these guidelines must be justified and their reason correctly documented.

ACKNOWLEDGMENT

The authors thank the support by Brazilian Society of Clinical Oncology and Brazilian Society of Urology.

This initiative was sponsored by the educational funds non-exclusive of Janssen and Bayer, without interference in the material content. The sponsors helped with the logistics of meetings.

CONFLICT OF INTEREST

Andre Deeke Sasse: Received fees from Bayer, Astellas and Janssen (Consulting).

Daniel Herchenhorn: Received fees from Bayer, Astellas, Janssen and Sanofi (Consulting and Lectures).

Diogo Assed Bastos: Received fees from Bayer, Astellas, Janssen and Sanofi (Consulting).

Fabio Augusto Barros Schutz: Received fees from Bayer, Astellas, Janssen and Sanofi (Consulting).

Fernando Cotait Maluf: Received fees from Bayer, Astellas, Janssen and Sanofi (Consulting).

Igor Alexandre Protzner Morbeck: Received fees from Bayer, Astellas and Janssen (Consulting and Lectures).

Oren Smaletz: Received fees from Bayer, Astellas, Janssenand Sanofi (Consulting).

Volney Soares Lima: Received fees from Janssen (Consulting) and Bayer (Lectures).

Ari Adamy Jr received fees from Janssen (Consulting).

Gustavo Franco Carvalhal received fees from Bayer, Astellas, Astra-Zeneca, Pfizer and Janssen due to Lectures in scientific events.

Lucas Mendes Nogueira received fees from Bayer, Astellas and Janssen, and Sanofi Aventis (Consulting). He was researcher in clinical trial sponsored by Bayer, Astellas, Janssen and GSK.

Rodolfo Borges dos Reis received fees from Bayer and Janssen (Consulting), and Astra Zeneca and Janssen (Lectures).

Other authors:

None declared

REFERENCES

1. Estimativas 2016 - Incidência de Câncer no Brasil. 2016. (Accessed 10/16/2016), available at <http://www.inca.gov.br/estimativa/2016/>.
2. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424-33.
3. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187-97.
4. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16:152-60.
5. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13:983-92. Erratum in: Lancet Oncol. 2012;13:e464.
6. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54.
7. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.
8. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502-12.
9. Gillessen S, Omlin A, Attard G, de Bono JS, Efstathiou E, Fizazi K, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol. 2015;26:1589-604.
10. Levels of Evidence. 2011. (Accessed 16/10/2016), available at <http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf>
11. Milholland AV, Wheeler SG, Heieck JJ. Medical assessment by a Delphi group opinion technic. N Engl J Med. 1973;288:1272-5.
12. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000;355:1491-8.
13. Carneiro A, Sasse AD, Wagner AA, Peixoto G, Kataguiri A, Neto AS, et al. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. World J Urol. 2015;33:1281-9.
14. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373:737-46.
15. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163-77.
16. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate câncer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14:149-58.

17. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377:813-22.
18. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 2005;6:392-400.
19. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al.AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014; 371:1028-38.

Correspondence address:
Lucas Nogueira, MD
Departamento de Urologia e Departamento de Cirurgia
Hospital das Clínicas, Universidade Federal de Minas Gerais
Rua da Paisagem, 480 / 10 andar
Nova Lima, MG, 34006-059, Brasil
E-mail: lucasnog@globo.com

ORIGINAL ARTICLE

Vol. 43 (3): 416-421, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0340

Metastatic prostate cancer in the modern era of PSA screening

Philip A. Fontenot Jr. [1], Avinash Nehra [1], William Parker [1], Hadley Wyre [1], Moben Mirza [1], David A. Duchene [1], Jeffrey Holzbeierlein [1], James Brantley Thrasher [1], Peter Van Veldhuizen [2], Eugene K. Lee [1]

[1] Department of Urology, University of Kansas Medical Center, Kansas City, Kansas, USA; [2] Division of Hematology/Oncology, University of Kansas Medical Center, Kansas City, Kansas, USA

ABSTRACT

Introduction: To characterize initial presentation and PSA screening status in a contemporary cohort of men treated for metastatic prostate cancer at our institution.
Materials and methods: We reviewed records of 160 men treated for metastatic prostate cancer between 2008-2014 and assessed initial presentation, categorizing patients into four groups. Groups 1 and 2 presented with localized disease and received treatment. These men suffered biochemical recurrence late (>1 year) or earlier (<1 year), respectively, and developed metastases. Groups 3 and 4 had asymptomatic and symptomatic metastases at the outset of their diagnosis. Patients with a first PSA at age 55 or younger were considered to have guideline-directed screening.
Results: Complete records were available on 157 men for initial presentation and 155 men for PSA screening. Groups 1, 2, 3 and 4 included 27 (17%), 7 (5%), 69 (44%) and 54 (34%) patients, respectively. Twenty (13%) patients received guideline-directed PSA screening, 5/155 (3%) patients presented with metastases prior to age 55 with their first PSA, and 130/155 (84%) had their first PSA after age 55, of which 122/130 (94%) had metastasis at the time of diagnosis.
Conclusion: Despite widespread screening, most men treated for metastatic prostate cancer at our institution presented with metastases rather than progressed after definitive treatment. Furthermore, 25 (16%) patients received guideline-directed PSA screening at or before age 55. These data highlight that, despite mass screening efforts, patients treated for incurable disease at our institution may not have been a result of a failed screening test, but a failure to be screened.

ARTICLE INFO

Keywords:
Prostate-Specific Antigen; Neoplasms; Prostate

Int Braz J Urol. 2017; 43: 416-21

Submitted for publication:
June 16, 2016

Accepted after revision:
December 20, 2016

Published as Ahead of Print:
March 17, 2017

INTRODUCTION

Despite being labeled an indolent disease, prostate cancer (CaP) remains the second leading cause of cancer death in American men (1). While most patients with CaP have a favorable prognosis, a minority will have an aggressive phenotype leading to a 2.58% lifetime risk of dying from disease (1, 2). In the United States, patient mortality from CaP has decreased over the past 3 decades (1991-present) based on 2014 SEER data, which is attributed to earlier detection with prostate specific antigen (PSA) screening and improved treatment modalities (1). However, despite widespread PSA screening, there remains no consensus on whether benefits outweigh harms of the test, as data are conflicting. This is highlighted by two large clinical trials

that examined the impact of PSA screening on CaP specific survival (3, 4).

The PSA screening controversy has led to various guidelines (5-13). In 2009, the American Urologic Association (AUA) recommended a first PSA test at age 40 for men with more than a 10-year life expectancy and did not specify a screening interval (5). In 2010, the National Comprehensive Cancer Network (NCCN) recommended an initial PSA test at age 40 with a screening interval of every 5 years in low risk men and annually in high-risk men (6). The American Cancer Society recommended an initial PSA between age 40-50 depending on patient risk of developing CaP (7). In 2012, the United States Preventative Services Task Force (USPSTF) recommended against PSA-based screening for CaP, stating that current evidence shows that the harms of PSA screening outweigh benefits (8).

Our study objective was to characterize and describe a cohort of patients treated for incurable disease during the contemporary era of PSA screening at our institution. We sought to determine their initial presentation (localized versus metastatic) as well as their PSA screening status prior to initial diagnosis (guideline-directed versus non-guideline directed).

MATERIALS AND METHODS

After institutional review board (IRB) approval was obtained (KUMC Study 0000852), we used the tumor registry at the University of Kansas Medical Center (KUMC) to identify all patients treated for stage IV CaP between June 2008 to December 2014. These dates correspond with the initiation of electronic medical records (EMR) at KUMC and represent a contemporary era of CaP therapy. We reviewed patient charts for accurate coding of stage IV CaP, past medical history, demographics, family history of CaP and ECOG performance status. Charts were examined to determine initial presentation with prostate cancer (localized versus metastatic) and their PSA screening status at or prior to diagnosis. For patients with missing data, outside records were thoroughly reviewed. Furthermore, we performed telephone interviews with patients or families for those with insufficient information. Patients with missing data were excluded from analysis.

We categorized subjects into one of four groups based on initial presentation with CaP. Patients in groups 1 and 2 presented with presumed localized disease, were treated with surgery or radiation, and had a late biochemical recurrence (BCR) (>1 year; Group-1) or early (<1 year; Group-2). These men eventually developed metastatic disease. Patients in groups 3 and 4 presented with asymptomatic and symptomatic metastatic disease, respectively, from the onset of diagnosis with prostate cancer.

Next, we evaluated if patients received guideline-directed PSA screening using a cut-point of age 55. During the time-frame of our study, the AUA guideline for PSA screening was a first PSA test at age 40 for men with more than a 10-year life expectancy, the NCCN recommended an initial PSA test at age 40, and the ACS recommended an initial PSA between age 40-50 depending on an individual's risk of CaP (5-7). We chose a cut-off of 55, as this encompassed these screening guidelines, as well as the most recent AUA guidelines (9). We classified patients into groups A through C based on PSA screening status. Patients in group A underwent PSA screening at or before age 55. Group B included those who presented with symptomatic metastases at or prior to age 55 with no prior PSA test. Patients in group C had their first PSA after age 55 and were considered to not have undergone guideline-directed PSA screening.

SPSS 22.2 (IBM, Armonk, New York) was used to perform statistical analysis, with all p-values reported for 2-sided analysis. Descriptive statistics were utilized to present our data, with chi-square and T-tests to assess significance. Kaplan-Meier curve was created to demonstrate overall survival.

RESULTS

We identified 252 patients coded as having both prostate cancer and stage IV cancer. 173 men had a diagnosis of metastatic CaP, while 79 had localized CaP plus metastatic disease of another etiology (i.e. bladder cancer) and thus were excluded. Thirteen patients were excluded for incomplete records. No patients that required telephone calls were included in the analysis to decrease the

risk of recall bias. We analyzed a total of 160 patients in our cohort (157 with complete records on initial presentation and 155 for PSA screening).

The mean ages at initial diagnosis of CaP, metastases, and death were 66, 68 and 73, respectively. Most patients were Caucasian (84%) while 12% of our cohort identified as African American. Mean PSA at diagnosis with metastatic disease was 427ng/mL (median 42ng/mL). Mean ECOG performance status was 0.5 (Table-1). At a median follow-up of 38 months (range 0-286 months), 71/160 (44%) of patients died of their disease, with a median overall survival in this population of 84.0 (range: 2-286) months (Figure-1). Patients had a median time from development or diagnosis of metastatic disease to death of 25.5 (range: 0-139) months.

When sorted by initial presentation, 27/157 (17%) patients initially received definitive therapy (radical prostatectomy or radiation) for presumed localized disease, had a BCR greater than 1 year after therapy and subsequently developed metastases. Seven (5%) men underwent definitive therapy for presumed localized disease, but had a BCR lower than 1 year after treatment and subsequently developed metastases. Sixty-nine (44%) patients presented initially with asymptomatic metastases while fifty-four (34%) patients presented to the physician with symptoms of metastatic disease, having CaP confirmed by biopsy (Table-2) In total, 78% of patients in our cohort (Groups 3 and 4) presented with metastatic disease at the outset of their prostate cancer diagnosis.

Table 1 - Patient Demographics.

Patients (n)	160
Age at Diagnosis (Mean)	66
Age at Metastasis (Mean)	68
Age at Death (Mean)	73
Race	N (%)
White	134 (84)
African American	19 (12)
Hispanic/Latino	2 (1)
Asian	1 (0.5)
Native American	1 (0.5)
Family History	N (%)
Yes	41 (25)
No	109 (68)
Mean PSA at Metastasis (ng/mL)	427
Median PSA at Metastasis (ng/mL)	42
ECOG at Presentation	Mean: 0.5 (0)

Figure 1 - Survival from time of diagnosis.

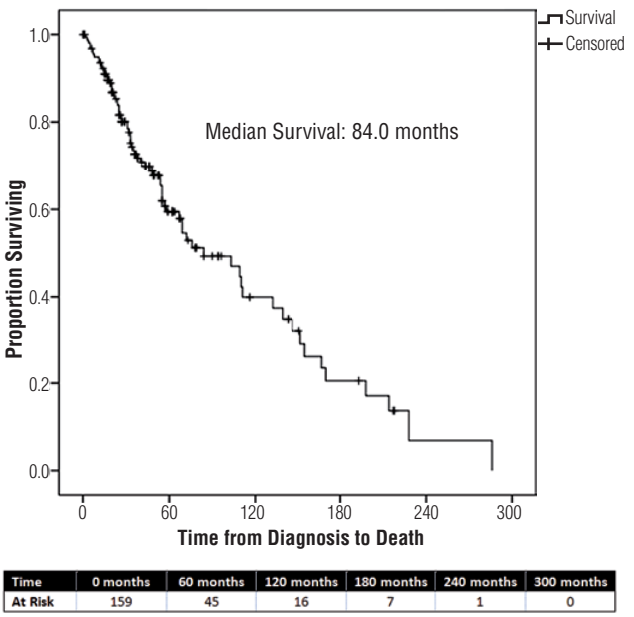


Table 2 - Presentation Category.

Group	Number of Patients (%)
1	27 (17)
2	7 (5)
3	69 (44)
4	54 (34)

Groups 1 and 2) presented with presumed localized disease and were treated with either surgery or radiation but recurred late (>1 year; Group 1) or early (≤1 year; Group 2).
Groups 3 and 4) were patients who presented with asymptomatic (Group 3) and symptomatic (Group 4) metastatic disease.

Next, we examined PSA screening characteristics in our patient cohort. Men in Group-A underwent guideline-directed PSA screening at or prior to age 55 and included 20/155 (13%) men. There were 5/155 (3%) men in Group-B who were diagnosed with metastatic CaP prior to age 55, which coincided with their first PSA test 130/155 (84%) patients were included in group C, of which 8/130 (6%) patients underwent screening prior to initial diagnosis of CaP and 122/130 (94%) had their first PSA test at the time of diagnosis with metastatic disease Table-3.

Table 3 - PSA Screening Category.

PSA Screening Category	N	Percent (%)
A	20	13
B	5	3
C	130	84

Group A) had guideline-directed screening, having their first PSA < or equal to age 55.
Group B) did not have a chance to be screened, as they presented with symptoms of metastasis at less than or equal to age 55.
Group C) did not have guideline-directed PSA screening, having their first PSA above age 55.

We characterized patient's PSA screening in terms of how they originally presented. In men who presented with presumed localized disease (Groups 1 and 2), 18% (6/34) were considered to have undergone guideline-directed PSA screening, compared to 15% (19/123) in patients who presented with metastatic disease (Groups 3 and 4). Conversely, in patients who presented with presumed localized disease (Groups 1 and 2), 76.5% (26/34) did not undergo guideline-directed PSA screening. In men who presented initially with metastatic disease (Group 3 and 4), 82.1% (101/123) did not have guideline-directed PSA screening (p=0.004). As expected, men who presented with presumed localized disease initially had a lower mean PSA at the time of metastatic development (37.6ng/mL) compared to men who presented initially with metastatic disease (538.1ng/mL), p=0.001.

DISCUSSION

Our report demonstrates that between June 2008 and December 2014, the majority of patients (123/157 (78%)) treated at our institution for metastatic CaP had initially presented with metastases at the outset of their disease. These findings support a recently published report which found 56% of a 113-patient cohort who died of CaP initially presented with metastases (14). Additionally, 130/155 (84%) of our patients did not undergo guideline-directed PSA screening, defined as having a first PSA at age 55 or younger. The PSA screening rate in our patient cohort is somewhat alarming, especially given that previous studies have estimated the overall prevalence of PSA screening in the USA to be 75% in men over age 50 (13). Our data suggests that patients at our institution who developed clinically significant, metastatic CaP and/or die of disease were more likely to present with incurable disease and not have undergone guideline-directed screening.

Guidelines and position statements on PSA screening vary and there remains no universal consensus on whether or not to perform, when to initiate or end, and at what intervals to repeat PSA screening (5-12). Nevertheless, the trend among organizations is to shift away from mass screening to a limited, opportunistic screening approach in the well-informed male (9). Again, as noted above, we chose age 55 as the cutoff for guideline-directed PSA screening in our study because it encompassed the new 2013 AUA CaP screening guideline and also took into account that the majority of organizations in previous years (during the time-frame of our study) recommended an initial PSA prior to this age (5-7, 9-11, 13).

The ERSPC, first published in 2009 and still on-going, represents the largest randomized CaP screening trial to date. The ERSPC trial showed a reduction in CaP specific mortality in a screened group compared to control in men ages 55-69 (3). The PLCO trial included 76.685 men, and randomized patients to a screened or "usual care" control group. No significant difference in CaP specific or overall mortality was found between the groups (4). Critics of the PLCO study argue that patients in the control group were also screened, 25% and 48%, had DREs and PSAs respectively, which may have negated any benefit of screening (15). Thus, while these two studies are

the largest, randomized trials on CaP screening to date, any difference between groups is muddied by the lack of a pure, unscreened control group.

Previous studies have demonstrated the number of patients who present with advanced disease in the modern era of PSA screening has decreased. Catalona et al. reported that 70% of CaP found through PSA screening were organ confined, compared with only 51% of cancers in a referred group of non-PSA-screened patients (16). Furthermore, data from the Center for Prostate Disease Research has shown a decrease in patients who initially present with metastatic disease from 19.8% in 1989 to 3.3% in 1998, which corresponds with the start of widespread PSA screening for CaP in the USA (17).

As noted, there is significant variation in the results of PSA screening studies. Theoretically, large, randomized controlled trials are performed to assess the utility of universal screening efforts. However, is it possible that some cohorts of patients are missed not only by community PSA screening efforts, but also clinical trials? Also, does inclusion in clinical trials bias a population to those who seek out medical care, as they must see a physician to enroll? While we did not look at patient perceived barriers to PSA screening in our study, there are other reports that have attempted to answer this question. Two major barriers that prevent men from getting screened are cost and lack of knowledge about CaP. Additional barriers cited include fear of the rectal exam or cancer, lack of time, resistance to seek healthcare when feeling well, and embarrassment (18-20).

As a retrospective study, this report clearly has limitations. Our patient cohort is small (N=160) and represents a single tertiary referral center, possibly leading to a selection bias for more aggressive and advanced cases. For example, patients who undergo routine PSA screening, are diagnosed with localized CaP, have definitive therapy, develop a BCR and minimal metastatic burden may stay at community practices for androgen deprivation therapy. Conversely, patients who present with more aggressive, metastatic disease may be quickly referred to our center. Second, a retrospective study design relies on the accuracy of medical records and/or patient recall. In order to mitigate possible inaccuracy, we utilized multiple information gathering strategies (i.e., utilizing patient's EMRs, reviewing outside records, and contacting patients or families). As stated, patients where telephone based recall was the only source of information for initial presentation or PSA screening were excluded to limit recall bias.

As a descriptive study, we focus on conveying the message that patients treated at our institution with diffuse disease are presenting with metastasis at the outset of the diagnosis and the majority of patients in this cohort are not being screened. While we used 55 years of age as the cut--off for what we considered "guideline" directed in this particular study, we do not advocate a certain age at which PSA screening should or should not be used based on these results. Furthermore, it is not our conclusion that men in our cohort would have been cured had they undergone a more standard screening protocol. Clearly, randomized controlled trials have been performed and are on-going to further answer these particular questions.

Despite widespread screening efforts during the time of this study, most patients in our cohort presented with metastatic disease and did not undergo guideline directed PSA screening. These data underscore the notion that despite mass screening during a contemporary time frame, patients treated for incurable disease at our institution may not represent a failure of the screening test, but instead a failure to be screened.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Howlader N, Noone AM, Krapcho M (eds), et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute: Bethesda, MD, April 2015. Online publication. Available from URL: <http://seer.cancer.gov/csr/1975_2012/>. Accessed: 5/5/2015.
2. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2011 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2014. On-line Publication. Available from URL: www.cdc.gov/uscs. Accessed: 5/5/2015.

3. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-8.
4. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-9. Erratum in: N Engl J Med. 2009;360:1797.
5. Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. J Urol. 2009;182:2232-41.
6. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, et al. NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw. 2016;14:509-19.
7. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010;60:70-98.
8. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:120-34.
9. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190:419-26.
10. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59:61-71.
11. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in câncer screening. CA Cancer J Clin. 2009;59:27-41.
12. Lim LS, Sherin K; ACPM Prevention Practice Committee. Screening for prostate cancer in U.S. men ACPM position statement on preventive practice. Am J Prev Med. 2008;34:164-70. Erratum in: Am J Prev Med. 2008;34:454.
13. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? JAMA. 2003;289:1414-20.
14. Patrikidou A, Loriot Y, Eymard JC, Albiges L, Massard C, Ileana E, et al. Who dies from prostate cancer? Prostate Cancer Prostatic Dis. 2014;17:348-52.
15. Eckersberger E, Finkelstein J, Sadri H, Margreiter M, Taneja SS, Lepor H, et al. Screening for Prostate Cancer: A Review of the ERSPC and PLCO Trials. Rev Urol. 2009;11:127-33.
16. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. JAMA. 1993;270:948-54.
17. Sun L, Gancarczyk K, Paquette EL, et al. Introduction to the department of defense center for prostate disease research multicenter national prostate cancer database, and analysis in the PSA era. Urol Oncol 2001; 6: 203-9.
18. Shelton P, Weinrich S, Reynolds WA Jr. Barriers to prostate cancer screening in African American men. J Natl Black Nurses Assoc. 1999;10:14-28.
19. Weinrich SP, Reynolds WA Jr, Tingen MS, Starr CR. Barriers to prostate cancer screening. Cancer Nurs. 2000;23:117-21.
20. Conde FA, Landier W, Ishida D, Bell R, Cuaresma CF, Misola J. Barriers and facilitators of prostate cancer screening among Filipino men in Hawaii. Oncol Nurs Forum. 2011;38:227-33.

Correspondence address:
Eugene K. Lee, MD
The University of Kansas Medical Center,
Department of Urology
3901 Rainbow Blvd, MS 3016,
Kansas City, KS, 66160
Fax: +1 913 588-6668
E-mail: elee@kumc.edu

ORIGINAL ARTICLE

Vol. 43 (3): 422-431, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0315

Predicting outcomes in partial nephrectomy: is the renal score useful?

André Costa Matos [1], Marcos F. Dall´Oglio [2], José Roberto Colombo Jr. [2, 3], Alexandre Crippa [4], João A. Q. Juveniz [2], Felipe Coelho Argolo [1]

[1] Hospital São Rafael, Salvador, BA, Brasil; [2] Departamento de Urologia, Faculdade de Medicina da Universidade de São Paulo, SP, Brasil; [3] Departamento de Uro-Oncologia,Instituto do Câncer do Estado de São Paulo, SP, Brasil; [4] Serviço de Urologia, Hospital do Servidor Público Municipal de São Paulo - HSPM, SP, Brasil

ABSTRACT

Introduction and Objective: The R.E.N.A.L. nephrometry system (RNS) has been validated in multiple open, laparoscopic and robotic partial nephrectomy series. The aim of this study was to test the accuracy of R.E.N.A.L. nephrometry system in predicting perioperative outcomes in surgical treatment of kidney tumors <7.0cm in a prospective model. *Materials and Methods:* Seventy-one patients were selected and included in this prospective study. We evaluate the accuracy of RNS in predicting perioperative outcomes (WIT, OT, EBL, LOS, conversion, complications and surgical margins) in partial nephrectomy using ROC curves, univariate and multivariate analyses. R.E.N.A.L. was divided in 3 groups: low complexity (LC), medium complexity (MC) and high complexity (HC). *Results:* No patients in LC group had WIT >20 min, versus 41.4% and 64.3% MC and HC groups respectively (p=0.03); AUC=0.643 (p=0.07). RNS was associated with convertion rate (LC:28.6% ; MC:47.6%; HC:77.3%, p=0.02). Patients with RNS <8 were most often subjected to partial nephrectomy (93% x 72%, p=0.03) and laparoscopic partial nephrectomy (56.8% x 28%, p=0.02), AUC=0.715 (p=0.002). The RNS was also associated with operative time. Patients with a score >8 had 6.06 times greater chance of having a surgery duration >180 min. (p=0.017), AUC=0.63 (p=0.059). R.E.N.A.L. score did not correlate with EBL, complications (Clavien >3), LOS or positive surgical margin. *Conclusion:* R.E.N.A.L. score was a good method in predicting surgical access route and type of nephrectomy. Also was associated with OT and WIT, but with weak accuracy. Although, RNS was not associated with Clavien >3, EBL, LOS or positive surgical margin.

ARTICLE INFO

Keywords:
Nephrectomy; Operative Time; Patients

Int Braz J Urol. 2017; 43: 422-31

Submitted for publication:
June 07, 2016

Accepted after revision:
October 01, 2016

Published as Ahead of Print:
February 13, 2017

INTRODUCTION

The widespread use of imaging modalities has increased the incidence of renal tumors, which are mostly identified from smaller and incidental renal masses. Thus, at present, more than 60% of such patients are diagnosed with T1 tumors (1). The literature supports that partial nephrectomy (PN) is oncologically similar to total nephrectomy (TN) (2) but is associated with fewer cardiovascular events (3); however, TN remains the most common form of treatment for newly diagnosed small RTs (4, 5). This could be explained by the superior feasibility of TN, especially laparoscopically (6), and the fact that the surgical access decision is subjective for each surgeon based on the tomography exam.

To standardize tumor assessment, minimize bias and improve clinical outcomes, the R.E.N.A.L. nephrometry system (RNS) was proposed in 2009 (7), based on five tumor characteristics (radius, exophytic extent, nearness to the renal sinus, anterior/posterior location and location relative to the polar lines). Since then, this tool has been validated in multiple retrospective open, laparoscopic and robotic partial nephrectomy series (8-12).

However, the authors did not use any statistical model to build the score and their variables won the same weight. We believe that, some anatomical features presented in R.E.N.A.L. score are more important than the others and should, specially in laparoscopic surgery, influence perioperative outcomes.

The aim of this study was to test the accuracy of R.E.N.A.L. score system in predicting perioperative outcomes in laparoscopic partial nephrectomy of kidney tumors ≤7.0cm, in a prospective model.

MATERIALS AND METHODS

Between January 2010 and June 2012, 320 patients underwent radical or partial nephrectomies at our institution for the treatment of renal cancer. Of these, 173 patients had tumors ≤7cm. Patients with chronic renal failure, solitary kidneys, renal tuberculosis, previous renal or upper abdomen surgeries or nephrolithiasis were excluded. We had also excluded patients without multiplanar CT scan that could disrupt R.E.N.A.L. interpretation. Seventy-one patients were selected and prospectively followed up.

The R.E.N.A.L. score was determined by the same observer based on criteria proposed by Uzzo (7). This system considers tumor size, the degree to which the tumor is endophytic, the proximity to the collecting system, the posterior or anterior location of the mass and its polarized location. Awarded for each component are 1 to 3 points, except for the anterior or posterior location, which receives a letter "A" or "P". Additionally, a suffix "h" is given to lesions that touch the main artery or vein. Thus, 3 groups were formed, according to tumor complexity: low (LC: patients with score 4-6), medium (MC: patients with score 7-9) and high (HC: patients with score 10-12).

All patients were initially indicated for partial laparoscopic nephrectomy, considered herein as a gold standard. The procedures were performed using the laparoscopic standard technique, briefly described as follows: Mobilization of the colon, dissection of the renal vascular pedicle and removal of the Gerota's fascia. Warm ischemia was achieved using a vascular clamp. Mannitol was administered 5 min before and after the vascular occlusion. The tumor was located and excised, along with its perinephric fat, using scissors. No frozen section analysis of the tumor bed was routinely performed. Hemostasis and closure of the calices were applied whenever necessary using figure-of-eight 2-0 Vicryl® SH needle sutures (Johnson & Johnson New Brunswick, NJ, USA). An approximation of the renal trauma was performed using 0 Vicryl® CT needle 'U' sutures anchored with the Hem-o-lok® Ligation System (Teleflex Incorporated, Limerick, PA USA). No ureteric stent was placed in any case. Patient baseline and tumor characteristics are depicted in Table-1.

We analyzed intra operative outcomes (operative time - OT, warm ischemia time - WIT, estimated blood loss - EBL, conversion to open approach, conversion to total nephrectomy) and complicationrates recorded during the first 90 days after surgery and classified them according to the Clavien-Dindo classification system (13). The operative time was considered long when >180 minutes (14-16), WIT when >20 minutes (17-19) and EBL when ≥1000mL (20). The pathological margin status of the specimens was also analysed.

Further, we divided the results into groups according to the ASA (American Society of Anesthesiologists), Charlson comorbidity index (21) to verify the association of comorbidities on the results.

The R.E.N.A.L. score were tested for their ability to predict surgical outcomes and complications using receiver operating characteristic (ROC) curves. The overall performance of the ROC analysis was quantified by computing the area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different from a result that could have been obtained by chance. Using ROC analysis, the optimal sensitivity and specificity of R.E.N.A.L. were determined using various

Table 1 - Clinicopathological data and surgical approaches.

Gender	
Male	39 (55%)
Female	32 (45%)
Age	60±12.7 (22-88)
IMC	27.6±4.5 (17.9-88)
ASA	
I	5 (7%)
II	60 (84.5%)
III	6 (8.5%)
Hypertension	32 (45.1%)
DM	9 (12.7%)
Smokers	19 (26.8%)
Charlson	
≤3	40 (56.3%)
>3	31 (44.3%)
Incidental	54 (76.1%)
Tumor size	4,1 (1,3 – 7,0)
Histological subtype	
Clear cells	34 (48%)
Others malignant	28 (39%)
Benign	9 (13%)
Patological Stage	
T1a	39 (55%)
T1b	21 (30%)
T2	6 (8%)
T3a	5 (7%)
Margin status	
Negative	67 (94%)
Positive	4 (6%)
Surgical intervention	
Laparoscopic partial nephrectomy	32 (45.1%)
Open partial nephrectomy	28 (39,4%)
Laparoscopic total nephrectomy	8 (11.3%)
Open total nephrectomy	3 (4.2%)
Pre-operative creatinine	0.9±0.18
Post-operative creatinine	1.0±0,24
Pre-operative hemoglobin	13.7±1.3
Post-operative hemoglobin	11,3±2,6

threshold values and Youden index method for the prediction of outcomes. Relative risk was calculated using Mantel-Haenszel analysis. The Fisher's exact test and chi-square test were used to compare proportions. We also performed univariate Cox regression analysis to select variables that showed significant associations with the dependent variables. Only these were included in the multivariate Cox proportional-hazards model in a stepwise method. Two-tailed p <0.05 was considered to indicate statistical significance. The analyses were conducted using SPSS statistical software (version 17.0).

RESULTS

Seventy-one patients were included in a intention to treat partial nephrectomy analysis. Clinical and pathological features are exposed in Table-1. No statistical difference was found in RNS groups regarding to age, BMI, ASA and Charlson score (Table-2).

SURGICAL OUTCOMES

Conversion rate

Of the 71 patients included, 26 had preemptive open conversion (2 total and 24 partial). Forty-five subjects initially underwent laparoscopic procedure, 8 were converted to laparoscopic total and 5 to open nephrectomy (4 partial and 1 total) (Figure-1).

ROC curve was performed to test the accuracy of RNS to predict conversion rate. The AUC was 0.715 (0.595-0.836) (p=0.002) (Figure-2). The best specificity cut-off was RENAL ≥9. Patients with RNS<9 were most often subjected to PN (93% x 72%, p=0.03) and LPN (56.8% x 28%, p 0.02) (Table-3).

Perioperative outcomes were not different in distinct surgical access. (Table-4)

Warm ischemia time

The median duration of ischemia increased with tumors anatomical complexities, according to the RNS (LC: 10 minutes; MC: 15 minutes; HC: 20 minutes - p<0.01). There were no patients in LC group with WIT ≥20min (LC 0xMC 41.4% x HC 64.3%, p=0.03)

Table 2 - Distribution of variables according to renal score.

	LC	MC	HC	p
Lengh of stay (days)	3.6	3.9	4.2	ns
Operative Time (min)	134	163	185	<0.05 *
Estimated blood loss (mL)	376	460	347	ns
Warm isquemia time (min)	10	15	20	<0.05**
Clavien ≥3	0	7 (16.6%)	1 (4.5%)	ns
ASA >2	1(14.3%)	4 (9.5%)	1 (4.5%)	ns
BMI	27.7	27.6	27.6	ns
Charlson ≤3	6 (85.7%)	36 (85.7%)	18 (85.4%)	ns
Incidental	7 (100%)	33 (78.6%)	14 (63.6%)	0.05
Positive margins	1(14.3%)	2 (4.8%)	1 (4.5%)	0.17
Clear cell histology subtype	2 (28.6%)	17 (44.7%)	15 (68.2%)	0.5
LPN	5 (71.4%)	22(52.4%)	5(22.7%)	0.01

We performed a ROC curve analysis and found an AUC=0.598, which was not significant (p=0.252); this finding demonstrates that there is no cutoff score of RNS that is able to predict a clamping time <20 or ≥20.

Operative time

The mean operative time was longer in HC (185 min) than in MC (163 min) or LC (134 min) p<0.05. The ROC curve demonstrated that the RNS could predict a prolonged surgery time, with an area under the curve of 0.63 (p=0.05) (Graph-1). Using the Youden index to predict the best cutoff point, we found R.E.N.A.L. ≥8 as a predictor of surgical time ≥180 minutes, with a sensitivity of 89.3% and specificity of 37.2%. The odds of having surgery time >180 min. was 4.94 times greater in patients with a score ≥8 (p=0.020).

Estimated blood loss

The average EBL in the groups were, respectively, 376, 460 and 347mL for LC, MC, HC. These values lacked both clinical and statistical difference. Seven patients had ≥1000mLof bleeding and 1 was transfused (2000mL of bleeding). There were no association with R.E.N.A.L. complexity groups: 1LC; 5MC; 1HC.

Margin status

No TN patients had positive surgical margins, although 4PN patients (4/60) had positive surgical margins, 3LPN and 1 OPN.

Post-operative complications

No patients presented with post-operative bleeding, urinary fistulas, pseudoaneurysms with clinical symptoms or deaths during the follow-up time. Eight (11.3%) patients had major complications (Clavien≥3). However, none of these complications were observed in LC group, instead occurring in 7 (16.6%) and 1 (4.5%) individuals in MC and HC groups, respectively.

In the logistic regression analysis,RNS, surgical approach (open or laparoscopic) and

Figure 1 - Conversion rate.

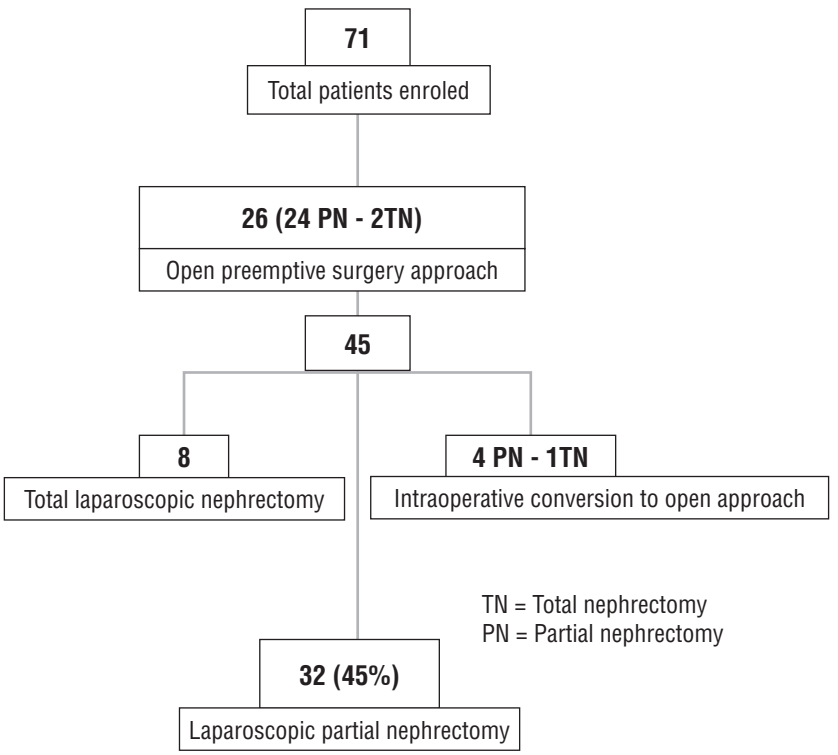
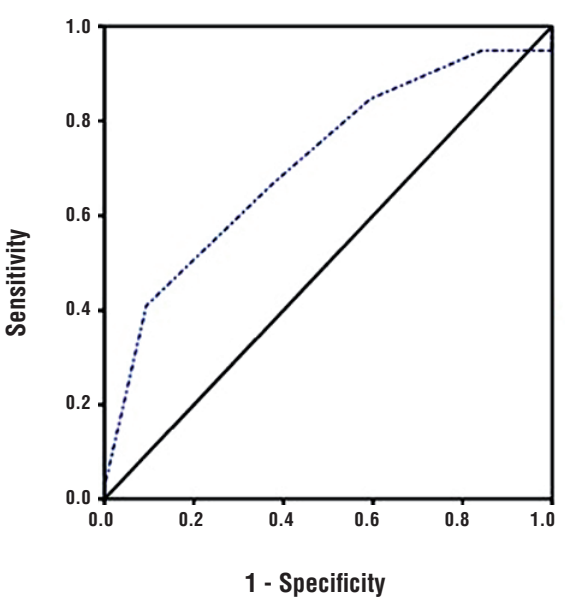


Figure 2- ROC curve: RENAL x conversion rate.



AUC: 0.715 (0.595 - 0.836) (p=0.002)

Table 3 - Conversion rate according to RENAL ≥9.

RENAL	LPN	Others	p
<9	25 (54.3%)	21 (45.7%)	0.02
≥9	7 (28%)	18 (72%)	

Table 4 - Perioperative outcomes and surgical approach.

	LPN	OPN	LTN	OTN	p
OT	174±51 (90-300)	155±50 (70-261)	189±77 (120-354)	133±38 (90-160)	NS
WIT	17 (10-35)	11.5 (8-30)	-	-	NS
EBL	376 (223 -529)	491 (318-662)	293 (123-465)	513 (-/1597)	NS
LOS	3,6+1,1 (1-6)	4,3+1,2 (3/7)	4,1+2,2 (2/9)	3,7+1,2 (3-5)	NS
Clavien-Dindo ≥3	3 (9.4%)	3 (10.7%)	2 (25%)		

OT = Operative time - mean (95%IC)
WIT = Warm ischemia time - median (95%IC)
EBL = Estimated blood loss - mean (95%IC)
LOS = Length of stay - mean (min - max)
LPN = Laparoscopic partial nephrectomy
OPN = Open partial nephrectomy
LTN = Laparoscopic total nephrectomy
OTN = Open total nephrectomy

operative time were not related to Clavien ≥3 (Table-5).

We found that the addition of each unit to the ASA score increased the chance of having Clavien ≥3 by 11.48 times (p=0.008). The ROC curve analysis got an AUC of 0.69 (p=0.084). The best number given by the Youden index was 3, with a sensitivity of 37.5% and specificity of 95.2%. From this value, we applied logistic regression with ASA categorizations, and the odds of having Clavien ≥3 were 12 times greater for individuals with an ASA >3 (95%CI=2-69; p=0.008).

Furthermore, age was significantly associated with major complications. We found that each additionalyear of age increased the chance of having Clavien ≥3 by 1.08 times (p=0.043). The AUC for this was 0.72 (p=0.043), demonstrating that age is a predictive variable for Clavien ≥3. Searching for the best cutoff according to the Youden method, we found that age ≥66 years had a sensitivity of 75.0% and a specificity of 68.3%. From this value, we applied logistic regression with age categorization and found that those with age ≥66 were 6.45 times more likely to have Clavien ≥3 (95%CI=1.2-34.8; p=0.030).

DISCUSSION

The majority of papers that have studied nephrometry score systems are retrospective. Thus, confounding factors are usually adjusted for in the statistical analysis. On the other hand, in our study, we adjusted for these factors within the methodology, performing the study prospectively and excluding patients with anatomical features that could interfere with the perioperative results. These stringent inclusion criteria led to a significant loss of sample size, which could have reduced

Table 5 - Predictors of Clavien≥3.

	OR	95% CI	p
RENAL	0.95	0.6-1.5	0.84
RENAL-L	0.76	0.5-1.2	0.82
ASA	11.48	1.9-69.5	0.008
Age ≥65	6.45	1.2-24.8	0.043
Surgical approach	0.9	0.8-1.3	0.783
Operative time	1.01	0.99-1.0	0.1

the power of our analysis. In the present study, we evaluate the accuracy of R.E.N.A.L. nephrometry system in predicting outcomes in partial nephrectomies for <7cm kidney cancers because we don't have literature to support routine elective partial nephrectomy in >7cm tumors.

From a technical point of view, the choice between partial or total nephrectomy is still very subjective and even experienced surgeons often are in doubt whether the tumor can be extirpated in order to preserve functional renal parenchyma and in a minimally invasive approach.With nephrometry scores using, one can obtain objective parameters to predict conversion rates.In our sample, we can identify patients with greater chances of conversion. Individuals with RNS≥9 are at high risk, and perhaps would be better approached by open surgery.

Funahashi et al. (22) retrospectively evaluated anatomical data of renal tumor associated with the access route to partial nephrectomy and found that the tumor's relationship to the renal surface (endophytic character) and the distance from the renal sinus affected the surgeon's decision to open access route or minimally invasive, and tumor size did not influence that decision.Gill et al. (23) in a similar analysis with 771 LPN and 1029 OPN reported that tumor size (2.6cm LPN vs. 3.3cm OPN) and endophytic character (34.4% LPN vs. 53.3% OPN) were significantly different between the two access routes (17).Naya et al. (8) evaluated factors that influence the frequency of LTN (68 patients) vs. LPN (74 patients). They found that the RNS up to 8 was the best cut off for patients selection for LPN.As these data are being validated by larger studies, it will allow better predict the chances of conversion, improving the anesthetic and surgical planning and patient preparation for this possibility. Moreover, technically favorable tumors should be most operated by LPN.

A systematic review from American Society of Anesthesiologists defines as prolonged surgery intervals from 2.5 hours to 4 hours (14). Also others references confirm these information based on increasing post operative complications (15, 16). Ng et al. (24) reported an OT of 3.5 hours in LPN. Marszalek et al. (25) had an average time of 139 min. We had a mean OT of 174 minutes in LPN and RNS was significantly associated with a prolonged surgery time. Data showed that RNS≥8 was a predictor of surgical time ≥180 minutes, with a sensitivity of 89.3%. This indicates that, in cases of a CT scan showing a renal mass with RNS <8, the surgeon could predict that rarely OT will exceed 3 hours.

Although controversial in literature, several clinical studies suggest that the maximum period of WIT time for preservation of renal function should not exceed 20min (17, 19, 26). Previous studies have reported differences in WIT among R.E.N.A.L. groups (9, 10). In our series, we found that WIT was statistically greater in the high complexity group. However, the difference was not clinically significant, as no group had a median WIT greater than 20 minutes. Advancing this analysis, we found that there were no cutoff scores of RENAL able to predict a clamping time <20 or ≥20 min. It is likely that the low mean WIT in our patients contributed to these results. To reduce WIT, our group unclamps the kidney vessels early, immediately after the first external parenchymal suture has been placed. Otherwise some

studies have demonstrated a correlation between RNS and WIT. Hayn et al. (27) found, in a series with 141 laparoscopic partial nephrectomies, WITs of 16, 23 and 31 minutes for the low, medium and high complexity groups, p<0.001.

The hemorrhagic shock scale proposed by ATLS (Advanced Trauma Life Support) consider bloodloss between 15-30% of body volume or 750 to 1500mL (Class II) a significant clinical bleeding, because patients experiment tachycardia, tachypnea and elevates plasma levels of catecholamins (20).RNS was not good predictors of EBL. In our series and in a recently published paper, intraoperative bleeding was not clinically different among RNS groups (LC: 135mL; MC: 210mL; HC: 314mL) (11). These results could be explained by a good intra-operative vascular control of the hilum and a good suture repair of the kidney parenchyma, achieved using open, laparoscopic or robotic techniques.

The overall incidence of urological complications after LPN has been reported at 9.0% (12). Simmons and Gill (28) found no correlation between tumor size and centrality with the incidence of complications after LPN, on either the univariate or multivariate analyses. According to a recently published paper (12), a higher RNS was significantly associated with an increased incidence of Clavien grade III. In our series, RNS did not show any relation to postoperative complications. On the other hand, the ASA score and patient's age were significantly associated with Clavien ≥3. In our sample, baseline patient characteristics were more important that anatomical tumor characteristics in predicting complications.

Turna et al. (29) reported a 2.4% incidence of postoperative urinary fistula after LPN, but no independent predictors of this outcome were found. Recently, another group (30) reported that each unit of increase in RNS was associated with an increased likelihood of a postoperative urine leak. We did not encounter any urinary leaks postoperatively, and no patients had to use a ureteral catheter. A first line suture performed with 2.0 Vicryl SH needle in all patients with a deep defect in the renal parenchyma may be sufficient to include the collecting system effectively.

From now, we have in literature 10 scores that use anatomic features involved in complexity of partial nephrectomies. Although some studies have been showing association between them and surgical outcomes, no one have accuracy strongly tested and validated (31).

CONCLUSIONS

There is a growing need to objectively measure the complexity of kidney tumors due to the use of minimally invasive procedures that require greater operative skill. In respect to ≤7cm tumors,R.E.N.A.L. score, in this data, was a good method in predicting surgical access route and type of nephrectomy. Also was associated with OT and WIT, but with weak accuracy. On the other hand, RNS was not associated with Clavien >3, EBL, LOS or positive surgical margin. These observations must be tested by other groups in a major population.

ABBREVIATIONS

ASA = American Society of Anesthesiologists
AUC = area under the curve
BMI = body mass index
EBL = estimated blood loss
HC = high complexity
LC = low complexity
LOS = length of stay
LPN = laparoscopic partial nephrectomy
MC = **medium complexity**
OPN = open partial nephrectomy
OT = operative time
PN = partial nephrectomy
RNS = R.E.N.A.L. nephrometry system
ROC curve = receiver operating characteristic curve
RTs = Renal Tumors
TN = total nephrectomy
WIT = warm ischemia time

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol. 2000;163:442-5.
2. Lesage K, Joniau S, Fransis K, Van Poppel H. Comparison between open partial and radical nephrectomy for renal tumours: perioperative outcome and health-related quality of life. Eur Urol. 2007;51:614-20.
3. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? J Urol. 2009;181:55-61.
4. Hollenbeck BK, Taub DA, Miller DC, Dunn RL, Wei JT. National utilization trends of partial nephrectomy for renal cell carcinoma: a case of underutilization? Urology. 2006;67:254-9.
5. Nuttall M, Cathcart P, van der Meulen J, Gillatt D, McIntosh G, Emberton M. A description of radical nephrectomy practice and outcomes in England: 1995-2002. BJU Int. 2005;96:58-61.
6. Patel SG, Penson DF, Pabla B, Clark PE, Cookson MS, Chang SS, et al. National trends in the use of partial nephrectomy: a rising tide that has not lifted all boats. J Urol. 2012;187:816-21.
7. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182:844-53.
8. Naya Y, Kawauchi A, Oishi M, Ueda T, Fujihara A, Naito Y, et al. Comparison of diameter-axial-polar nephrometry and RENAL nephrometry score for treatment decision-making in patients with small renal mass. Int J Clin Oncol. 2015;20:358-61.
9. Altunrende F, Laydner H, Hernandez AV, Autorino R, Khanna R, White MA, et al. Correlation of the RENAL nephrometry score with warm ischemia time after robotic partial nephrectomy. World J Urol. 2013;31:1165-9.
10. Mayer WA, Godoy G, Choi JM, Goh AC, Bian SX, Link RE. Higher RENAL Nephrometry Score is predictive of longer warm ischemia time and collecting system entry during laparoscopic and robotic-assisted partial nephrectomy. Urology. 2012;79:1052-6.
11. Simhan J, Smaldone MC, Tsai KJ, Canter DJ, Li T, Kutikov A, et al. Objective measures of renal mass anatomic complexity predict rates of major complications following partial nephrectomy. Eur Urol. 2011;60:724-30.
12. Liu ZW, Olweny EO, Yin G, Faddegon S, Tan YK, Han WK, et al. Prediction of perioperative outcomes following minimally invasive partial nephrectomy: role of the R.E.N.A.L nephrometry score. World J Urol. 2013;31:1183-9.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
14. Smetana GW, Lawrence VA, Cornell JE. Annals of Internal Medicine Clinical Guidelines Preoperative Pulmonary Risk Stratification for Noncardiothoracic Surgery : Systematic Review for the American College of Physicians. 2006. Available at. <http://annals.org/aim/article/722320/preoperative-pulmonary-risk-stratification-noncardiothoracic-surgery-systematic-review-american-college>
15. Fleisher L. Risk of Anesthesia. In: Miller R, editor. Anesthesia. 7th ed. Philadelphia: Churchil Livingstone; 2010; pp. 969-99.
16. Pires CP CE. Complicações respiratórias. In: SAESP, editor. Tratado de Anestesiologia. 7th ed. São Paulo: Atheneu; 2010; pp. 2703–15.
17. Marberger M. Renal ischaemia: not a problem in laparoscopic partial nephrectomy? BJU Int. 2007;99:3-4.
18. Thompson RH, Blute ML. At what point does warm ischemia cause permanent renal damage during partial nephrectomy? Eur Urol. 2007;52:961-3.
19. Funahashi Y, Hattori R, Yamamoto T, Kamihira O, Kato K, Gotoh M. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. Eur Urol. 2009;55:209-15.
20. American College of Surgeons. Advanced Trauma Life Support for Doctors: Student Course Manual. 8th ed. Chicago: American College of Surgeons; 2008.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
22. Funahashi Y, Murotani K, Yoshino Y, Sassa N, Ishida S, Gotoh M. The renal tumor morphological characteristics that affect surgical planning for laparoscopic or open partial nephrectomy. Nagoya J Med Sci. 2015;77:229-35.
23. Gill IS, Kavoussi LR, Lane BR, Blute ML, Babineau D, Colombo JR Jr, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol. 2007;178:41-6.
24. Ng CS, Gill IS, Ramani AP, Steinberg AP, Spaliviero M, Abreu SC, et al. Transperitoneal versus retroperitoneal laparoscopic partial nephrectomy: patient selection and perioperative outcomes. J Urol. 2005;174:846-9.
25. Marszalek M, Chromecki T, Al-Ali BM, Meixl H, Madersbacher S, Jeschke K, et al. Laparoscopic partial nephrectomy: a matched-pair comparison of the transperitoneal versus the retroperitoneal approach. Urology. 2011;77:109-13.
26. Thompson RH, Frank I, Lohse CM, Saad IR, Fergany A, Zincke H, et al. The impact of ischemia time during open nephron sparing surgery on solitary kidneys: a multi-institutional study. J Urol. 2007;177:471-6.
27. Hayn MH, Schwaab T, Underwood W, Kim HL. RENAL nephrometry score predicts surgical outcomes of laparoscopic partial nephrectomy. BJU Int. 2011;108:876-81.

28. Simmons MN, Ching CB, Samplaski MK, Park CH, Gill IS. Kidney tumor location measurement using the C index method. J Urol. 2010;183:1708-13.
29. Turna B, Frota R, Kamoi K, Lin YC, Aron M, Desai MM, et al. Risk factor analysis of postoperative complications in laparoscopic partial nephrectomy. J Urol. 2008;179:1289-94.
30. Bruner B, Breau RH, Lohse CM, Leibovich BC, Blute ML. Renal nephrometry score is associated with urine leak after partial nephrectomy. BJU Int. 2011;108:67-72.
31. Hou W, Yan W, Ji Z. Anatomic features involved in technical complexity of partial nephrectomy. Urology. 2015;85:1-7.

Correspondence address:
André Costa Matos, MD
Hospital São Rafael
Avenida Anita Garibaldi
Centro Empresarial Garibaldi, 1815/Sala 219 B
Ondina, Salvador, Bahia, 41253-190, Brasil
Telephone: +55 712626-3030
E-mail: andrecostamatos@yahoo.com.br

ORIGINAL ARTICLE

Vol. 43 (3): 432-439, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0118

Validation of preoperative variables and stratification of patients to help predict benefit of cytoreductive nephrectomy in the targeted therapy ERA

Brandon J. Manley [1], Eric H. Kim [1], Joel M. Vetter [1], Aaron M. Potretzke [1], Seth A. Strope [1]

[1] *Washington University School of Medicine, Division of Urology, St. Louis, Missouri, USA*

ABSTRACT

Objectives: To further elucidate which patients with metastatic renal cell carcinoma (mRCC) may benefit from cytoreductive nephrectomy (CN) before targeted therapy (TT), and to assess the overall survival of patients undergoing CN and TT versus TT alone.
Materials and Methods: We identified 88 patients who underwent CN at our institution prior to planned TT and 35 patients who received TT without undergoing CN. Preoperative risk factors described in the literature were assessed in our patient population (serum albumin, liver metastasis, symptomatic metastasis, clinical ≥T3 disease, retroperitoneal and supradiaphragmatic lymphadenopathy). Patients were stratified by number of pretreatment risk factors and overall survival (OS) was compared.
Results: TT patients had significantly more risk factors compared to CN patients (3.06 vs. 2.11, p<0.01). Patients who received TT alone had median OS of 5.8 months. All but one patient receiving TT alone had two or more risk factors. A comparison of the CN and TT groups was performed by constructing Kaplan-Meier curves. There was no significant difference in median OS for those patients with exactly two risk factors (447 vs. 389 days, p=0.24), and those with three or more risk factors (184 vs. 155 days, p=0.87).
Conclusions: Using previously described pretreatment risk factors we found that patients with two or more risk factors derived no significant survival advantage from CN in the TT era. These risk factors should be incorporated in the assessment of patients for CN.

ARTICLE INFO

Keywords:
Carcinoma, Renal Cell; Kidney Neoplasms; Nephrectomy; Risk Factors; Comorbidity

Int Braz J Urol. 2017; 43: 432-9

Submitted for publication:
March 06, 2015

Accepted after revision:
December 18, 2016

Published as Ahead of Print:
January 19, 2017

INTRODUCTION

Based on the results of two landmark randomized controlled trials (1-3), cytoreductive nephrectomy (CN) is recommended as a part of the treatment for many patients with metastatic RCC (mRCC). Multiple studies have addressed appropriate patient selection for CN (4-7). Various pretreatment risk factors have been proposed, including serum albumin, serum lactate dehydrogenase (LDH), retroperitoneal or supradiaphragmatic lymphadenopathy, liver metastasis, symptomatic metastasis on presentation, and clinical T3 or greater disease (6). However, validation of these risk factors in an independent data set is lacking, especially among those treated with targeted therapy (TT) alone. Importantly, previous studies included patients who received immunotherapy, rather than TT, which is not consistent with contemporary practice.

To better determine the benefits of CN in the TT era, we retrospectively reviewed patients at our institution who received TT alone (TT group) or CN followed by planned TT (CN group).

We assessed the ability of previously identified risk factors (6) to discriminate survival in our population. Patients were stratified by the number of risk factors present, and the overall survival of patients undergoing CN and planned TT was compared to those receiving TT alone.

MATERIALS AND METHODS

Patient population

After Institutional Review Board approval, we retrospectively reviewed all mRCC patients who received systemic TT from 2005 to 2013 at our institution. We defined TT as patients who received tyrosine kinase inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, or vascular endothelial growth factor (VEGF) inhibitors. We identified 100 patients who underwent CN at our institution prior to initiation of planned TT, and 39 other patients who received TT without undergoing CN. Of the CN patients, eight were excluded due to unavailable pretreatment imaging and four were excluded due to missing survival data. Of the TT patients, two were excluded due to incomplete clinical data and two were excluded due to prior immunotherapy. Thus, our final cohort consisted of 123 patients: 88 patients who received CN and 35 who were treated with TT alone. Histologic subtype for the CN patients consisted of: 71% clear cell, 17% sarcomatoid, 7% papillary type II, 5% other (including collecting duct, chromophobe, and squamous differentiation). Subtype classification for the TT alone patients could not be determined as all patients were diagnosed based on biopsy of their metastatic site, which presented histologic limitations.

Clinical variables and outcomes

The following clinical variables were collected: age, adult comorbidity evaluation (ACE) score (8), Karnofsky performance status, serum albumin, serum lactate dehydrogenase (LDH), clinical T stage, presence of liver metastasis, symptomatic metastasis, and retroperitoneal or supradiaphragmatic lymphadenopathy. Clinical T stage was based on the 2010 American Joint Committee on Cancer (AJCC) staging system. AJCC clinical N and M stage were not recorded, as the data points pertaining to lymphadenopathy and metastasis were selected for their previously demonstrated significance (9). Pretreatment albumin was not available for 11 of the 123 patients (8%) included in our study. Pretreatment LDH was not available in 81of 123 patients (65%). Although we chose to remove LDH from our primary analysis, a sensitivity analysis was performed using multiple imputation to ensure no significant changes occurred due to missing data. Pretreatment risk factors used in our primary analysis were: serum albumin below laboratory normal range, clinical T3 or T4 disease, presence of liver metastasis, symptomatic metastasis, and retroperitoneal or supradiaphragmatic lymphadenopathy >1cm. Survival data was gathered using available medical records and the Social Security death index. Our final query of the death index was on October 6, 2013.

Statistical analysis

Baseline patient characteristics

Continuous variables were compared with the paired t-test, and categorical variables were compared with chi-squared testing. Statistical significance was defined by $p<0.05$ (two-tailed).
Median overall survival for CN patients stratified by risk factor group versus TT only.

An attempt was made to validate the findings of Culp et al. in which they ascertained risk of death based on number of risk factors in CN patients (6). Therefore, CN patients were stratified by the number of pretreatment risk factors present. TT patients were not subdivided and considered the referent for this analysis. Univariate Cox proportional hazards analysis was performed for each CN risk factor group and compared to all TT patients. Culp et al. conducted a Cox proportional hazards analysis for CN patients with three or fewer and four or more risk factors. As LDH was removed from our analyses, the model was completed for CN patients with two or fewer risk factors and those with three or more risk factors.

Survival analysis

Kaplan-Meier estimated overall survival (OS) was compared between CN and TT groups stratified by the number of pretreatment risk fac-

tors present. As only one patient with fewer than two risk factors received TT alone without CN, all patients with fewer than two risk factors were excluded from the Kaplan-Meier analysis. There was no comparator group for patients with fewer than two risk factors receiving CN. The remaining patients were stratified into two groups: exactly two risk factors or three to five risk factors. Log rank p-values were calculated to compare survival curves. Multivariate cox proportional hazards analysis was also performed adjusting for age and comorbidity.

Sensitivity analysis

Multiple imputation analysis was performed for missing data. For each missing variable, multiple imputations were derived at random on the basis of the distribution of each variable within our data. All statistical analyses were then repeated with imputed values for LDH and albumin to ensure no changes resulted from missing data. All statistical analyses were completed using R software, version 2.15.1 using the package 'survival' for the survival analysis (10) and the package 'MICE' for multivariate imputation and analysis (11).

RESULTS

Baseline patient clinical characteristics are provided in Table-1. Mean number of risk factors was significantly greater for the TT group as compared to the CN group (3.06±1.08 vs. 2.11±1.17, p<0.01). Significantly more patients in the TT group had symptomatic metastasis (77% vs. 53%, p=0.02) and supradiaphragmatic lymphadenopathy (63% vs. 30%, p<0.01) as compared to the CN group. After CN, 14/88 (15.9%) CN patients did not undergo the previously planned TT; justifications included death (7.50%), refusal (2,14%), no evidence of disease (2, 14%), and decision in consultation with medical oncology to undergo active surveillance (3,21%).

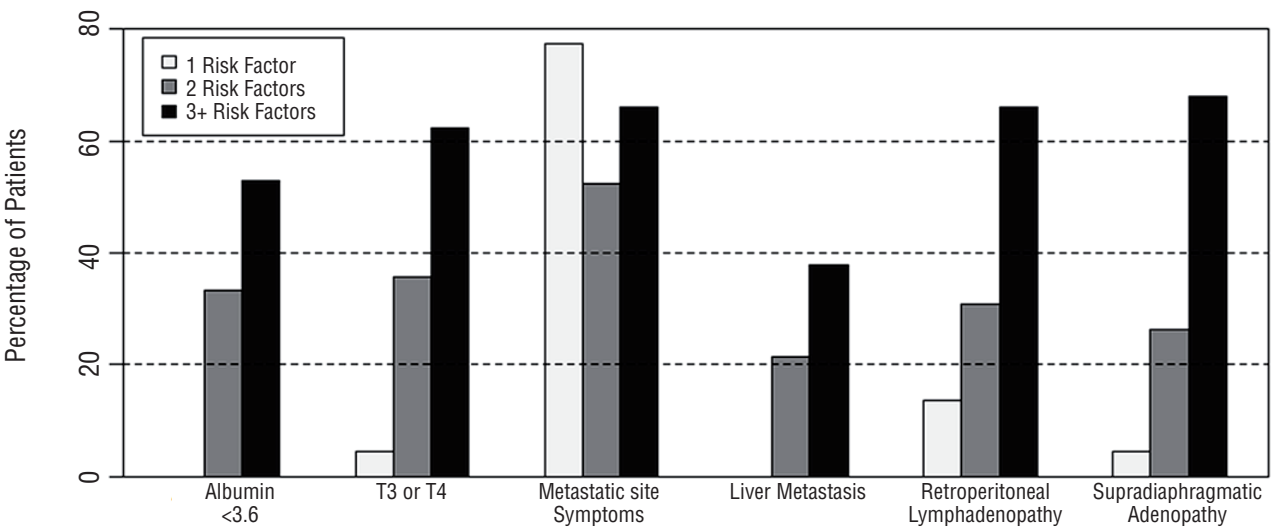
Figure-1 illustrates the distribution and frequency of individual risk factors stratified by the total number of risk factors present for each patient. For patients with exactly one risk factor, symptomatic metastasis was seen most frequently (17/22=77%). For patients with exactly two risk factors, symptomatic metastasis was also seen most frequently (24/42=57%), but all risk factors were represented. For patients with three or more factors, all risk factors were similarly represented:

Table 1 - Baseline patient clinical characteristics.

Variable	CN	TT	p-value
Number of patients	88	35	
Mean age (SD), years	57.4 (10.4)	57.8 (10.4)	0.87
Mean ACE score (SD)	1.22 (0.96)	1.26 (1.01)	0.83
Karnofsky performance ≤ 60 (%)	10/88 (11%)	12/35 (34%)	**<0.01**
Mean number of risk factors (SD)	2.11 (1.17)	3.06 (1.08)	**<0.01**
Albumin ≤ 3.5 (%), g/dL	61/88 (69%)	20/35 (57%)	0.20
Clinical stage ≥ T3 (%)	36/88 (41%)	13/35 (37%)	0.70
Liver metastasis (%)	18/88 (20%)	11/35 (31%)	0.20
Symptomatic metastasis (%)	47/88 (53%)	27/35 (77%)	**0.02**
Retroperitoneal LAD (%)	32/88 (36%)	19/35 (54%)	0.07
Supradiaphragmatic LAD (%)	26/88 (30%)	22/35 (63%)	**<0.01**

CN = cytoreductive nephrectomy; **TT =** targeted therapy; **SD =** standard deviation; **ACE =** adult comorbidity evaluation; **LAD =** lymphadenopathy

Figure 1 - Distribution of individual risk factors among patients stratified by total number of risk factors present.



clinical stage ≥T3 (32/53=60%), symptomatic metastasis (33/53=62%), retroperitoneal lymphadenopathy (33/53=62%), and supradiaphragmatic lymphadenopathy (33/53=62%).

Median OS for CN patients stratified by risk factor group compared to all TT patients are provided in Table-2. TT patients were not stratified and served as the referent group. Patients who received TT alone without CN had a global median OS of 5.8 months. Patients who received CN and had two or fewer factors demonstrated median OS of 22.1 months. In univariate analysis, when compared to all TT patients as a referent, this represented significantly greater OS (HR=0.39, 95% CI 0.23-0.65). OS did not significantly differ between all TT patients and CN patients with three or more risk factors (HR=1.29, 95% CI 0.74-2.23).

Table-3 demonstrates the median OS from our Kaplan-Meier analysis for both the CN and TT groups stratified by their number of risk factors. No patients in the TT group had zero risk factors, and only one had one risk factor. Due to this we were not able to carry out comparative analysis between CN patients with 0-1 risk factors and TT patients with 0-1 risk factors. Stratification was performed to provide CN and TT groups with exactly two and three or more risk factors. Figure-2 illustrates the estimated survival curves for patients with exactly two risk factors. No significant difference in median OS was noted between CN and TT only (447 vs. 389 days, p=0.24) for a difference of about 2 months. Figure-3 illustrates the estimated survival curves for patients with three or more factors. For these patients, no significant difference in median OS was noted between CN and TT only (184 vs. 155 days, p=0.87), for a difference of about 1 month. Furthermore, after stratification by number of risk factors present and multivariate analysis controlling for age and comorbidities, CN did not demonstrate a benefit in either those with exactly two risk factors (HR=1.37, 95% CI 0.56–3.38) or three or more risk factors (HR=0.87, CI 0.47–1.63).

All analyses were repeated using the imputed values for LDH and albumin levels. The association of increasing numbers of risk factors and worsening survival remained intact in this analysis. CN was not associated with improvement in survival for patients with two or more risk factors in these analyses.

DISCUSSION

We found that median overall survival for patients undergoing CN decreased as their number of preoperative risk factors increased. When the CN patients were stratified by preoperative risk factors and compared to the TT patient group

Table 2 - Median overall survival for CN patients stratified by risk factor group versus TT only.

Patient Group	N	HR	95% CI	P-value	Median OS, months
TT Only	35	Reference	-	-	5.8
CN					
Risk Factors					
0	6	0.47	0.11-1.99	0.30	15.5
1	21	0.30	0.15-0.63	**<0.01**	28.3
2	30	0.49	0.27-0.88	**0.02**	14.9
3	23	1.08	0.59-1.96	0.80	7.2
4	4	1.31	0.45-3.80	0.62	4.7
5	4	5.64	1.72-18.5	**<0.01**	2.0
< 2	57	0.39	0.23-0.65	**<0.01**	22.1
> 3	31	1.29	0.74-2.23	0.37	6.1

CN = cytoreductive nephrectomy; **TT =** targeted therapy; **HR =** hazard ratio; **CI =** confidence interval; **OS =** overall survival

Table 3 - Kaplan-Meier analysis with median overall survival for both the cytoreductive nephrectomy and targeted therapy groups stratified by number of risk factors.

	Cytoreductive Nephrectomy		Targeted Therapy	
Factors	Count	Median Overall Survival (days)	Count	Median Overall Survival (days)
0	6	466.5	0	*
1	21	850	1	*
2	30	447	12	389
3	23	215	10	156
4	4	142.5	8	232
5	4	60.5	4	152

***** = unable to calculate due insufficient data

as a whole, we found an apparent survival advantage for CN in patients with fewer than or equal to two risk factors (Table-2). However, after stratifying both CN and TT patients by the number of preoperative risk factors present, we found no differences in survival when exactly two or three or more pretreatment risk factors were present for each group, based on Kaplan-Meier analysis (Figures 2 and 3). Likewise, multivariate analysis controlling for age and ACE did not demonstrate a benefit of CN for patients with two or more risk factors.

An attempt was made to validate the findings by Culp et al. in their analysis of risk factors in CN patients (Table-2) (6). Like the group from M.D. Anderson, we used the medical therapy cohort as the referent group. The noted difference in the present univariate analysis is that we were unable to include LDH as an assessed risk factor due to missing data in

Figure 2 - Kaplan-Meier estimated survival comparing patients in cytoreductive nephrectomy group (CN) to targeted therapy group (TT) for patients with exactly two risk factors.

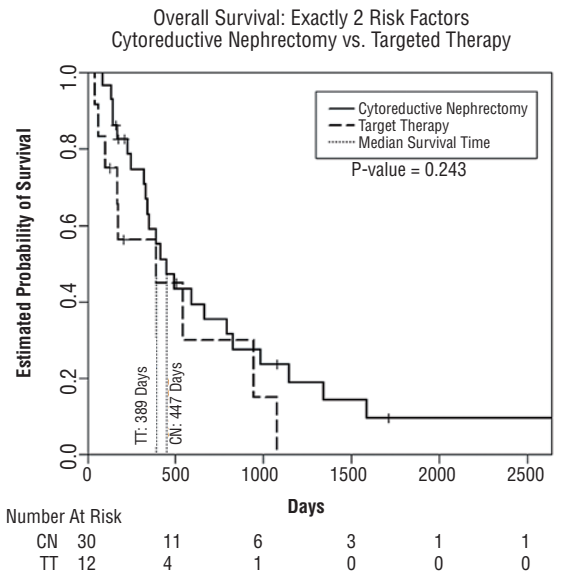
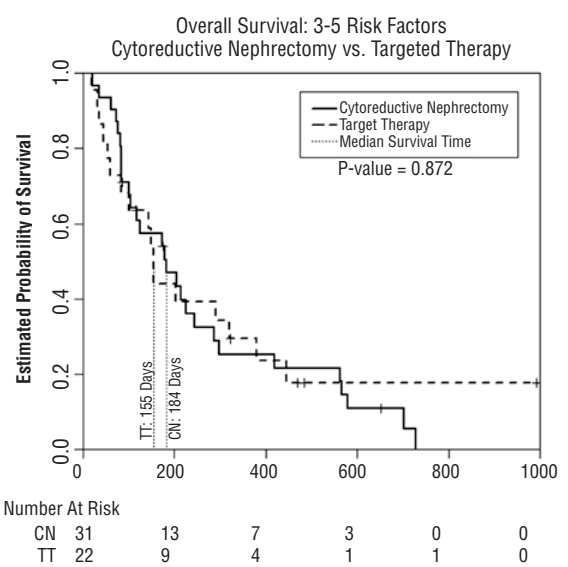


Figure 3 - Kaplan-Meier estimated survival comparing patients in cytoreductive nephrectomy group (CN) to targeted therapy group (TT) for patients with three to five risk factors.



a large portion of our cohort (65%). Also, in our preliminary analysis patients with three risk factors did not derive a benefit from CN. Therefore, rather than assess patients with three or fewer and four or more risk factors as was done by Culp and colleagues, we stratified CN patients by two or fewer and three or more risk factors. Ultimately, our results mirror those of Culp et al. The analysis is challenging given the heterogeneity and inherent bias in the targeted therapy group, wherein nearly every patient had two or more risk factors. To account for these differences, we derived conclusions from Kaplan-Meier survival curves and multivariate Cox proportional hazards models. In agreement with several other studies, we found the actual benefit of CN may be limited to a select patient population (6, 7, 12). In cases where two or more risk factors were present, patients did not appear to benefit from CN in our stratified analysis.

Interestingly, only a single patient with fewer than two risk factors received TT alone, highlighting a selection bias for patients undergoing CN versus receiving primary TT. In practical terms, it appears that urologists and medical oncologists are already selecting patients at highest risk to forgo extirpative therapy. This seems to be largely based on intuition as our cohort largely predates the work by Culp et al. that defined these risk factors (6).

Often, patients are unable to complete the planned medical therapy after CN. In the present cohort, 14/88 (15.9%) CN patients did not undergo the intended TT. In 2010, Kutikov et al. published their series of 141 patients who underwent CN (13). The authors found that 31% of patients did not undergo the intended systemic therapy. In this group, the medical therapy was omitted due to rapid disease progression (30%), decision for surveillance by oncology (21%), patient refusal (23%), and death (19%). Additionally, of the patients who did receive TT after CN, approximately half of the patients (33/69=47%) received a second-line TT due to either progression of disease or medication intolerability, and the decision of what medication to use as a second or third-line therapy was made at the discretion of the treating medical oncologist. Future studies with larger sample sizes may be able to identify patient and tumor factors predictive of the need for second or third-line TT.

Previous population-based studies have demonstrated a benefit for patients treated with

CN (14-16). However, these population-based studies are not able to compare CN and TT patients with similar pretreatment risk factors. This inability to accurately assess disease burden between treatment groups is a clear limitation. Furthermore, many previous studies have included patients who received immunotherapy, presented with asynchronous metastasis, and received radiotherapy (6, 14-16). Although our patient population is relatively small, we have removed many of these confounding factors. The present study includes mRCC patients treated only in the TT era, with no treatment contamination with immunotherapy or radiotherapy. Additionally, we stratify not only our CN patients by pretreatment risk factors but also our TT patients as well. With both CN and primary TT patients stratified by number of risk factors, our study provides additional insight as to which patients may derive benefit from CN. For patients with exactly two and three to five risk factors, we found that performing CN prior to TT over TT alone provides minimal or no improvement in survival. While our study is underpowered to prove that this small survival improvement is statistically significant, even in an appropriately powered study this improvement must also be balanced with the known increased risk of surgical complications in mRCC patients (17).

Our study is not without limitations. It is logical to assume based on our data that the perceived overall health and corresponding prognosis of each patient biased the initial treatments offered. Although the healthier patients, as judged by the surgeon, are more likely to receive CN, we found no evidence for improved survival over TT when data were analyzed stratified by the number of risk factors present. As stated previously, the overwhelming majority of patients with zero to one risk factor underwent CN at our institution, which prevents accurate comparisons between CN and primary TT in this lower risk patient population. Although the TT alone group is a heterogenous treatment group (receiving TKI, mTOR inhibitors, and VEGF inhibitors), the patients who were able to receive TT after CN were expected to have similar heterogeneity in their TT treatments. The choice of specific TT agents to use and when to withdraw or change therapy was made at the discretion of the treating medical oncologist and patient, and was not defined by an institutional or study protocol. While 15.9% of patients in the CN group did not complete the intended TT, this limitation is common in the literature (13). Furthermore, the histologic subclassification in the TT alone group could not be determined as biopsies were performed on metastatic sites and limited in tissue. Future studies with larger sample sizes should examine the histologic subclassification of mRCC and identify if a strong association between histology and survival exists even when diagnosed at a metastatic stage. Finally, our results are from a tertiary care center, and may not reflect the full spectrum of metastatic RCC patients seen in community practice.

Paramount to the practicing urologic surgeon is the relative weight of the risks and benefits of CN. In a population-based series of 16,285 patients by Trinh et al., the overall complication rate was 31% (17). Moreover, the complication rate was increased in those with numerous comorbidities and more than one metastatic site. Additionally, the in hospital mortality rate was 5%, and was significantly greater in those with age ≥75 (7.9%), three or more comorbidities (7.7%), and two or more metastatic sites (7.4%). While the possible benefit of CN is enticing, the results presented herein show it may be prudent to forgo surgery in those with advanced disease or with significant medical illness. Avoiding costly complications and untoward patient suffering is of vital concern.

CONCLUSIONS

Using previously described preoperative risk factors we found that patients with two or more risk factors derived no significant survival advantage from CN in the TT era. These risk factors should be incorporated in the assessment of patients for CN.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345:1655-9.
2. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001;358:966-70.
3. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol. 2004;171:1071-6.
4. Leibovich BC, Han KR, Bui MH, Pantuck AJ, Dorey FJ, Figlin RA, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer. 2003;98:2566-75.
5. Leibovich BC, Cheville JC, Lohse CM, Zincke H, Frank I, Kwon ED, et al. A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. J Urol. 2005;174:1759-63.
6. Culp SH, Tannir NM, Abel EJ, Margulis V, Tamboli P, Matin SF, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer. 2010;116:3378-88.
7. You D, Jeong IG, Ahn JH, Lee DH, Lee JL, Hong JH, et al. The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy. J Urol. 2011;185:54-9.
8. Piccirillo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer. 1996;77:834-42.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471-4.
10. A Package for Survival Analysis in S. 2015 available at <https://CRAN.R-project.org/package=survival> (Accessed December 8, 2016).
11. van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. . Journal of Statistical Software 2011;45:1-67.
12. Choueiri TK, Xie W, Kollmannsberger C, North S, Knox JJ, Lampard JG, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endotelial growth factor targeted therapy. J Urol. 2011;185:60-6.
13. Kutikov A, Uzzo RG, Caraway A, Reese CT, Egleston BL, Chen DY, et al. Use of systemic therapy and factors affecting survival for patients undergoing cytoreductive nephrectomy. BJU Int. 2010;106:218-23.
14. Warren M, Venner PM, North S, Cheng T, Venner C, Ghosh S, et al. A population-based study examining the effect of tyrosine kinase inhibitors on survival in metastatic renal cell carcinoma in Alberta and the role of nephrectomy prior to treatment. Can Urol Assoc J. 2009;3:281-289.
15. Aben KK, Heskamp S, Janssen-Heijnen ML, Koldewijn EL, van Herpen CM, Kiemeney LA, et al. Better survival in patients with metastasised kidney cancer after nephrectomy: a population-based study in the Netherlands. Eur J Cancer. 2011;47:2023-32.
16. Zini L, Capitanio U, Perrotte P, Jeldres C, Shariat SF, Arjane P, et al. Population-based assessment of survival after cytoreductive nephrectomy versus no surgery in patients with metastatic renal cell carcinoma. Urology. 2009;73:342-6.
17. Trinh QD, Bianchi M, Hansen J, Tian Z, Abdollah F, Shariat SF, et al. In-hospital mortality and failure to rescue after cytoreductive nephrectomy. Eur Urol. 2013;63:1107-14.

Correspondence address:
Seth A. Strope, MD
4960 Children's Place
Campus Box 8242
St. Louis, MO 63110, USA
Telephone: +1 314 454-8049
E-mail: stropes@wudosis.wustl.edu

ORIGINAL ARTICLE

Vol. 43 (3): 440-454, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0521

Analysis of various potential prognostic markers and survival data in clear cell renal cell carcinoma

Tastekin Ebru [1], Oz Puyan Fulya [1], Akdere Hakan [2], Yurut-Caloglu Vuslat [3], Sut Necdet [4], Can Nuray [1], Ozyilmaz Filiz [1]

[1] Department of Pathology, Faculty of Medicine, Trakya University, Edirne, Turkey; [2] Department of Urology, Faculty of Medicine, Trakya University, Edirne, Turkey; [3] Department of Radiation Oncology, Faculty of Medicine, Trakya University, Edirne, Turkey; [4] Department of Biostatistics, Faculty of Medicine, Trakya University, Edirne, Turkey

ABSTRACT

Purpose: Clear cell renal cell cancers frequently harbor Von Hippel-Lindau gene mutations, leading to stabilization of the hypoxia-inducible factors (HIFs) and their target genes. In this study, we investigated the relationship between vascular endothelial growth factor (VEGF), HIF-1α, HIF-2α, p53 positivity, microvessel density, and Ki-67 rates with prognostic histopathologic factors (Fuhrman nuclear grade, stage, and sarcomatoid differentiation) and survival in clear cell renal cell carcinomas.

Material and Methods: Seventy-two nephrectomy specimens diagnosed as clear cell renal cell carcinoma between 2000 and 2012 were reevaluated. Immunohistochemically VEGF, HIF-1α, HIF-2α, p53, CD34 (for microvessel density evaluation), and Ki-67 antibodies were applied to the tumor areas. The relationships of these antibodies with prognostic factors and survival rates were evaluated with statistical analyses.

Results: Mean survival time was 105.6 months in patients with ccRCC. Patients with high expression of VEGF, HIF-1α and HIF-2α positivity, a high Ki-67 proliferation index, and a high microvessel density evaluation score had a shorter survival time ($p<0.05$).

Conclusions: Our findings supported that with the use of these immunohistochemical markers, prognosis of renal cell carcinoma may be predicted at the first step of patient management. New treatment modalities targeted to HIF-1α and HIF-2α might be planned as well as VEGF-targeted therapies in the management of clear cell renal cell carcinomas.

ARTICLE INFO

Key words:
Carcinoma; Carcinoma, Renal Cell; Survival Rate

Int Braz J Urol. 2017; 43: 440-54

Submitted for publication:
September 17, 2015

Accepted after revision:
April 30, 2016

Published as Ahead of Print:
September 01, 2016

INTRODUCTION

Renal cell carcinoma (RCC) is the third most common urological malignancy and represents 5% of all cancer diagnoses. Clear cell renal cell cancers (ccRCCs) represent 70% of all renal cancers, and several clinical and histopathologic factors are implicated in the prognosis of renal cancers. Since the World Health Organization updated its classification of kidney tumors in 2004, many studies on histological subtypes, stage, Fuhrman nuclear grade (FNG), prognostic histopathologic factors, and the relationships of these prognostic factors and various immunohistochemical antibodies were conducted. Various studies were conducted to detect the angiogenic and diagnostic factors of ccRCCs and to find new evaluation criteria (1).

Sporadic ccRCC is caused by Von Hippel-Lindau (VHL) tumor suppressor gene mutations

located on chromosome 3p in up to 90% of cases. This gene plays a critical role in hypoxia response, including stimulation of neoangiogenesis. According to the most recent studies, common angiogenesis and abnormal blood vessel growth have a direct correlation with the prognosis of renal cell carcinoma (2-5).

The best-documented function of the VHL gene is its role in the oxygen-sensing pathway comprising the substrate recognition component of the E3 ubiquitin ligase complex. This complex targets hypoxia inducible factors (HIFs) for polyubiquitination and proteasomal degradation. The HIF heterodimer can translocate to the nucleus and transactivate the target genes, many of which promote adaptation to acute or chronic hypoxia, including vascular endothelial growth factor (VEGF), which promotes angiogenesis (2, 6). The mutation or inactivation of VHL genes leads to uncontrolled expression of HIF-1α that leads to increased HIF-1α levels in a cell. This complex leads to the transcription of genes that are susceptible to hypoxia and are related to cell survival, regulation of pH levels, glucose metabolism, and angiogenesis, such as VEGF, platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-α), erythropoietin, and carbonic anhydrase 9 (6). VEGF is the most potent endothelial cell-specific angiogenesis factor. It increases vascular permeability that leads to endothelial cell proliferation, migration, and tube formation (7). Many studies on the influence of VEGF and HIFs on prognosis have been conducted. The relation of these antibodies to targeted therapies, nuclear grading, and tumor size and sarcomatoid differentiation (SD) are increasingly intriguing subjects for studies. These factors offer hints about the progress, strategy, and results of the treatment or chances of relapse. In addition, RCC, a clinically angiogenic activity, has a direct relation with the expression of VEGF. This led to VEGF inhibition-based treatment methods used today against RCC (8).

Immunohistochemically, p53 positivity, and a high Ki-67 proliferating index are associated with cell proliferation. Many studies on the Ki-67 proliferating index and mutant p53 positivity as independent prognostic factors in RCC have been conducted (9). In addition, as an important indicator in RCC prognosis, angiogenesis assessment can be carried out using CD34 antibodies to measure microvessel density (MVD) levels. Recent studies have focused on the importance of these factors in determining the average life expectancy (7, 9, 10).

In this study, we investigated the relationship of VEGF, HIF-1α, HIF-2α, p53 positivity, MVD, and Ki-67 rates with prognostic histopathologic factors (FNG, stage, and SD), and survival in ccRCCs.

MATERIALS AND METHODS

Study population and clinical and pathological analysis

The surgical pathology reports of all patients who underwent nephrectomy for RCC between 2000 and 2012 at Department of Pathology, Trakya University Medical Faculty, were reviewed. The follow-up time was a minimum of 2 months and a maximum of 168 months in this study. The surgical pathology reports of all patients who underwent nephrectomy for RCC between 2000 and 2012 at Trakya University Medical Faculty, Department of Pathology were reviewed. The follow-up time was a minimum of 2 months and a maximum of 168 months in this study.

Thirty-two (44.4%) of the patients died during the study and the death reasons for the all patients were clear cell RCC. The pathology reports, as well as the clinical and follow-up data, were retrospectively analyzed. The tumor slides of all patients were reexamined by the Department of Pathology. Histological factors were reevaluated blindly and independently by two pathologists (E.T. and F.O.P.).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (152/2014-17/10). We obtained clinical and pathological data for all enrolled patients from our database and analyzed the results. Informed consent was obtained from all individual participants included in the study.

Histological evaluation

Tumor grade was based on the Fuhrman nuclear grade system (11), and the tumors were staged according to AJCC/UICC TNM, 7th edition (12). SD was assessed on histologic sections and was graded into two categories, present or absent.

Immunohistochemical analysis

Before the study, control tissues (from data sheets) were obtained from the archive for each antibody, and then the control staining of these materials was performed. Of these antibodies, Ki-67, p53, and HIF-1α showed nuclear staining, VEGF and CD34 showed cytoplasmic staining, and HIF-2α showed nuclear and cytoplasmic staining. Cytoplasmic staining has been approved as significant for HIF-1α by some researchers (13). Considering the molecular characteristics of HIF-1α and HIF-2α, we used approved positive nuclear staining in this study.

VEGF evaluation

The immunostaining of VEGF (Clone SP28) was evaluated as a percentage of the cytoplasmic staining pattern in tumor cells. At least 10 high-power fields, including tumors, were evaluated. Moderate cytoplasmic staining was observed in healthy renal tubules (6), and the intensity and percentage of the tumor cells stained with VEGF were evaluated (14). The percentages of VEGF-positive tumor cells were scored as 0 (no staining), 1 (1–25% positive cells), 2 (26–50% positive cells) and 3 (>50% positive cells). The VEGF staining intensity was also scored as 0 (negative), 1 (weak), 2 (intermediate), and 3 (strong). The sum of the percentage and intensity scores was evaluated, and a final score was noted as 0 (negative), 1–2 (weak), 3 (moderate), or 4–6 (strong expression). Cases were divided into two groups, group 1 (score 0–3) and group 2 (score 4–6).

HIF-1α and HIF-2α evaluations

HIF-1α (Clone H1alpha67) and HIF-2α (Clone D9E3) immunoreactivity was assessed separately for staining distribution and intensity. For the HIF-1α and HIF-2α assessment, the staining intensity was scored as 0 (negative), 1 (weak), 2 (medium), and 3 (strong). The extent of the staining was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%) according to the percentages of the positive staining areas in relation to the entire carcinoma area. The sum of the intensity and extent score was used as the final staining score (0–7) for HIF-1α and HIF-2α. Tumors that had a final staining score of 2 and higher were considered positive, and tumors that had a final staining score lower than 2 were considered negative (6, 13).

p53 evaluation

For p53 (Clone DQ-7) assessment, 1000 tumor cells were evaluated, and cases with nuclear staining were considered positive (9).

Ki-67 evaluation

For detection of the Ki-67 (Clone SP26) proliferating index, 1000 tumor cells were counted, and the average value was determined statistically (9).

MVD (CD34 antibody) evaluation

For MVD assessment, the areas of the tumor containing the most capillaries and small venules (i.e., areas of the most intense neovascularization) were examined with a light microscope. Tumors are frequently heterogeneous in microvessel density, but the areas with the highest neovascularization were found by scanning the tumor sections at low power (40X and 100X). CD34 antibody (Clone QBEnd-10) was applied to identify the highest number of discrete microvessels in the tumor areas. Microvessels in sclerotic areas within the tumor, where microvessels are sparse, and immediately adjacent areas of unaffected kidney tissue were not considered in the vessel counts. Any brown-staining endothelial cell or endothelial cell cluster that was clearly separate from adjacent microvessels, tumor cells, and other connective tissue elements was considered a single, countable microvessel. Vessel lumens, although usually present, were not necessary for a structure to be defined as a microvessel, and red cells were not used to define a vessel lumen. Vessel count was performed on a 200X field in five areas, and the average value was determined statistically (10).

Survival data

Survival information was obtained from the university's patient follow-up unit.

Statistical analysis

Patients were classified by their survival status (alive vs. dead). Results are shown as mean±standard deviation, median (minimum–maximum) or number (percentage). The Student t test was used for comparison of age between the alive and dead groups. Gender, FNG, stage, SD, VEGF, HIF-1α, HIF-2α, and P53 values between the alive and dead groups were compared with the chi-square test. The Ki-67 and MVD values between the alive and dead groups were compared with the Mann-Whitney U test. Relationships between VEGF, HIF-1α, HIF-2α, P53, Ki-67, and MVD with FNG, stage, and SD were analyzed with point-biserial correlation analysis. Survival function of patients with ccRCC was analyzed by using the Kaplan-Meier survival analysis according to the stage, FNG, SD, VEGF, and HIF-1α. Then, the log-rank test was used for comparison of survival status. Cut-off values were determined by using the ROC analysis for Ki-67 and MVD, and then the sensitivity, specificity, and area under the curve (AUC) values were calculated based on these cut-off points. A multivariable Cox regression analysis was used to investigate the effect of stage, FNG, SD, VEGF, and HIF-1 alpha on survival.

Statistical analyses were performed using SPSS 20.0 (IBM SPSS Inc., Chicago, IL, USA) and MedCalc11.1.1.0 (MedCalc Software bvba, Ostend, Belgium) statistical software.

RESULTS

Demographic data

Seventy-two patients with ccRCC were included in the study. Forty-nine patients were male, and 23 were female (68.1% and 31.9%). Their ages were between 26 and 80 years. Forty (55.6%) of the patients were alive during the study. Patients who were alive had a mean age of 58.48±8.11 years, and deceased patients had a mean age of 65.94±8.65 years. The number of patients according to stage were 25, 17, 21, and 9 in stages 1, 2, 3, and 4, respectively. Most of the patients were localized in FNG 2 (30 patients) and FNG 3 (27 patients). The FNG 1 group included only 5 patients, and the FNG 4 group included 9 patients. Although 11 patient's tumors showed SD, 61 patient's tumors did not.

Survival evaluation revealed a general survival rate of 78.21% and a mean survival time of 86.6 months (86.59±4.8) in ccRCC. The median follow-up time was 76 months (min 1.5–max 168.3 months). The mean survival time was 105.6 months in patients with ccRCC. The 1-, 5- and 10-year survival rates were 95.8%, 72.8%, and 48.8% respectively. Survival time was shorter in patients with advanced stage ($p<0.001$), high grade ($p<0.001$), and SD positivity ($p<0.001$). Forty-four of the 72 patients had metastatic ccRCC. According to the medical oncology clinical data, 32 patients were treated with tyrosine kinase inhibitors, and 18 patients received mTOR inhibitors.

Table-1 and Figure-1 show the patient's demographic data, histopathologic prognostic features (FNG, stage, SD), and their relationships with survival. Immunohistochemical staining features are shown in Figure-2 and listed in Tables 2 and 3; microscopic features and immunohistochemical staining examples of ccRCCs are shown in Figures 2 and 3.

VEGF and survival status

With the VEGF antibody, only 4 cases did not show staining, while the others had different levels of staining. Twenty-seven (37.5%) cases had strong staining for VEGF, and only 6 of them (22.22%) were survivors. We observed a direct relation between the VEGF score and the stage, Fuhrman nuclear grade, and SD positivity ($r=0.935$, $p<0.001$; $r=0.692$, $p<0.001$; $r=0.394$, $p<0.001$, respectively). We observed that although the VEGF stain score increased, the mean survival rates decreased. The mean survival time for cases with a VEGF stain score of 1 was 142.91 months, on average, in cases with score 2, 106.3 months, and in cases with score 3, as low as 56.09 months ($p<0.01$; see Table-4).

HIF-1α and survival status

Twenty-two cases (30.5%) showed a positive reaction with HIF-1α; 7 of these cases (31.8%)

Table 1 - Clinical and pathological characteristics of patients.

	Alive	Dead	P
Age (year±SD)	58.48±8.1	65.94±8.6	<0.001*
Gender	**(n/%)**	**(n/%)**	
Male	27 (%68)	22 (%69)	0.910
Female	13 (% 32)	10 (%31)	
Fuhrman Grade	**(n/%)**	**(n/%)**	
1	5 (%13)	0 (%0)	
2	25 (%62)	5 (%16)	<0.001*
3	10 (%25)	17 (%53)	
4	0 (%0)	10 (%31)	
Stage	**(n/%)**	**(n/%)**	
1	20 (%50)	5 (%16)	
2	10 (%25)	7 (%22)	<0.001*
3	10 (%25)	11 (%34)	
4	0 (%0)	9 (%28)	
SD	**(n/%)**	**(n/%)**	
+	0 (% 0)	11 (%34)	<0.001*
-	40 (%100)	21 (%66)	

SD = Sarcomatoid differentiation

were survivors. We observed a direct correlation between HIF-1α positivity and FNG (r=0.264; p<0.05) and stage (r=0.277; p<0.05). No statically significant relation between HIF-1α and SD was observed (p=0.25). A shorter survival time was present in cases of HIF-1α positivity. Cases with HIF-1α positivity had an average survival time of 63 months, while cases with negativity had an average survival time of 120 months (p<0.05; see Table-4).

HIF-2α and survival status

Twelve cases (16.6%) showed a positive reaction with HIF-2α, and 7 of these cases (31.8%) were survivors. No statically significant relation between HIF-2α, FNG, stage, and SD was found. We observed a shorter average survival time for patients with HIF-2α positivity. The mean survival time for the HIF-2α-positive cases was 88 months and for the negative cases was 107 months (p<0.05; see Table-4).

Figure 1 - Relationship of histopathological and immunohistochemical characteristics with survive. A) Survival function of patients with RCC, B) Survival function of patients with RCC by stage, C) Survival function of patients with RCC by Fuhrman Nuclear Grade, D) Survival function of patients with RCC by Sarcomatoid differentiation. E) Survival function of patients with RCC by VEGF, F) Survival function of patients with RCC by HIF-1 Alpha.

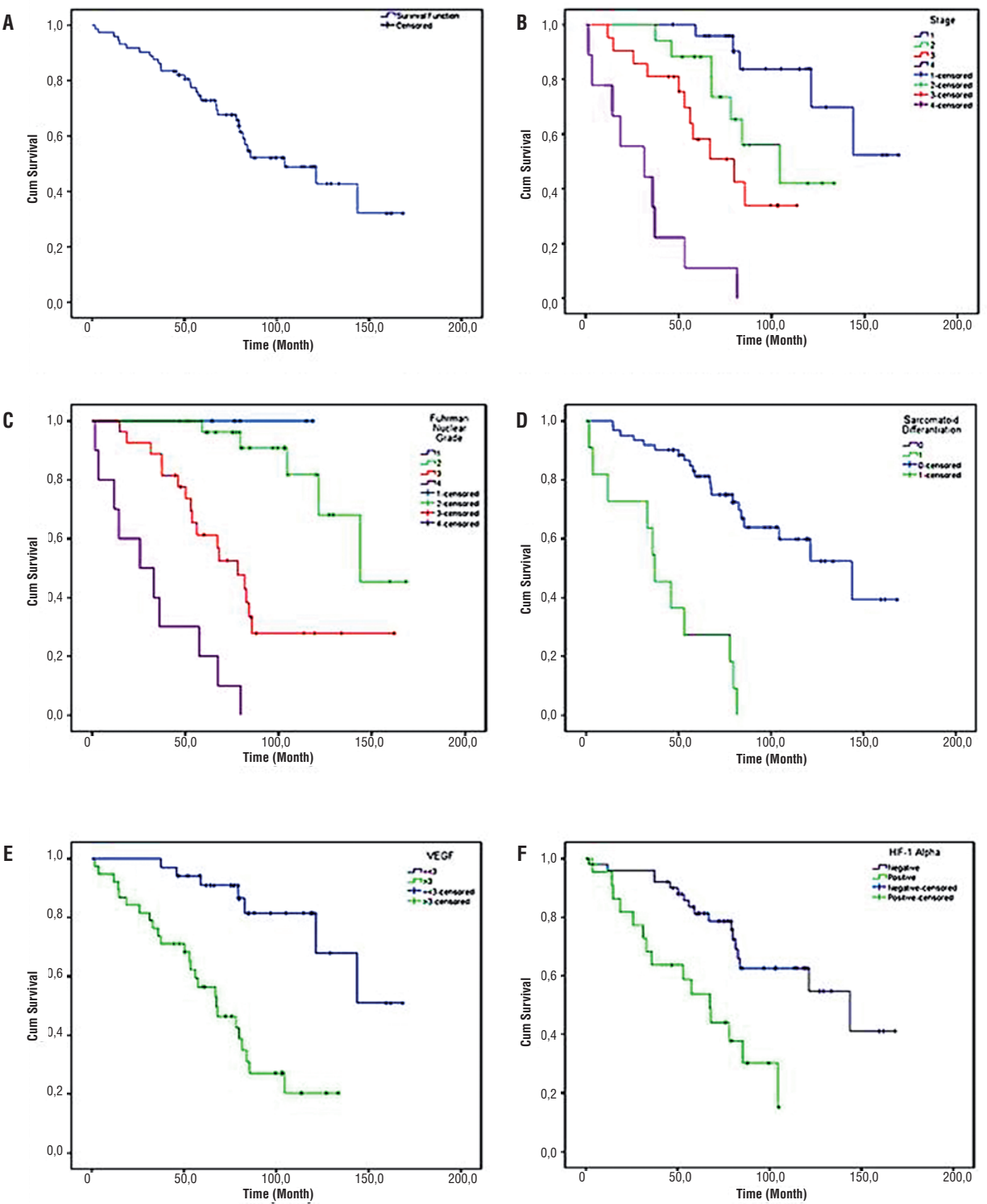


Figure 2 - Microscopic features of clear cell renal cell carcinomas. A) Fuhrman grade 1 tumor (H&EX100), B) Fuhrman grade 3 tumor (H&EX200), C and D) Sarcomatoid differentiation in clear cell renal cell carcinoma (H&EX50).

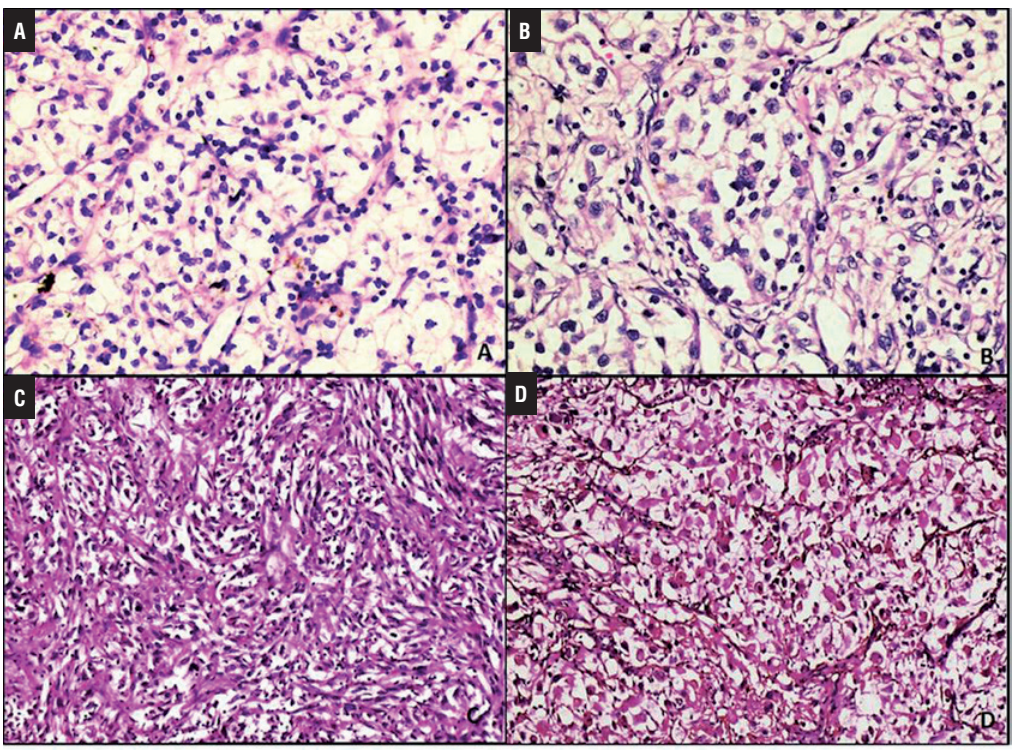


Table 2 - Distribution of immunohistochemical characteristics of patients.

	Alive	Dead	p
VEGF	**(n/%)**	**(n/%)**	
0-3	27 (%68)	7 (%22)	0.002*
4-6	13 (%32)	25 (%78)	
HIF-1 alpha	**(n/%)**	**(n/%)**	
+	7 (%18)	15 (%47)	0.007*
-	33 (%82)	17 (%53)	
HIF-2 alpha	**(n/%)**	**(n/%)**	
+	5 (%13)	7 (%22)	0.289
-	35 (%87)	25 (%78)	
P53	**(n/%)**	**(n/%)**	
+	1 (%3)	5 (%13)	0.041*
-	39 (%87)	27 (%87)	
Ki 67 (median/min-max)	70.5(10-289)	145.5 (27-453)	<0.001*
MVD (median/min-max)	141.5 (91-400)	280 (98-250)	<0.001*

VEGF = Vascular endothelial growth factor; **HIF** = Hypoxia inducible factor; **MVD** = Micro vessel density

Table 3 - Distrubution of immunohistochemical markers between the stages, Fuhrman nuclear grade and sarcomatoid differentiation.

		HIF-1 alpha		HIF-2 alpha		VEGF						
		(-)	(+)	(-)	(+)	0	1	2	3	4	5	6
STAGE (n)	**1** (n=25)	4	21	4	21	1	11	23	0	0	0	0
	2 (n=17)	5	12	4	13	0	0	0	9	8	0	0
	3 (n=21)	8	13	3	18	0	0	0	0	10	9	2
	4 (n=9)	5	4	1	8	0	0	0	0	0	3	6
FNG (n)	**1** (n=5)	2	3	2	3	1	1	3	0	0	0	0
	2 (n=30)	5	25	2	28	0	9	9	4	5	3	0
	3 (n=27)	8	19	6	21	0	1	1	5	11	6	3
	4 (n=10)	7	3	2	8	0	0	0	0	2	3	5
SD (n)	**(-)** (n=61)	17	44	11	50	1	11	13	8	15	9	4
	(+) (n=11)	5	6	1	10	0	0	0	1	3	3	4

FNG = Fuhrman nuclear grade; **SD** = Sarcomatoid differentiation; **VEGF** = Vascular endothelial growth factor; **HIF** = Hypoxia inducible factor; **SD** = Sarcomatoid differentiation

p53 and survival status

Six cases (8.3%) showed a positive reaction for p53, and only 1 of these cases (16.7%) was a survivor. A relation and a direct correlation were observed between p53 positivity and FNG (r=0.263; p<0.05). A similar relation and correlation were also observed between p53 positivity and SD (r=0.290, p<0.05). We observed a shorter average survival time for patients with p53 positivity. The p53 positive cases had a mean survival time of 42 months, while negative cases had a mean survival time of 111 months (p<0.05; see Table-4).

Ki-67 and survival status

The Ki-67 proliferation index and FNG, stage, and SD had a positive statically significant relationship (r=0.644, p<0.001; r=0.738 p<0.001; r=0.349, p<0.01, respectively). The mean Ki-67 value for was 57.5 for deceased patients and 27.6 for survivors (p<0.001; see Table-4).

MVD and survival status

MVD and FNG, stage, and SD had a positive statically significant relationship (r=0.652, p<0.001; r=0.640, p<0.001; r=0.347, p<0.01, respectively). The mean MVD value was 46.5 for deceased patients and 28.5 for survivors (p<0.001; see Table-4). The effect of stage, FNG, and SD on survival status was evaluated with multivariable Cox regression analysis. The survival rate was negatively affected by stage 1-4, FNG 3 and 4, and SD positivity (Table-5).

Immunohistochemical data inter-correlation

VEGF had statically significant relationships with HIF-1α (r=0.566; p<0.001), MVD (r=0.669; p<0.01), and the Ki-67 proliferation index (r=0.764; p<0.001). In addition, HIF-1α had a similar statically significant relationship with HIF-2α (r=0.270; p<0.05), p53 (r=0.234; p<0.05), the Ki-67 proliferation index (r=0.350, p<0.05),

Figure 3 - Immunohistochemical staining examples of ccRCCs. A) Widespread, strongly HIF 1α positivity (X400), B) Widespread, moderate HIF 2α positivity (X400), C) Widespread, moderate (X200) and D) focally, strong VEGF positivity (X400), E) Numerous CD34 positive moderate sized and F) small sized vessels (arrow) (X100), G) Nuclear Ki-67 positivity (X200), H) Nuclear p53 positivity (X200) (arrow in G and H: nuclear staining).

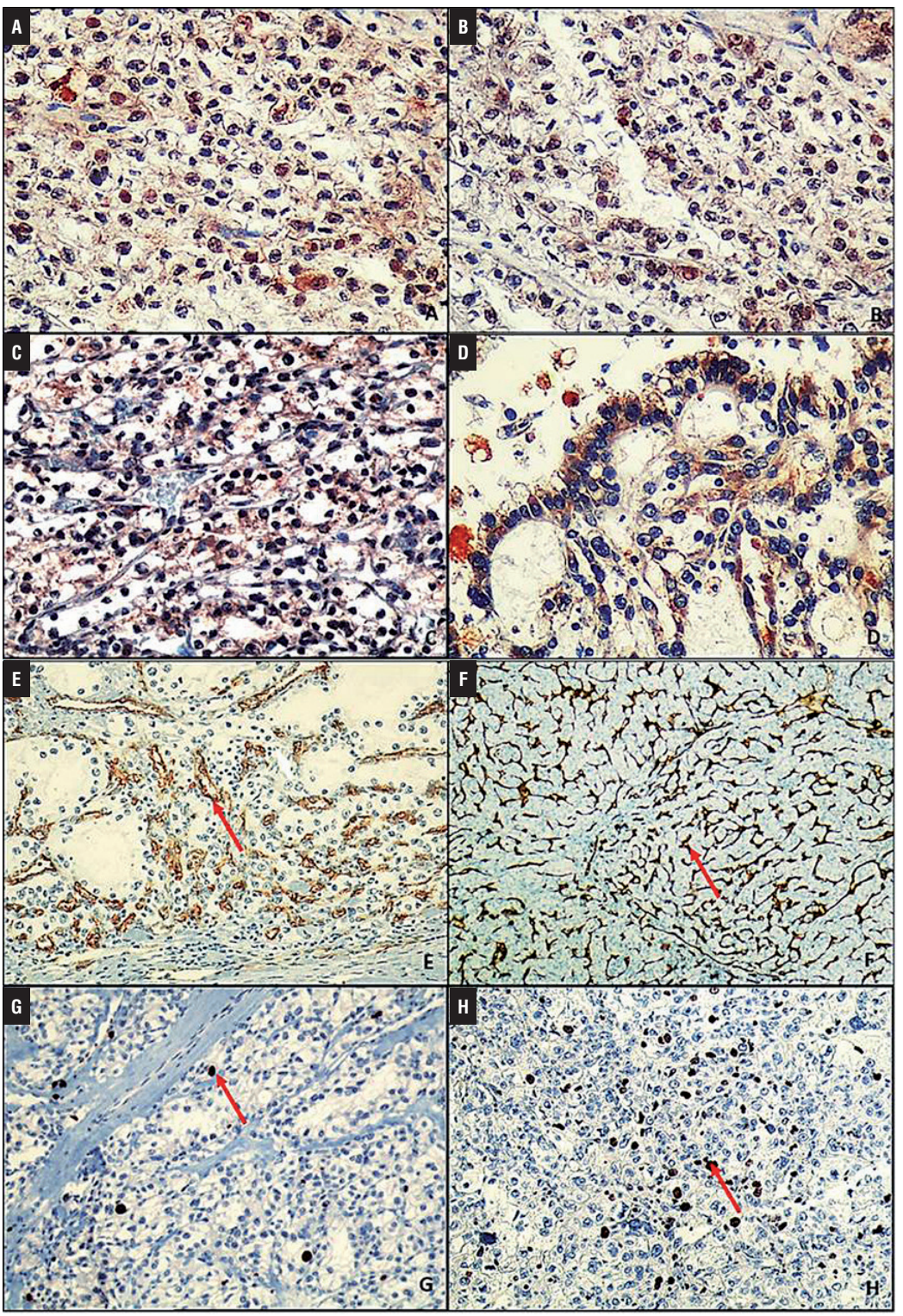


Table 4 - Comparison of the pathological and immunohistochemical characteristics.

	Prognostic factor		
	Pathological characteristic	r	p
VEGF	Fuhrman	0.692	<0.001*
	Stage	0.935	<0.001*
	SD	0.394	<0.001*
HIF-1 alpha	Fuhrman	0.264	<0.05*
	Stage	0.277	<0.05*
	SD	0.137	0.25
HIF-2 alpha	Fuhrman	0.073	0.54
	Stage	0.043	0.72
	SD	0.086	0.47
p53	Fuhrman	0.263	<0.05*
	Stage	0.086	0.47
	SD	0.290	<0.05*
Ki-67	Fuhrman	0.644	<0.001*
	Stage	0.738	<0.001*
	SD	0.349	<0.01*
MVD	Fuhrman	0.652	<0.001*
	Stage	0.640	<0.001*
	SD	0.347	<0.01*

VEGF = Vascular endothelial growth factor; **HIF** = Hypoxia inducible factor; **MVD** = Micro vessel density; **SD** = Sarcomatoid differantiation

Table 5 - The effect of stage, FNG and SD on survival.

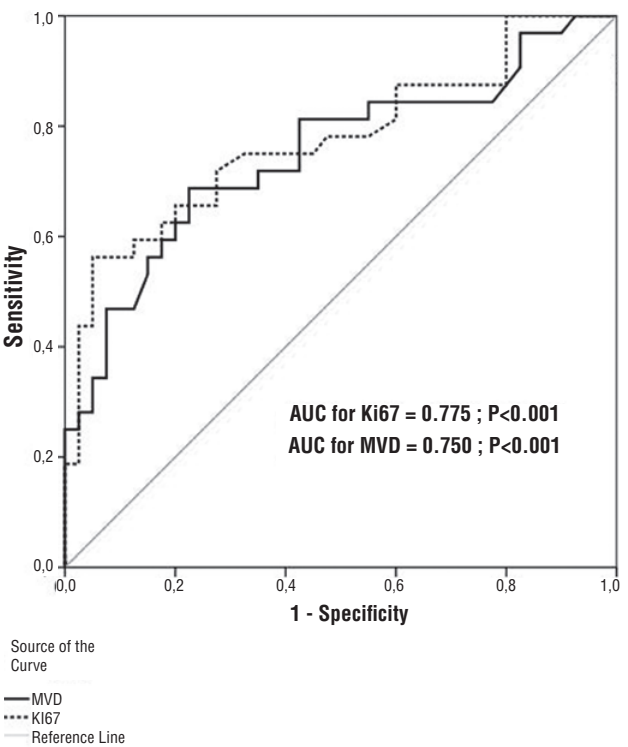
	Cox regression-Multivariate			
		HR	95% CI for HR	p
Stage	I-II		reference	
	III-IV	2.694	1.163 – 6.241	0.021
FNG	I-II		reference	
	III-IV	5.286	1.885 – 14.819	0.002
SD	(-)		reference	
	(+)	2.575	1.111-5.971	0.027

FNG = Fuhrman nuclear grade; **SD** = Sarcomatiod differentiation

and MVD (r=0.399, p<0.05). The Ki-67 proliferation index and MVD also had a statically significant relationship (r=0.618; p<0.01; see Table-4).

We evaluated the mortality difference for Ki-67 and MVD with ROC analysis. At the time of diagnosis, Ki-67 had a cut-off point >132 at 56.2% sensitivity and 95% specificity. MVD had a cut-off value of >180 and, at this point, 68.7% sensitivity and 77.5% specificity (Figure-4).

Figure 4 - ROC Curve analysis for Ki-67, and MVD



DISCUSSION

Genetic and molecular prognostic factors specific to disease in RCC are an important topic for all current research related to this field. Recent studies have increased our understanding of the molecular biology of RCC, leading to the development of better-guided molecular treatment methods. Based on this information, immunohistochemical indicators are becoming more common of a subject for studies to predict the prognosis of patients with ccRCC and to determine treatment methods (9).

In this study, immunohistochemically VEGF, HIF-1α, HIF-2α, p53, CD34 (for MVD evaluation), and Ki-67 antibodies were applied to the tumor areas, and the relationships of these antibodies with prognostic factors (FNG, stage, and SD) and survival rates were evaluated. We observed that VEGF and HIF-1α proteins that play an important role in tumor angiogenesis, p53 gene mutation related to apoptosis, the Ki-67 proliferation index, prognostic properties of the tumor (FNG, stage, SD) related to each other or independently affect patient's survival may lead to poor prognosis. The development of new treatment methods and agents will lead to new horizons, especially in metastatic RCCs.

VEGF and prognosis

Angiogenesis-related growth factors, in which the Von Hippel-Lindau gene plays a role regarding regulation, are the most important objectives in the treatment of ccRCCs. VEGF is a critical cytokine regarding tumor angiogenesis. RCC, a clinically vascular tumor, has a direct correlation with VEGF expression. For this reason, ccRCC and VEGF inhibition are associated in treatment. Chang et al. reported higher levels of VEGF expression in ccRCC than in healthy kidney parenchyma (15). Furthermore, recent studies have shown correlations between VEGF expression and microvascular density, tumor size, nuclear grade, stage, and prognosis in ccRCC (6, 16).

Recent studies on ccRCC showed that expression of VEGF was directly related to stage, capsular invasion, size, and nuclear grade in ccRCC (8, 16, 17). In the present study, consistent with other studies, patients with a high FNG and stage and with SD, had high staining scores.

Yilmazer et al. (18) showed that the expression of VEGF was correlated with vascular density. Cases with high VEGF stain scores had also high MVD. Our findings are compatible with the finding as we observed a positive correlation between MVD and the VEGF staining score. Burgesser et al. (6) reported that the expression of VEGF was directly related to the proliferation index. Our results were compatible with theirs. Samples with a high stain score had low average survival rates. These findings show that VEGF related to a poor

prognosis in many tumors is also related in the same way with ccRCC.

HIF-1α, HIF-2α and prognosis

Because HIF-α activates related genes in the regulation of angiogenesis, glucose metabolism, pH control, epithelial proliferation, and apoptosis, it is related to progression in many types of cancer. In the kidney, a substantial amount of HIF-1α is released from many cells; HIF-2α is released from interstitial fibroblast and endothelial cells (19). Many studies, including Byun et al. (20), have revealed significant associations between HIF-2α and tumor stage. Dornbusch et al. (2) reported similar results in 2013. However, Haase (21) reported that in the kidney's normal tubular epithelial cells gene expression related to HIF is more under HIF-1α control. According to their study on RCC tumors, with VHL mutations, while the HIF-2α level is high, HIF-1α is not. Sowter et al. (19) conducted a study on the role of HIF proteins and demonstrated that in RCC the HIF-2α network has a fundamental role in many stages of cancer development. Raval et al. (22), in a study of the effects of HIF subgroups in VHL-related RCC, emphasized that HIF-2α has a tumor-growing effect and HIF1-α stops tumor growth. In the present study, similar to the Byunn et al. (20) results, we found that although RCCs with high HIF-1α staining scores are related to FNG, stage, and SD, the HIF-2α staining scores are not. In the HIF-1α- and HIF-2α-positive samples, the average survival rate decreased. In the literature review, Lidgren et al. (13) tracked HIF-1α positivity in RCC samples with low degree, early stage, and high survival rates and accepted HIF-1α positivity as an indicator of a good prognosis; while Klatte et al. (23) found HIF-1α positivity in RCC with renal cells and found no relationship between stage, FNG, and HIF-1α staining. However, HIF-1α and HIF-2α positivity was found to be related to a poor prognosis and low survival rates in many tumor types and ccRCCs in the literature, as in the present study.

According to various studies about angiogenesis in the available literature, VEGF and HIF-1α are the most important. However, the results are controversial and inconsistent (19, 20).

Most studies also focused on tumor microvascular density, because it is directly associated with the expression of angiogenic factors. Minardi et al. reported a direct relationship between HIF-1α expression and vascular density (24). The data from the present study were compatible with this report. HIF-1α expression was correlated with higher MVD and Ki-67 proliferation index values. One point that should be discussed, which is an issue of conflict in different publications, is the staining property of HIF-1α. Taking molecular properties into account, HIF-1α is activated only in the nucleus and is subject to translocation (3). In some studies, cytoplasmic staining and nuclear staining are considered positive, while in other studies only cytoplasmic staining is positive (13). Some studies have shown that staining patterns differ between tumors and non-tumor tissues or in VHL mutant or non-mutant samples. The differences in the literature indicate that the staining pattern continues to be a matter of debate (25).

p53 and prognosis

p53 expression in RCCs is disputed. In the literature (9), p53 expression is related to a poor prognosis and SD. In the findings of the present study, high-grade p53 positivity was highly correlated with SD, one of the indicators of a poor prognosis in ccRCC. No relation was observed between p53 positivity and stage. The antibody's positivity is not related to MVD and the proliferation index. Phouc et al. (26) demonstrated that a high staining score of the p53 gene in RCCs is inversely related to survival. Olumi et al. (27), in a study with a low number of samples, did not find a relationship between the p53 gene in RCCs and survival; however, the data for p53 staining in the present study show a statically significant relationship between p53 positivity and survival. The p53-positive samples had lower survival rates and lower average lifetime.

Ki-67 and prognosis

Studies on the effects of Ki-67, which is an indicator of active cell proliferation, on prognosis in patients with RCC have been conducted. Bakır and Özekinci (28) reported a relationship between high Ki-67 positivity and advanced pathological

stage and poor prognosis. They reported that more than 9% proliferation with Ki-67 is an independent indicator of poor prognosis. Itoi et al. (29) reported that Ki-67 is an independent prognostic factor in RCC while p53 is not a sufficient prognostic indication. Our findings showed that the Ki-67 proliferation index and the stained nucleus number are directly proportionate and are related to stage, FNG, and SD. An increase in the Ki-67 proliferation index is also accompanied by a decrease in survival time. This finding was statistically significant and in agreement with the literature.

MVD (CD34 antibody) and prognosis

CD34 is a molecule related to the abluminal endothelial microprocess that causes vascular sprouting in the tumor's stroma in the angiogenesis stage, used in measuring microvessel density. The CD34 antibody is better than other antibodies for use in microvessel measurements to detect prognosis (8). Yılmazer et al. (18) reported that in advanced stage tumors, the vascular density was high ($p<0.05$). Kavantzas et al. (7) showed that higher vascular density was related to a higher nuclear grade. However, MacLennan (4) found no significant correlation between vascular density and tumor stage. Nativ et al. (30) showed that vascular density was lower in tumors with a higher FNG. The present data show that in patients with indicators of poor prognosis such as a high FNG, advanced stage, and SD MVD was high. Bürgesser et al. reported that tumors with higher HIF-1α expression had higher MVD (6). The present data are comparable with these findings. Bürgesser et al. reported that higher vascular density was related to lower survival rates (6). The data of the present study confirm theirs.

MVD and Ki-67 values and cut-off values

The cut-off value we observed for MVD and the Ki-67 evaluation is a new and low-sensitive suggestion. However, new studies with a higher number of patients the importance of these findings must be noted. The cut-off value detected in larger studies might be helpful in treatments for breast carcinomas, for example.

RCC is very resistant to standard chemotherapy. Biological and immune-based therapies and treatment options for patients with RCC are limited, and the response rates are low. Immunotherapy with interferon-α and interleukin-2 once represented the standard treatment for RCC; however, both are associated with substantial toxicity, and response rates are limited (2). Understanding of the pathogenesis of ccRCC has facilitated the development of new RCC-targeting therapies. The discovery of VHL inactivation and HIF activation of genes and other pathways that are important for tumor progression has aided the development of new drugs that target angiogenesis and proliferation pathways. Drugs that target the VEGF pathway have been approved for RCC. Although these new agents may improve survival rates, none are curative. At present, no predictive biomarkers have been established for these drugs. Given that these drugs inhibit this pathway at the protein level, target protein expression might be associated with response to therapy. Some attempts have been made to develop predictive biomarkers that are primarily centered on VHL mutations and the HIF and VEGF levels.

Another aspect of this subject is that showing protein expression levels with immunohistochemical staining might be a supportive method for predicting RCC survival features, treatment regimens, and management of patient. An evaluation of the literature on RCCs showed the relationships of angiogenetic and prognostic factors, with each other and with immunohistochemical indicators, are debatable.

In this study, we suggested that VEGF staining scores, HIF-1α, HIF-2α, p53 positivity, MVD, and Ki-67 counts may be used for the prediction of prognosis in patients with ccRCC. In addition, new treatment regimens targeted to this pathway may be planned. Especially, these therapeutic agents may be a gleam of hope for patients with metastatic ccRCC.

CONCLUSIONS

In conclusion, although there have been different reports, the correlation between HIF-1α, HIF-2α, VEGF, and p53 positivity, high MVD, and the Ki-67 proliferation index with prognostic histopathological features and survival rates

was consistent with most of the findings in the literature. Differences in the staining scores of immunohistochemical antibodies provide preliminary information about patient survival. In light of these findings, new target-oriented treatments may be improved to target the HIF-1α and HIF-2α pathway, as well as VEGF-targeted therapies that were used. In the future, immunohistochemical evaluation criteria should be standardized, new studies should be planned with comprehensive case series, and results should be supported with molecular studies. Prospective and more standardized studies should be planned to specify the role of angiogenic factors in ccRCC and the results standardized for the prediction of the treatment and management of disease.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300. Erratum in: CA Cancer J Clin. 2011;61:133-4.
2. Dornbusch J, Zacharis A, Meinhardt M, Erdmann K, Wolff I, Froehner M, et al. Analyses of potential predictive markers and survival data for a response to sunitinib in patients with metastatic renal cell carcinoma. PLoS One. 2013;8:e76386.
3. Eichelberg C, Junker K, Ljungberg B, Moch H. Diagnostic and prognostic molecular markers for renal cell carcinoma: a critical appraisal of the current state of research and clinical applicability. Eur Urol. 2009;55:851-63.
4. MacLennan GT, Bostwick DG. Microvessel density in renal cell carcinoma: lack of prognostic significance. Urology. 1995;46:27-30.
5. Gossage L, Eisen T. Alterations in VHL as potential biomarkers in renal-cell carcinoma. Nat Rev Clin Oncol. 2010;7:277-88.
6. Bürgesser MV, Riva V, Ojeda SM, Muñoz Morales D, Calafat P, Diller A. Expression of VEGF-A, HIF-1 A, CD34 and Ki67 in clear cell renal cell carcinomas and their relationship with conventional prognostic markers. Rev Fac Cien Med Univ Nac Cordoba. 2014;71:7-15.
7. Kavantzas N, Paraskevakou H, Tseleni-Balafouta S, Aroni K, Athanassiades P, Agrogiannis G, Patsouris E. Association between microvessel density and histologic grade in renal cell carcinomas. Pathol Oncol Res. 2007;13:145-8.
8. Jacobsen J, Rasmuson T, Grankvist K, Ljungberg B. Vascular endothelial growth factor as prognostic factor in renal cell carcinoma. J Urol. 2000;163:343-7.
9. Rioux-Leclercq N, Turlin B, Bansard J, Patard J, Manunta A, Moulinoux JP, et al. Value of immunohistochemical Ki-67 and p53 determinations as predictive factors of outcome in renal cell carcinoma. Urology. 2000;55:501-5.
10. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis--correlation in invasive breast carcinoma. N Engl J Med. 1991;324:1-8.
11. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655-63.
12. Greene FL, American Joint Committee on C, American Cancer S. (2002) AJCC cancer staging manual, Springer-Verlag, New York.
13. Lidgren A, Hedberg Y, Grankvist K, Rasmuson T, Bergh A, Ljungberg B. Hypoxia-inducible factor 1alpha expression in renal cell carcinoma analyzed by tissue microarray. Eur Urol. 2006;50:1272-7.
14. Karavasilis V, Malamou-Mitsi V, Briasoulis E, Tsanou E, Kitsou E, Kalofonos H, et al. Angiogenesis in cancer of unknown primary: clinicopathological study of CD34, VEGF and TSP-1. BMC Cancer. 2005;5:25.
15. Chang SG, Jeon SH, Lee SJ, Choi JM, Kim YW. Clinical significance of urinary vascular endothelial growth factor and microvessel density in patients with renal cell carcinoma. Urology. 2001;58:904-8.
16. Tomisawa M, Tokunaga T, Oshika Y, Tsuchida T, Fukushima Y, Sato H, et al. Expression pattern of vascular endothelial growth factor isoform is closely correlated with tumour stage and vascularisation in renal cell carcinoma. Eur J Cancer. 1999;35:133-7.
17. Zhang X, Yamashita M, Uetsuki H, Kakehi Y. Angiogenesis in renal cell carcinoma: Evaluation of microvessel density, vascular endothelial growth factor and matrix metalloproteinases. Int J Urol. 2002;9:509-14.
18. Yilmazer D, Han U, Onal B. A comparison of the vascular density of VEGF expression with microvascular density determined with CD34 and CD31 staining and conventional prognostic markers in renal cell carcinoma. Int Urol Nephrol. 2007;39:691-8.
19. Sowter HM, Raval RR, Moore JW, Ratcliffe PJ, Harris AL. Predominant role of hypoxia-inducible transcription factor (Hif)-1alpha versus Hif-2alpha in regulation of the transcriptional response to hypoxia. Cancer Res. 2003;63:6130-4. Erratum in: Cancer Res. 2003;63:8562.
20. Byun SS, Yeo WG, Lee SE, Lee E. Expression of survivin in renal cell carcinomas: association with pathologic features and clinical outcome. Urology. 2007;69:34-7.
21. Haase VH. Hypoxia-inducible factors in the kidney. Am J Physiol Renal Physiol. 2006;291:F271-81.

22. Raval RR, Lau KW, Tran MG, Sowter HM, Mandriota SJ, Li JL, et al. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. Mol Cell Biol. 2005;25:5675-86.
23. Klatte T, Seligson DB, Riggs SB, Leppert JT, Berkman MK, Kleid MD, et al. Hypoxia-inducible factor 1 alpha in clear cell renal cell carcinoma. Clin Cancer Res. 2007;13:7388-93.
24. Minardi D, Lucarini G, Filosa A, Milanese G, Zizzi A, Di Primio R, et al. Prognostic role of tumor necrosis, microvessel density, vascular endothelial growth factor and hypoxia inducible factor-1alpha in patients with clear cell renal carcinoma after radical nephrectomy in a long term follow-up. Int J Immunopathol Pharmacol. 2008;21:447-55.
25. Kubis HP, Hanke N, Scheibe RJ, Gros G. Accumulation and nuclear import of HIF1 alpha during high and low oxygen concentration in skeletal muscle cells in primary culture. Biochim Biophys Acta. 2005;1745:187-95.
26. Phuoc NB, Ehara H, Gotoh T, Nakano M, Yokoi S, Deguchi T, et al. Immunohistochemical analysis with multiple antibodies in search of prognostic markers for clear cell renal cell carcinoma. Urology. 2007;69:843-8.
27. Olumi AF, Weidner N, Presti JC. p53 immunoreactivity correlates with Ki-67 and bcl-2 expression in renal cell carcinoma. Urol Oncol. 2001;6:63-7.
28. Bakır S, Özekinci S: The prognostic significance of the KI-67 and CD-44 in renal cell carcinomas. Dicle Med J. 2005; 32: 123-30.
29. Itoi T, Yamana K, Bilim V, Takahashi K, Tomita F. Impact of frequent Bcl-2 expression on better prognosis in renal cell carcinoma patients. Br J Cancer. 2004;90:200-5.
30. Nativ O, Sabo E, Reiss A, Wald M, Madjar S, Moskovitz B. Clinical significance of tumor angiogenesis in patients with localized renal cell carcinoma. Urology. 1998;51:693-6.

Correspondence address:
Ebru Tastekin, MD
Department of Pathology, Faculty of Medicine
Trakya University, Edirne, Turkey
FAX: +90 532 600-3001
E-mail: ebrutastekin@hotmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 455-461, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0114

The change in serum Thiol/Disulphide homeostasis after transrectal ultrasound guided prostate biopsy

Hüsnü Tokgöz [1], Selim Taş [1], Özlem Giray [2], Soner Yalçınkaya [1], Özlem Tokgöz [3], Cemile Koca [4], Murat Savaş [1], Özcan Erel [4]

[1] Department of Urology, Antalya Training and Research Hospital, Antalya, Turkey; [2] Department of Biochemistry , Antalya Training and Research Hospital, Antalya, Turkey; [3] Department of Radiology, Antalya Training and Research Hospital, Antalya, Turkey; [4] Department of Biochemistry, Yildirim Beyazit University, School of Medicine, Ankara, Turkey

ABSTRACT

Objectives: The aim of this prospective clinical study was to investigate variations in a novel oxidative stress marker (thiol/disulphide homeostasis) in men who underwent transrectal ultrasound guided prostate biopsy (TRUSB).

Materials and Methods: A total of 22 men undergoing TRUSB of the prostate were enrolled in the study. Patients with abnormal digital rectal examination and/or total prostate specific antigen (PSA) over 4ng/mL underwent TRUSB with 12 cores. Serum samples were obtained before and just after the procedure to evaluate the possible changes in thiol/disulphide homeostasis. Mean age, total PSA and free PSA, prostate volume and histopathological data were also recorded.

Results: Mean age of the study population was 65.05±8.89 years. Significant decreases in native and total thiol levels were documented after the biopsy procedure. However, serum disulphide levels and disulphide/native thiol, disulphide/total thiol and native/total thiol ratios did not significantly change after TRUSB. No correlation was observed between oxidative parameters and total PSA and free PSA levels, prostate volume and histopathology of the prostate. However, mean patient age was significantly correlated with mean native and total thiol levels.

Conclusion: Significant decreases in serum native and total thiol levels related to the prostate biopsy procedure suggest that TRUSB causes acute oxidative stress in the human body. Since our trial is the first in the current literature to investigate these oxidative stress markers in urology practice, additional studies are warranted.

ARTICLE INFO

Keywords:
Biopsy; Prostate; Oxidative Stress; Ultrasonography

Int Braz J Urol. 2017; 43: 455-61

Submitted for publication:
February 02, 2016

Accepted after revision:
October 30, 2016

Published as Ahead of Print:
January 03, 2017

INTRODUCTION

Prostate cancer is a major health problem globally and the incidence is rising. After the entry into health care the use of conventional ultrasounds, Watanabe et al. described the first transrectal ultrasonography in 1967 (1). During the '80s, transrectal ultrasound guided prostate biopsy (TRUSB) became a primary technique for the detection of prostate cancer. Because cancers cannot be accurately visualized by conventional ultrasound, sextant biopsy was developed by Hodge et al. (2). Subsequent investigators proposed obtaining more cores to improve the diagnostic accuracy of TRUSB (3, 4). Over the past decade, a significant number of modifications have been made to the techniques for prostate cancer biopsy. Currently, routine 12-core (extended) biopsy

is recommended as an office-based, diagnostic standard for evaluating patients with increasing PSA levels (5). Like all biopsy procedures, TRUSB is an invasive technique and, although rare, may be associated with complications such as acute prostatitis, hematuria and rectal bleeding. As such, it exerts stress on the human body.

Oxidative stress in the body occurs due to the imbalance between antioxidants and reactive oxygen radicals, and leads to various systemic disorders. In 2014, Drs. Erel and Neselioglu developed a novel and automated assay which determined plasma thiol/disulphide homeostasis (6). Thiols may undergo an oxidative reaction via oxidants and form disulphide bonds. A disulphide bond is a covalent bond and the linkage is also called a disulphide bridge. The formed disulphide bonds might be reduced to thiol groups; hence, dynamic thiol/disulphide homeostasis is maintained. So, thiol/disulphide homeostasis may already be regarded as an oxidative stress marker like lipid hydroperoxide, total antioxidant/oxidant status and paraoxonase. It has been shown that an abnormal thiol disulphide homeostasis state is involved in the pathogenesis of various diseases, namely diabetes mellitus, cardiovascular diseases, cancer, rheumatoid arthritis, chronic renal disease, acquired immunodeficiency syndrome (AIDS), liver disease and some neurological disorders (Parkinson disease, Alzheimer disease, Friedreich ataxia, multiple sclerosis and amyotrophic lateral sclerosis) (7-16).

Currently, it remains unclear whether TRUSB causes oxidative stress in the human body. In the current literature, no study has been published that evaluates serum or urinary oxidative stress levels in men who underwent TRUSB. In our study, we investigated the changes in dynamic thiol/disulphide homeostatic state in men undergoing TRUSB for abnormal digital examination or serum total prostate specific antigen (PSA) elevation. In addition, correlation between clinical parameters and levels of oxidative stress markers were also evaluated. Our hypothesis is that TRUSB causes acute oxidative stress in the human body resulting in significant changes in serum levels of oxidative stress markers.

MATERIALS AND METHODS

The approval of the hospital ethics committee was obtained and 22 males were included in this prospective clinical study. Each patient provided informed consent prior to participation in the study. These patients with abnormal digital rectal examinations or serum total PSA levels of greater than 4ng/mL were previously referred to our clinic for TRUSB. All of the patients were asymptomatic before the procedure. Those with bleeding diathesis or on anticoagulation therapy, with a history of radical prostatectomy or radiotherapy, or with regular drug use were excluded. In addition, men with known systemic diseases like coronary artery disease, diabetes mellitus, liver disease, chronic renal failure, rheumatoid arthritis, or with cancer diagnosis that would affect serum oxidative stress parameters were also excluded. Patients with known neurological disorders were not included in the study. All patients received standard antibiotic prophylaxis of ciprofloxacin 500mg twice daily for 3 days, begun 1 day before the procedure. All prostate biopsies were carried out under TRUS guidance, and an automatic biopsy gun with an 18-gauge needle was used to obtain 12 core biopsies. All of the patients received a rectal enema before the procedure. Patients were examined in the left lateral decubitus position with a 9±5MHz curved-array transrectal probe, and the prostate volume and ultrasonographic appearance in the longitudinal and transverse planes were recorded. Age, histopathologic results of biopsy specimens, serum total PSA and free PSA levels, rectal examination findings of patients and prostate volumes were also recorded.

Just before the biopsy procedure, 10cc of blood was taken from the left arm using a biochemistry tube. One hour after the biopsy, another 10cc blood was taken. Collected serum samples were centrifuged at 1500g for 10 minutes to obtain the supernatant serum fraction and those samples were kept at -80°C until analysis. Thiol/disulphide homeostasis tests were performed in the same way as Drs. Erel and Neselioglu previously described in their paper (6). Two parallel vessels were used for samples. To determine total thiol, 10µL

sample was treated with 10µL sodium borohydride in 50% methanol–water solution (v/v; R1), which reduces dynamic disulfide bonds to free thiol groups. Excess reductants were eliminated using 110µL 6.715mM formaldehyde and 10.0mM ethylenediaminetetraacetic acid (EDTA) in Tris buffer 100mM (pH 8.2). For native thiol, 10µL sample was treated with 10µL, 10mM sodium chloride in 50% methanol–water solution (v/v; R1') and 110µL 6.715mM formaldehyde and 10.0mM EDTA in Tris buffer 100mM (pH 8.2). Then, the DTNB (5,50-dithiobis-[2-nitrobenzoic acid]) solution was added. The first absorbance was taken only after adding R1 and R1' for total and native thiol, respectively, and the second absorbance was taken after the application of formaldehyde and DTNB solutions, and when the reaction trace forms a plateau (assay duration was approximately 10 min). First absorbance was subtracted from the second. The main wavelength is 415nm, and the secondary wavelength is 700nm. All the chemicals were purchased from Merck Chemicals (Darmstadt, Germany) and Sigma-Aldrich Chemie (Milwaukee, Wisconsin, USA). The amount of dynamic disulphide was calculated by taking half of the difference between total thiol and native thiol groups. In this way, native and total thiols were calculated. Afterwards, serum disulphide levels and the disulphide/native thiol, disulphide/total thiol and native/total thiol ratios were determined.

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corporation). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of two related (paired) continuous variables, the paired samples t-test was used. To evaluate the correlations between measurements, Pearson correlation coefficient was used. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Mean age of the study population was 65.05±8.89 years (median age was 66). Mean serum total PSA and free PSA levels, prostate volume and histopathological results of biopsy specimens of all patients are given in Table-1. Significant decreases in mean native and total thiol levels were documented after the biopsy procedure when compared to levels before biopsy ($p < 0.05$, paired samples t test) (Table-2) (Figures 1 and 2). However, mean serum disulphide levels were not significantly changed after the biopsy procedure ($p=0.22$, paired samples t test) (Table-2). Similarly, the percentage of disulphide/native thiol, disulphide/total thiol and native/total thiol ratios were not significantly changed after TRUSB (Table-2).

In the correlation analysis, there was a significant negative correlation between mean patient age and mean pre-biopsy (correlation

Table 1 - Clinical data of men who underwent transrectal ultrasound guided prostate biopsy.

Variables	
Age*	65.05±8.89
Total PSA (ng/ mL)*	18.25±6.69
Free PSA (ng/ mL)*	3.13±0.77
Prostate volume (cc)*	60.27±29.96
Histopathology	
BPH	10 (45.5%)
Chronic prostatitis	2 (9.1%)
ASAP	1 (4.5%)
High grade PIN	2 (9.1%)
Prostate adeno cancer	7
Gleason score 3+3	3 (13.6%)
Gleason score 3+4	1 (4.5%)
Gleason score 4+5	1 (4.5%)
Gleason score 5+4	2 (9.1%)
Total (number of patients, %)	**22 (100%)**

SD = Standard deviation; **PSA =** Prostate-specific antigen; **Ng/mL =** nanogram per mililiter; **cc =** cubic centimeter; **BPH =** Benign prostatic hyperplasia; **ASAP =** Atypical small acinar proliferation; **PIN =** prostatic intraepithelial neoplasia; *mean±SD

Table 2 - Changes in the levels of oxidative stress markers after the biopsy procedure with relevant p values.

	Before biopsy	After biopsy	*p** value
Native thiol (µmol/L)	441.54±44.88	432.84±36.54	**0.04**
Total thiol (µmol/L)	470.22±47.46	460.17±40.46	**0.03**
Disulphide (µmol/L)	14.32±2.65	13.65±2.68	0.22
Disulphide/ native thiol %	3.25±0.54	3.14±0.47	0.38
Disulphide/ total thiol %	3.04±0.48	2.94±0.42	0.38
Native / total thiol %	93.90±0.96	94.10±0.83	0.39

Data were expressed as mean±standard deviation
Statistically significant p values were written as bold
* Paired samples t test

Figure 1 - Native thiol levels were significantly lower in men who underwent transrectal ultrasound guided prostate biopsy when compared to the levels just before biopsy (p=0.04, paired samples t test).

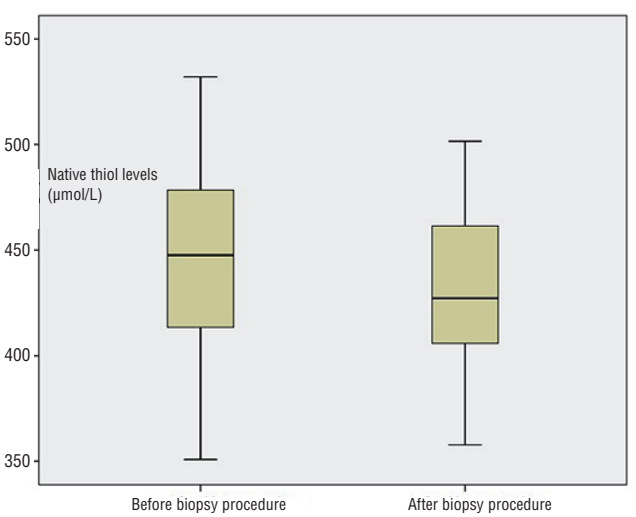
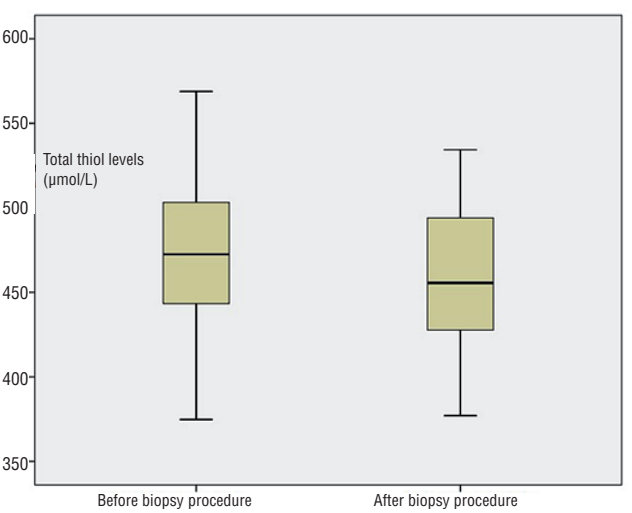


Figure 2 - Total thiol levels were significantly lower in men who underwent transrectal ultrasound guided prostate biopsy when compared to the levels just before biopsy (p=0.03, paired samples t test).



coefficient=-0.480, p=0.024, Pearson correlation analysis) and post-biopsy native thiol levels (correlation coefficient=-0.593, p=0.004, Pearson correlation analysis). Additionally, a significant negative correlation was also noticed between age and pre-biopsy (correlation coefficient=-0.444, p=0.039) and post-biopsy total thiol levels (correlation coefficient=-0.545, p=0.009). However, no statistically significant correlation was observed between any of the oxidative stress parameters and the total and free PSA levels, prostate volume and histopathology of the prostate (p >0.05, Pearson correlation analysis).

DISCUSSION

There is no study published which investigates changes in thiol/disulphide homeostasis in urological disorders. However, the investigation of serum levels of different oxidative stress markers is not new. Recently, Ener et al. evaluated the oxidative stress status and antioxidant capacity in patients with painful bladder syndrome, and used serum total antioxidant capacity, total oxidant status, binding capacity of exogenous cobalt to human albumin, serum advanced oxidation protein products, paraoxonase, arylesterase, IgE, and

C-reactive protein as oxidative markers (17). Some investigators researched the levels of oxidative markers either in urine or semen (18, 19). When compared to these conventional oxidative stress markers, the novel assay developed by Drs. Erel and Neselioglu provides an easy, relatively cheap, practical, fully automated (optionally manual) spectrophotometric assay for the determination of plasma dynamic thiol/disulphide homeostasis (6). Kundi et al. investigated its use in patients with acute myocardial infarction and found significant changes in serum levels of native thiols, total thiols and disulphide when compared to controls (20). Ates et al. have shown that thiol oxidation increases in prediabetics as well as in type 1 diabetics (21, 22). They also observed a correlation between serum disulphide levels and blood glucose and HbA1c levels. Some other authors also evaluated thiol/disulphide homeostasis in asphalt workers, in patients with masked and primary hypertension, in women with idiopathic recurrent pregnancy loss and pre-eclampsia, and in patients with inflammatory bowel disease (23-30).

This trial is the first to show significant changes in dynamic thiol/disulphide homeostasis in men undergoing TRUSB of the prostate. This means that thiol oxidation increased in men who underwent biopsy of the prostate. It is acknowledged that any biopsy procedure may cause acute oxidative stress in biopsied organs and increase the levels of oxidative stress markers in tissues (31-33). So, trauma to any organ or any systemic disorder may lead to increases in serum levels of oxidative stress parameters. We performed 12-core biopsies to all cases in the study group. It may be considered that serum native and total thiol levels could be correlated with the biopsy core numbers. We hypothesize that increasing the number of biopsy cores may aggravate the thiol oxidation in plasma. To identify whether this is the case or not, another study should be designed to compare serum levels of thiols in men undergoing 12-core and 24-core--saturation biopsies. However, the study groups should be age-matched because age was the only parameter that was significantly correlated with native and total thiol levels in our study. So, older age at biopsy might increase the risk of morbidity and oxidative stress caused by the biopsy procedure. Similarly, as in our study, negative correlations between age and thiol levels were also documented by some other researchers (20, 21). They found inverse correlations between native and total thiol levels and patient age. In their studies, native and total thiol levels decreased with increasing age.

In the study population, out of 22 men, 7 cases were diagnosed with prostate adenocarcinoma. Regarding histopathological diagnosis, when subgroups were formed no significant differences in serum levels of oxidative markers were noticed. But as the cancer group is too small to make reliable statistical analyses, we cannot make a discrete conclusion. Future studies with larger study population are necessary to investigate the correlation between serum thiol levels and histopathology of the prostate.

Potential limitations of this study should be considered. One could reasonably attempt to form an independent control group composed of non-treated healthy subjects. But we thought that it would be more homogenous and reliable to evaluate the same patients in terms of changes in the levels of oxidative stress parameters. Thus, the effect of TRUSB on the human body could be investigated in detail. Another limitation is that our sample size is relatively small, but prospective studies including men with similar ages in larger series may provide more valuable data. We performed two sensitivity tests (repeated measures analysis of variance for both native and total thiol levels). For native thiol levels, we observed a power of 0.520 and for total thiol levels we observed a power of 0.592. Therefore, the sensitivity in this study might be regarded as at least 0.520. In addition, changes in the levels of native and total thiols should also be evaluated in the long term. Thus, consecutive serum sampling at 1-week intervals after the biopsy procedure could be done and alterations or normalization in serum levels of native and total thiols might be determined. However, while the study was ongoing, we did not know which marker levels would vary significantly. So, the focus of our study was assessment of acute oxidative stress. Acute and chronic oxidative stress may lead to different consequences, and evaluation of chronic stress could form the aim of another trial. Finally, we did not compare our

data with other oxidative stress parameters such as lipid hydroperoxide, total antioxidant/oxidant status and paraoxonase. However, a MEDLINE search produced many studies related to the use of thiol/disulphide homeostasis as an oxidative stress marker for many clinical disorders (6-16).

In conclusion, an advantage of this novel marker is that it is easily calculated, readily available, and relatively cheap. Significant decreases in serum native and total thiol levels (as the components of thiol/disulphide homeostasis) related to the prostate biopsy procedure suggest that TRUSB causes acute oxidative stress in the human body. Thus, unnecessary biopsies should be avoided. Patient age at biopsy might affect oxidative stress during biopsy. So, men with older age may have an increased risk of oxidative stress caused by the prostate biopsy itself.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Watanabe H, Kato H, Kato T, Morita M, Tanaka M. [Diagnostic application of ultrasonotomography to the prostate]. Nihon Hinyokika Gakkai Zasshi. 1968;59:273-9.
2. Hodge KK, McNeal JE, Stamey TA. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol. 1989;142:66-70.
3. Rodríguez-Patrón Rodríguez R, Mayayo Dehesa T, Burgos Revilla FJ, Alonso González M, Lennie Zucharino A, García González R. [Results of a series of transrectal ultrasound guided biopsy of the prostate in 6000 patients. Part II: PSA derived parameters]. Arch Esp Urol. 2005;58:623-34.
4. Stamey TA. Making the most out of six systematic sextant biopsies. Urology. 1995;45:2-12.
5. Tsivian M, Kimura M, Sun L, Mouraviev V, Mayes JM, Polascik TJ. Predicting unilateral prostate cancer on routine diagnostic biopsy: sextant vs extended. BJU Int. 2010;105:1089-92.
6. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.
7. Matteucci E, Giampietro O. Thiol signalling network with an eye to diabetes. Molecules. 2010;15:8890-903.
8. Go YM, Jones DP. Cysteine/cystine redox signaling in cardiovascular disease. Free Radic Biol Med. 2011;50:495-509.
9. Prabhu A, Sarcar B, Kahali S, Yuan Z, Johnson JJ, Adam KP, et al. Cysteine catabolism: a novel metabolic pathway contributing to glioblastoma growth. Cancer Res. 2014;74:787-96.
10. Tetik S, Ahmad S, Alturfan AA, Fresko I, Disbudak M, Sahin Y, et al. Determination of oxidant stress in plasma of rheumatoid arthritis and primary osteoarthritis patients. Indian J Biochem Biophys. 2010;47:353-8.
11. Rodrigues SD, Batista GB, Ingberman M, Pecoits-Filho R, Nakao LS. Plasma cysteine/cystine reduction potential correlates with plasma creatinine levels in chronic kidney disease. Blood Purif. 2012;34:231-7.
12. Sbrana E, Paladini A, Bramanti E, Spinetti MC, Raspi G. Quantitation of reduced glutathione and cysteine in human immunodeficiency virus-infected patients. Electrophoresis. 2004;25:1522-9.
13. Calabrese V, Lodi R, Tonon C, D'Agata V, Sapienza M, Scapagnini G, et al. Oxidative stress, mitochondrial dysfunction and cellular stress response in Friedreich's ataxia. J Neurol Sci. 2005;233:145-62.
14. Smeyne M, Smeyne RJ. Glutathione metabolism and Parkinson's disease. Free Radic Biol Med. 2013;62:13-25.
15. Steele ML, Fuller S, Maczurek AE, Kersaitis C, Ooi L, Münch G. Chronic inflammation alters production and release of glutathione and related thiols in human U373 astroglial cells. Cell Mol Neurobiol. 2013;33:19-30.
16. Kuo LM, Kuo CY, Lin CY, Hung MF, Shen JJ, Hwang TL. Intracellular glutathione depletion by oridonin leads to apoptosis in hepatic stellate cells. Molecules. 2014;19:3327-44.
17. Ener K, Keske M, Aldemir M, Özcan MF, Okulu E, Özayar A, et al. Evaluation of oxidative stress status and antioxidant capacity in patients with painful bladder syndrome/interstitial cystitis: preliminar results of a randomised study. Int Urol Nephrol. 2015;47:1297-302.
18. Hagan S, Khurana N, Chandra S, Abdel-Mageed AB, Mondal D, Hellstrom WJ, et al. Differential expression of novel biomarkers (TLR-2, TLR-4, COX-2, and Nrf-2) of inflammation and oxidative stress in semen of leukocytospermia patients. Andrology. 2015;3:848-55.
19. Yang S, Pinney SM, Mallick P, Ho SM, Bracken B, Wu T. Impact of Oxidative Stress Biomarkers and Carboxymethyllysine (an Advanced Glycation End Product) on Prostate Cancer: A Prospective Study. Clin Genitourin Cancer. 2015;13:e347-51.
20. Kundi H, Ates I, Kiziltunc E, Cetin M, Cicekcioglu H, Neselioglu S, et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med. 2015;33:1567-71.
21. Ates I, Kaplan M, Inan B, Alisik M, Erel O, Yilmaz N, et al. How does thiol/disulfide homeostasis change in prediabetic patients? Diabetes Res Clin Pract. 2015;110:166-71.
22. Ates I, Kaplan M, Yuksel M, Mese D, Alisik M, Erel Ö, et al. Determination of thiol/disulphide homeostasis in type 1 diabetes mellitus and the factors associated with thiol oxidation. Endocrine. 2016;51:47-51.

23. Yilmaz ÖH, Bal C, Neşelioglu S, Büyükşekerci M, Gündüzöz M, Eren F, et al. Thiol/disulfide homeostasis in asphalt workers. Arch Environ Occup Health. 2016;71:268-272.
24. Ateş İ, Ozkayar N, Altay M, Yilmaz FM, Topçuoğlu C, Alışık M, et al. Is disulphide/thiol ratio related to blood pressure in masked hypertension? Clin Exp Hypertens. 2016;38:150-4.
25. Ozler S, Oztas E, Tokmak A, Ergin M, Isci E, Eren F, et al. The association of thiol/disulphide homeostasis and lipid accumulation index with cardiovascular risk factors in overweight adolescents with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2016;84:516-23.
26. Erkenekli K, Sanhal CY, Yucel A, Bicer CK, Erel O, Uygur D. Thiol/disulfide homeostasis in patients with idiopathic recurrent pregnancy loss assessed by a novel assay: Report of a preliminary study. J Obstet Gynaecol Res. 2016;42:136-41.
27. Yuksel M, Ates I, Kaplan M, Alışık M, Erel Ö, Saygılı F, et al. The dynamic thiol/disulphide homeostasis in inflammatory bowel disease and its relation with disease activity and pathogenesis. Int J Colorectal Dis. 2016;31:1229-31.
28. Ozler S, Erel O, Oztas E, Ersoy AO, Ergin M, Sucak A, et al. Serum Thiol/Disulphide Homeostasis in Preeclampsia. Hypertens Pregnancy. 2015;34:474-485.
29. Ates I, Ozkayar N, Inan B, Yilmaz FM, Topcuoglu C, Neselioglu S, et al. Dynamic thiol/disulphide homeostasis in patients with newly diagnosed primary hypertension. J Am Soc Hypertens. 2016;10:159-66.
30. Korkmaz V, Kurdoglu Z, Alisik M, Cetin O, Korkmaz H, Surer H, et al. Impairment of thiol-disulfide homeostasis in preeclampsia. J Matern Fetal Neonatal Med. 2016;29:3848-53.
31. Kumar A, Hammad A, Sharma AK, Mc-Cardle F, Rustom R, Christmas SE. Oxidative stress in kidney transplant biopsies. Exp Clin Transplant. 2015;13:207-13.
32. Resim S, Kurutas EB, Gul AB, Eren M, Benlioglu C, Efe E, et al. The Levels of Oxidative Stress Biomarkers in Rats as a Response to Different Techniques of Testicular Biopsy. Indian J Surg. 2015;77:310-3.
33. Singh L, Singh G, Sharma A, Sinha A, Bagga A, Dinda AK. A comparative study on renal biopsy before and after long-term calcineurin inhibitors therapy: na insight for pathogenesis of its toxicity. Hum Pathol. 2015;46:34-9.

Correspondence address:
Hüsnü Tokgöz, MD
Antalya E.A. Hastanesi D-Blok Kat:6
Muratpaşa/ Antalya 07070, Turkey
Telephone: + 90 505 527-2396
E-mail: h_tokgoz@hotmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 462-469, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0479

Lateral decubitus position vs. lithotomy position: which is the best way to minimize patient's pain perception during transrectal prostate biopsy?

Phil Hyun Song [1], Young Hwii Ko [1]

[1] *Department of Urology, College of Medicine, Yeungnam University, Daegu, Korea*

ABSTRACT

Introduction: Considering the distinctive nature in terms of psychological stress and anal tone of position which is generally selected between lithotomy and left lateral decubitus (LLD), we postulated its effect on pain perception during biopsy, and investigated their association.

Materials and Methods: A prospective study for comparison of two biopsy positions which were perform in a different working day was conducted for 208 men (lithotomy position=86, LLD=122). The decision on the position was made solely based on the patient's preference for the biopsy day, and all procedures were performed according to the identical protocol (12-core biopsy with intrarectal lidocaine gel), probe, and needle. The maximal degree of pain during the entire process was assessed using a visual analogue scale (VAS), immediately after biopsy. After propensity matching, a total of 152 patients were finally selected (lithotomy group=76, LLD=76), then peri-biopsy parameters were compared.

Results: Between groups, no differences were observed across all variables including age, obesity, prostate volume, serum PSA, international prostate symptom score, and cancer detection rate, except mean (±standard deviation) VAS score (3.89±2.01 vs. 4.58±2.22, p=0.049). VAS score showed significant association solely with patient's position (Pearson's coefficient=-0.165, p=0.042). In multiple linear regression models regarding the effect of clinical variables on VAS score, patient position was a single independent predictor favoring lithotomy position to decrease perceived pain (B=-0.928, p=0.024).

Conclusions: These data suggest lithotomy position as a proper way to perform transrectal prostate biopsy with routine use of topical lidocaine gel in comparison with conventional LLD position.

ARTICLE INFO

Keywords:
Pain Measurement; Patient Positioning; Biopsy

Int Braz J Urol. 2017; 43: 462-9

Submitted for publication:
October 01, 2015

Accepted after revision:
February 29, 2016

Published as Ahead of Print:
January 27, 2017

INTRODUCTION

In identification of prostate cancer, the most common malignant disease in Caucasians also with persistently increasing incidence in Asian populations, the use of extended number of biopsy cores became a contemporary standard in performance of transrectal ultrasound guided prostate biopsy (TRBx), by enhanced detection rate in comparison with a traditional six-core scheme (1, 2). After initial biopsy, the number of patients who requires repeat biopsy also grows with the increased life span and widespread use of active surveillance as a recommendable clinical option

in management of low risk prostate cancer (3). In addition, along with increasing incidence of biopsy led by increased public awareness of the disease as well as escalation of biopsy cores obtained, the number of subjects who consider the procedure uncomfortable and painful is also increasing (4). Thus, efforts to minimize the discomfort associated with the procedure are crucial not only in detection, but also in a proper control of the disease through the patient's life expectancy.

Although techniques including intrarectal lidocaine gel, periprostatic nerve block, and intravenous sedation with opioid drug, have been suggested to decrease the discomfort (5-7), the majority of patients still experience a considerable degree of pain (8). In an attempt to obtain a further relief, the effect of position which is generally selected between lithotomy and conventional left lateral decubitus (LLD) position had been researched (9-11). However, outcomes from several western studies reached contrasting conclusions, and there are no data for Asian population, who have a relatively smaller prostate. Considering the distinctive nature in terms of psychological stress, physician's movement, and anal tone of each position, we postulated its effect on pain perception during the procedure, and investigated their association in Korean men in a prospective manner.

MATERIAL AND METHODS

The patients enrolled

Our indications for prostate biopsy were identical, including elevated serum prostate specific antigen (PSA) level over 3.5ng/mL and/or an abnormal digital rectal examination (DRE). In our institution, TRBx was performed in lithotomy position or LLD position and the decision on the position was made solely based on the patient's preference for the biopsy date (lithotomy position on Monday and Friday; LLD position on Tuesday and Thursday). Biopsy in a lithotomy position was performed by a single urologist in the operative room and in a LLD position by a single radiologist in the radiologic department. At the initiation of this study, both physicians had over 10 years' experience (minimal 500 cases each) in TRBx using identical position. Patients with anal and/or rectal pathologies, chronic pelvic pain syndrome, presence of urinary tract infection, or contraindication for the lithotomy position were excluded in this study. After approval of the local review board, 208 patients (122 subjects in LLD and 86 subjects in lithotomy position) were enrolled in this prospective study conducted from September 2013 to February 2014. Propensity score matching was then performed to control the imbalances between the groups, and 152 patients were finally selected for each group (76 subjects in LLD and 76 subjects in lithotomy position).

Institutional transrectal prostate biopsy procedure

Entire procedures were performed according to the same protocol in terms of prophylactic antibiotics, local analgesics before the procedure, the number of biopsy cores, the model of needle and ultrasonography, and post procedural management regardless of the patient's position. Anticoagulants or antiplatelets were routinely stopped for a minimum of 7 days before biopsy. Based on our institutional policy, all patients undergoing TRBx required hospitalization, and a cleansing enema was routinely performed prior to the day before the procedure. After overnight fasting following enema, the procedures were performed at a similar time (between 8-10AM). Ciprofloxacin 250mg was administered intravenously 1 hour before the procedure, and oral ciprofloxacin was prescribed for 3 additional days after the procedure. Immediately before biopsy, 10mL of 2% lidocaine gel was applied to the rectum for 5 minutes. To improve efficacy and reduce procedure time, TRBx was performed using a team based approach consisting of 4 participants, including a qualified physician who manipulated the probe and decided on the biopsy target area and depth, a senior resident with minimal 2 years' experience assisting the procedure applying biopsy needles and obtaining the specimen, a junior resident who adjusted and maintained the patient's position, and a scrub nurse who handled the specimen obtained from the biopsy needle. Specimens from 12 sites across the prostate (2 from the base, 2 from the mid lobe, 1 from the apex, and 1 from the transitional zone for each prostate lobe) were obtained

using an 18-gauge 20-cm disposable needle (Baxter, USA), under the guidance of the same model of ultrasonography device (Hitachi HIGH VISION 5500; Hitachi Aloka Medical, Ltd, Tokyo, Japan) using the UST-675P prostate probe. When typical hypoechoic lesions suspicious of tumor were identified during procedure, additional biopsies were performed.

The highest degree of pain across the entire procedure from insertion of probe to completion of biopsy was assessed by a third person (non-physician coordinator) who was not participating in the procedure at the time of questioning, using a visual analogue scale (VAS) graded from 0 to 10 (0=painless, 10=intolerable pain), immediately after biopsy.

Matching the patients and statistical analysis

Comparison of variables between lithotomy and LLD position was performed using chi-square test and Student's T-test. Based on this comparison, the parameters that showed a statistically significant difference between groups were selected, and then used for propensity score matching. Propensity scores were calculated for each patient using multivariable logistic regression.

The relationship between clinical variables and VAS was analyzed using simple correlation (Pearson's correlation) and multivariable analysis using linear regression models. All statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA) using two-sided tests with a significance level of 5%.

RESULTS

Basic demographics and matching the patient

The characteristics of the patients are summarized in Table-1. Before matching, the patients in lithotomy position had significantly severe lower urinary tract symptoms, which was assessed using international prostate symptom score (IPSS; 15.49±6.19 vs. 13.24±9.11, p=0.042) and marginally higher pre-biopsy PSA (22.76±27.50ng/dL vs. 16.01±18.81ng/dL, p=0.005). Propensity score matching was then performed for 4 pre-biopsy variables, including IPSS, PSA, prostate volume, and age, considering previously reported links between the last two variables for the first two variables. For finally selected 152 patients, statistical similarity was obtained for all pre-biopsy variables (Table-1).

After biopsy, the overall cancer detection rate was 36.8%, which was similar across each group (p=0.867) despite of significantly more biopsy cores were obtained in lithotomy position (12.30±0.673 vs. 12.08±0.271, p=0.009). During the procedure, while no differences were observed in overall distribution of VAS and equinoctial distribution using cutoff score of 5 (p=0.157 and 0.099), the mean value of VAS was significantly lower in the lithotomy position group (3.89±2.01 vs. 4.58±2.22, p=0.049), when it was treated as continuous variables.

Clinical variables associated with VAS

In simple correlation analysis, VAS score showed significant association solely with patient's position preferring lithotomy position to decrease perceived pain (Pearson's coefficient=-0.165, p=0.042, Table-2). In multiple linear regression models (stepwise method, R^2=0.042, p=0.024) regarding the effect of clinical variables on VAS score, patient position was a single independent predictor (B=-0.928, p=0.024, Table-3) favoring lithotomy position.

DISCUSSION

TRBx procedure was generally believed to be well tolerable for the majority of patients (11). However, contrary to the traditional perception by the urologist, the pain or discomfort of patients associated with biopsy is not mild or negligible. Some kind of discomfort or pain during the procedure is reported by 52-96% of patients and 20% of them suffer from severe pain (12, 13). Even by DRE alone, 73% of patients reported moderate or higher discomfort (14). A clear tendency between the degree of pain during biopsy and the number of biopsy cores was consistently reported by prospective trials (15, 16). Regardless of the number of biopsy cores, the incidence of severe pain score increased generally from the first to the last biopsy (15). Tolerance of biopsy remained unchanged throughout the procedure in 53.2% and became

Table 1 - Characteristics of the enrolled patients.

		Before matching (n=208)				After matching (n=152)			
		Total	LLD position (n=122)	lithotomy position (n=86)	p-value	Total	LLD position (n=76)	lithotomy position (n=76)	p-value
Pre-biopsy variables	**Age (years)**	67.81±8.33	67.73±8.881	67.93±7.539	0.861	67.16±8.45	66.72±9.19	67.59±7.67	0.528
	Prostate volume (g)	42.17±25.86	40.33±20.25	44.78±32.14	0.258	42.84±27.86	40.56±21.14	45.12±33.24	0.315
	Pre-biopsy PSA (ng/dL)	22.99±18.8	16.01±18.81	22.76±27.50	0.050	18.77±22.87	16.11±17.88	21.44±26.82	0.151
	Number of biopsy (%)								
	first	180 (86.5)	103 (84.4)	77 (89.5)		135 (88.8)	67 (88.2)	68 (89.5)	
	second	21 (10.1)	15 (12.3)	6 (7.0)	0.456	12 (7.9)	7 (9.2)	5 (6.6)	0.763
	third	7 (3.4)	4 (3.3)	3 (3.5)		5 (3.3)	2 (2.6)	3 (3.9)	
	Nodule on DRE (%)								
	with palpable nodule	9 (5.4)	5 (5.3)	4 (5.4)		6 (4.9)	2 (3.4)	4 (6.3)	
	without palpable nodule	159 (94.6)	89 (94.7)	70 (94.6)	0.620	116 (95.1)	56 (96.6)	60 (93.8)	0.682
	BMI (kg/m^2)	23.82±2.67	23.71±2.57	23.97±2.77	0.485	23.86±2.60	23.92±2.45	23.79±2.76	0.754
	Prior history of DM (%)								
	with DM	36 (17.3)	20 (16.4)	16 (18.6)		31 (20.4)	16 (21.1)	15 (19.7)	
	without DM	172 (82.7)	102 (83.6)	70 (81.4)	0.712	121 (79.6)	60 (78.9)	61 (80.3)	1.000
	Pyuria at time of biopsy (%)				0.601				
	with pyuria	10 (4.8)	6 (4.9)	4 (4.7)		6 (3.9)	4 (5.3)	2 (2.6)	0.681
	without pyuria	198 (95.2)	116 (95.1)	82 (95.3)		146 (96.1)	72 (94.7)	74 (97.4)	
	Total IPSS	14.12±8.15	13,24±9.11	15.49±6.19	0.042	15.28±7.94	15.07±9.40	15.49±6.19	0.745
Intra & post - biopsy variables	**VAS score**	4.29±2.20	4.54±2.28	3.89±2.02	0.041	4.24±2.14	4.58±2.22	3.89±2.01	0.049
	0	4 (2.1)	4 (3.4)	-	0.105	3 (2.0)	3 (3.9)	-	0.157
	1	11(5.6)	4 (3.4)	7 (9.2)		10 (6.6)	3 (3.9)	7 (9.2)	
	2	37 (19.0)	19 (16.0)	18 (23.7)		27 (17.8)	9 (11.8)	18 (23.7)	
	3	22 (11.3)	11 (9.2)	11 (14.5)		19 (12.5)	8 (10.5)	11 (14.5)	
	4	38 (19.5)	24 (20.2)	14 (18.4)		30 (19.7)	16 (21.1)	14 (18.4)	
	5	19 (9.7)	15 (12.6)	4 (5.3)		11 (7.2)	7 (9.2)	4 (5.3)	
	6	37 (19.0)	23 (19.3)	14 (18.4)		32 (21.1)	18 (23.7)	14 (18.4)	
	7	8 (4.1)	4 (3.4)	4 (5.3)		6 (3.9)	2 (2.6)	4 (5.3)	
	8	15 (7.7)	11 (9.2)	4 (5.3)		13 (8.6)	9 (11.8)	4 (5.3)	
	9	-	-	-		-	-	-	
	10	4 (2.1)	4 (3.4)	-		1 (0.7)	1 (1.3)	-	
	Number of biopsy core	12.13±0.627	12.02±0.589	12.29±0.648	0.006	12.19±0.524	12.08±0.271	12.30±0.673	0.009
	12 core (%)	179 (86.1)	112 (91.8)	67 (77.9)		129 (84.9)	70 (92.1)	59 (77.6)	0.022
	over 12 core (13-16%)	29 (13.9)	10 (8.2)	19 (22.1)	0.007	23 (15.2)	6 (7.9)	17 (22.4)	
	Pca detected (%)	85 (40.9)	54 (44.3)	31 (36.0)	0.254	56 (36.8)	29 (38.2)	27 (35.5)	0.867

SD = standard deviation; **BMI** = body mass index; **PSA** = prostate-specific antigen; **IPSS** = International prostate symptom score; **VAS** = visual analogue scale

Table 2 - Outcome of simple correlation among clinical variables associated with VAS.

Variables	Pearson's coefficeint	p-value
Age	-0.068	0.402
Prostate volume	0.005	0.954
Pre-biopsy PSA (ng/dL)	-0.003	0.974
Number of biopsy	0.067	0.410
Number of biopsy core	-0.036	0.661
The presence of nodule on DRE	-0.176	0.053
BMI (kg/m²)	-0.060	0.463
Prior history of DM	0.041	0.620
Pyuria at time of biopsy	-0.015	0.856
Total IPSS	-0.117	0.152
Identification of Pca	-0.015	0.852
Position at the time of biopsy	-0.165	0.042

PSA = prostate-specific antigen; **DRE** = Digital rectal examination; **BMI** = body mass index; **DM** = Diabetes mellitus; **Pca** = Prostate cancer

Table 3 - Outcome of multiple linear regression model among clinical variables associated with VAS.

Variables	P value	B (95% CI)
Age	0.199	-0.115
Prostate volume	0.071	-0.161
Pre-biopsy PSA (ng/dL)	0.546	0.055
Number of biopsy	0.336	0.086
Number of biopsy core	0.655	-0.041
The presence of nodule on DRE	0.247	-0.104
BMI (kg/m²)	0.272	-0.098
Prior history of DM	0.827	-0.020
Pyuria at time of biopsy	0.746	-0.029
Total IPSS	0.613	-0.045
Identification of Pca	0.434	-0.070
Position at the time of biopsy	0.024	-0.928 (-0.119~ -1.644)

PSA = prostate-specific antigen; **DRE =** Digital rectal examination; **BMI =** body mass index; **DM =** Diabetes mellitus; **Pca =** Prostate cancer

worse as the test proceeded in the remaining patients (17). Familiarity with the procedure at the repeat biopsy did not decrease pain or anxiety at al. (18).

In contrast, only 4% and 11% of patients reported no pain or discomfort, respectively, and 3% had no complaint during TRBx (18). Of men who were interviewed, 19% would not wish to undergo the procedure again without aid of analgesia, and 6% would like biopsies to be done under general anesthesia (19). Because the biopsy itself is still invasive in nature, a high degree of discomfort associated with it may result in failure of the patient to return for the future biopsy even though it will be necessary.

Perception of pain is a highly subjective psychological phenomenon, which can be influenced by various factors. As for the predictor of severe pain during TRBx, several reports have suggested preoperative anxiety, which

was reported in 64% of biopsy events (18), pain on insertion of the transrectal ultrasonic probe (15) or during DRE (20), and age of the patients (19). However, all of these previously reported characteristics were not chosen or adjustable by the physician, without providing a substantial clue to minimize the discomfort at the time of the procedure despite usefulness in identification of the risk group. Conversely, the outcomes from this series suggest lithotomy position as a simple method for the majority of subjects who have no limitation in range of motion in the hip joint. A significant decrease of mean VAS score was observed in lithotomy position in comparison with LLP, and a multivariable model showed lithotomy position as a single significant predictor to minimize VAS score.

Then, what is the potential explanation for our findings? While the mechanism of pain associated with TRBx is complex, recent studies have gradually enlightened this area. Between lithotomy position and LLP, there exist two fundamental differences; the visibility of the procedure by the subject or eye contact by the physician which thereby influences the embarrassment of the subject, and the convenience in relaxation of pelvic floor muscle which affects the anal sphincter contraction thereby enabling easier probe insertion and lesser pain perception. Because a sense of vulnerability or defenselessness associated with patient positioning may interfere with physical and psychological distress (14), lithotomy position which allows the patient to identify visual information on the progress of the procedure improves the tolerance of the patient while the position of the legs in this position obviously creates additional discomfort. A more direct relationship between patient's positioning and the degrees of pelvic floor muscle relaxation was recently identified. Using electromyographic evaluation with eight--channels for 29 women, Resende et al. demonstrated that the lateral positon presented a significantly greater myoelectrical signal of pelvic floor resting tone among lithotomy, supine, and lateral positions (21). In the same context, several randomized controlled trails which assessed the effect of topical muscle relaxant during TRBx consistently confirmed the effectiveness and safety in diminishing the patient's discomfort, particularly during the insertion of an ultrasound probe (22, 23).

Our hypothesis regarding the positive influence of lithotomy position on TRBx was supported by other research, which demonstrated that use of a larger probe (74mm) results in much higher VAS pain perception than same size and smaller (58mm) probe in the absence of injectable local anesthesia (24). In addition, probe insertion was reported to produce a significantly higher pain scale than biopsy using a 12 core prostate biopsy scheme (25). Due to the similarities of the procedure, discomfort during DRE can reflect that of the patient during TRBx, and several studies have reported an association between the patient's position and pain during DRE (20, 26). Among four positions including LLD and supine position, more than half of their patients chose the supine position for DRE (27).

The authors also recognize several limitations of this series. First, while the data were collected prospectively, we cannot randomize the subjects based only on the position, mainly because of uneven distribution of patient's preference on the date. Instead, we adjusted the discrepancies of each group by propensity matching, and selected subjects demonstrated similar pre-biopsy characteristics across all variables except the number of biopsy core, which was rather significantly higher in lithotomy position. However, the number of biopsy core was not significantly associated with VAS both in univariable and multivariable analysis. Second, despite similar expertise of each physician on the procedure, there may exist a habitual difference which may affect the pain perception of the patients. In addition, the environmental difference of OR and radiologic department may act as an isolated variable. Third, different from the majority of reported series, our procedure was performed after hospitalization. Our institutional policy, based on prior reports on discomfort and complications related to the TRBx, requires hospitalization which facilitates the routine use of enema preparation before the procedure and detailed counselling from the coordinator or physician, both of which may have a positive effect on VAS score. Thus, prostate biopsy in different settings may not lead to reproduction of a similar result

with us, and we believe these distinctive natures as a main reason for inconsistent conclusions on the advantage of lithotomy position during TRBx in prior series which used different biopsy setting in terms of the use of analgesics, the number of biopsy cores, and the number and experiences of physicians (9-11).

It is also obvious that not all men experience severe endurable pain during the procedure. However, in performing prostate biopsy, one of the goals should be to minimize the patient's discomfort associated with the procedure in era of active surveillance strategy in which the acceptance of repeat biopsy is crucial. In acquisition of this, our data indicating an obvious influence of position on pain may contribute to establishment of the best clinical setting for TRBx.

CONCLUSIONS

The position of the patient was a single factor associated with pain perception during transrectal prostate biopsy with an extended biopsy scheme. With routine use of topical lidocaine gel, lithotomy position significantly decreased the patient's pain without compromising detectability of prostate cancer. Based on these findings, we suggest lithotomy position as a proper way to perform TRUS guided prostate biopsy in comparison with conventional lateral decubitus position.

ACKNOWLEDGMENT

This work was supported by the 2015 Yeungnam University Research Grant.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol. 2003;169:125-9.
2. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol. 2013;63:214-30.
3. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. European Association of Urology. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65:124-37.
4. Lee C, Woo HH. Current methods of analgesia for transrectal ultrasonography (TRUS)-guided prostate biopsy -- a systematic review. BJU Int. 2014;113:48-56.
5. Inal G, Yazici S, Adsan O, Ozturk B, Kosan M, Cetinkaya M. Effect of periprostatic nerve blockade before transrectal ultrasound-guided prostate biopsy on patient comfort: a randomized placebo controlled study. Int J Urol. 2004;11:148-51.
6. Ozden E, Yaman O, Göğüs C, Ozgencil E, Soygür T. The optimum doses of and injection locations for periprostatic nerve blockade for transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, placebo controlled study. J Urol. 2003;170:2319-22.
7. Berger AP, Frauscher F, Halpern EJ, Spranger R, Steiner H, Bartsch G, et al. Periprostatic administration of local anesthesia during transrectal ultrasound-guided biopsy of the prostate: a randomized, double-blind, placebo-controlled study. Urology. 2003;61:585-8.
8. Collins GN, Lloyd SN, Hehir M, McKelvie GB. Multiple transrectal ultrasound-guided prostatic biopsies--true morbidity and patient acceptance. Br J Urol. 1993;71:460-3.
9. Bruyère F, Faivre d'Arcier B, Haringanji DC, Boutin JM, Haillot O, Lanson Y. Effect of patient position on pain experienced during prostate biopsy. Urol Int. 2007;78:351-5.
10. Kilciler M, Demir E, Bedir S, Erten K, Kilic C, Peker AF. Pain scores and early complications of transrectal ultrasonography-guided prostate biopsy: effect of patient position. Urol Int. 2007;79:361-3.
11. Lodeta B, Lodeta M. Prostate Biopsy in the Left Lateral Decubitus Position is Less Painful than Prostate Biopsy in the Lithotomy Position: A Randomized Controlled Trial. Korean J Urol. 2012;53:87-91.
12. Bastide C, Lechevallier E, Eghazarian C, Ortega JC, Coulange C. Tolerance of pain during transrectal ultrasound-guided biopsy of the prostate: risk factors. Prostate Cancer Prostatic Dis. 2003;6:239-41.
13. Zisman A, Leibovici D, Kleinmann J, Siegel YI, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of pain, anxiety and erectile dysfunction. J Urol. 2001;165:445-54.
14. Clements R, Aideyan OU, Griffiths GJ, Peeling WB. Side effects and patient acceptability of transrectal biopsy of the prostate. Clin Radiol. 1993;47:125-6.

15. Romero FR, Romero AW, Brenny Filho T, Bark NM, Yamazaki DS, de Oliveira FC. Patients' perceptions of pain and discomfort during digital rectal exam for prostate cancer screening. Arch Esp Urol. 2008;61:850-4.
16. Chopra S, Rowe EW, Laniado M, Patel A. A prospective study analysing the effect of pain on probe insertion, and the biopsy strategy, on the patients' perception of pain during TRUS-guided biopsy of the prostate. N Z Med J. 2008;121:39-43.
17. Horninger W, Reissigl A, Fink K Results of a prospective randomised study comparing the prostate cancer detection rates in PSA screening volunteers undergoing 10 vs 14 transrectal ultrasound guided biopsies: J Urol 1998;159 suppl:180.
18. Rodríguez-Patrón Rodríguez R, Mayayo Dehesa T, Lennie Zucharino A, González Galán A, Peral Amorós M. Complications of prostatic echo-guided transrectal biopsy and tolerance depending on the patient and the operator. Study of 205 patients. Arch Esp Urol. 2002;55:509-21.
19. Zisman A, Leibovici D, Kleinmann J, Siegel YI, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of pain, anxiety and erectile dysfunction. J Urol. 2001;165:445-54.
20. Irani J, Fournier F, Bon D, Gremmo E, Doré B, Aubert J. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. Br J Urol. 1997;79:608-10.
21. Djavan B, Zlotta A, Remzi M, Ghawidel K, Basharkhah A, Schulman CC, et al. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. J Urol. 2000;163:1144-8.
22. Resende AP, Petricelli C, Zanetti MRD. Which of the recumbent positions promoves better pelvic floor muscle relaxation? ICS 2010 abstract number 1015
23. Rochester MA, LE Monnier K, Brewster SF. A double-blind, randomized, controlled trial of topical glyceryl trinitrate for transrectal ultrasound guided prostate biopsy. J Urol. 2005;173:418-20.
24. McCabe JE, Hanchanale VS, Philip J, Javle PM. A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. BJU Int. 2007;100:536-8.
25. Koprulu S, Cevik I, Unlu N, Dillioglugil O. Size of the transrectal ultrasound probe makes no difference in pain perception during TRUS-Bx under adequate local anesthesia. Int Urol Nephrol. 2012;44:29-33.
26. Philip J, McCabe JE, Roy SD, Samsudin A, Campbell IM, Javlé P. Site of local anaesthesia in transrectal ultrasonography-guided 12-core prostate biopsy: does it make a difference? BJU Int. 2006;97:263-5.
27. Furlan AB, Kato R, Vicentini F, Cury J, Antunes AA, Srougi M. Patient's reactions to digital rectal examination of the prostate. Int Braz J Urol. 2008;34:572-5.

Correspondence address:
Young Hwii Ko, MD
Department of Urology
College of Medicine, Yeungnam University
317-1 Daemyung-dong, Nam-gu, Daegu, 705-035, Korea
Fax: +82 536 275-535
E-mail: urokyh@naver.com

ORIGINAL ARTICLE

Vol. 43 (3): 470-475, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0441

Impact of personalized three-dimensional (3D) printed pelvicalyceal system models on patient information in percutaneous nephrolithotripsy surgery: a pilot study

Hasan Anil Atalay [1], H. Lütfi Canat [1], Volkan Ülker [2], İlter Alkan [1], Ünsal Özkuvanci [3], Fatih Altunrende [1]

[1] Department of Urology, Okmeydani Training and Research Hospital, Sisli, Istanbul, Turkey; [2] Department of Urology, İzmir Tepecik Training and Research Hospital, Izmir, Istanbul, Turkey; [3] Department of Urology, Istanbul Medical School, Çapa, Istanbul, Turkey

ABSTRACT

Objective: To investigate the impact of personalized three dimensional (3D) printed pelvicalyceal system models on patient information before percutaneous nephrolithotripsy surgery.
Material and Methods: Patients with unilateral complex renal stones with indicatation of percutaneous nephrolithotripsy surgery were selected. Usable data of patients were obtained from CT scans as Digital Imaging and Communications in Medicine (DICOM) format. Mimics software version 16.0 (Materialise, Belgium) was used for segmentation and extraction of pelvicalyceal systems. DICOM format were converted to Stereolithography file format. Finally, fused deposition modeling was used to create plasticine 3D models of pelvicalyceal systems. A questionnaire was designed for patients to assess personalized 3D models effect on patient's understanding their conditions before percutaneous nephrolithotripsy surgery (PCNL). The day before surgery, each patient was seen by a urologist to deliver information about surgery. Questionnaire forms were asked to patients complete before and after presentation of 3D models and the results of the questions were compared.
Results: Five patient's anatomically accurate models of the human renal collecting system were successfully generated. After the 3D printed model presentation, patients demonstrated an improvement in their understanding of basic kidney anatomy by 60% (p=0.017), kidney stone position by 50% (p=0.02), the planned surgical procedure by 60% (p=0.017), and understanding the complications related to the surgery by 64% (p=0.015). In addition, overall satisfaction of conservation improvement was 50% (p=0.02).
Conclusion: Generating kidney models of PCSs using 3D printing technology is feasible, and understandings of the disease and the surgical procedure from patients were well appreciated with this novel technology.

ARTICLE INFO

Keywords:
Calculi; Technology; Lithotripsy

Int Braz J Urol. 2017; 43: 470-5

Submitted for publication:
August 04, 2016

Accepted after revision:
January 15, 2017

Published as Ahead of Print:
March 17, 2017

INTRODUCTION

Three-dimensional (3D) printing is a new technology that has developed rapidly in recent years. This new approach holds significant benefits for medical procedures such as maxillofacial reconstruction (1). It has also been used for forensics, orthopedics, and rare complex interventions (2). Non-biological 3D printing models are being applied in the Urology field for planning surgeries, resident education, and patient information (3, 4).

Percutaneous nephrolithotripsy (PCNL) is a standard, safe, and efficient method for treating renal stones larger than 2cm in size (5). Access

through an appropriate calyx and knowledge of the complex 3D internal anatomy is essential for a successful PCNL. In the past, intravenous urography (IVU) and ultrasonography were used to analyze pelvicalyceal systems (PCSs) and stone anatomy. With advances in CT technology (e.g., rapid spiral acquisition and reconstruction software), it is now possible to provide accurately--reconstructed 3D images of the PCS that have been used successfully to facilitate successful PCNLs (6).

There is now a growing interest in providing information to support patient's participation in choosing treatments and deciding on strategies for managing their health problems (7). Information materials are no substitute for good verbal discussions, but consultations are usually short and plenty of evidence exists that patients do not receive the information they want and need (8). For this reason, the ability to generate 3D models from patient data is allowing physicians to inform patients in ways never seen before (9).

In this study, our aim was to assess whether personalized 3D printed models of PCSs can improve patient's understanding of their conditions before PCNL surgeries.

MATERIAL AND METHODS

Creating 3D Printed Models from Medical Imaging

Creating 3D models from medical imaging data is a multi-step process. First, usable data must be obtained from CT scans, magnetic resonance images, or ultrasound images. In our hospital (Okmeydani Teaching and Research Hospital), we used CT (Toshiba Alexion™ multislice CT) scan data from five patients. Data from CT scans in Digital Imaging and Communications in Medicine (DICOM) format are important because low-resolution images can result in inaccurate models (10).

Second, segmentation, or extraction and isolation of the area of interest, of the data must be performed. We sent our DICOM-formatted data to a bioengineer (Biotechnica Engineering Co Ltd, Istanbul) for segmentation. Numerous software programs are available for use with DICOM datasets. In our case, Mimics software version 16.0 (Materialise, Belgium) was used.

Finally, data must be saved in a file format recognized by the 3D printer software. The most commonly used format is the Stereolithography (stl) file format.

3D Printing

Recent advances in 3D printing technology have produced new processes that allow the use of a variety of materials factors. Acrylonitrile butadiene styrene (ABS) has been used for creating 3D models of PCSs. The most important mechanical properties of ABS are impact resistance, toughness, high radiodensity, and low cost. We used fused deposition modeling, an inexpensive technology popular with consumers. These printers use a polymer filament that is heated to a liquid state in a printer head and deposited in predefined locations corresponding to the model shape (Stratasys Inc.) (11).

Evolution of Personalized 3D Printed Models from Patients

A survey questionnaire with open ended questions of ordinal 10-point rating scales (1-poor/fair/good, 10-very good/excellent) was given to patients which consisted of 3 components: a) overall satisfaction of conversation (1 item), b) model assistance in understanding the disease and procedure (3 items) and c) understanding the complications related to the surgery (1 item). The day before surgery, each patient was seen by a urologist, the IVU images and CT scans were used as a teaching aid to deliver information about surgery and the disease. After the conversation, the questionnaire form asked patients to complete and then 3D printed models were presented to patients and they completed the questionnaire form again. Results of the questions were compared before and after the presentation of the 3D models.

Statistics

A total of 25 questions were asked to patients. Median total scores of responses for each category, before and after 3D printed model presentation, was compared (Wilcoxon test). Statistical analyses were performed using

SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA)

RESULTS

From June 2015 to January 2016, 5 patients with a unilateral staghorn renal stone and clinical indication of percutaneous nephrolithotomy were selected. Our first aim was to successfully create a 3D model of the pelvicalyceal systems. After two attempts we successfully generated anatomically accurate human renal collecting system. Overall collecting systems were clearly presented with regards to the virtual reconstructions. Fused deposition modeling with Acrylonitrile butadiene styrene (ABS) was used to generate anatomically-correct size and shape renal collecting system. The consumable costs of the model are low, at around 100$, and the print time for the 3D model is approximately 2 hours (Figures 1 and 2).

Patients demonstrated an improvement in their understanding of basic kidney anatomy, planned surgical procedure and understanding the complications related to the surgery after viewing their personal 3D kidney models. After the 3D printed model presentation, it was found that the mean improvement rate of total scores was higher. Patients demonstrated an improvement in their understanding of basic kidney anatomy by 60% (p=0.017), kidney stone position by 50% (p=0.02), the planned surgical procedure by 60 % (p=0.017), and understanding the complications related to the surgery by 64% (p=0.015). In addition, overall satisfaction of conservation improvement was 50% (p=0.02).

DISCUSSION

Accurate information which patients find useful has the potential to enhance the quality and appropriateness of health care. However, using

Figure 1 - Patient 1 A) Posterior view of collecting system, B) Coronal view of collecting system, C) Anterior view of collecting system, D) Posterior view of 3D printed model, E) Posterior-lateral view of 3D printed model, F) Anterior view of 3D printed model.

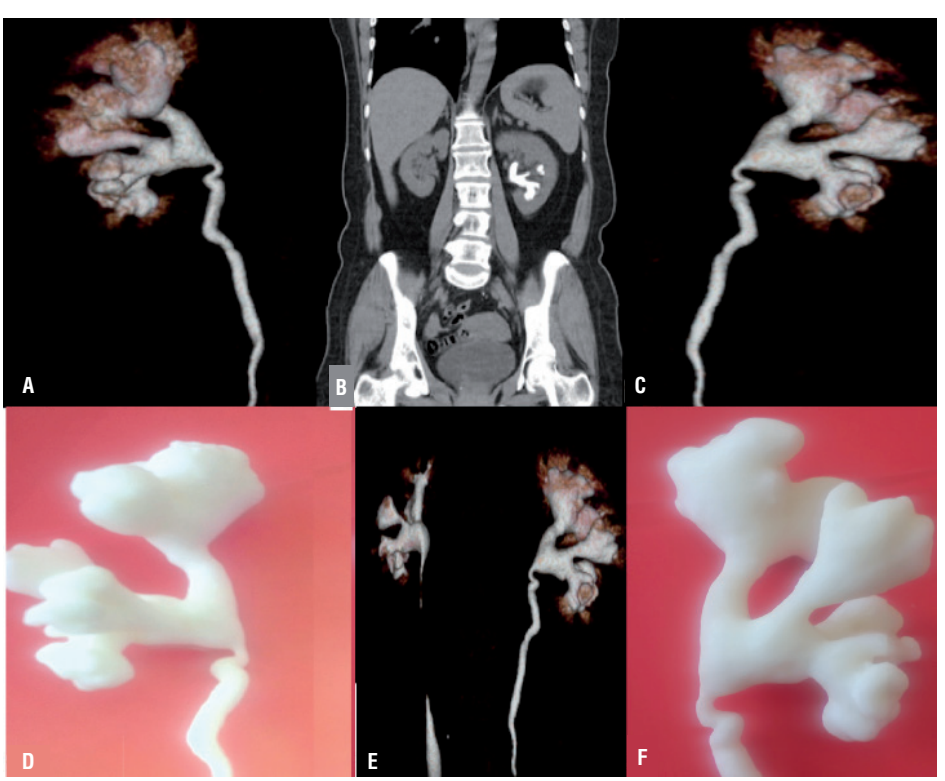
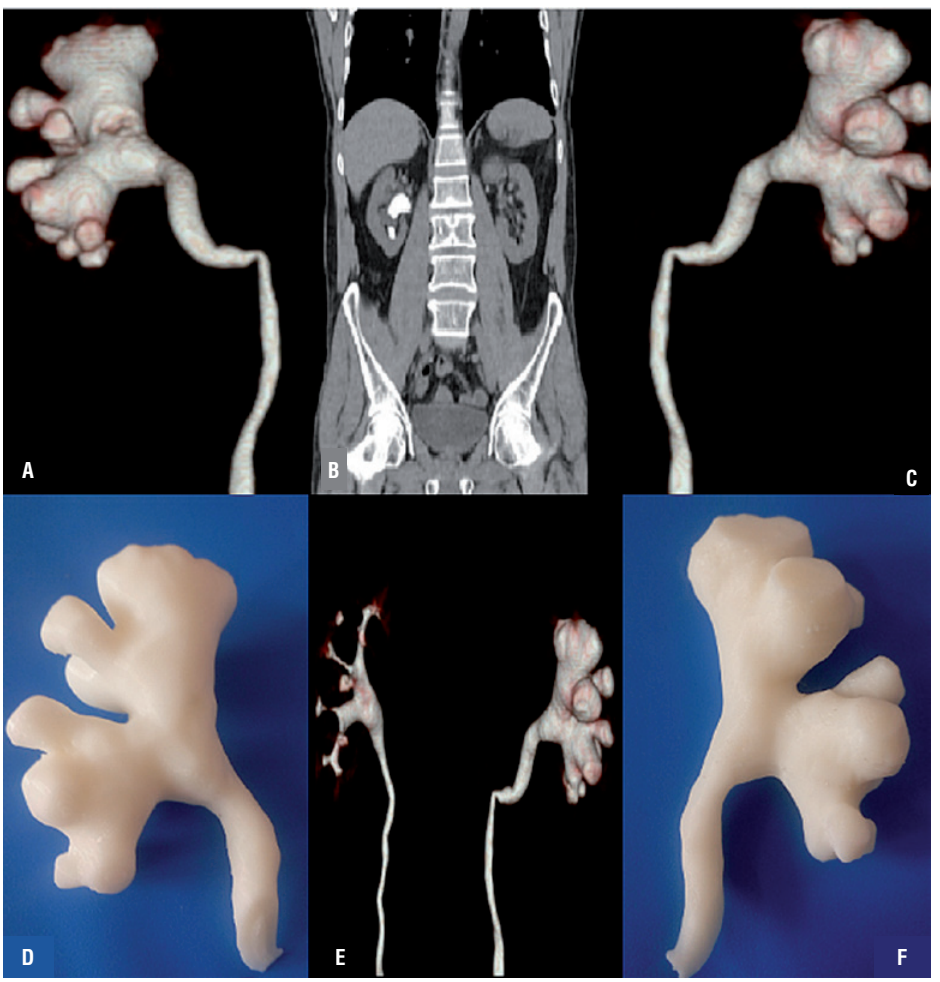


Figure 2 - Patient 2 A) Posterior view of collecting system, B) Coronal view of collecting system, C) Anterior view of collecting system, D) Posterior view of 3D printed model, E) Posterior-lateral view of 3D printed model, F) Anterior view of 3D printed model.



only 2D images makes it very difficult for surgeons to inform their patients about the surgery and the complications. This is why new modalities have been developed for patient information (12). PCNL is an effective method but various factors have a negative impact on the success rate and complications of PCNL surgery. Several studies have revealed that increasing stone burden and multiple tracks correlate with decreased stone--free rate and increased bleeding (13). Although staghorn stones required multiple tracks to have a stone free status. The ultimate goal would be complete stone clearance with no complications.

In the present study, we have created 5 physical, patient-specific, anatomically identical human renal collecting system 3D models before operative intervention, based on CT imaging of patients with unilateral staghorn renal stones. 3D models of the PCS can provide not only necessary images but are also feasible in planning collecting system access for planning PCNL surgery in complex staghorn renal stones.

Printed models have been used for preoperative planning in complex orthopedic and craniofacial procedures and neurosurgery (14, 15). There have been a few reports about bio-modeling for planning endourologic procedures and usefulness as an education tool for patients (16). While creating a 3D model, CT scan slice thickness has to be 5mm or up to 3mm because low resolution images

can result in discrepancy between the generated model and actual anatomy (17). But the increased radiation dose delivered with CT scans thinner then 5mm, is a cause of concern. The high-dose could increase 75 per cent of the radiation exposure compared to low-dose CT, according to the literature reports (18, 19).

Generating anatomically identical 3D models of renal collecting systems allows surgeons and patients to interact with the renal unit in a tangible way than using conventional images. In this study, it has shown that this interaction with models is an effective educational tool for patients resulting in an improvement over conventional imaging. With the 3D models, patients were better able to understand the renal anatomy and renal physiology, and the complications related to the surgery compared to CT scans and IVU images.

This study has shown that, physician and patient communication were improved after presentation of personalized physical 3D models. 3D physical models are valuable for patient satisfaction of conservation with a 50% improvement. Despite given detailed information with IVU and CT images about planned surgery and complications that may occur, patient's initial reference level of understanding was low. It is very difficult for patients to understand IVU and CT images and it can also be difficult for physicians to inform patients about the surgery and associated complications. After the presentation of 3D models, we witnessed how they helped patients raise and ask their own questions, enhancing their understanding. Improving patient education by the use of personalized 3D printed models appears to be a promising way to efficiently enhance the quality of personal exchange between a patient and his surgeon and influence overall patient satisfaction. In addition, patient education level is effective on the disclosure process.

Moreover, using this kind of personalized 3D models not only for patient counseling but also for students, residents and fellow's surgical teaching could help achieve better cost-effectiveness. Indeed, such models, in making easier 3D anatomical understanding, may certainly be useful tools to enhance surgical strategy discussion and improve preoperative planning.

CONCLUSIONS

Generating kidney models of pelvicalyceal systems with 3D printing technology is feasible; understanding of the disease and the surgical procedure from patients were well appreciated with this novel technology.

ABBREVIATIONS

3D = Three dimensional
CT = Computed tomography
IVU = Intravenous urography
PCNL = Percutaneous nephrolithotripsy
PCS = Pelvicalyceal systems
DICOM = Digital Imaging and Communications in Medicine
Q = Questions

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Mehra P, Miner J, D'Innocenzo R, Nadershah M. Use of 3-d stereolithographic models in oral and maxillofacial surgery. J Maxillofac Oral Surg. 2011;10:6-13.
2. Akiba T, Inagaki T, Nakada T. Three-dimensional printing model of anomalous bronchi before surgery. Ann Thorac Cardiovasc Surg. 2014;(20 Suppl):659-62.
3. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. Urology. 2014;83:500-6.
4. Silberstein JL, Maddox MM, Dorsey P, Feibus A, Thomas R, Lee BR. Physical models of renal malignancies using standard cross-sectional imaging and 3-dimensional printers: a pilot study. Urology. 2014;84:268-72.
5. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016;69:468-74.
6. Hubert J, Blum A, Cormier L, Claudon M, Regent D, Mangin P. Three-dimensional CT-scan reconstruction of renal calculi. A new tool for mapping-out staghorn calculi and follow-up of radiolucent stones. Eur Urol. 1997;31:297-301.
7. Coulter A. Partnerships with patients: the pros and cons of shared clinical decision-making. J Health Serv Res Policy. 1997;2:112-21.

8. Lynn C. Sbaih. What seems to be the matter: communication between hospitals and patients? Audit Commission HMSO, London, 1993, ISBN 0-11886-100-X.
9. Costello JP, Olivieri LJ, Su L, Krieger A, Alfares F, Thabit O, et al. Incorporating three-dimensional printing into a simulation-based congenital heart disease and critical care training curriculum for resident physicians. Congenit Heart Dis. 2015;10:185-90.
10. Wong JY, Pfahnl AC. 3D printing of surgical instruments for long-duration space missions. Aviat Space Environ Med. 2014;85:758-63.
11. Masood SH, Song WQ. Development of new metal/polymer materials for rapid tooling using fused deposition modelling. Materials and Design. 2004;25:587-94.
12. Evans JH, Collier J, Crook I, Garrud P, Harris P, MacKinlay DR, et al. Using multimedia for patient information--a program about nocturnal enuresis. Br J Urol. 1998;(81 Suppl 3):120-2.
13. Eguchi T, Takasuna K, Kitazawa A, Fukuzawa Y, Sakaue Y, Yoshida K, et al. Three-dimensional imaging navigation during a lung segmentectomy using na iPad. Eur J Cardiothorac Surg. 2012;41:893-7.
14. Turna B, Nazli O, Demiryoguran S, Mammadov R, Cal C. Percutaneous nephrolithotomy: variables that influence hemorrhage. Urology. 2007;69:603-7.
15. D'Urso PS, Askin G, Earwaker JS, Merry GS, Thompson RG, Barker TM, et al. Spinal biomodeling. Spine (Phila Pa 1976). 1999;24:1247-51.
16. Bernhard JC, Isotani S, Matsugasumi T, Duddalwar V, Hung AJ, Suer E, et al. Personalized 3D printed model of kidney and tumor anatomy: a useful tool for patient education. World J Urol. 2016;34:337-45.
17. Rengier F, Mehndiratta A, von Tengg-Kobligk H, Zechmann CM, Unterhinninghofen R, Kauczor HU, et al. 3D printing based on imaging data: review of medical applications. Int J Comput Assist Radiol Surg. 2010;5:335-41.
18. Poletti PA, Platon A, Rutschmann OT, Schmidlin FR, Iselin CE, Becker CD. Low-dose versus standard-dose CT protocol in patients with clinically suspected renal colic. AJR Am J Roentgenol. 2007;188:927-33.
19. Huda W, Bissessur K. Effective dose equivalents, HE, in diagnostic radiology. Med Phys. 1990;17:998-1003.

Correspondence address:
Hasan Anil Atalay, MD
Department of Urology
Okmeydani Training and Research Hospital
Sisli, Istanbul, 3475, Tukey
Telephone: + 90 533 323-4133
E-mail: anilatalay@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 476-480, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0324

Evaluation of the Spies™ modalities image quality

Esteban Emiliani [1], Michele Talso [1], Mohammed Baghdadi [1], Aarón Barreiro [1], Andrea Orosa [1], Pol Serviàn [1], Pavel Gavrilov [1], Silvia Proietti [1], Olivier Traxer [1,2]

[1] Department of Urology, Hôpital Tenon, Université Pierre et Marie Curie - Paris VI, Paris, France; [2] GRC lithiase (Grouped Recherche Clinique) Université Paris VI, Pierre et Marie Curie, Paris, France

ABSTRACT

Introduction: The Spies™ system (Karl-Storz®) was introduced into digital ureteroscopy to improve endoscopic vision. To date, there is no data to either indicate which of the Spies modalities is better for improving diagnosis and treatment procedures, nor to compare the modalities in terms of image quality. The aim of this study was to evaluate and compare the image quality of five Spies™ modalities (SM) to the standard white light in an in-vitro model.

Materials and Methods: Two standardized grids and 3 stones of different composition were recorded in white light and the 5SM (Clara, Chroma, Clara+Chroma), Spectra A and B) using 4 standardized aqueous scenarios. Twelve templates were done in order to simultaneously compare the same objective in the different modalities. Six urologists, five medical students, five urology residents, and five persons not involved with urology evaluated each video on a scale of 1 (very bad) to 5 (very good).

Results: Comparing white light to SM, subjects scored better the quality of Clara and Clara+Chroma than white light ($p=0.0139$ and $p<0.05$) and scored worse Spectra A and B ($p=0.0005$ and $p=0.0023$)). When comparing Clara to the other SM, it was ranked equivalent to Clara+Chroma ($p=0.67$) and obtained a higher rank than Chroma, Spectra A and B ($p<0.05$, $p=0.0001$ and $p=0.0001$). In the multivariate analysis mean scores were higher among urologists.

Conclusion: In all analyzed scenarios, the subjects ranked Clara and Clara+Chroma as the modalities with better image quality compared to white light.

ARTICLE INFO

Keywords:
Ureteroscopy; Diagnosis; Lithotripsy; Technology

Int Braz J Urol. 2017; 43: 476-80

Submitted for publication:
June 07, 2016

Accepted after revision:
September 15, 2016

Published as Ahead of Print:
March 13, 2017

INTRODUCTION

Since the arrival of digital ureteroscopy, several new technologies have been used to improve endoscopic vision. Examples of such technologies include the NBI™ system (Olympus®) (1); the photodynamic diagnosis (2) or the Storz Professional Image Enhancement System: Spies™ system (Karl-Storz®, Tuttlingen, Germany) integrated in the Karl-Storz® FlexXC™ ureteroscope that uses five different modalities of visual enhancement besides the standard white light. This system captures an image in white light through a red, green and blue (RGB) camera and performs a digital reprocessing to modify and generate the new image modality desired (3).

To date there is no evidence regarding which of the five modalities is better to improve diagnosis or treatment procedures, nor data comparing the modalities in terms of image quality; also, the company does not recommend its use for any specific situation (4).

The aim of this study was to evaluate and compare the image quality of the five Spies™ modalities (SM) to the standard white light in an in-vitro model.

MATERIALS AND METHODS

The Spies™ system, integrated in the FlexXC™ ureteroscope, uses five different modalities of visual enhancement to improve tumor diagnosis. Aside from the standard white light it uses the following modalities: Spectra A and B by color spectral separation using different color filter settings that allow better contrast between tissues, Clara: by manipulating the image brightness to achieve better views of dark spots, Chroma by increasing color contrast and Clara+Chroma by combining both (3).

To evaluate the image quality, two standardized grids or test patterns of colors and resolution specifically designed to test image quality (Edmund Optics, Barrington, NJ®) (5, 6) and 3 stones of different composition (monohydrate calcium oxalate, dehydrate calcium oxalate and uric acid) were used in 4 different standardized scenarios using the K-box™ simulator (Coloplast®): 110cc of saline solution, 110cc of sterile water, 110cc of saline solution mixed with 20cc of pure contrast and 110cc of saline solution mixed with 3cc of iodine solution 0.3%. A total of 72 videos were made after recording the three objects in all of the six modalities in the four scenarios. To conserve the image quality, the videos were made in high definition with a calibrated Karl-Storz® recording device.

Twelve templates were done randomizing the position of the videos to simultaneously compare the same objectives recorded in the different modalities (Figure-1) in order to perform an absolute scale of merit from 1 (very bad) to 5 (very good).

Figure 1 - Example of the templates used to evaluate the same object in the different scenarios.

1) Sharpness grid template in the different Spies modes in saline solution (**a:** White light, **b:** Clara, **c:** Chroma, **d:** Clara+Chroma, **e:** Spectra A, **f:** Spectra B).
2) Stone view template in the different Spies modes in Sterile Water (**a:** White light, **b:** Clara, **c:** Chroma, **d:** Clara+Chroma, **e:** Spectra A, **f:** Spectra B).
3) Stone view template in the different Spies modes in saline solution mixed with 3 cc of iodine solution. (**a:** White light, **b:** Clara, **c:** Chroma, **d:**Clara+Chroma, **e:** Spectra A, **f:** Spectra B).
4) Color grid template in the different Spies modes in saline solution with contrast. (**a:** White light, **b:** Clara, **c:** Chroma, **d:** Clara+Chroma, **e:** Spectra A, **f:** Spectra B)

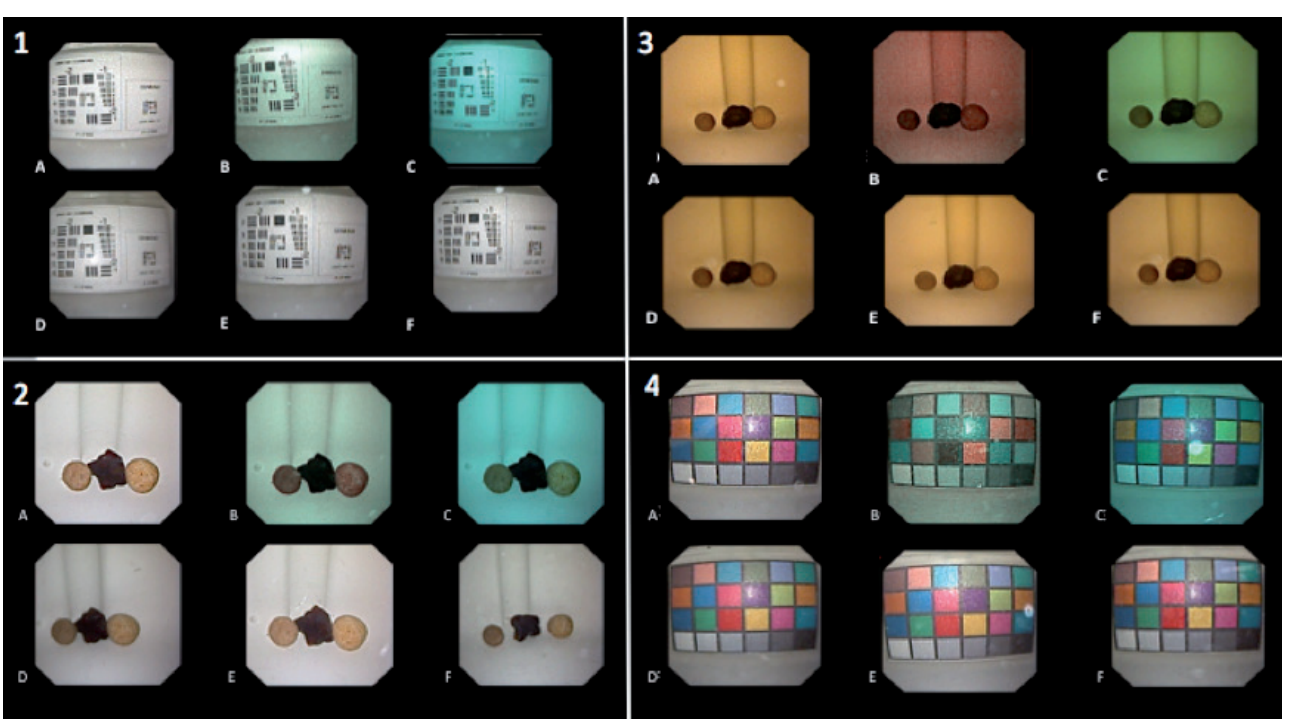


Image quality was measured subjectively as in real endoscopy. A random group of six urologists, five medical students, five urology residents, and five persons not involved with the ureteroscopic procedure evaluated each video and ranked the image quality. Subjects were asked to rate perceived image degradation, sharpness of the objects, and presence of artifacts that could distort the image. Scores were tabulated by the sum of the 1-5 score for each image with each solution.

Statistical analysis was performed with the STATA 13.0 software. A T Student's test and multivariate logistic regression analysis was employed to compare Spies™ versus standard white light as control. P<0.05 was considered statistically significant.

RESULTS

Eight females and 13 males evaluated the videos; the mean age was 37 years (22-56). Eleven subjects had a refractive error corrected with either glasses or contact lenses. The groups were homogeneous in terms of gender, age, profession and refraction errors. The mean score in terms of image quality for each modality was: White light: 40, Clara: 46, Chroma: 41, Clara+Chroma: 45, Spectra A: 29 and Spectra B: 31. When comparing white light with the SM the subjects scored better the quality of Clara and Clara+Chroma (p=0.0139 and p<0.05 respectively) and worse Spectra A and B (p=0.0005 and p=0.0023 respectively). When comparing Clara (the modality best ranked) and the other SM, the former was equivalent to Clara+Chroma (p=0.67) and obtained a higher rank than Chroma, Spectra A and B (p<0.05, p=0.0001 and p=0.0001 respectively). Results are summarized in Table-1.

In the subgroup where the quality of the view of the stones was ranked, Clara and Clara+Chroma modalities were ranked as the best, being better rated than white light (p=0.0001 and p=0.0001 respectively). The image quality of the stone video in Spectra A and B had a worse scoring than white light (p=0.0055 and p=0.0052 respectively). There were no statistical differences between the aqueous scenarios using the same SM (p>0.05). Results are summarized in Table-2.

In the multivariate analysis stratified by profession into urologist/residents and non-urologists (students, other), the mean scores were higher among the urologists (45 vs. 31, respectively). There were no differences between groups in terms of gender, corrected view or age.

DISCUSSION

Digital ureteroscopy has brought diverse advantages for diagnostic and treatment procedures. Aside from a clear improvement in the image quality when compared to fiber optics, it has shown a significant reduction of operative times when treating stones (7).

Another benefit of digital ureteroscopy is a set of the novel integrated tools that have been developed to enhance ureteroscopic visualization

Table 1 - Scores of all modalities.

Modality	Mean score	Score range	*White light vs. Spies Modalities	**Clara vs. Spies Modalities
White light	40	(19-60)		
Clara	46	(24-60)	p=0.0139	
Chroma	41	(19-60)	p=0.94	p < 0.05
Clara+Chroma	45	(29-60)	p< 0.05	p=0.6767
Spectra A	29	(12-58)	p=0.0005	p=0.0001
Spectra B	31	(12-58)	p=0.0023	p=0.0001

* Comparison between the Spies modes and white light

** Comparison between the Spies modes and Clara (The Spies mod best ranked)

Table 2 - Scores of all modalities when qualifying the stone images. Comparison between the Spies modes and white light.

Modality	Mean score	Score range	White light vs. Spies Modalities
White light	13	(4-20)	
Clara	17	(10-20)	p=0.0001
Chroma	13	(4-20)	p=1
Clara+Chroma	16	(10-20)	p=0.0001
Spectra A	10	(4-19)	p=0.0055
Spectra B	19	(4-20)	p=0.0052

through light absorption by increasing brightness and contrast or color spectral separation.

As conservative treatment can be offered to patients with upper urinary tract carcinoma with low grade, non-invasive and small tumors (8), there is an increasing interest in developing image enhancement machinery integrated into flexible ureteroscopes. The challenge of adequate diagnosis arises in cases of doubtful small and flat lesions where radiological and cytological evaluations may have low accuracy (3, 9, 10). For these situations, aside from Spies™, the NBI™ system (Olympus®) was developed specifically to increase tumor diagnosis accuracy, contrary to Spies™ in which the company does not recommend its use for any specific situation (4). In the upper urinary tract NBI™ system has initially demonstrated improved tumor detection rates by 22.7% compared to white light, however further evaluation is needed in order to recommend its daily clinical use (1, 11, 12). Likewise, to our knowledge there are no studies regarding the upper urinary tract tumor diagnosis with Spies™.

The SM best ranked overall was Clara and Clara+Chroma compared to white light and the other SM. Clara manipulates the image brightness, Chroma intensifies color contrast and Clara+Chroma combines both. As Chroma and Clara+Chroma theoretically increase sharpness (which means a more detailed image boundary, sharp and not blurred) an image with better quality may be perceived and could explain why it was considered better than the other modalities.

Spectra A and B looks for tissue differentiation by filtering color spectra. Spectra A filters red to remove the base redness of urothelium while gains contrast in the remaining colors. Spectra B decreases red spectrum while increasing the green and blue for the same purpose. Although a color grid was used to record the videos, the color accuracy was not evaluated as the two SMs are intended to modify it. In this study the image quality of Spectra A and B had the worse score compared to white light and the other SM (In both grid and stones evaluation). Although the system takes high definition images the digital manipulation of an image may decrease the image quality. This could explain the low image quality assessment, as in this process some distortion or artifacts may be seen in the image. As the Spectra modes are commonly used to compete with other technologies for tumor diagnosis, according to these results, further in vivo studies are needed to assess whether this image quality deterioration may decrease the probability of tumor diagnosis and/or stone treatment.

In the multivariate analysis stratified by profession into urologist/residents and non-urologists (students, other), the mean scores were higher among the urologists (45 vs. 31 respectively). The subjective perception of urologists based on personal experiences and the knowledge of fiber optic and digital scopes may influence this decision. Knowing the surgical intention of the image and what surgical skills could be achieved with it, even if the image is not impeccable could increase the evaluation points.

Further, presently there is an increasing amount of urologists that use the SM as a working device for tumor ablation and stone laser treatment as surgeons may feel more confortable with the new endoscopic vision of the object to treat. This is the reason why stones of different components were evaluated. Our findings in the subgroup where

the quality of the view of the stones was ranked may suggest that Clara and Clara+Chroma may be the best option for this purpose. This follows the company's concept that this tool can also be used to achieve a better image for treatment purposes.

A limitation of this study is that it was not initially intended to describe image quality in tumors specifically, but to give an overall evaluation of the quality of the system and to explore other possible uses. This preliminary study provides information for further in vivo assessments to evaluate whether the use of Spies™ may increase the effectiveness of endoscopic procedures including ureteroscopy, cystoscopy and percutaneous nephroscopy; either for stones or tumor treatments by increasing image quality.

CONCLUSIONS

In this in vitro study Clara and Clara+Chroma were ranked as the best Spies™ modalities with better image quality compared to white light or other Spies™ modalities. Spectra A and B had the lowest rates in all scenarios analyzed.

ACKNOWLEDGMENTS

The European Association of Urology supported Dr. Esteban Emiliani with the EUSP clinical fellowship program. Jeremie Berg, Hôpital Tenon, Paris, France, for his assistance with the experiments.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Traxer O, Geavlete B, de Medina SG, Sibony M, Al-Qahtani SM. Narrow-band imaging digital flexible ureteroscopy in detection of upper urinary tract transitional-cell carcinoma: initial experience. J Endourol. 2011;25:19-23.
2. Ahmad S, Aboumarzouk O, Somani B, Nabi G, Kata SG. Oral 5-aminolevulinic acid in simultaneous photodynamic diagnosis of upper and lower urinary tract transitional cell carcinoma - a prospective audit. BJU Int. 2012;110:E596-600.
3. Bus MT, de Bruin DM, Faber DJ, Kamphuis GM, Zondervan PJ, Laguna Pes MP, et al. Optical diagnostics for upper urinary tract urothelial cancer: technology, thresholds, and clinical applications. J Endourol. 2015;29:113-23.
4. Karl Storz FlecXc brochure: (Cited on 15 Mar 2017). available at. <https://www.karlstorz.com/cps/rde/xbcr/karlstorz_assets/ASSETS/3347684.pdf>
5. USAF 1951 Edmund Optics, Barrington, NJ. [cited 2015 Dec 23]. Available at. <http://www.edmundoptics.com/test-targets/resolution-test-targets/1951-usaf-glass-slide-resolution-targets/1790/>.
6. Color Checker Edmund Optics, Barrington, NJ. [cited 2015 Dec 23]. Available at.< http://www.edmundoptics.com/test-targets/color-gray-level-test-targets/x-rite-colorchecker/1815/>.
7. Somani BK, Al-Qahtani SM, de Medina SD, Traxer O. Outcomes of flexible ureterorenoscopy and laser fragmentation for renal stones: comparison between digital and conventional ureteroscope. Urology. 2013;82:1017-9.
8. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol. 2015;68:868-79.
9. Messer J, Shariat SF, Brien JC, Herman MP, Ng CK, Scherr DS, et al. Urinary cytology has a poor performance for predicting invasive or high-grade upper-tract urothelial carcinoma. BJU Int. 2011;108:701-5.
10. Sudakoff GS, Dunn DP, Guralnick ML, Hellman RS, Eastwood D, See WA. Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. J Urol. 2008;179:862-7.
11. Meyer F, Al Qahtani S, Gil-Diez de Medina S, Geavlete B, Thomas A, Traxer O. Narrow band imaging: description of the technique and initial experience with upper urinary tract carcinomas. Prog Urol. 2011;21:527-33.
12. Audenet F, Traxer O, Yates DR, Cussenot O, Rouprêt M. Potential role of photodynamic techniques combined with new generation flexible ureterorenoscopes and molecular markers for the management of urothelial carcinoma of the upper urinary tract. BJU Int. 2012;109:608-13.

Correspondence address:
Olivier Traxer, MD
Department of Urology
Tenon Hospital
Pierre and Marie Curie University
4 Rue de la Chine. 75020 Paris, France
Telephone: + 3 406 8589-9442
E-mail: olivier.traxer@aphp.fr

ORIGINAL ARTICLE

Vol. 43 (3): 481-488, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0643

Emergency percutaneous nephrostomy versus emergency percutaneous nephrolithotomy in patients with sepsis associated with large uretero-pelvic junction stone impaction: a randomized controlled trial

Chi-Sen Hsu [1], Chung-Jing Wang [2], Chien-Hsing Chang [2], Po-Chao Tsai [2], Hung-Wen Chen [3], Yi-Chun Su [3]

[1] Department of Infection, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.; [2] Division of Urology, Department of Surgery, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.; [3] Department of Emergency, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.

ABSTRACT

Introduction: A randomized trial was conducted prospectively to evaluate the efficacy, related complications, and convalescence of emergency percutaneous nephrolithotomy compared to percutaneous nephrostomy for decompression of the collecting system in cases of sepsis associated with large uretero-pelvic junction stone impaction.

Materials and Methods: The inclusion criteria included a WBC count of 10.000/mm^3 or more and/or a temperature of 38°C or higher. Besides, all enrolled patients should maintain stable hemodynamic status and proper organ perfusions. A total of 113 patients with large, obstructive uretero-pelvic junction stones and clinical signs of sepsis completed the study protocol. Of those, 56 patients were placed in the emergency percutaneous nephrostomy group, while the other 57 patients were part of the percutaneous nephrolithotomy group. The primary end point was the time until normalization of white blood cells (WBC) at a count of 10.000/mm^3 or less, and a temperature of 37.4°C or lower. The secondary end points included the comparison of analgesic consumption, length of stay, and related complications. Statistical analysis was performed using SPSS® version 14.0.1. The Mann-Whitney U test, chi-square test, and Fisher's exact test were used as appropriate.

Results: The length of hospital stays (in days) was 10.09±3.43 for the emergency percutaneous nephrostomy group and 8.18±2.72 for the percutaneous nephrolithotomy group. This set of data noted a significant difference between groups. There was no difference between groups in regard to white blood cell count (in mm^3), time to normalization of white blood cell count (in days), body temperature (in °C), time to normalization of body temperature (in days), C-reactive proteins (in mg/dL), time taken for C-reactive proteins to decrease over 25% (in days), procalcitonin (in ng/mL), or complication rates.

Conclusions: This study confirms that emergency percutaneous nephrolithotomy may be as safe as early percutaneous nephrolithotomy in a selected low risk patients with sepsis-associated large, obstructive stone.

ARTICLE INFO

Keywords:
Sepsis; Nephrostomy, Percutaneous; complications [Subheading]

Int Braz J Urol. 2017; 43: 481-8

Submitted for publication:
November 11, 2015

Accepted after revision:
December 03, 2016

Published as Ahead of Print:
January 18, 2017

INTRODUCTION

Although urolithiasis is one of the most common urological diseases, it can be lethal when a urinary tract infection associated with obstructive uropathy due to upper urinary tract calculi results in bacteremia and sepsis (1). The efficacy of percutaneous nephrostomy and retrograde ureteral catheterization in decompressing the collecting system has been firmly established (2, 3). Furthermore, the high success and low complication rates of these drainage procedures have made both alternatives attractive to radiologists and urologists. Percutaneous nephrolithotomy (PCNL) remains the important contraindication for large renal calculi with untreated urinary tract infections (UTI) (4). Antegrade lithotripsy is generally not advocated for patients who are severely ill (5). However, advances in endoscopic instruments and techniques and surgeon's familiarity with the procedure have significantly shortened operation times and increased the success rate. A randomized trial was conducted with its focus being evaluation of the efficacy, related complications, and convalescence of emergency percutaneous nephrolithotomy compared to percutaneous nephrostomy for decompression of the collecting system in cases of sepsis associated with large uretero-pelvic junction stone impaction.

MATERIALS AND METHODS

The study was approved (STM No. 06B-008) and its related work was undertaken in Chia-Yi city and overseen by our Institutional Review Board at St. Martin De Porres Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients were asked to sign an informed consent form before granting their participation. The study was designed to be a randomized, controlled trial and was carried out from January, 2007 to July, 2013. A sample size of 45 patients was required in order to detect a 30% difference in the proportions of the trial parameters (e.g. complication rates, such as time until WBC normalization at 10.000/mm^3 or less and a temperature of 37.4°C or lower, length of stay) in the treatment groups at a significance level of 0.05 and a power of 80%. Adult patients admitted to the emergency room or to the hospital with large (>20mm), obstructive uretero-pelvic junction stones and clinical signs of sepsis were asked to participate in this randomized study. The inclusion criteria included a WBC count of 10.000/mm^3 or more and/or a temperature of 38°C or higher. Besides, all enrolled patients should maintain stable hemodynamic status and proper organ perfusions. Patients were excluded from the study if they had uncorrected coagulopathy, urinary diversion, pregnancy, a solitary kidney, severe sepsis, septic shock, and an unwillingness or were otherwise unable to commit to the study's follow-up protocol.

Preoperative and admission-related data included urinalysis, urine culture, blood culture, complete blood count, biochemistry study, renal ultrasound, plain kidney-ureter-bladder X-film, intravenous urography, and whole abdominal computed tomography (CT) were obtained and evaluated upon admission. Intraoperative findings, stone composition, and outcome were also recorded. Stone length was calculated according to the longest diameter, and the stone burden was calculated by multiplying its length by its width. The stone-free rate and position of double-J were assessed postoperatively using plain kidney-ureter-bladder X-film and non-contrast computerized tomography before removal of nephrostomy tube.

All patients were initially given empirical parenteral antibiotics, which included first to fourth generation cephalosporins, aminoglycosides, quinolones, monobactams, and penicillins upon admission. The parenteral antibiotics were shifted to appropriate ones according to the results of urine culture till the signs of infection subsided. Patients were prescribed oral Ketorolac 10mg three times per day to minimize urinary tract symptoms as needed, and allowed the use of sublingual buprenorphine 0.2mg on demand as needed. Overall dosages were documented and compared. Patients were randomized to re-

ceive emergency percutaneous nephrolithotomy or percutaneous nephrostomy according to a random numbers Table. The primary end point was the time taken until WBC normalization at 10.000/mm^3 or less and a temperature of 37.4^{o}C or lower. The secondary end points were the comparison of analgesic consumption, length of stay, and related complications.

In the emergent percutaneous nephrolithotomy group, patients were placed in a prone position under endotracheal general anesthesia. All procedures were performed under sonographic guidance along the middle or upper calyx without retrograde ureteric catherization, and by percutaneous nephroscope (20.8Fr. Wolf) combined with 30Fr. Amplatz sheath, low pressure continuous normal saline irrigation, and the lithoclast (0.8mm probe, Swiss LithoClast®) to disintegrate the stones. The nephroscope ensued under direct vision after consecutive dilatation of the percutaneous nephrostomy tract. Simultaneously, lithotripsy was performed by hitting the stone's center, breaking it into pieces as small as possible, and using the probe tip as the reference. When fragment size was deemed small enough, fragments were then retrieved from the uretero-pelvic junction under direct vision with a nephroscopic grasper. Surgery was concluded when no fragments remained in the entirety of the uretero-pelvic junction. Double-J ureteral stent and nephrostomy tube were placed routinely and double-J ureteral stent was left indwelling for two weeks. All procedures were performed by the same urologist to ensure uniform skill and experience level. Operation time was recorded starting from the insertion of percutaneous nephrostomy puncture needles until the placement of the nephrostomy tube.

In the emergency percutaneous nephrostomy group, emergency percutaneous nephrostomy (14Fr. nephrostomy tube) was performed in the angiography suite by a board-certified interventional radiologist using sonographic guidance with the patient under local anesthesia. Elective percutaneous nephrolithotomy was performed within 72 hours of diagnosis if the patient was hemodynamically stable (blood pressure of more than 110/60mmHg, heart rate of no more than 90 beats per minute, respiratory rate of no more than 20 breaths per minute and renal function within normal limits) after the initial parenteral antibiotics treatment.

All the enrolled patients were discharged after confirmation of double-J ureteral stent in situ and disappearance of all signs of infection (WBC normalization less than 8.000/mm3 and body temperature lower than 37.4^{o}C).

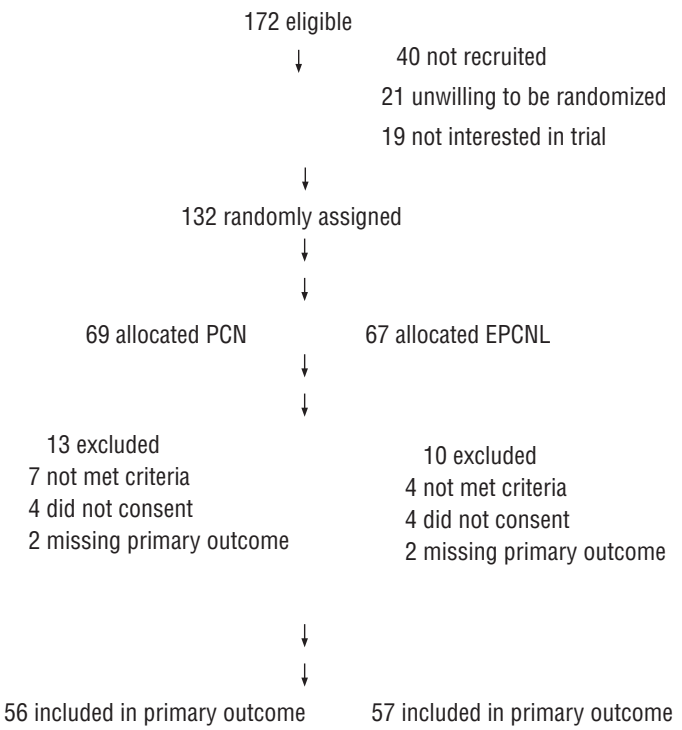
Statistical analysis was performed using SPSS® version 14.0.1. The Mann-Whitney U test, chi-square test, and Fisher's exact test were all used as appropriate. P-values lower than 0.05 were considered significant.

RESULTS

A total of 172 patients were eligible and prospectively randomized into two groups before they entered the operation room. In the percutaneous nephrostomy group, a total of 69 patients were available for consideration. Among the 69 patients, 7 did not meet the inclusion criteria with stable hemodynamic status and proper organ perfusions, and an additional 4 refused to sign the consent forms and were removed from the study. In all, a total of 58 patients were enrolled and received emergency percutaneous nephrostomy. Elective percutaneous nephrolithotomy treatment within 72 hours of diagnosis was made available if patients were deemed hemodynamically stable after their initial parenteral antibiotics treatment. In the emergency percutaneous nephrolithotomy group, a total of 67 patients were available. Among the 67 patients, 4 did not meet the inclusion criteria with stable hemodynamic status and proper organ perfusions, and an additional 4 refused to sign the consent forms and were removed from the study. In all, a total of 59 patients were enrolled and received emergency percutaneous nephrostomy. In both groups, there were 2 patients who were eventually unable to receive their allocation of treatment due to an inability to follow-up post-randomization. Thus, analysis was done with 56 and 57 patients as the denominator in each randomization arm (Figure-1).

No significant statistical difference was observed in patient age, gender distribution, body mass index, stone size, stone burden, stone

Figure 1 - Summary of study disposition.



Numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow.

composition, stone laterality, operation times, or infected organisms (Table-1).

The length of hospital stays (in days) was 10.09±3.43 for the emergency percutaneous nephrostomy group and 8.18±2.72 for the percutaneous nephrolithotomy group. This set of data noted a significant difference between groups (Table-2). There was no difference observed between groups with regard to white blood cell count (mm^3), time to normalization of white blood cell count (in days), body temperature (in ^oC), time to normalization of body temperature (in days), C-reactive proteins (in mg/dL), time taken for C-reactive proteins to decrease over 25% (in days), procalcitonin (in ng/mL), or complication rates (thrombocytopenia) (Table-2). However, analgesic consumptions were 30.89±10.83 in the emergency percutaneous nephrostomy group and 39.82±14.45 in the percutaneous nephrolithotomy group, with a significant difference. No patients suffered from postoperative exacerbation of the clinical condition and there were no postoperative mortalities in our study. All the uretero-pelvic junction stones were evacuated completely. The status of stone free was defined as total absence of residual stones and confirmed by non-contrast computerized tomography.

DISCUSSION

According to the European Association of Urology Guidelines on Urolithiasis (4), a large, obstructive renal stone with all signs of urinary tract infection is an urological emergency. Urgent decompression is often necessary to prevent further complications in infected kidneys presenting with hydronephrosis, secondary to stone-induced, unilateral, or bilateral renal obstructions. Currently, two options exist for urgent decompression of obstructed collecting systems: placement of an indwelling ureteral stent, or percutaneous placement of a nephrostomy

Table 1 - Patients Demographics and Perioperative Data.

Characteristic	PCN group N=56	EPCNL group N=57	P value
Age (year) [a]			**0.462**
Mean	58.91±11.18	58.12±12.53	
Range	33-76	39-89	
Gender [b]			**0.751**
Male	36 (64.29)	35 (61.40)	
Female	20 (35.71)	22 (38.60)	
Body mass index [a]	25.49±2.69	25.13±2.79	0.503
Male [a]	25.54±2.72	25.46±2.38	0.958
Female [a]	25.41±2.70	24.60±3.33	0.266
Stone sizes(mm)			
Length(mm) [a]	24.88±2.79	25.47±3.80	0.901
Width(mm) [a]	15.04±4.23	14.40±2.61	0.815
Stone burden [a]	376.68±127.34	366.46±81.98	**0.654**
Laterality [b]			**0.774**
Right	30 (53.57)	29 (50.88)	
Left	26 (46.43)	28 (49.12)	
Operative times (mins) [a]	33.43±6.13	33.96±.31	0.647
Culture organisms [c]			**0.997**
Escherichia coli	18 (32.14)	17 (29.82)	
Proteus mirabilis	8 (14.29)	9 (15.79)	
Pseudomonas aeruginosa	8 (14.29)	9 (15.79)	
Staphylococcus aureus	4 (7.14)	6 (10.53)	
β-Hemolytic Streptococcus species	2 (3.57)	1 (1.75)	
Candida albicans	2 (3.57)	2 (351)	
Multiple organisms	2 (3.57)	3 (5.26)	
Negative cultures	12 (21.43)	10 (17.54)	
Appearance of kidney urine			**0.886**
Cloudy	2 (3.57)	3 (5.26)	
Turbid	23 (41.07)	24 (42.11)	
Blood-stained	12 (21.43)	13 (22.81)	
Purulent	19 (33.93)	18 (31.58)	

Values are presented as mean±standard deviation or number (%); [a] Mann-Whitney U test; [b] Chi-square test; [c] Fisher's exact test

Table 2 - Surgical Results and Complications.

	PCN group	EPCNL group	P value [a]
Length of hospital stay(days)	10.09±3.43	8.18±2.72	0.001**
Respiration rate(time/min)	27.65±21.28	28.01±21.36	087
Pulse rate(beats/min)	94.24±22.57	95.03±23.04	0912
White blood count (mm^3)	21760.71±7137.20	21420.68±5730.93	0.968
Time to normalization of White blood count (days)	4.89±1.71	4.30±1.46	0.062
Body temperature (ºC)	39.59±0.85	39.61±0.80	0.689
Time to normalization of body temperature (days)	2.63±1.38	2.49±1.44	0.438
C-reactive protein (mg/dL)	66.22±26.49	64.11±27.43	0.520
C-reactive protein decreased over 25% (days)	3.11±1.09	3.37±1.05	0.159
Procalcitonin (ng/mL)	26.98±20.78	25.89±28.72	0.240
Ketorolac (mg)	30.89±10.83	39.82±14.45	0.001**
Buprenorphine dosage (mg)	0.26±0.80	0.08±0.15	0.013*
Complications			
Thrombocytopenia [b]	8 (14.29)	6 (10.53)	0.544

Values are presented as mean±standard deviation or number (%).
*p<0.05; **p<0.01
[a] Mann-Whitney U test; [b] Chi-square test

tube. For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective. It is recommended that for sepsis presenting with obstructive stones, it is urgent for the collecting system to be decompressed, using either percutaneous drainage or ureteral stenting. Definitive treatment of the stone should be delayed until sepsis is resolved.

We conducted this randomized trial in order to evaluate the efficacy, related complications, and convalescence of emergency percutaneous nephrolithotomy when compared to percutaneous nephrostomy for decompression of the collecting system in cases of sepsis associated with large uretero-pelvic junction stone impaction. In our study, the inclusion criteria were broad enough to encompass cases with positive and negative cultures. Blood cultures may not always return positive for septicemia due to a variety of factors including fastidious organisms, prior antimicrobial therapy, growth inhibitory factors in the blood, and sampling error. Emergency percutaneous nephrolithotomy did not increase the incidence of complication rates (10.53%), and was lower when compared with the 14.29% incidence rate of percutaneous nephrostomy. The length of hospital stay was notably lower in the emergency percutaneous nephrolithotomy group. On the other hand, consumption of analgesics was notably lower in the emergency percutaneous nephrostomy group. As for the clinical normalization of index parameters (time until normalization of white blood cell count, body temperature, time until normalization of body temperature, C-reactive protein decrease of over 25%, and procalcitonin), there was no significant difference observed between the groups. It can be concluded, therefore, that emergency percutaneous nephrolithotomy neither leads to increased bacteremia nor is it significantly more hazardous when dealing with issues of acute obs-

truction. Besides, the superiority of emergency PCNL over emergency percutaneous nephrostomy includes obviation of multiple procedures, morbidities associated with ureteral stents or nephrostomy tubes, risk associated with drainage procedure, etc.

Traditionally, percutaneous nephrolithotomy has been contraindicated in unstable patients with sepsis because internal instrumentation is not advocated for such patients. Percutaneous nephrolithotomy, on the other hand, may be contraindicated or should be performed with extra care in patients presenting with bleeding diathesis (disseminated intravascular coagulopathy, severe thrombocytopenia, or prolonged prothrombin and partial thromboplastin times), cardiopulmonary insufficiency resulting in aggravation of respiratory symptoms when placed in a prone position, severe spinal dysraphism, and other causes of an abnormal body habitus, ectopic kidneys, and retrorenal colon. Lee et al. reports that 65 of 69 (94.2%) patients with urosepsis improved dramatically following percutaneous drainage (6). In our sample, all patients treated with percutaneous nephrolithotomy improved postoperatively. Lang and Price report a mortality rate of 8% after emergency percutaneous nephrostomy and 12% for surgical treatment of urosepsis secondary to obstruction (7). Even though a direct comparison cannot be made because their study was performed 30 years ago, there were no deaths after percutaneous nephrolithotomy in our study.

Fortunately, all the uretero-pelvic junction stones were evacuated completely. The status of stone free was achieved and confirmed by non-contrast computerized tomography. Although we achieved positive results with emergency percutaneous nephrolithotomy for obstructive uretero-pelvic junction stones, our study limitations involved the exclusion of patients with a single uretero-pelvic junction stone combined with multiple renal stones, uncorrected coagulopathy, and unstable hemodynamic sepsis. Emergency percutaneous nephrolithotomy is still contraindicated in bleeding diathesis, tumor in the presumptive access tract area, potential malignant kidney tumor, and pregnancy. Low risk patients with initial favorable response to treatment is the group to offer emergency PCNL.

Systemic inflammatory response syndrome (SIRS) defines a clinical response to a nonspecific insult of either infectious or noninfectious origin. SIRS is determined in the presence of two or more of the following variables: an elevated temperature over 38.0°C, a subnormal temperature below 36.0 °C, a heart rate greater than 90 beats per minute, a respiratory rate greater than 20 breaths per minute, PaCO2 below 32 Torr, a white blood cell count over 12.000/mm^3 or under 4.000/mm^3, or over 10% immature (band form) forms (8-14). Sepsis is the systemic response to infection and is defined as the presence of SIRS in addition to a documented or presumed infection.

CONCLUSIONS

This study confirms that emergency percutaneous nephrolithotomy may be as safe as early percutaneous nephrolithotomy in a selected low risk patients with sepsis-associated large, obstructive stone.

ABBREVIATIONS

PCN = Percutaneous Nephrostomy
PCNL = Percutaneous Nephrolithotomy
CT = computed tomography
UTI = urinary tract infections

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Amano T, Matsui F, Takashima H, Takemae K. [Analysis of patients with septic shock due to urosepsis brought on by ureteral calculi]. Hinyokika Kiyo. 2003;49:1-4.
2. Ramsey S, Robertson A, Ablett MJ, Meddings RN, Hollins GW, Little B. Evidence-based drainage of infected hydronephrosis secondary to ureteric calculi. J Endourol. 2010;24:185-9.
3. Lynch MF, Anson KM, Patel U. Percutaneous nephrostomy and ureteric stent insertion for acute renal deobstruction. Consensus based guidelines. Br J Med Surg Urol 2008;1;120-5.

4. Türk C, Knoll T, Petrik A, Sarica K, Skolarikos A, Straub M, Seitz C. EUA Guidelines on Urolithiasis p21, 2015.available at >http://uroweb.org/wp-content/uploads/22-Urolithiasis_LR_full.pdf>
5. Thuroff JW, Gilfrich CP. Percutaneous endourology and ureterorenoscopy; in Tanagho EA,McAninch JW (eds): Smith's General Urology,ed 16. New York, McGraw-Hill. 2000; pp. 121-139.
6. Lee WJ, Patel U, Patel S, Pillari GP. Emergency percutaneous nephrostomy: results and complications. J Vasc Interv Radiol. 1994;5:135-9.
7. Lang EK, Price ET. Redefinitions of indications for percutaneous nephrostomy. Radiology. 1983;147:419-26.
8. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644-55.
9. Hayden WR. Sepsis and organ failure definitions and guidelines. Crit Care Med. 1993;21:1612-3.
10. Young GB, Bolton CF, Austin TW. Definitions for sepsis and organ failure. Crit Care Med. 1993;21:808.
11. Ackerman MH. The systemic inflammatory response, sepsis, and multiple organ dysfunction: new definitions for an old problem. Crit Care Nurs Clin North Am. 1994;6:243-50.
12. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250-6.
13. Zhao H, Heard SO, Mullen MT, Crawford S, Goldberg RJ, Frendl G, et al. Na evaluation of the diagnostic accuracy of the 1991 American College of Chest Physicians/Society of Critical Care Medicine and the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society sepsis definition. Crit Care Med. 2012;40:1700-6.
14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.

Correspondence address:
Chung-Jing Wang, MD
Division of Urology
Saint Martin De Porres Hospital
Chiayi, Taiwan, R.O.C
Fax: + 886 52 788-535
E-mail: jing@stm.org.tw

ORIGINAL ARTICLE

Vol. 43 (3): 489-495, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0451

Hyberbaric oxygen as sole treatment for severe radiation – induced haemorrhagic cystitis

Athanasios Dellis [1], Athanasios Papatsoris [2], Vasileios Kalentzos [3], Charalambos Deliveliotis [2], Andreas Skolarikos [2]

[1] 2nd Department of Surgery, National and Kapodistrian University of Athens, Aretaieion Academic Hospital, Greece; [2] 2nd Department of Urology, University of Athens, Sismanoglio General Hospital, Athens, Greece; [3] Department of Diving and Hyperbaric Oxygen, Naval and Veterans Hospital, Athens, Greece

ABSTRACT

Purpose: To examine the safety and efficacy of hyperbaric oxygen as the primary and sole treatment for severe radiation-induced haemorrhagic cystitis.
Materials and methods: Hyperbaric oxygen was prospectively applied as primary treatment in 38 patients with severe radiation cystitis. Our primary endpoint was the incidence of complete and partial response to treatment, while the secondary endpoints included the duration of response, the correlation of treatment success-rate to the interval between the onset of haematuria and initiation of therapy, blood transfusion need and total radiation dose, the number of sessions to success, the avoidance of surgery and the overall survival.
Results: All patients completed therapy without complications with a mean follow-up of 29.33 months. Median number of sessions needed was 33. Complete and partial response rate was 86.8% and 13.2%, respectively. All 33 patients with complete response received therapy within 6 months of the haematuria onset. One patient needed cystectomy, while 33 patients were alive at the end of follow-up.
Conclusions: Our study suggests the early primary use of hyperbaric oxygen for radiation-induced severe cystitis as an effective and safe treatment option.

ARTICLE INFO

Keywords:
Urinary Bladder; Cystitis; Hematuria; Oxygen Inhalation Therapy

Int Braz J Urol. 2017; 43: 489-95

Submitted for publication:
August 08, 2016

Accepted after revision:
October 01, 2016

Published as Ahead of Print:
March 13, 2017

INTRODUCTION

The use of hyperbaric oxygen (HBO) as a treatment modality of radiation-induced lesions is not new, while about a decade ago the European Society for Therapeutic Radiology and Oncology and the European Committee for Hyberbaric Medicine underlined the indications of HBO in the treatment of radio-induced manifestations in normal tissue (1), including the prevention of osteoradionecrosis after dental extraction, the treatment of mandibular osteoradionecrosis in combination with surgery and the treatment of haemorrhagic cystitis resistant to conventional treatments. There are several studies published on HBO therapy for radiation cystitis, but most of them have discrepancies regarding their design and methodology since they are retrospective and not randomized or comparative; they lack control group and HBO is used as a secondary treatment. Herein, we present our updated results of a study, whose initial results concerning patients recruited until 2010 have been already published (2). Our present study includes the first and sole prospective series on HBO therapy of severe radiation cystitis in patients who have not received any previous treatment.

MATERIALS AND METHODS

Inclusion/Exclusion criteria

Since September 2007 we have prospectively enrolled 38 patients with severe radiation cystitis (initially grade IV post-radiation haematuria, according to the RTOG and the EORTC acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis) (Table-1) (3). All patients enrolled suffered from severe haemorrhagic cystitis with haematuria requiring transfusion. All patients should have only had a urethral catheter and bladder irrigation as initial and unique treatment of their radiation-induced haemorrhagic cystitis and may have started transfusions prior to HBO therapy. Patients with severe emphysema or other severe chronic obstructed airway disease, a history of spontaneous pneumothorax, of tympanic membrane spontaneous perforation or otological reconstruction were excluded from our study, as well as patients with active viral infection, history of treatment with cisplatin or doxorubicin, active bladder malignancy and uncorrected bleeding disorders.

Evaluation and Treatment

On admission to hospital all patients underwent the standard laboratory examinations (2) including full blood count and complete clotting and biochemistry profile measurements. Urine samples were examined for common urinalysis, urine culture and cytology. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen was scheduled for staging purposes and to exclude other bladder pathology. All patients underwent cystoscopy under anesthesia and bladder biopsies were taken by one surgeon (A.D) to confirm histological changes consistent with radiation cystitis and to exclude bladder malignancy. A large diameter urethral catheter (22F-24F) was placed to secure prompt bladder irrigation.

All patients were initially scheduled to receive 30HBO sessions in a walk-in multi-place hyberbaric chamber with intend to increase them up to 45 sessions until the haematuria resolved. According to the routine protocol of our department, all patients are planned to receive 100% oxygen at a 1.8 atmospheres absolute pressure per session for 90 minutes per day, five days a week - Monday to Friday. When complete response to HBO was reached the treatment was ceased. In case of worsening or relapse of haematuria during follow-up, HBO therapy was re-initiated under the same schedule. In case no benefit was gained from the initial treatment, more than 45 treatments were needed, severe complications occurred, or if patients declined

Table 1 - Classification of haematuria events for both acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis (3).

	Radiation morbidity	
Haematuria morbidity	Acute* (RTOG**)	Late* (RTOG/EORTC***)
Grade I	NA	Minor telangiectasia (microscopic haematuria)
Grade II	NA	Generalized telangiectasia (macroscopic haematuria)
Grade III	Gross haematuria with or without clot passage	Severe generalized telangiectasia (frequent macroscopic haematuria)
Grade IV	Haematuria requiring transfusion	Severe haemorrhagic cystitis
Grade V	Death from uncontrolled haematuria	Death from uncontrolled haematuria

s*Acute morbidity defined as treatment related complications occurring within 90 days from first radiotherapy session
**RTOG: Radiation Therapy Oncology Group
***EORTC: European Organization for Research and Treatment of Cancer

further therapy, HBO was considered as a failure and patients were referred for further treatment (conservative or surgical).

Within 4 weeks of treatment completion, all patients underwent cystoscopy under anesthesia by the same surgeon to confirm treatment result and/or to compare with the pre-treatment status. Bladder biopsy was performed in only 19 initial patients and was further abandoned, because pathology reports were stable and we considered we should therefore avoid any morbidity. This procedure was further reserved only for patients with subjectively abnormal bladder mucosa.

Study endpoints

Primary endpoint was the success rate measured by the incidence of complete and partial response to treatment. Complete response was defined as the complete cessation of bleeding and the lack of need for transfusion in combination with the disappearance of endoscopic findings and concomitant normal bladder findings in repeat biopsies where available. Partial response was defined as a decrease in the grade of RTOG/EORTC scoring criteria, the existence of microscopic haematuria or the persistence of mild macroscopic haematuria not requiring transfusion or other urgent treatment. Secondary endpoints include the duration of HBO response without the need for further treatment, the number of sessions needed to achieve success, the avoidance of surgery and the overall survival.

Statistical analysis

Descriptive statistics and comparisons were made using the SPSS 16 (SPSS Inc. Chicago IL) statistical package with $p<0.05$ being significant. Statistical analysis was performed using the chi-square and t test, as appropriate.

RESULTS

Since September 2007 thirty-eight patients (thirty-three men and five women) were enrolled in our study. Mean patient age was 70.3 years (range 56 to 82). Indications for radiation therapy included prostate cancer for twenty-eight, muscle-invasive bladder cancer for seven, rectal cancer for one and cervical cancer for two patients. Mean radiation dose was 63.8Gys (range 32 to 80), while there were no data available in 3 patients. Mean interval between completion of radiation therapy and onset of haematuria was 21.4 months (range 1 to 210). Mean interval between completion of radiation therapy and the onset of HBO therapy was 24.7 months (range 2 to 212 months). Mean time interval between the onset of the hematuria to the HBO treatment was 5.4 months (range 1-48). Mean transfusion need prior to and during the treatment was 7.6 red blood cells packs (range 3 to 16). In particular, 11 patients were transfused with up to 6 units and 27 patients with more than 6 units.

Pre-treatment patient evaluation revealed no bladder infection or tumour in any case. Pathology reports were stable and included histological findings consistent with post-radiation cystitis in all cases; that were: diffuse mucosal edema, vascular telangiectasia, submucosal haemorrhage and interstitial or smooth muscle fibrosis. Severe ischemia of the bladder wall as a result of obliterative endarteritis, was also occasionally present.

All patients completed HBO therapy without experiencing any severe HBO-related complications and were followed-up for a mean period of 29.3 months (range 3 to 94). Mean HBO therapy sessions were 33 (range 20 to 78). Thirty-three patients (86.8%) had complete response while five patients (13.2%) experienced partial response with marked improvement in their haematuria (grade II). For the thirty-three patients with complete response who received HBO therapy within 6 months of the haematuria onset, the mean time interval was 4.9 months (range 1-6), while in the remaining five patients with partial response the mean time interval was 22 months (range 8-48) ($p<0.001$). All demographics and results of our study are detailed in Table-2. One patient from the complete response group had a recurrence of grade II haematuria at 6 months of follow-up and received 18 additional HBO treatments. All aforementioned patients with complete response remained stable for the rest of the follow-up. Three patients with partial response received 15 additional treatments and they had not had haematuria since then. The

Table 2 - Demographics and results of our study on hyperbaric therapy in the treatment of radiation-induced bladder complications.

	n
Patients	38
Men	33
Women	5
Age (years)	70.3 (56-82)*
Indications	
Prostate Cancer	28
Muscle-Invasive Bladder Cancer	7
Rectal Cancer	1
Cervical Cancer	2
Radiation Dose (Gys)	63.8 (32-80)*
Not Available Data	3
Interval Between haematuria to HBO (months)	5.4 (1-48)*
Interval between Radiotherapy to haematuria (months)	21.4 (1-210)*
Interval between radiotherapy to HBO (months)	24.7 (2-212)*
Transfusion	7.6 (3-16)*
≤6 units	11
>6 units	27
Follow-up (months)	29.3 (3-94)*
HBO sessions	33 (20-78)*
Response	
Complete	33 (86.8%)
Partial	5 (13.2%)

*mean (range)

two last patients experienced severe haematuria 6 months after the end of HBO therapy and following a full consent one underwent cystectomy and urinary diversion, while the other was offered a successful embolisation with sporadic episodes of low severity macroscopic haematuria since then.

Post-hyperbaric treatment cystoscopy revealed a subjectively normal bladder mucosa in thirty two patients, which was confirmed by a histologically normal mucosa in 17 of the patients who had complete response. The embolised patient showed improved but persistent findings of radiation cystitis. The pathologic examination of the cystectomy specimen revealed, apart from findings of radiation cystitis, a transitional T2G3 muscle invasive bladder cancer (MIBC).

Regarding our study endpoints, complete response rate was 86.8% and partial response rate was 13.2%, giving an overall success rate of primary therapy of 100%. It should be underlined that all 33 patients with complete response received HBO therapy within 6 months of the haematuria onset compared to the remaining 5 patients with partial response who received HBO therapy ranging from 8 to 48 months from the haematuria onset. Thirty-three patients were alive at the end of follow-up.

DISCUSSION

Pelvic radiation may result in either acute or chronic bladder injuries (4) that lead to radiation-induced haemorrhagic cystitis, in 5-10% of cases (5). Bladder complications may occur within two months to more than twenty years following completion of pelvic radiotherapy (1, 6) with haemorrhage being present in 9% of cases (1).

Severe RTOG/EORCT grade III or worse bladder morbidity has been reported at 1% at 5 years, 1.4% at 10 years and 2.3% at 20 years following radiotherapy for cervical cancer (7). Radiation for prostate cancer may lead to moderate or severe haematuria in 3-5% of cases (8).

Traditionally, severe radiation cystitis has been treated in various ways (1). Continuous or intermittent bladder irrigation with large bore catheters usually constitutes the first-line treatment. Intravesical instillations with alum, silver nitrate, phenol, formalin or hyaluronic acid have been used as a second-line treatment, while the third-line therapy is consisted of several oral and intravenous agents, such as aminocaproic acid, traxenamic acid, corticosteroids, estrogens, antibiotics, prostaglandins and sodium pentosan-polysulphate. These agents are administered either concomitantly with first or second-line treatment options or as a pure third-line treatment. Unfortunately, traditional treatments are not well validated in terms of efficacy and constitute results from non-randomized trials in most of the cases grossly underpowered. Furthermore, there are no prospective studies comparing oral, intravesical and intravenous treatments between them or with HBO, apart from one randomized study between

intravesical hyaluronic acid instillation and HBO therapy with similar results (9). However, all these treatments do not cure the radiation-induced cystitis, nor prevent recurrence of severe haematuria. Moreover, some of them may have serious systematic side effects or may exacerbate bladder fibrosis which was initiated by radiation treatment, leading to a small-capacity low-compliant urinary bladder (1, 8, 10-17). More than a decade ago, a Cochrane Database systematic literature review on non-surgical interventions for late radiation cystitis in patients who underwent radical radiotherapy to the pelvis concluded that in the absence of randomized controlled studies it is impossible to set definitive rules for treatment (5). Recently, there have been reports of KTP laser use in an attempt of haemostasis with minimal mucosal destruction with promising results as a final step before definitive treatment (18, 19). In case of intractable haemorrhage, arterial embolization or ligation and/or cystectomy represent definitive treatment, at the cost of increased morbidity.

Urothelial cellular changes due to radiotherapy are caused by water radiolysis. This results in increase of activated free oxygen radicals that cause cell-membrane injury by lipid peroxidation and immediate cell death. Furthermore, DNA damage caused directly by radiation energy per se and indirectly by free oxygen radicals results in replication failures and further cell death (20). Additionally, pelvic radiotherapy initially causes mucosal edema and inflammation. Telangiectasia, submucosal haemorrhage and interstitial fibrosis may follow. Obliterative endarteritis of small blood vessels leads to acute and chronic ischemia of the bladder wall and eventually to smooth muscle fibrosis due to cellular hypoxia. The later chronic endarteritis is successfully described as "the three-H model" (21, 22).

Hyperbaria related to HBO therapy increases bladder's tissue oxygen tension (17). Hyperoxia enhances neovascularization and growth of normal tissue (8, 23). Angiogenesis is stimulated by tissue macrophages responding to the steep oxygen gradient. Interestingly, the tissue oxygen remains almost in normal levels for many years following HBO therapy, implying that the hyperoxia-induced angiogenesis is essentially permanent (8).

Vasoconstriction and cease of bleeding as well as improvements of tissue healing and immune function constitute additional beneficial effects of HBO (23).

The use of HBO should not be thought as a treatment modality that cures everything although there are cases where irrelevant improvements to HBO therapy have been reported (24). Especially, as far as radiation-induced haemorrhagic cystitis is concerned, several series of patients treated with HBO have been published (6, 8, 10-17, 21, 25-30). The vast majority are retrospective reviews and case series with only a few ones (6, 17, 26, present study) being prospective in nature. Furthermore, a recent review raised concerns on whether HBO therapy shows clear clinical benefit on radiation cystitis (25). In all these studies HBO was used as a secondary treatment option. In experimental setting (23) HBO may correct the underlying pathophysiology of radiocystitis, leading to permanent cure.

To the best of our knowledge, our study is the first and sole prospective study on only severe haematuria patients. It is the first study using HBO as primary therapy for radiation-induced cystitis and the first in which post-treatment cystoscopic and histologic findings were included as study's endpoints. Furthermore, apart from the absolute overall success rate of HBO as primary therapy, complete response rate in 86.8% of cases is the highest in literature. The highest efficacy of our suggested method is further amplified by the fact that patients are stable with no or minor radiotherapy--induced morbidity for a relatively long follow--up period. As a result, we can therefore conclude that primary treatment of severe post-radiation haemorrhagic cystitis with HBO has proved to be effective and safe both for the bladder structure itself and for patients and should be underlined that none of our patients had to discontinue HBO therapy due to HBO side effects. Initiation of therapy within 6-months of haematuria onset seems to be of utmost benefit, since in this early setting HBO therapy is assumed to break the vicious circle of chronic sloughing and resultant scarring in cases of hypoxic irradiated bladder tissues (16). Finally, we support the findings of other series (10, 11), indicating that when HBO fails, the urologist

should consider other underlying causes such as malignancy.

Our study has several drawbacks. First of all, it is not randomized or controlled, but given the fact that cystectomy represents the alternative definitive treatment for radiation cystitis we believe it will be difficult to randomize patients. Secondly, due to strict inclusion criteria, since it is the only prospective study with severe haemorrhagic cystitis patients all of which needed transfusion, the number of patients enrolled in our study is relatively small.

CONCLUSIONS

The early primary use of hyperbaric oxygen to treat severe radiation-induced haematuria (especially within the first six months from the haematuria onset) is an effective and safe treatment option with excellent initial results. Increasing patient recruitment, precise and longer follow-up is warranted to extract careful and permanent conclusions. Prospective randomized controlled trials uniformly designed in order to avoid variability in treatment strategies, will eventually provide more precise information.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Pasquier D, Hoelscher T, Schmutz J, Dische S, Mathieu D, Baumann M, et al. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. Radiother Oncol. 2004;72:1-13.
2. Dellis A, Deliveliotis C, Kalentzos V, Vavasis P, Skolarikos A. Is there a role for hyberbaric oxygen as primary treatment for grade IV radiation-induced haemorrhagic cystitis? A prospective pilot-feasibility study and review of literature. Int Braz J Urol. 2014;40:296-305.
3. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341-6.
4. Payne H, Adamson A, Bahl A, Borwell J, Dodds D, Heath C, et al. Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges. BJU Int. 2013;112:885-97.
5. Denton AS, Clarke NW, Maher EJ. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis. Cochrane Database Syst Rev. 2002;3:CD001773.
6. Vilar DG, Fadrique GG, Martín IJ, Aguado JM, Perelló CG, Argente VG, et al. Hyperbaric oxygen therapy for the management of hemorrhagic radio-induced cystitis. Arch Esp Urol. 2011;64:869-74.
7. Levenback C, Eifel PJ, Burke TW, Morris M, Gershenson DM. Hemorrhagic cystitis following radiotherapy for stage Ib cancer of the cervix. Gynecol Oncol. 1994;55:206-10.
8. Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. J Urol. 2003;169:2200-2.
9. Shao Y, Lu GL, Shen ZJ. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012;109:691-4.
10. Rijkmans BG, Bakker DJ, Dabhoiwala NF, Kurth KH. Successful treatment of radiation cystitis with hyperbaric oxygen. Eur Urol. 1989;16:354-6.
11. Norkool DM, Hampson NB, Gibbons RP, Weissman RM. Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. J Urol. 1993;150:332-4.
12. Lee HC, Liu CS, Chiao C, Lin SN. Hyperbaric oxygen therapy in hemorrhagic radiation cystitis: a report of 20 cases. Undersea Hyperb Med. 1994;21:321-7.
13. Del Pizzo JJ, Chew BH, Jacobs SC, Sklar GN. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: long-term followup. J Urol. 1998;160:731-3.
14. Mathews R, Rajan N, Josefson L, Camporesi E, Makhuli Z. Hyperbaric oxygen therapy for radiation induced hemorrhagic cystitis. J Urol. 1999;161:435-7.
15. Mayer R, Klemen H, Quehenberger F, Sankin O, Mayer E, Hackl A, et al. Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer. Radiother Oncol. 2001;61:151-6.
16. Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. Urology. 2005;65:649-53.
17. Bevers RF, Bakker DJ, Kurth KH. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. Lancet. 1995;346:803-5.
18. Talab SS, McDougal WS, Wu CL, Tabatabaei S. Mucosa-sparing, KTP laser coagulation of submucosal telangiectatic vessels in patients with radiation-induced cystitis: a novel approach. Urology. 2014;84:478-83.
19. Martinez DR, Ercole CE, Lopez JG, Parker J, Hall MK. A Novel Approach for the Treatment of Radiation-Induced Hemorrhagic Cystitis with the GreenLightTM XPS Laser. Int Braz J Urol. 2015;41:584-7.
20. Smit SG, Heyns CF. Management of radiation cystitis. Nat Rev Urol. 2010;7:206-14.

21. Degener S, Pohle A, Strelow H, Mathers MJ, Zumbé J, Roth S, et al. Long-term experience of hyperbaric oxygen therapy for refractory radio- or chemotherapy-induced haemorrhagic cystitis. BMC Urol. 2015;15:38.
22. Mendenhall WM, Henderson RH, Costa JA, Hoppe BS, Dagan R, Bryant CM, et al. Hemorrhagic radiation cystitis. Am J Clin Oncol. 2015;38:331-6.
23. Buras J. Basic mechanisms of hyperbaric oxygen in the treatment of ischemia-reperfusion injury. Int Anesthesiol Clin. 2000;38:91-109.
24. Dellis AE, Skolarikos A, Vavasis P, Spyropoulos E, Kalentzos VN. Spontaneous hydrocele resolution after hyperbaric oxygen treatment: a clinical case report. Undersea Hyperb Med. 2010;37:199-201.
25. Hoggan BL, Cameron AL. Systematic review of hyperbaric oxygen therapy for the treatment of non-neurological soft tissue radiation-related injuries. Support Care Cancer. 2014;22:1715-26.
26. Oscarsson N, Arnell P, Lodding P, Ricksten SE, Seeman-Lodding H. Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery. Int J Radiat Oncol Biol Phys. 2013;87:670-5.
27. Oliai C, Fisher B, Jani A, Wong M, Poli J, Brady LW, et al. Hyperbaric oxygen therapy for radiation-induced cystitis and proctitis. Int J Radiat Oncol Biol Phys. 2012;84:733-40.
28. Tahir AR, Westhuyzen J, Dass J, Collins MK, Webb R, Hewitt S, et al. Hyperbaric oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study. Asia Pac J Clin Oncol. 2015;11:68-77.
29. Liss MA, Osann K, Cho J, Chua WC, Dash A. Severity of hematuria effects resolution in patients treated with hyperbaric oxygen therapy for radiation-induced hematuria. Urol Int. 2013;91:451-5.
30. Shilo Y, Efrati S, Simon Z, Sella A, Gez E, Fenig E, et al. Hyperbaric oxygen therapy for hemorrhagic radiation cystitis. Isr Med Assoc J. 2013;15:75-8.

Correspondence address:
Athanasios Dellis, MD, PhD
2nd Department of Surgery,
Aretaieion Academic Hospital,
School of Medicine,
National and Kapodistrian University of Athens,
5, Granikou St., 15125,
Maroussi, Athans, Greece
E-mail: aedellis@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 496-504, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0468

Randomized crossover trial of amoxapine versus vitamin B_{12} for retrograde ejaculation

Jianlin Hu [1,2], Koichi Nagao [1], Toshihiro Tai [1], Hideyuki Kobayashi [1], Koichi Nakajima [1]

[1] Department of Urology, Reproduction Center, Toho University School of Medicine, Omori Hospital, Tokyo, Japan; [2] Department of Reproductive Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

ABSTRACT

Objective: To compare the efficacy and safety of amoxapine and vitamin B_{12} for treating retrograde ejaculation (RE).

Materials and Methods: Between May 2009 and November 2012, this open-label, randomized, crossover study enrolled 26 men suffering with RE at Department of Reproductive Medicine, Omori Hospital. Patients were randomly allocated into two groups (n=13 each). The amoxapine-B_{12} group received amoxapine (50 mg daily for 4 weeks, orally) followed (after a 1-week washout period) by vitamin B_{12} (500 µg three-times daily for 4 weeks). The B_{12}-amoxapine group received the opposite regimen. All patients masturbated to ejaculation at least twice during each treatment period. The primary outcome was antegrade ejaculation of semen, as reported by the patient, on more than one occasion during either treatment period (defined as treatment success). Any adverse events were noted. Success rates were compared between treatments using Fisher's exact test.

Results: One patient (B_{12}-amoxapine group) withdrew for personal reasons (breakdown of marital relations); all other patients completed the study. Overall success rate was 88% (22/25). Success rate was higher for amoxapine than for vitamin B_{12} (80%, 20/25 vs 16%, 4/25; P<0.0001). 18 patients were responsive to amoxapine but not to vitamin B_{12}, 2 patients were responsive to vitamin B_{12} but not amoxapine, 2 patients were responsive to both drugs, and 3 patients had no response to either drug. One patient (4%) reported sleepiness and 2 (8%) reported constipation while receiving amoxapine. No adverse events were reported during vitamin B_{12} treatment.

Conclusions: Amoxapine may be an effective, safe and well-tolerated therapy for RE.

ARTICLE INFO

Keywords:
Ejaculation; Drug Therapy; Amoxapine; Infertility, Male

Int Braz J Urol. 2017; 43: 496-504

Submitted for publication:
August 18, 2016

Accepted after revision:
December 18, 2016

Published as Ahead of Print:
Febraury 02, 2017

INTRODUCTION

Retrograde ejaculation (RE) is defined as a substantial redirection of seminal fluid from the posterior urethra into the bladder and mainly caused by bladder neck dysfunction (1). Men suffering from RE present with total or sometimes partial absence of semen, despite the sensation of an orgasm, after intercourse or masturbation (2). Current treatment methods are based on two different strategies (3). The first is pharmacologic intervention or surgical management in order to restore antegrade ejaculation by increasing bladder neck tone. The second is urinary sperm retrieval or electroejaculation; this aims to facilitate fertility by obtaining spermatozoa with invasive methods and then applying artificial reproductive technologies.

To date, there has been little guidance on RE management. Nevertheless, pharmacotherapy can be tried as a first-line treatment because it is simple, time-saving, cost-effective and non-invasive. Clinically, imipramine, a tricyclic antidepressant agent (TCA), is commonly used to treat RE due to a variety of causes. However, the overall success rate does not exceed 50%, and adverse effects are reported frequently (4-7). On the other hand, studies of RE therapy, including the use of imipramine medication, have many deficiencies. Most previous investigations of RE therapy are case studies or lack a suitable control, partly because the incidence of RE is not very high. It has been reported that RE accounts for less than 2% of cases of subfertility presenting to a fertility clinic (3). Thus, it can be challenging to obtain a sufficiently large sample size for validate statistical comparisons.

Amoxapine, a tetracyclic antidepressant that is chemically distinct from TCAs, has been reported to result in far fewer adverse events than imipramine in patients treated for depression (8). Amoxapine also selectively blocks neuronal reuptake of norepinephrine and, to a lesser extent, serotonin, and thus upregulates peripheral sympathetic activity to contract the bladder neck; therefore, it also exerts actions that are potentially beneficial in the treatment of RE. Successful treatment of RE with amoxapine has been described in a case report (9). Based on these very limited previous data, we hypothesized that amoxapine would show clinical benefit as a therapy for RE. Therefore, the objective of this randomized crossover trial was to compare the efficacy and safety of amoxapine in the treatment of RE with those of vitamin B_{12}, which was used as a negative control.

MATERIALS AND METHODS

Study design

This was an open-label, randomized, crossover study comparing the treatment efficacy, adverse effects and tolerability of amoxapine and vitamin B_{12} in the management of RE.

Patients

The study participants were recruited between May 2009 and November 2012 at the Assisted Reproduction Center, Omori Hospital. The inclusion criteria were: 1) male; 2) aged between 18 to 60 years old; 3) patient reported an absence of antegrade ejaculation but experienced a sensation of orgasm after intercourse or masturbation; and 4) a definitive diagnosis of primary RE or secondary RE (e.g. associated with diabetes mellitus, pelvic surgery or depression) was made on the basis of the detailed medical history, physical examination findings and results of imaging and laboratory investigations, as described below.

The diagnosis of RE was made using a standard protocol. During the initial visit to our reproduction center, all patients underwent a standard evaluation of the male reproductive system according to Japanese reproductive health guidelines (10). A detailed medical history was obtained, and erectile function was evaluated using the International Index of Erectile Function (IIEF-5) questionnaire. We also used ultrasonography to measure the testis volume as well as to evaluate the epididymal and prostatic structures. Furthermore, the presence of the vas deferens and seminal vesicles were confirmed to exclude patients with obstructive problems such as congenital bilateral absence of the vas deferens (CBAVD), ejaculatory duct cyst or dysplasia of seminal vesicles, *etc*. In addition, we conducted laboratory blood testing, including determination of serum concentrations of glucose and sex hormones such as testosterone (T), estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL). Examination of semen in the urine was conducted according to World Health Organization guidelines (11). Patients were asked to supply a semen sample by masturbation in our reproduction center after 3 to 5 days of abstinence, and post-masturbatory urine was then collected for analysis. If sperm were found in the post-centrifuge sample (centrifuged at 3000g for 15 minutes and viewed at $^{\times}200$ magnification) and the fructose-resorcinol--hydrochloric acid test was positive (colored), the diagnosis of RE was then confirmed.

Men were excluded if any of the following criteria applied: 1) moderate-to-severe erectile dysfunction (IIEF-5 score $\leq$ 12); 2) obstructive or non-obstructive azoospermia (absence of vas de-

ferens or absence of sperm in post-masturbatory urine); 3) low sexual desire; 4) serum concentrations of sex hormones not within the normal range; or 5) unable to suspend current pharmacologic treatment for other underlying illnesses (e.g., patients using α1-adrenoceptor antagonists for the treatment of hypertension, angle-closure glaucoma, patients using monoamine oxidase inhibitors, acute and recovery phase of myocardial infarction). Ultimately, 26 patients with confirmed RE were enrolled in this study.

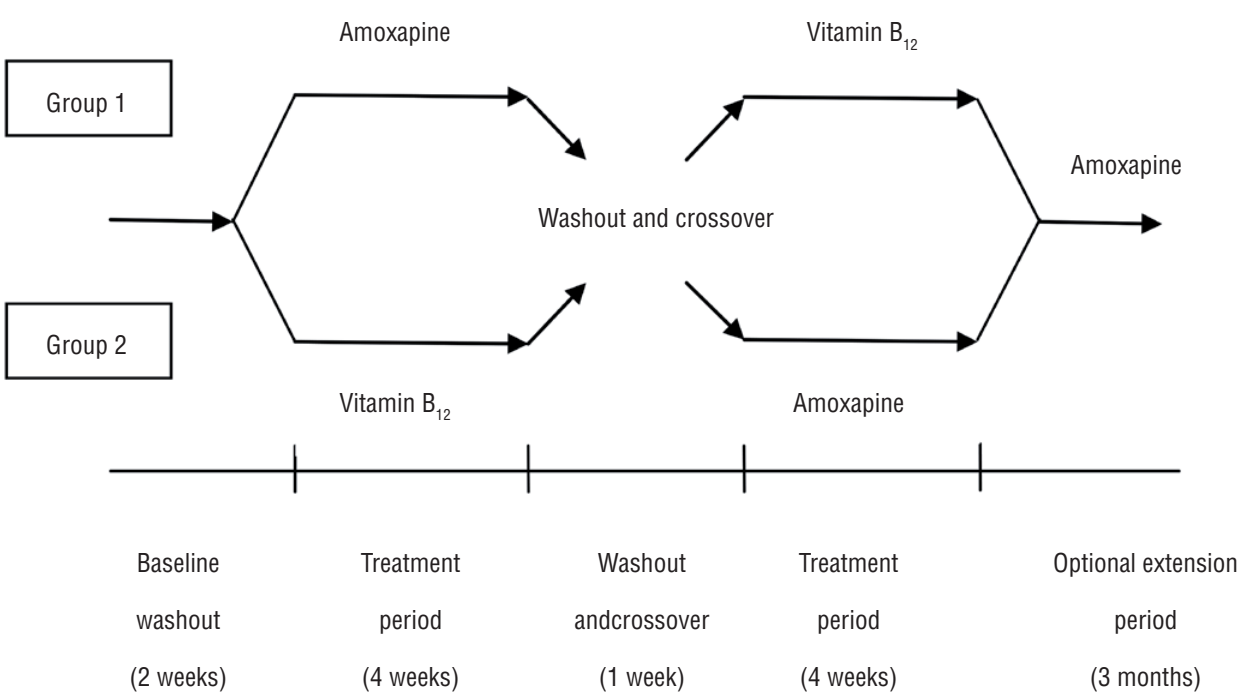
The following baseline demographic and clinical characteristics were recorded for each enrolled patient: age, duration of RE, type of RE (primary or secondary), marital status, and desire for infertility treatment.

This study was approved by the ethics committee of Toho University (approval number 20-105). All patients were informed of the study objectives and design and gave written informed consent before their participation. There were no important changes to the methods after trial commencement.

Grouping and intervention

The study comprised a 2-week baseline period, two 4-week treatment periods (separated by a 1-week washout period), and an optional 3-month extension period (Figure-1). Briefly, the patients were randomly divided into two groups (n = 13 each) using an allocation sequence generated with a random number table; the random allocation sequence was implemented using sequentially numbered, opaque, sealed envelopes. As this was an open-label study, neither the patient nor investigators were blinded to the treatment used once the allocation had been made. After a 2-week washout period (for drugs used to treat other underlying illnesses, particularly drugs that might affect ejaculation, such as antipsychotics and α_1-adrenoceptor antagonists), patients allocated to the amoxapine-B_{12} group took amoxapine (Pfizer, Japan) 50 mg daily (orally at bedtime) for 4 weeks. After a 1-week washout period, the medication was changed to vitamin B_{12} (Otsuka, Japan) 500 µg three times daily (orally after meals) for another 4 weeks. Patients in the B_{12}-amoxapine group received the opposite regimen.

Figure 1 - Study design.



Outcome measures

Patients were followed up at the end of each 4-week treatment period. The primary outcome measure was the percentage of patients in which antegrade ejaculation was recovered during the treatment period ('success rate'). Assessment of this outcome measure was as follows. All patients were instructed to masturbate at least twice during each 4-week treatment period. Recovery of antegrade ejaculation was defined as the ejaculation of white fluid (semen) on more than one occasion during the 4-week treatment period, as reported by the patient at the follow-up consultation. The recovery of antegrade ejaculation was taken to indicate that the pharmacologic intervention had been successful in that particular patient. The success rates were compared between the two medical therapies.

The patients entering the 3-month study extension were followed-up for at least a further 3 months after treatment. During the 3-month study extension, patients with fertility requirements were prescribed amoxapine according to the above regimen and encouraged to attempt timed intercourse at 2 to 0 days before their partner's ovulation. The occurrence of successful pregnancy during the 3-month extension period was recorded as a secondary outcome measure. If pregnancy did not occur during that time, artificial reproduction techniques such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) were recommended for consideration.

Any adverse events reported by the patients during the treatment periods were recorded.

There were no changes to the trial outcomes after the trial had commenced.

Statistical analysis

All analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL USA). The data were analyzed using descriptive statistics and are presented as median, range, frequency or percentage, as appropriate. The success rates were compared between groups using Fisher's exact test. In all statistical tests, statistical significance was defined as a P value < 0.05.

RESULTS

A total of 26 patients were randomized in a 1:1 ratio into the two groups. One patient in the B_{12}-amoxapine group withdrew during the first treatment period for personal reasons (breakdown of marital relations and divorce). Ultimately, 25 patients successfully completed the study (13 patients in the amoxapine-B_{12} group and 12 patients in the B_{12}-amoxapine group) and were included in the final analysis (Figure-2).

Table-1 shows the demographic characteristics of the patients. The age ranged from 28 to 54 years (median, 40.8 years) while the duration of RE ranged from 2 months to 25 years (median, 4.5 years). Among the 25 patients, 22 (88%) had a previous history of normal ejaculation and were diagnosed as having secondary RE. The cause of RE was diabetes mellitus in 15/22 patients (68.2%), postsurgical complications of radical resection of rectal carcinoma in 6/22 patients (27.3%), and depression in 1/22 patients (4.5%). Due to the absence of a previous history of normal ejaculatory experiences, RE was considered idiopathic or primary in 3/25 patients (12%). A total of 11 patients (44%) were married, 10 of whom (40% of the total) sought treatment for infertility and entered the 3-month period of extended treatment with amoxapine. During follow-up, the wives of two patients (20%, 2/10) became pregnant naturally and the wife of another patient (10%, 1/10) became pregnant by intracytoplasmic sperm injection 6 months later.

The treatment outcomes (i.e. numbers of patients in which antegrade ejaculation was recovered during the treatment period) for amoxapine and vitamin B_{12} are shown in Table 2. The overall success rate in all patients was 88% (22/25 patients). The success rate was significantly higher for amoxapine than for vitamin B_{12} (80%, 20/25, 95% CI: 59%-93% vs 16%, 4/25, 95% CI: 5%-36% respectively; $P < 0.0001$; Figure-3). In total, 18 patients (72%, 18/25, 95% CI: 51%-88%) were responsive to amoxapine (i.e. recovered antegrade ejaculation) but not to vitamin B_{12}. In contrast, only 2 patients (8%, 2/25, 95% CI: 1%-26%) were responsive to vi-

Figure 2 - Enrollment and follow up of study subject.

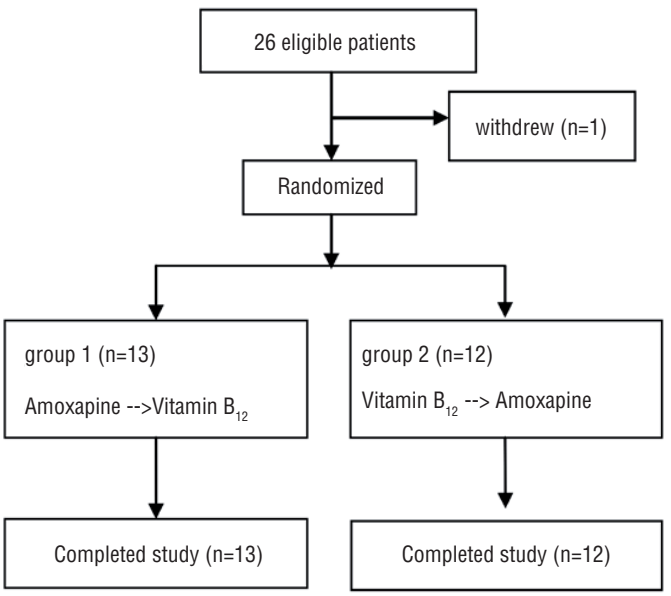


Table 1 - Demographic characteristics of the patients (n = 25).

Variables		
Age (years)	Range	28~54
	Median	40.8
Duration of RE (years)	Range	0.17~25
	Median	4.5
RE type (n)	Primary	3
	Secondary	22
Marriage status (n)	Married	11
	Unmarried	14
Desire for infertility treatment (n)	Yes	10
	No or presently not	15

RE = Retrograde ejaculation.

tamin B_{12} but not to amoxapine. A further 2 patients (8%, 2/25, 95% CI: 1%-26%) were responsive to both drugs, and 3 patients (12%, 3/25, 95% CI: 3%-31%) had no response to either drug.

Adverse events

One patient (4%, 1/25) reported sleepiness and two patients (8%, 2/25) reported constipation while receiving amoxapine. No adverse events were reported during treatment with vitamin B_{12}.

DISCUSSION

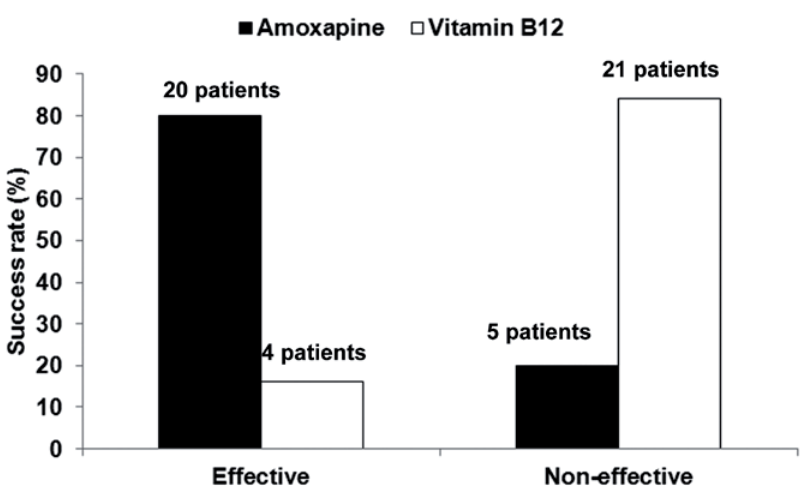
The main finding of the present study was that amoxapine showed higher efficacy compared with vitamin B_{12} in the treatment of RE, with a to-

Table 2 - Pharmacologic treatment outcomes.

Cause	n	Efficacy (recovery of antegrade ejaculation)				Total efficacy	
		Amoxapine (n)	Vitamin B12 (n)	Both (n)	Neither (n)	Amoxapine (n)	Vitamin B12 (n)
DM	15	14	0	0	1	14	0
RRRC	6	4	1	1	0	5	2
Depression	1	0	0	1	0	1	1
Idiopathic	3	0	1	0	2	0	1
Total	**25**	**18**	**2**	**2**	**3**	**20**	**4**

DM = Diabetes mellitus; **RRRC =** Radical resection of rectal carcinoma.

Figure 3 - Comparison of success rates for amoxapine and vitamin B_{12}. Fisher's exact test, $P < 0.05$.



tal of 80% (20/25) of all patients responding to the drug. Furthermore, amoxapine was well tolerated, with only mild adverse events reported in a small proportion of patients (12%, 3/25). Therefore, low--dose amoxapine may be safe and effective for the management of RE.

Amoxapine is an N-demethylated dibenzoxazepine and has antidepressant properties that resemble those of imipramine. With an elimination half-life of 8 to 30 hours, amoxapine is usually administered to adults at a dose of 200 to 300 mg daily. Amoxapine was reported to have comparable efficacy and faster onset at improving selected symptoms of depression, as compared with imipramine, and adverse events were less frequent (8). In our study, 20 patients treated with amoxapine reported semen ejaculation, a significantly higher success rate than that in patients receiving vitamin B_{12} (success rate: 80% vs 16%, respectively; $P < 0.0001$). We chose a daily amoxapine dose of 50 mg, after referring to a guideline for treating RE with imipramine. This dosage is about 25% of that normally used to treat depression and therefore would be expected to result in a low rate of adverse events. We observed no major adverse effects. Only 3 patients reported adverse events (mild sleepiness and constipation), which confirms that amoxapine at this dosage not only shows efficacy in treating RE but also is safe and well tolerated.

Another advantage of amoxapine administration is that it shows clinical benefit in the

treatment of RE due to different causes. As Kamischke and Nieschlag noted in their review (12), neurogenic causes, such as pelvic surgery and diabetes mellitus, are responsible for a large number of RE cases. Among our patients, 60% had diabetes mellitus and 24% had undergone retroperitoneal lymph node dissection as part of surgical treatment for rectal carcinoma. These patients were clearly at high risk for RE due to sympathetic nerve impairment and thus were candidates for treatment with drugs that increase sympathetic tone. In our study, most men, including 1 patient with mild depression, successfully achieved antegrade ejaculation while receiving amoxapine. These results indicate that amoxapine can be used successfully to treat RE due to various causes. There was a total of 5 patients (20%) who did not respond to treatment with amoxapine. A possible explanation for the non-response to amoxapine was that the underlying pathology was severe or anatomic, i.e., that damage to organic structures could not be addressed by medical treatment alone.

It is clear that the bladder neck has an important role in normal ejaculation (13). Dysfunction of the autonomic nervous system and impairment of the internal urethral sphincter can inhibit bladder closure during expulsion of semen. The etiologies can be pharmacologic (e.g., use of an α-adrenoceptor blocker), anatomic (e.g., congenital abnormalities), neurogenic (e.g., retroperitoneal surgery, diabetic autonomic neuropathy or multiple sclerosis) and even idiopathic (14). As a result, semen can reflux into the bladder through the bladder neck, leading to total or partial absence of antegrade ejaculation despite the presence of orgasm (i.e., RE).

Pharmacotherapy for RE attempts to restore bladder neck function by either increasing sympathetic tone or decreasing parasympathetic activity (3). The medications used can be sympathomimetic, anticholinergic or antihistaminic and are recommended for men without spinal cord injuries or anatomic anomalies of the urethra who are not receiving medicines for other underlying illnesses (2). In a recent systematic review, the overall antegrade ejaculation rate was 28% (11/40) for sympathomimetic drugs, 22% (11/50) for anticholinergic drugs, and 39% (5/13) for the combination of sympathomimetics and anticholinergics (3). Although the efficacy of combination therapy seemed to be higher than that of mono-therapy, the numbers of patients in these studies were too small for any firm conclusions to be drawn.

Pharmacotherapy is more convenient, less invasive and more easily tolerated than other treatment methods for RE such as surgical management (15-17), electroejaculation (18) and urinary sperm retrieval (19-21). Moreover, most non-pharmacotherapy only addresses infertility and does not directly treat RE. Pharmacotherapy offers patients the possibility of resuming normal intercourse and natural pregnancy. The data in the present study showed that 56% (14/25) of the patients were unmarried and that 60% (15/25) did not require fertility treatment. To these patients, recovery of normal ejaculation may be more important than immediate improvement of fertility. Pharmacotherapy should be considered as the most appropriate first-line therapy for such patients.

Imipramine was found to be effective and safe for the treatment of RE due to anatomic and physiologic causes (4-7, 22, 23). However, the overall success rate did not exceed 50% (4-7). Although the success rates for treating RE due to post-retroperitoneal lymph node dissection were reported to be nearly 100% (22, 23), these studies lacked controls and the sample sizes were small. The adverse effects of imipramine were reported to be mild and included dizziness, weakness, palpitation, nausea and sweating. The overall rates of adverse effects in two studies were 45.45% (22) and 36.36% (7), respectively.

This study has several limitations. First, we were not able to include a placebo suitable for double blinding. Although vitamin B_{12} is commonly used for neuroprotection (24), it has to be given 3 times daily. Therefore, it cannot be excluded that the open-label design of the study may have introduced a degree of bias into the results. Second, the treatment outcomes were reported by the patients, which does not permit an objective evaluation of spermatozoa characteristics; this may have increased the likelihood of false positive results. However, an advantage of this method of assessment is that the patients were able to have sex and masturbate freely, without a timetable,

and unnecessary nervousness and anxiety could therefore be avoided. Third, the study did not include an active control group such as imipramine, so it was not possible to compare the efficacy and safety of amoxapine with other drugs currently used to manage RE. Fourth, the sample size was relatively small for a randomized controlled trial. Since RE is uncommon, it is very difficult to recruit large numbers of patients. We enrolled as many patients as possible during a three-and-a-half-year period. Moreover, amoxapine is a tetracyclic antidepressant, and treatment for RE is off-label and without guideline support. Therefore, our study is just an exploratory study but not a confirmatory study. Since the difference in success rates between the amoxapine and vitamin B_{12} groups was large, our results can be considered reliable despite the small sample size. Future research should consider the effects of amoxapine on spermatozoa characteristics and compare amoxapine with imipramine or other drugs used to treat RE.

Our findings indicate that amoxapine has a significantly higher efficacy than vitamin B_{12} in the treatment of RE. Adverse events during treatment with amoxapine were mild and infrequent, and the drug was well tolerated. In summary, low-dose amoxapine may be a safe and effective drug for treating RE caused by a variety of reasons.

ABBREVIATIONS

RE = Retrograde ejaculation
TCA = Tricyclic antidepressant agent
IIEF-5 = International Index of Erectile Function
T = Testosterone
E2 = Estradiol
LH = Luteinizing hormone
FSH = Follicle stimulating hormone
PRL = Prolactin
IVF = *in vitro* fertilization
ICSI = intracytoplasmic sperm injection

CONFLICT OF INTEREST

None declared.

Funding

This article was supported in part by a Japan China Sasakawa Medical Fellowship.

REFERENCES

1. Kondoh N. Ejaculatory dysfunction as a cause of infertility. Reprod Med Biol. 2012; 11:59-64.
2. Colpi G, Weidner W, Jungwirth A, Pomerol J, Papp G, Hargreave T, et al. EAU guidelines on ejaculatory dysfunction. Eur Urol. 2004;46:555-8.
3. Jefferys A, Siassakos D, Wardle P. The management of retrograde ejaculation: a systematic review and update. Fertil Steril. 2012;97:306-12.
4. Okada H, Fujioka H, Tatsumi N, Kanzaki M, Inaba Y, Fujisawa M, et al. Treatment of patients with retrograde ejaculation in the era of modern assisted reproduction technology. J Urol. 1998;159:848-50. Erratum in: J Urol 1998;159:1650.
5. Xiao Y. Treatment of functional retrograde ejaculation with acupuncture and TCM herbal drugs. J Tradit Chin Med. 2002;22:286-7.
6. Gilja I, Parazajder J, Radej M, Cvitković P, Kovacić M. Retrograde ejaculation and loss of emission: possibilities of conservative treatment. Eur Urol. 1994;25:226-8.
7. Arafa M, El Tabie O. Medical treatment of retrograde ejaculation in diabetic patients: a hope for spontaneous pregnancy. J Sex Med. 2008;5:194-8.
8. Kinney JL, Evans RL Jr. Evaluation of amoxapine. Clin Pharm. 1982;1:417-24.
9. Hibi H, Ohori T, Yamada Y. DPP-IV inhibitor may affect spermatogenesis. Diabetes Res Clin Pract. 2011;93:e74-5.
10. Medicine JSfR (2010) Guidbook for Reproductive Medicine. Kanehara, Tokyo.
11. Organization WH (2010) WHO Laboratory Manual for the Examination and Processing of Human Semen. World Health Organization, Geneva.
12. Kamischke A, Nieschlag E. Treatment of retrograde ejaculation and anejaculation. Hum Reprod Update. 1999;5:448-74.
13. Thomas AJ Jr. Ejaculatory dysfunction. Fertil Steril. 1983;39:445-54.
14. Barazani Y, Stahl PJ, Nagler HM, Stember DS. Management of ejaculatory disorders in infertile men. Asian J Androl. 2012;14:525-9.
15. Ramadan AE, el-Demiry MI, Ramadan AE. Surgical correction of post-operative retrograde ejaculation. Br J Urol. 1985;57:458-61.
16. Abrahams JI, Solish GI, Boorjian P, Waterhouse RK. The surgical correction of retrograde ejaculation. J Urol. 1975;114:888-90.
17. Dees JE. Congenital epispadias with incontinence. J Urol. 1949;62:513-22.
18. Rosenlund B, Sjöblom P, Törnblom M, Hultling C, Hillensjö T. In-vitro fertilization and intracytoplasmic sperm injection in the treatment of infertility after testicular cancer. Hum Reprod. 1998;13:414-8.

19. Hotchkiss RS, Pinto AB, Kleegman S. Artificial insemination with sêmen recovered from the bladder. Fertil Steril. 1954;6:37-42.
20. Nikolettos N, Al-Hasani S, Baukloh V, Schöpper B, Demirel LC, Baban N, et al. The outcome of intracytoplasmic sperm injection in patients with retrograde ejaculation. Hum Reprod. 1999;14:2293-6.
21. Philippon M, Karsenty G, Bernuz B, Courbiere B, Brue T, Saïas-Magnan J, et al. Successful pregnancies and healthy live births using frozen-thawed sperm retrieved by a new modified Hotchkiss procedure in males with retrograde ejaculation: first case series. Basic Clin Androl. 2015;25:5.
22. Ochsenkühn R, Kamischke A, Nieschlag E. Imipramine for successful treatment of retrograde ejaculation caused by retroperitoneal surgery. Int J Androl. 1999;22:173-7.
23. Nijman JM, Jager S, Boer PW, Kremer J, Oldhoff J, Koops HS. The treatment of ejaculation disorders after retroperitoneal lymph node dissection. Cancer. 1982;50:2967-71.
24. Nachum-Biala Y, Troen AM. B-vitamins for neuroprotection: narrowing the evidence gap. Biofactors. 2012;38:145-50.

Correspondence address:
Koichi Nagao, MD
Department of Urology
Reproduction Center
Toho University School of Medicine
Omori Hospital
Tokyo, 143-8541, Japan
Fax: + 86 21 6408-5875
E-mail: hello570@126.com

ORIGINAL ARTICLE

Vol. 43 (3): 505-511, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0468

Validation of self – confidence scale for clean urinary intermittent self – catheterization for patients and health – caregivers

Cintia Fernandes Baccarin Biaziolo [1], Alessandra Mazzo [2], José Carlos Amado Martins [3], Beatriz Maria Jorge [4], Rui Carlos Negrão Batista [5], Silvio Tucci Júnior [6, 7]

[1] Programa de Pós-Graduação em Mestrado Profissional de Tecnologia e Inovação em Enfermagem da Escola de Enfermagem de Ribeirão Preto da Universidade de São Paulo - USP - Ribeirão Preto,SP, Brasil; [2] Departamento de Enfermagem Geral e Especializada da Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo - USP - Ribeirão Preto, SP, Brasil; [3] Departamento de Enfermagem Cirúrgica da Escola Superior de Enfermagem de Coimbra, Portugal; [4] Departamento de Enfermagem Fundamental da Escola de Enfermagem de Ribeirão Preto da Universidade de São Paulo - USP - Ribeirão Preto (SP), Brasil; [5] Escola Superior de Enfermagem de Coimbra, Portugal; [6] Divisão de Urologia, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo- USP - Ribeirão Preto,SP, Brasil; [7] Departamento de Cirurgia e Anatomia da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo- USP - Ribeirão Preto (SP), Brasil

ABSTRACT

Objective: To validate a measurement instrument for clean intermittent self-catheterization for patients and health-caregivers.
Material and Methods: Methodological study of instrument validation performed at a Rehabilitation Center in a University hospital for patients submitted to clean intermittent self-catheterization and their health-caregivers. Following ethical criteria, data were collected during interview with nurse staff using a Likert question form containing 16 items with 5 points each: "no confidence"=1, "little confidence"=2, "confident"=3, "very confident"=4 and "completely confident"=5. Questionnaire called "Self-Confident Scale for Clean Intermittent Self-catheterization" (SCSCISC) was constructed based on literature and previously validated (appearance and content).
Results: The instrument was validated by 122 patients and 119 health-caregivers, in a proportion of 15:1. It was observed a good linear association and sample adequacy KMO 0.931 and X2=2881.63, p<0.001. Anti-image matrix showed high values at diagonal suggesting inclusion of all factors. Screen plot analysis showed a suggestion of items maintenance in a single set. It was observed high correlation of all items with the total, alpha-Cronbach 0.944. The same results were obtained in subsamples of patients and health-caregivers.
Conclusion: The instrument showed good psychometric adequacy corroborating its use for evaluation of self-confidence during clean intermittent self-catheterization.

ARTICLE INFO

Keywords:
Nursing; Intermittent Urethral Catheterization; Gestalt Therapy

Int Braz J Urol. 2017; 43: 505-11

Submitted for publication:
November 12, 2015

Accepted after revision:
July 28, 2016

Published as Ahead of Print:
March 13, 2017

INTRODUCTION

Some neurologic diseases affect micturition, including elimination and storage capacity, or complete emptying of bladder, resulting in neurogenic bladder. Usually it is caused by neurological disturbances due to function, obstruction or inability to voluntary control of micturition (1).

Medical diagnosis of neurogenic bladder is established based on clinical exam, laboratory and image exams (X-rays, ultrasound), urodynamic evaluation and clinical behavior of patient (2). Its prognosis is related to early diagnosis and adequate treatment. The objective of treatment is to preserve urinary tract, preventing infections and other complications (3) as well as to reintegrate patients to their daily activities.

Among several treatment alternatives, clean intermittent self-catheterization has been used since 1947. However, only from 1972 on, the technique was widely accepted, using clean and no sterile technique, without prejudice to patients (4).

However, the procedure harms daily activities of patients and their relatives, is bothersome and mostly is continuous, and must be performed several times a day. During clean intermittent self-catheterization (CISC), it is usual to observe difficulty to obtain adequate material and familial support that may cause depression and withdrawal of daily activities related to health care (5). Success of clean intermittent self-catheterization technique improves self-esteem, return to daily micturition routine and also to daily activities (6). In that context, the role of rehabilitation nurses and the use of adequate strategies to warrant compliance of patient and family members are very important. Some authors point out that patient's confidence is related to education and follow-up strategies (7). Also, self-assurance to perform the procedure stimulates a better health care (8, 9).

Self-confidence is always related to behavior or tasks. Frequently, it is related to repetition and perception of weaknesses and individual potentialities (8). It refers to individual judgement of skills to organize and execute action plans required to achieve behavioral patterns (8).

In daily routine of a rehabilitation center of a University Hospital, we have been seen patients that use clean intermittent self-catheterization and searched instruments that support continuity of treatment, monitoring patient's self-confidence. Since those instruments are unavailable, we decided to validate a questionnaire. Based on literature, we constructed a question form (8, 10-13) and decided to validate it in relation to form and content in order to evaluate self-confidence of patients and health-caregivers. The instrument was called "Self-Confidence Scale for Clean Intermittent Self-Catheterization" (SCSCISC). It is a Likert question form of 16 items and 5 points per item: "not confident"=1, "little confident"=2, "confident"=3, "very confident"=4, and "completely confident"=5.

The questionnaire was validated in relation to appearance and content in two steps. At first step, a group of 7 specialists, including urologic nurses and physicians of the Rehabilitation Center validated the question form, and in the second step, it was validated by a group of 9 patients and health-caregivers that used clean intermittent self-catheterization (14-15). In the present study, the objective was to validate SCSCISC as an instrument for measurement of self-confidence of patients and health-caregivers.

MATERIALS AND METHODS

Methodological study of instrument validation performed at a rehabilitation center of a University Hospital of Sao Paulo State, Brazil.

Sample

The study was developed in patients and their health-caregivers with neurologic bladder, that used intermittent self-catheterization of urinary bladder, and that participate in a rehabilitation program. The sample included 241 subjects (122 patients and 119 health-caregivers).

Self-Confidence Scale for Clean Intermittent Urinary Self-Catheterization (SCSCISC)

This is a Likert-type question form including 16 items graded with five points: "not confident"=1, "little confident"=2, "confident"=3, "very confident"=4, and "completely confident"=5 (14, 15).

Data collection

Data collection for validation of the scale was performed by the authors during a nurse consulting routinely performed at the rehabilitation program.

Patients and health-caregivers were interviewed and answered a socio-economic question form and SCSCISC.

Data analysis

Data were codified and doubly applied in Excel spreadsheets and posteriorly exported and analyzed by SPSS program (Statistical Package for Social Science), version 22.0. S.

In order to determine validity and reliability of scale, it was used descriptive statistics, measuring central tendency and dispersion (media, mode, medium, percent, variance, standard deviation) in order to verify sample adequacy (16) and statistical inference (factorial analysis and estimate of intern consistency). In order to evaluate obtained results, $p<0.05$ was assumed as statistically significant.

Ethical Aspects

This study was approved by the Ethical Committee in Research of the Nurse School of Ribeirao Preto (number 146/2012). According to resolution # CNS 466/2012, patients and health-caregivers were invited to participate on the study and signed a free consent form. Anonymity and liberty to quit were maintained throughout the study.

RESULTS

During the period of the study 241 subjects were interviewed, including 122 (50.2%) patients and 119 health-caregivers (49.4%). 84 (70.6%) health-caregivers were related to patient (mother, father, brother, wife).

Among patients, 78 (64.0%) were male and among health-caregivers 85 (71.4%) were female. In relation to age, most patients were 11 to 20 years old and health-caregivers 31 to 40 years old.

In relation to urinary catheterization, almost all patients (106, 86.9%) and health-caregivers (106, 89.0%) were trained at the hospital of the study. In relation to frequency, most performed catheterization four times a day.

SCSCISC showed good suitability of the database, in a proportion of 15:1, in relation to case number and respective quantity of variables.

There was a good linear correlation among variables (100% of correlation superior to 0.30).

Kaiser Meyer Olking suitability test of sample showed proper adequacy of sample for analysis (16), with a value of 0.931. Using Barlet sphericity test it was obtained statistically significant values with $X^2=2881.63$ $p<0.001$, indicating the existence of relation of the variables.

Anti-image matrix corroborates to sample adequacy of each variable to be used in factorial analysis, with elevated values at diagonal (0.896 "what to do when there is blood in the urine" to 0.964 "how to withdraw the catheter"), suggesting inclusion of all variables for factorial analysis.

In order to obtain the factors of SCSCISC, it was performed a factorial analysis of the main components of the 16 items of scale using the main component method and orthogonal varimax rotation.

Following analysis and Screen-plot observation it was possible to identify the suggestion of items maintenance in one single set. Considering the data, the sample size, the factorial analysis, the Screen-plot convergence and that scale division explained 56.5% of variance, it was maintained, at final analysis, only one set of factors at the scale.

As explained in Table-1, it was checked the variance proportion of each variable, explained by the extracted components (communalities) and factorial burden of each item. Due to the size of the sample, it was decided to maintain the items with factorial burden superior to 0.40 (17).

In relation to analysis of items set that compose SCSCISC and their relation to data using the Cronbach alpha test (Table-2) testing the proposed items and their correlation, it was obtained a high correlation of all items with the whole scale, resulting in a high alpha value (0.944). All items contributed to the good alpha value; the suppression of any item would harm the scale.

Due to impossibility to use SCSCISC in a completely new sample, the sample was divided

Table 1 - Matrix of correlation of items of Varimax rotated factors with Kaiser normalization for a single factor (N=241).

Items I feel I am capable of	Single Factor 1
1 - Perform urinary catheterization	0.572
2 - Choose the best time to perform the procedure	0.556
3 - Choose the correct material to perform the material	0.648
4 - Wash my hands	0.719
5 - Perform genital hygiene	0.744
6 - Open the material	0.723
7 - Choose to use or not the lubricant	0.437
8 - Insert the catheter	0.624
9 - Verify how much catheter must be inserted	0.666
10 - Decide how much time to keep urine dripping	0.710
11 - How to withdraw the catheter	0.746
12 - To measure the collected urine	0.654
13 - What to do when there is blood in the urine	0.624
14 - What to do when there is no urine	0.631
15 - How to discard urine	0.609
16 - How to write down the obtained quantity of urine	0.645

Table 2 - Homogeneity of Items and Cronbach Internal Consistency Coefficients of SCSCISC scale in totality (N=241).

Items	Medium	Standard Deviation	Correlation with total (corrected)	Alpha if item is suppressed
1	3.90	1.062	0.675	0.941
2	3.63	1.084	0.684	0.941
3	3.85	1.038	0.738	0.940
4	4.24	975	0.685	0.941
5	4.18	982	0.718	0.940
6	4.12	1.018	0.759	0.940
7	3.71	1.258	0.568	0.944
8	3.99	1.074	0.716	0.940
9	3.78	1.095	0.775	0.939
10	3.78	1.152	0.808	0.938
11	3.91	1.033	0.819	0.938
12	3.72	1.145	0.736	0.940
13	2.73	1.431	0.562	0.945
14	3.00	1.386	0.609	0.944
15	3.95	1.069	0.737	0.940
16	3.75	1.233	0.712	0.940

in two sub-samples (A and B) obtained by randomization provided by SPSS®. At the analysis of subsamples the tests of original sample were replicated and it was observed similar results in relation to reliability of the scale (Cronbach alpha of subsample A 0.942 and 0.931 of subsample B), good correlation and maintenance of scale with a single set of factors.

Also, the sample was divided in two categories (PATIENTS and HEALTH-CAREGIVERS). In these subsamples the same testes were again replicated and it were found similar results related to reliability of the scale (Cronbach alpha PATIENT 0.947 and HEALTH CAREGIVER 0.940), good correlation and maintenance of scale with only one set of factors.

The results are presented inTable-3.

DISCUSSION

During rehabilitation of a patient that needs urinary catheterization, nurses are very important to prepare the patient and/or health caregivers, in relation to capacitation and to management and purchasing of material. When patient and health-caregiver develop self-confidence for the procedure, performance is more efficient and motivates the rehabilitation process.

In this study, 241 subjects were interviewed with almost 50% of patients and 50% of health caregivers, both responsible for the rehabilitation of urinary bladder using clean intermittent urinary catheterization. The institution trained those individuals (where the study was performed) after primary diagnosis. The methods are perfected by initiatives of the university and the personal. Self-confidence is one of the several aspects that are been implemented (5).

Self-confidence may be related to the self-efficacy theory that is constantly associated to a behavior or task. It originates from repeated experiences and realistic perception of individual difficulties and potentials. Individuals with higher sense of self-confidence are prone to challenges and correction of failures (18, 19).

Table 3 - Descriptive statistics of every dimension of the scale.

Items	N	Minimum	Maximum	Medium	Standard deviation
1	241	1	5	3.90	1.062
2	241	1	5	3.63	1.084
3	241	1	5	3.85	1.038
4	241	2	5	4.24	0.975
5	241	1	5	4.18	0.982
6	241	1	5	4.12	1.018
7	241	1	5	3.71	1.258
8	241	1	5	3.99	1.074
9	241	1	5	3.78	1.095
10	241	1	5	3.78	1.152
11	241	1	5	3.91	1.033
12	241	1	5	3.72	1.145
13	241	1	5	2.73	1.431
14	241	1	5	3.00	1.386
15	241	1	5	3.95	1.069
16	241	1	5	3.75	1.233
General	241	1.63	5	3.76	0.837

Self-confidence of clean intermittent urinary catheterization is related to success and continuity of treatment. Since there were no validated instruments to measure this aspect, it was proposed this question form (SCSCISC). In order to validate it, it was used an adequate number of participants according to observed results and the reference (16).

The proposed instrument showed high correlation of all items with total, indicating a correct reliability index (Alpha=0.944). SCSCISC measures self-confidence of patients and health caregivers.

Statistical and factorial analysis maintained all 16 items in one factor (56.5% of variance), corroborated by Screen-plot, showing adequacy of proposed items in the instrument.

Sample descriptive values related to self-confidence (Table-3) indicate that the higher values were related to hand hygiene and lower values related to "what to do when there is blood in the urine".

Such results are in accordance to other studies and stress the easy incorporation of relevance related to hand hygiene, topic vastly debated for a long time by public services to prevent hospital infection by professionals (20). In relation to urethral trauma this is a difficulty also to professionals (21). The professional must recognize and use lubricants adequately, know potentials and difficulties of different compounds of urethral catheters and present the best evidences to patients and/or health caregivers during the learning process.

The limiting aspect of the present study is the use of sample of patients and health caregivers in one only set. However, when separately analyzed, the subsamples show the same results as the whole set. In view of the rehabilitation process of patients and the role of health caregivers, the authors decided to create a single instrument to measure self-confidence of urinary catheterization.

Self-confidence is intrinsically related to self-efficacy. Health professionals are responsible for the development, follow-up, motivation and measurement of self-confidence of patients and health caregivers in relation to intermittent urinary catheterization. Nurses are essentials for urinary rehabilitation and the proposed instrument is relevant in this process.

CONCLUSIONS

This study validated a 16 items instrument (SCSCISC) in the form of a Likert scale to measure self-confidence of patients and health caregivers during intermittent urinary catheterization. It showed correct psychometric adequacy even when samples were singly studied (patients and health caregivers).

It is recommended replication of data and of the scale in new samples in order to evaluate self-confidence of patients and health caregivers during clean intermittent urinary catheterization, in order to improve quality of capacitation and treatment success.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Reis RB, Zequi SC, Zeratti Filho M. Urologia Moderna. Lemar. 2013.
2. Guyton AG, Hall JE. Tratado de Fisiologia Médica. Elsevier. 2011.
3. Sociedade Brasileira de Urologia. Bexiga Urinária: Cateterismo intermitente. Projeto Diretrizes. Associação Médica Brasileira e Conselho Federal de Medicina. 2008.
4. Seth JH, Haslam C, Panicker JN. Ensuring patient adherence to clean intermittent self-catheterization. Patient Prefer Adherence. 2014;8:191-8.
5. Mazzo A, Souza-Junior VD, Jorge BM, Nassif A, Biaziolo CF, Cassini MF, et al. Intermittent urethral catheterization-descriptive study at a Brazilian service. Appl Nurs Res. 2014;27:170-4.
6. Mangnall J. Important considerations of intermittent catheterisation. NRC Journal. 2013; 15:776-81.
7. Newman DK, Willson MM. Review of intermittent catheterization and current best practices. Urol Nurs. 2011;31:12-28.
8. Bandura A. Perceived self-efficacy in cognitive development and functioning. Educational psychologist. 1993;28:117-48.
9. Bandura A: Self-efficacy in changing societies. Cambridge University Press. 1995.

10. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA; Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol. 2010;31:319-26.
11. Geng V, Cobussen-Boekhorst H, Farrell J, Gea-Sánchez M, Pearce I, Schwennesen T, et al. Catheterisation: indwelling catheters in adults: urethral and suprapubic. Arnhem (The Netherlands): European Association of Urology Nurses (EAUN); 2012; pp. 112.
12. Mazzo A, Gaspar AACS, Mendes IAC, Trevizan MA, Godoy S, Martins JCA. Urinary catheter: myths and rituals present in preparation of patients. Acta Paul Enferm. 2012; 25:889-94.
13. Mazzo A, Martins JC, Jorge BM, Batista RC, Almeida RG, Henriques FM, et al. Validation of the self-confidence scale of nursing care in urinary retention. Rev Lat Am Enfermagem. 2015;23:814-20.
14. Silva DR, Mazzo A, Jorge BM, Souza Júnior VD, Fumincelli L, Almeida RG. Intermittent Urinary Catheterization: The Impact of Training on a Low-fidelity Simulator on the Self-confidence of Patients and Caregivers. Rehabil Nurs. 2015.
15. Fumincelli L, Mazzo A, Jorge BM, Souza-Júnior VD, Silva DRA. Cateterismo urinário intermitente limpo: impacto do treino em simulador de baixa fidelidade na autoconfiança de pacientes e cuidadores. 2º Congresso Internacional de Simulação Realística da Rede São Camilo; 27-29 ago 2014; São Paulo, BR. 2014; pp. 21.
16. Pestana MH, Gageiro JN: Análise de Dados para Ciências Sociais:A complementaridade do SPSS. Lisboa, Sílabo. 2005.
17. Hair Jr JF: Multivariate Data Analysis. Upper Saddle River, Prentice Hall. 2010.
18. Bandura A. Self-efficacy determinants of anticipated fears and calamities. J Personal Soc Psychol. 1983;45:464-9.
19. Perry P. Concept analysis: confidence/self-confidence. Nurs Forum. 2011;46:218-30.
20. Brasil. Agência Nacional de Vigilância Sanitária (ANVISA). Higienização das mãos em serviços de saúde. Brasília/DF: 2007. available at. <www.anvisa.gov.br/hotsite/higienizacao_maos/manual_integra.pdf>.
21. Fink R, Gilmartin H, Richard A, Capezuti E, Boltz M, Wald H. Indwelling urinary catheter management and catheter-associated urinary tract infection prevention practices in Nurses Improving Care for Healthsystem Elders hospitals. Am J Infect Control. 2012;40:715-20.

Correspondence address:
Alessandra Mazzo, MD
Av. Bandeirantes, 3900, Campus Universitário
Monte Alegre, Ribeirão Preto, SP, 14040-902, Brasil
E-mail: amazzo@eerp.usp.br

ORIGINAL ARTICLE

Vol. 43 (3): 512-517, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0198

Laparoscopic management of recurrent ureteropelvic junction obstruction following pyeloplasty: a single surgical team experience with 38 cases

Francesco Chiancone [1], Maurizio Fedelini [1], Luigi Pucci [1], Clemente Meccariello [1], Paolo Fedelini [1]

[1] *Urologic Clinic, AORN Cardarelli Hospital, Naples, Italy*

ABSTRACT

Purpose: To describe and analyze our experience with Anderson-Hynes transperitoneal laparoscopic pyeloplasty (LP) in the treatment of recurrent ureteropelvic junction obstruction (UPJO).

Materials and methods: 38 consecutive patients who underwent transperitoneal laparoscopic redo-pyeloplasty between January 2007 and January 2015 at our department were included in the analysis. 36 patients were previously treated with dismembered pyeloplasty and 2 patients underwent a retrograde endopyelotomy. All patients were symptomatic and all patients had a T1/2>20 minutes at pre-operative DTPA (diethylene-triamine-pentaacetate) renal scan. All data were collected in a prospectively maintained database and retrospectively analyzed. Intraoperative and postoperative complications have been reported according to the Satava and the Clavien-Dindo system. Treatment success was evaluated by a 12 month-postoperative renal scan. Total success was defined as T1/2≤10 minutes while relative success was defined as T1/2between 10 to 20 minutes. Post-operative hydronephrosis and flank pain were also evaluated.

Results: Mean operating time was 103.16±30 minutes. The mean blood loss was 122.37±73.25mL. The mean postoperative hospital stay was 4.47±0.86 days. No intraoperative complications occurred. 6 out of 38 patients (15.8%) experienced postoperative complications. The success rate was 97.4% for flank pain and 97.4% for hydronephrosis. Post-operative renal scan showed radiological failure in one out of 38 (2.6%) patients, relative success in 2 out of 38 (5.3%) patients and total success in 35 out of 38 (92.1%) of patients.

Conclusion: Laparoscopic redo-pyeloplasty is a feasible procedure for the treatment of recurrent ureteropelvic junction obstruction (UPJO), with a low rate of post-operative complications and a high success rate in high laparoscopic volume centers.

ARTICLE INFO

Keywords:
Laparoscopy; Hydronephrosis; Recurrence; Kidney Pelvis

Int Braz J Urol. 2017; 43: 512-7

Submitted for publication:
March 31, 2016

Accepted after revision:
November 11, 2016

Published as Ahead of Print:
January 23, 2017

INTRODUCTION

The failure of laparoscopic pyeloplasty can be early or late. In the early failure, the manifestation is often with pain, fever or a worsening of hydronephrosis after removing the ureteral stent. Routine follow-up after a pyeloplasty consists of ultrasonography, intravenous urography, computed tomography and renal scan. Criteria of success are radiologic and/or clinical improvement or resolution of obstruction. Renal scintigraphic criteria seems to be the best criteria to take into consideration a successful pyeloplasty. About 75% of patients who experienced obstruction after a lapa-

roscopic pyeloplasty based on scintigraphic criteria were asymptomatic, showing a bad correlation between obstruction and symptoms (1). Moreover, the patients can have a nonobstructive significant hydronephrosis and a residual atonic pelvis after pyeloplasty. In that case they can exhibit delayed t1/2 in the "indeterminate" or "obstructed" range (2).

Late failure can also occur two or more years after surgery (3). There are only a few reports of laparoscopic management of recurrent UPJO.

The largest series concerning transperitoneal laparoscopic redo-pyeloplasty have a successful rate of 83% (4) and 88% (5) (involving respectively 36 and 17 patients). The aim of this study was to describe and analyze our experience with Anderson-Hynes transperitoneal laparoscopic pyeloplasty (LP) in the treatment of recurrent ureteropelvic junction obstruction (UPJO).

MATERIALS AND METHODS

We enrolled thirty-eight consecutive patients who underwent laparoscopic redo-pyeloplasty between January 2007 and January 2015 at our department.

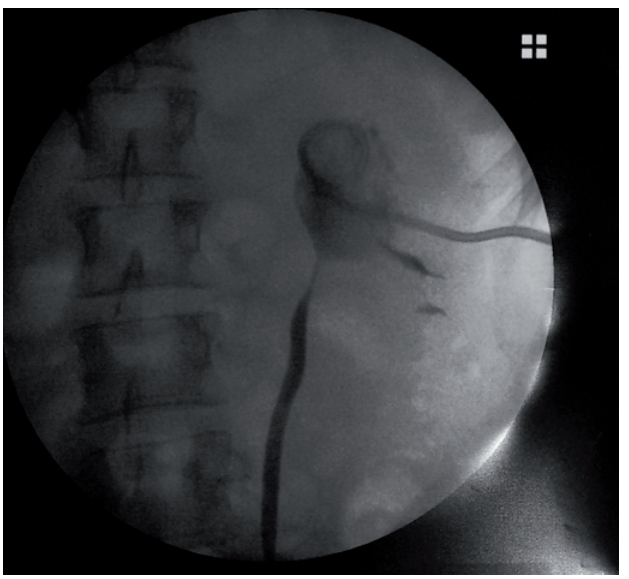
All patients were symptomatic and experienced several episodes of pain. The visual analog scale (VAS) was used to assess pain intensity at the time of colic.

All patients were studied preoperatively with renal ultrasonography (US), renal scan, and intravenous urography (IVU) or a CT scan (CT). In all patients, diagnostic tools showed severe hydronephrosis. All patients had immediately a temporary urinary derivation. 28 patients who had not fever (73.7%) underwent an ureteral stent insertion, while 10 patients (26.3%) who had fever underwent a placement of percutaneous nephrostomic tube (Figure-1).

In all cases a transperitoneal pyeloplasty using the Anderson-Hynes technique was performed, by a single surgical laparoscopic team (6).

Intraoperative and postoperative complications have been classified and reported according to Satava (7) and the Clavien-Dindo system (8).

Figure 1 - Shows a recurrent UPJO (ureteropelvic junction obstruction) with a percutaneous nephrostomic tube.



Treatment success was evaluated by 12 months postoperative DTPA (diethylene-triamine-pentaacetate) renal scan, hydronephrosis and flank pain. Total success was defined as T1/2≤10 minutes while relative success was defined as T1/2 between 10 to 20 minutes (9). All patients underwent a periodical clinical and radiological follow-up. All data were collected in a prospectively maintained database and retrospectively analyzed. Descriptive statistics of categorical variables focused on frequencies and proportions. Means and standard deviation were reported for continuously coded variables.

SURGICAL PROCEDURE

All procedures were performed in lateral decubitus after placement of the ureteral catheter in retrograde fashion and a retrograde ureterography was performed. An open Hasson approach was initially performed using a Hasson cannula. A 0º telescopic and 2 multi-disposal metal trocars (1 x 10-11mm, 1 x 5mm) were used. Dissection was performed by using monopolar scissors and bipolar forceps. The proximal ureter was spatuled with a lateral incision after resection and removal of the stenotic ureteropelvic junction. When we encountered a ventrally crossing vessel we opted

to transpose dorsally to the UPJ. The anastomosis was performed using a running 5-0 absorbable suture. A double-J stent was routinely inserted in retrograde fashion but in male patients this step was completed at the end of the laparoscopic intervention under fluoroscopic and cistoscopic control (6).

RESULTS

Table-1 depicts patient's demographics and baseline characteristics. The mean age was 26.6±6.5. Body mass index (BMI) was 25.6±2.5. Out of the 38 cases, 16 (42.1%) were males and 22 (57.9%) were females. 12 out of 38 (31.6%) patients performed their first laparoscopic transperitoneal pyeloplasty at our hospital. In two patients, a kidney stone was associated to UPJO. 24 out of 38 (63.2%) patients performed their first pyeloplasty at other hospitals (14 out of 24 procedures were performed using the retroperitoneal open technique and 10 out of 24 using the laparoscopic transperitoneal technique). Two patients (5.3%) underwent a retrograde endopyelotomy at other hospitals. In 28 cases surgical indication was recurrence of UPJO, in 4 cases it was recurrence of UPJO associated with the presence of an abnormal crossing vessel, in 2 cases it was a twisted anastomosis and in 4 cases it was a recurrence of UPJO associated with an incorrect angle of the anastomosis (Figure-2). In 20 (52.6%) cases UPJO was on right side while in 18 (47.4%) cases it was on the left side.

Mean stricture length was 0.99±0.45cm (range, 0.2-2.2cm) on IVU or retrograde pyelography. All patients were symptomatic and reported at least one episode of severe flank pain (VAS score 7-10) (10). All patients had a T1/2>20 minutes at pre-operative renal scan. 10 out of 38 (26.3%) cases reported at least one episode of fever.

Mean operating time was 103.16±30 minutes and all procedures were fully performed laparoscopically. The mean blood loss was 122.37±73.25 milliliters and no blood transfusions were necessary. The mean postoperative hospital stay was 4.47±0.86 days. Foley catheter was removed postoperatively after 2.9±0.75 days and peritoneal drainage tube was removed if its output didn't increase within 24 hours after catheter removal. The anomalous crossing vessel was transposed to ureteropelvic junction UPJ dorsally due to evident obstruction in all four patients. The double-J stent was removed after 29.9±5.4 days postoperatively. No intraoperative complications occurred according the Satava system.

Table 1 - Demographics and baseline characteristics of the 38 patients.

Variable	Value
	Mean±SD
Age at surgery (years)	26.6±6.5
BMI (kg/m^2)	25.6±2.5
	N±(%)
Males	16 (42.1%)
Females	22 (57.9%)
Right side	20 (52.6%)
Left side	18 (47.4%)
Symptomatic(pain)	38 (100%)
Fever	10 (26.3%)
Preoperative renal scan:	
T1/2>20 minutes	38 (100%)
First treatment:	
Laparoscopic transperitoneal pyeloplasty (our hospital)	12 (31.6%)
Laparoscopic transperitoneal pyeloplasty (other hospitals)	10 (26.3%)
Retroperitoneal open pyeloplasty (other hospitals)	14 (36.8%)
Retrograde endopyelotomy (other hospitals)	2 (5.3%)
Surgical indication:	
Recurrence of UPJO	28 (73.7%)
Recurrence of UPJO and abnormal crossing vessel	4 (10.5%)
Twisted anastomosis	2 (5.3%)
Recurrence of UPJO and incorrect angle of the anastomosis	4 (10.5%)
	Mean±SD
Mean stricture length (cm)	0.99±0.45

Figure 2 - a, b) shows a recurrent UPJO (ureteropelvic junction obstruction) due to an abnormal crossing vessel and (c, d) a recurrent UPJO due to a twisted anastomosis.

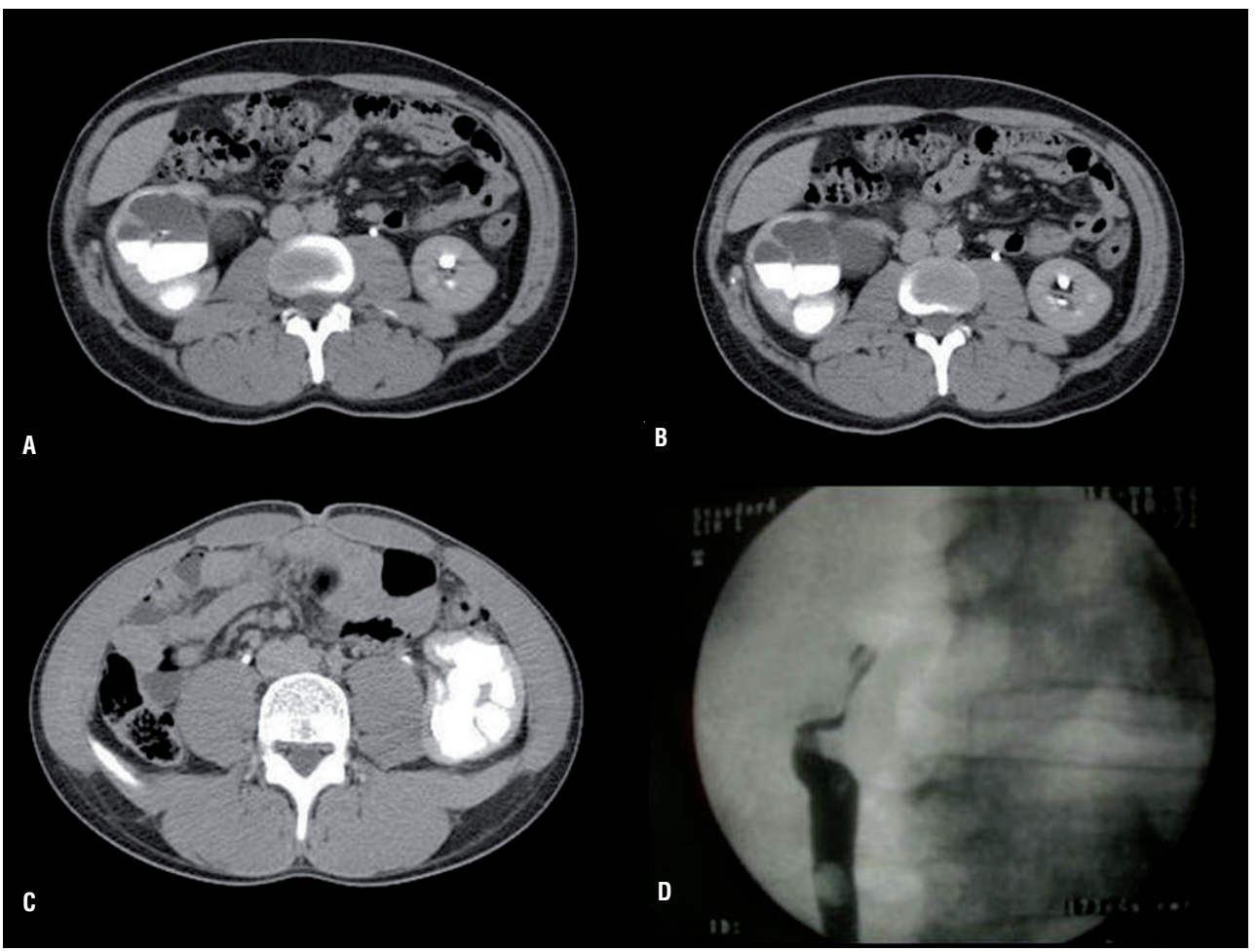


Table-2 reports post-operative complications according Clavien-Dindo classification and their management. 6 out of 38 patients (15.8%) experienced postoperative complications: hematuria (2 patients; 5.3%; Clavien-Dindo I), postoperative pain that required analgesics (2 patients; 5.3%; Clavien-Dindo I), urinary tract infection (1 patient; 2.6%; Clavien-Dindo II), urine leakage (1 patient; 2.6%; Clavien-Dindo IIIa).

The success rate was 97.4% (36 out of 38 patients) for flank pain using the VAS, and 97.4% (36 out of 38 patients) for hydronephrosis. Postoperative DTPA renal scan at 12 months showed radiological failure in 1 out of 38 (2.6%) patients, relative success in 2 out of 38 (5.3%) patients and total success in 35 out of 38 (92.1%) of patients. The radiologic failure, associated to flank pain and hydronephrosis, occurred in the patient that experienced the urine leakage. The patient underwent a laparoscopic pyeloplasty at our hospital for the third time with relative success at post-operative DTPA renal scan. The mean clinical and radiological follow-up was of 42.5±24.6 months.

DISCUSSION

Failure of pyeloplasty can be related to different factors. Even if anatomical features play a role, it is most likely secondary to technical issues. In our series one patient had a failure 15 years postoperatively, although most failures presented within 12 months of follow-up.

Table 2 - Post-operative complications according to Clavien-Dindo classification and their management.

	Grade	n(%)	Management
Hematuria	I	2/38 (5.3%)	delayed catheter removal
Postoperative pain	I	2/38 (5.3%)	analgesics
Urinary tract infection	II	1/38 (2.6%)	prolonged antibiotics
Urine leakage	IIIa	1/38 (2.6%)	percutaneous nephrostomy catheter placement and late removal of double-J stenting
Overall		6/38 (15.8%)	

To obtain a successful pyeloplasty some basic surgical principles should be observed: scrupulous preservation of the vascularity of ureter and pelvis, performing of a widely patent and watertight anastomosis, and careful tissue handling (11). It is important also to perform a "tension free" anastomosis, an anatomic reconstruction of ureteropelvic junction. Care should be taken to avoid kinking or twisting of anastomosis. In order to avoid a twisted anastomosis it is important to perform a good isolation of the pelvis and of the ureter and to pay attention to the first suture point.

Moreover, each crossing blood vessel should be recognized and in case of evident obstruction should be transposed. Some lower pole vessels could not be recognized as the main cause of UPJO during the first operation. In fact, they could have become adherent to an inflamed renal pelvis and could have inferiorly displaced by a big renal pelvis without an important cause of obstruction (12). Patients with a failed pyeloplasty have often an excessive amount of scaring and peripelvic fibrosis, and this finding could be associated to urinary extravasation, or an excessive tissue reaction to the first surgical procedure (13). In fact, one most delicate surgical step is the insertion of the ureteral stent. If the stent is inserted incorrectly, it will cause intraoperative complications or induce moderate to severe postoperative complications as urinary extravasation or fistulas, which lead to peripelvic fibrosis. The urinary extravasation could have caused the only radiological failure in our series.

Nowadays, several options are used for managing the failed pyeloplasty: antegrade or retrograde laser endopyelotomy, balloon dilation, redo-pyeloplasty and ureterocalicostomy. Open redo-pyeloplasty is associated with best outcomes compared with endopyelotomy (14, 15) and it has been the gold standard for years. With the advent of laparoscopy, laparoscopic redo-pyeloplasty has become a realistic alternative to redo open pyeloplasty, even if this approach is still anecdotal in literature. Although laparoscopic redo pyeloplasty may require a longer operative time to release peripelvic and periureteric fibrosis, hospital stay and postoperative complications were less than open redo pieloplasty (16).

Sundaram et al. reported the largest series of laparoscopic redo-pyeloplasty (36 patients) with a successful rate of 83% (4). Nevertheless, only 3 out of 36 (8.3%) patients underwent a pyeloplasty, while in our study 36 out of 38 (94.7%) patients were previously treated with dismembered pyeloplasty.

In our series the success rate was 97.4% for flank pain and 97.4% for hydronephrosis and total success at 12-month post-operative renal scan was achieved in 35 out of 38 (92.1%) of patients.

Radiological failure rate was 2.6%. It was similar to the failure rate previously described for the treatment of the primary UPJO (6). This can be explained by the fact that all procedures were performed by a well-trained and very experienced

laparoscopic surgical team. Laparoscopic redopyeloplasty can be a very challenging procedure because some adjuvant maneuvers may be required to success, like the use of a pelvis flap or ureterocalicostomy (17). In situations where ureteric and renal pelvis repair are not possible ileal interposition or autotransplantation can be also considered. The high rate of success in our series can be related to the short length of the failed stenosis without the need for additional challenging maneuvers. In the most complex cases we need to perform the isolation of all kidney and distal ureter in order to perform a tension free anastomosis and to avoid the twisting of the anastomosis.

Some limitations of the study herein include, firstly, the short follow-up time. Another limitation is that all procedures were performed by a single surgical team with significant expertise in laparoscopic surgery, which may restrict the generalizability of our results to centers with more limited laparoscopic experience. Moreover, this is a retrospective observational non-comparative study.

CONCLUSIONS

Laparoscopic redo-pyeloplasty is a feasible procedure for the treatment of recurrent ureteropelvic junction obstruction (UPJO), with a low rate of post-operative complications and a high success rate in high laparoscopic volume centers.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Grimsby GM, Jacobs MA, Gargollo PC. Success of Laparoscopic Robot-Assisted Approaches to Ureteropelvic Junction Obstruction Based on Preoperative Renal Function. J Endourol. 2015;29:874-7.
2. AJ Krill, CJ Palestro. Principles of Nuclear Medicine Imaging. In: LS Palmer and JS Palmer (ed.), Pediatric and Adolescent Urological Imaging- Springer New York Heidelberg Dordrecht London. 2014; †Part I, Cap. 6, pp. 102.
3. Madi R, Roberts WW, Wolf JS Jr. Late failures after laparoscopic pyeloplasty. Urology. 2008;71:677-80.
4. Sundaram CP, Grubb RL 3rd, Rehman J, Yan Y, Chen C, Landman J, et al. Laparoscopic pyeloplasty for secondary ureteropelvic junction obstruction. J Urol. 2003;169:2037-40.
5. Jarrett TW, Chan DY, Charambura TC, Fugita O, Kavoussi LR. Laparoscopic pyeloplasty: the first 100 cases. J Urol. 2002;167:1253-6.
6. Fedelini P, Verze P, Meccariello C, Arcaniolo D, Taglialatela D, Mirone VG. Intraoperative and postoperative complications of laparoscopic pyeloplasty: a single surgical team experience with 236 cases. J Endourol. 2013;27:1224-9.
7. Kazaryan AM, Røsok BI, Edwin B. Morbidity assessment in surgery: refinement proposal based on a concept of perioperative adverse events. ISRN Surg. 2013;2013:625093.
8. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-96.
9. Pouliot F, Lebel MH, Audet JF, Dujardin T. Determination of success by objective scintigraphic criteria after laparoscopic pyeloplasty. J Endourol. 2010;24:299-304.
10. Shih MT, Juho YC, Meng E, Sun GH, Cha TL, Wu ST, et al. Pain severity in renal colic: a retrospective evaluation of initial visits in patients at a medical center. Int Surg J 2016;3:480-3.
11. Novick, AC. and Streem, SB. Surgery of the kidney. In: Campbell's Urology, 7th ed. Edited by PC. Walsh, A. B. Retik, E. D. Vaughan, Jr. and A. J. Wein. Philadelphia: W. B. Saunders Co., vol. 3, sect. XIV, 1998; chapt. 97, pp. 3041–3043
12. Rehman J, Landman J, Sundaram C, Clayman RV. Missed anterior crossing vessels during open retroperitoneal pyeloplasty: laparoscopic transperitoneal Discovery and repair. J Urol. 2001;166:593-6.
13. Persky L, McDougal WS, Kedia K. Management of initial pyeloplasty failure. J Urol. 1981;125:695-7.
14. Thomas JC, DeMarco RT, Donohoe JM, Adams MC, Pope JC 4th, Brock JW 3rd. Management of the failed pyeloplasty: a contemporary review. J Urol. 2005;174:2363-6.
15. Braga LH, Lorenzo AJ, Skeldon S, Dave S, Bagli DJ, Khoury AE, et al. Failed pyeloplasty in children: comparative analysis of retrograde endopyelotomy versus redo pyeloplasty. J Urol. 2007;178:2571-5.
16. Piaggio LA, Noh PH, González R. Reoperative laparoscopic pyeloplasty in children: comparison with open surgery. J Urol. 2007;177:1878-82.
17. Ross JH, Streem SB, Novick AC, Kay R, Montie J. Ureterocalicostomy for reconstruction of complicated pelviureteric junction obstruction. Br J Urol. 1990;65:322-5.

Correspondence address:
Francesco Chiancone, MD
Urologic Clinic, AORN Cardarelli Hospital
Via A. Cardarelli 9, 80131, Naples, Italy
Telephone: + 39 340 863-9711
E-mail: francescok86@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 518-524, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0366

Which intraperitoneal insufflation pressure should be used for less postoperative pain in transperitoneal laparoscopic urologic surgeries?

Ali Akkoc [1], Ramazan Topaktas [1], Cemil Aydin [1], Selcuk Altin [1], Reha Girgin [1], Omer Faruk Yagli [2], Aykut Bugra Sentürk [3], Ahmet Metin [4]

[1] Department of Urology, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey; [2] Department of Urology, Kartal Yavuz Selim State Hospital, Istanbul, Turkey; [3] Department of Urology, Hitit University, Training and Research Hospital, Corum, Turkey; [4] Department of Urology, Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey

ABSTRACT

Purpose: To determine whether using different intraperitoneal insufflation pressures for transperitoneal laparoscopic urologic surgeries decreases postoperative pain.
Materials and Methods: 76 patients who underwent transperitoneal laparoscopic upper urinary tract surgery at different insufflation pressures were allocated into the following groups: 10mmHg (group I, n=24), 12mmHg (group II, n=25) and 14mmHg (group III, n=27). These patients were compared according to age, gender, body mass index (BMI), type and duration of surgery, intraoperative bleeding volume, postoperative pain score and length of hospital stay. A visual analog scale (VAS) was used for postoperative pain.
Results: Demographic characteristics, mean age, gender, BMI and type of surgeries were statistically similar among the groups. The mean operation time was higher in group I than group II and group III but this was not statistically significant (P=0.810). The mean intraoperative bleeding volume was significantly higher in group I compared with group II and group III (P=0.030 and P=0.006). The mean length of postoperative hospital stays was statistically similar among the groups (P=0.849). The mean VAS score at 6h was significantly reduced in group I compared with group III (P=0.011). At 12h, the mean VAS score was significantly reduced in group I compared with group II and group III (P=0.009 and P<0.001). There was no significant difference in the mean VAS scores at 24h among three groups (P=0.920).
Conclusion: Lower insufflation pressures are associated with lower postoperative pain scores in the early postoperative period.

ARTICLE INFO

Keywords:
Pain, Postoperative; Pneumoperitoneum; Laparoscopy; Urology

Int Braz J Urol. 2017; 43: 518-24

Submitted for publication:
June 21, 2016

Accepted after revision:
September 20, 2016

Published as Ahead of Print:
February 22, 2017

INTRODUCTION

Laparoscopic urologic surgeries have proven to be safe and effective compared with open surgery, offering the benefits of decreased blood loss, less postoperative pain, shorter hospital stay, rapid convalescence and earlier return to normal activities and work, smaller incisions and improved cosmetic effect (1-4). Although laparoscopic surgery reduces postoperative pain (POP), POP is still substantial and constitutes the main clinical problem after laparoscopic urologic procedures.

We surgeons always aim to inprove the quality of care given to patients. One of the strategies studied for less POP over the last years is to lower artificial intraperitoneal pressure level during laparoscopic procedure. Normal and low laparoscopic insufflation pressure are defined as 12-15 and 5-7mmHg, respectively (5). It has been shown that the use of lower pressure pneumoperitoneum reduces the adverse hemodynamic effects of laparoscopic surgery (6, 7). However, its effect on POP remains controversial.

We could find no study addressing the relationship between insufflation pressure and POP in transperitoneal or retroperitoneal laparoscopic urologic surgical procedures. This prospective study was aimed to compare POP in patients underwent transperitoneal laparoscopic upper urinary tract surgery (TLUS) at different insufflation pressures.

MATERIALS AND METHODS

We had included in this prospective study a total of 78 patients submitted to TLUS between July 2013 and March 2016 for various upper urinary tract pathologies including atrophic or hydronephrotic nonfunctioning kidney, renal cyst, ureteral stone, renal pelvic stone and ureteropelvic junction obstruction. The patients were allocated into three different intraperitoneal insufflation pressure groups. But two patients submitted to laparoscopic simple nephrectomy were excluded from the study because we had to increase intraperitoneal pressure for management of intraoperative bleeding. The operations were performed in 10mmHg and 14mmHg pressures. There were 24 patients in group I (10mmHg), 25 patients in group II (12mmHg), and 27 patients in group III (14mmHg). All laparoscopic procedures were performed by four surgeons. Approval was obtained from the local ethics committee, and written informed consent was obtained from all participants.

Exclusion criteria were pediatric population, oncology cases (due to the need of an additional incision to remove specimen), uncontrolled diseases such as severe hypertension, diabetes mellitus and asthma, neurologic diseases, chronic pain patients, prior abdominal surgery, a history of renal surgery or a solitary renal unit and American Society of Anaesthesiology (ASA) grade 3 or more.

In all cases, the same general anesthesia protocol was used. After induction of anesthesia, a nasogastric tube and a urinary catheter were inserted. All patients were placed in a modified (70 degree) lateral decubitus position with the umblicus over the break in the Table. Pneumoperitoneum was induced in all groups using a Veress needle and CO_2 was insufflated at a rate of 2L/min until intraabdominal pressures of 10, 12 and 14mmHg were reached. Intraperitoneal insufflation at these pressures was held constant by automatic regulation of the CO_2 inflow. Firstly, an 11mm trocar was placed, the abdomen was inspected by a 0º, 10mm rigid laparoscope for any injury due to Veress needle or port placements. Then, another 11mm trocar and 5mm trocar were used and these trocars were inserted under direct vision. When necessary, an additional 5mm fourth trocar was selectively used for proper exposure or traction. The surgical procedures were performed according to techniques used in transperitoneal laparoscopy by the types of surgery. Small specimens were retrieved through the 11mm trocar without trocar removal. Large benign specimens were removed after the specimen in the entrapment bag was fragmented by use of scissors without extension of the incision at the end of procedure. A double J stent was used intraoperatively in the twenty patients who were submitted to ureterolithotomy, pyelolithotomy and pyeloplasty. In all cases, residual CO_2 in peritoneum was evacuated at the end of the procedure by compressing the abdomen. We routinely placed a drainage tube through the lower trocar. After the laparoscopic surgery was completed, all patients were injected with 5mL of 5mg/mL bupivacaine (Marcaine 0.5%, AstraZeneca, Istanbul, Turkey) at all trocar areas.

All patients were routinely prescribed postoperative analgesia, with 20mg tenoxicam (Oksamen L, Mustafa Nevzat, Istanbul, Turkey) administered intravenously at 6 and 18 hours, postoperatively. After 24 hours, the same analgesic was administered to all patients if required. All of the patients were prescribed an oral analgesic drug for use as needed for pain after discharge.

The following study parameters of patients were recorded: age, gender, BMI, type and duration of surgery, intraoperative bleeding volume, postoperative pain score and length of hospital stay. The operation time was calculated from the first trocar insertion to the last trocar extraction. Evaluation of pain was performed postoperatively at 6, 12 and 24 hours. We asked patients to disregard localized and sharp pain around the port incision to exclude parietal pain. The patients were instructed by the physician to complete the visual analogue scale (VAS), ranging from 0 to 10 (0, no pain; 10, the most severe pain), to evaluate any diffuse, dull aching pains in the abdomen or shoulder, representing visceral and referred visceral pains.

All data were analyzed statistically using one-way analysis of variance (ANOVA) followed by the Bonferroni test for multiple comparisons, using the Statistical Package for Social Sciences (SPSS) software for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). The data are expressed as means±standard deviations (SD). P value of <05 was considered statistically significant.

RESULTS

During a 33-month period, we included in the study 76 patients who were submitted to TLUS including simple nephrectomy (LSN, n=28), renal cyst decortication (LRCD, n=28), ureterolithotomy (LUL, n=8), pyelolithotomy (LPL, n=6) and pyeloplasty (LPP, n=6). The mean age, gender, BMI and type of surgeries were statistically similar among the groups. The characteristics of the patients and types of surgeries are shown on Table-1. The mean intraoperative bleeding volumes were 115.42±49.87, 85.20±34.70, and 79.25±34.30mL in group I, group II, and group III, respectively, and significantly higher in group I compared with group II and group III (P=0.030 and P=0.006). It was higher in group II than group III but this was not statistically significant (P=1.000) (Table-2). The mean operation time was higher in group I than group II and group III but this was not statistically significant (P=0.810). The mean length of postoperative hospital stays were similar among groups (P=0.849) (Table-2).

The VAS scores at 6h were 4.13±1.12, 4.88±1.24, and 5.14±1.26 in group I, group II, and group III, respectively, and significantly reduced in group I compared with group III (P=0.011). At 12h, the mean VAS scores were 2.75±0.73, 3.52±1.01, and 3.74±0.85 in group I, group II and, group III, respectively and significantly reduced in group I compared with group II and group III (P=0.009 and P<0.001). There was no significant difference in the VAS scores at 24h among three groups (P=0.920) (Table-2). No patients required any additional analgesic agents for POP management.

DISCUSSION

Laparoscopy based on refinements in technology and instrumentation developed rather slowly and lately in urology and was adopted from gynecologists and general surgery, so initially it has been based on the transperitoneal approach (8). Since the introduction of laparoscopy in urologic practice, the clinical outcomes of laparoscopic surgery have shown decreased peri- and postoperative morbidity and mortality, shorter hospitalization and convalescence times, smaller incisions and improved cosmesis, and reduced POP compared with open surgery.

Patients in need of upper tract intervention for renal cyst, nonfunctioning kidney, ureteropelvic junction obstruction, or renal pelvic and ureteral stone or for oncological purposes may benefit from those advantages provided by TLUS. Although the duration of hospital stay and recovery time tend to be shorter than that after open surgery, POP is one of the most common complaints and still causes considerable discomfort and increased stress response following laparoscopic urologic procedures.

The types of POP in laparoscopic surgeries are deep intraabdominal pain (visceral pain), incisional pain (parietal pain) and shoulder pain (referred visceral pain) (9, 10). Although visceral pain may also depend on the extent of intraabdominal surgery, incisional pain is related to the number and size of access devices and also to the technique of incision closure and drainage. The reason of shoulder pain is not clear,

Table 1 - Characteristics of the patients and types of surgeries.

	Group 1 (N=24)	Group 2 (N=25)	Group 3 (N=27)	P Value
Age (years)	37.17±14.75	37.96±14.14	39.00±14.33	0.901
BMI (kg/m^2)	25.25±2.80	25.00±3.05	25.40±3.37	0.893
Gender				
(Male: Female)	13:11	11:14	13:14	0.782
Type of surgery				
LRCD	9	9	10	
LSN	9	9	10	
LUL	2	3	3	0.990
LPL	2	2	2	
LPP	2	2	2	

Table 2 - Postoperative pain scores, perioperative and postoperative parameters.

	Group 1 (N=24)	Group 2 (N=25)	Group 3 (N=27)	P Value
VAS (6h)	4.13±1.12	4.88±1.24	5.14±1.26	0.011[a]
VAS (12h)	2.75±0.73	3.52±1.01	3.74±0.85	<0.001[b]
VAS (24h)	1.95±0.75	2.04±0.74	2.00±0.62	0.920
Operation time (min)	111.17±56.17	102.40±50.65	103.00±51.70	0.810
Intraoperative blood loss (mL)	115.42±49.87	85.20±34.70	79.25±34.30	0.004[c]
Hospital stay (days)	3.50±2.20	3.88±2.68	3.67±2.07	0.849

[a]Group I < Group III p=0.011.
[b]Group I < Group II p=0.009, Group I < Group III p<0.001.
[c]Group I > Group II p=0.030, Group I > Group III p=0.006.

but it is commonly assumed that the continual stretching of the peritoneum during and after the pneumoperitoneum is responsible. Clinically, incisional and deep abdominal pain dominate over shoulder pain (5). There are several causes of pain following laparoscopic surgery due to the effect of CO_2 pneumoperitoneum, peritoneal stretching, diaphragmatic irritation, diaphragmatic injury and shoulder abduction during surgery (11, 12). Pneumoperitoneum affects the visceral pain component and theoretically, a low pressure should cause less pain than a high pressure (9) but this issue is still controversial.

Topcu and colleagues evaluated POP following gynecologic laparoscopy in a prospective randomized trial using three different intraabdominal pressures (8, 12, 15mmHg) (13). They showed a positive correlation between the VAS score following laparoscopic surgery and intraperitoneal insufflation pressure values. In the late postoperative period at 12h and 24h, they detected significantly lower pain score in the low pressure group. Additionally, in the early postoperative period at 6h, the VAS score was lower in the low pressure group, but this difference was not statistically significant. In our study, the VAS scores

at 6h were significantly reduced with 10mmHg pressure group compared with 14mmHg pressure group. At 12h, the VAS scores were significantly reduced in 10mmHg pressure group compared with 12 and 14mmHg pressure groups. There was no significant difference in the VAS scores at 24h among three groups.

In a prospective randomized double blind trial using 9 or 13mmHg intraabdominal pressure during laparoscopic cholecystectomy, it was reported that the low pressure pneumoperitoneum did not increase the duration of surgery, the frequency and intensity of shoulder tip pain were significantly lower in the low pressure group, and that the dose requirement for analgesic drugs was significantly lower in the low pressure group (14). In our study, there was no significant difference in the operation times and length of postoperative hospital stays among three different insufflation groups, and no patients required any additional analgesic agents for pain management.

In another study, Joshipura et al. reported that the use of low pressure had significant advantages for pulmonary function preservation, POP, analgesic usage, and hospital stay compared with the use of high pressure in pneumoperitoneum during laparoscopic cholecystectomy (15). Similarly, Wallace et al. compared 7.5 and 15mmHg intraabdominal pressures for laparoscopic cholecystectomy and reported that after operation the low pressure group had significantly less pain, better preservation of pulmonary function and shorter hospitalization (16). Some studies, however, have shown that the pressure levels did not affect pain scores. Celik and colleagues compared low (8mmHg), standard (12mmHg) and high-pressure (15mmHg) for laparoscopic cholecystectomy and reported that intraabdominal pressure has no effect on postoperative visceral pain, but has effect on duration of anesthesia and operation (17). Another study demonstrated no difference in low pressure and standard pressure pneumoperitoneum in the outcomes of laparoscopic cholecystectomy. And routine use of lower pressure pneumoperitoneum in laparoscopic cholecystectomy would not be recommended unless in selected straightforward cases (18). Similarly, Perrakis et al. reported that there was no difference in postoperative abdominal pain and analgesic consumption between low (8mmHg) and high (15mmHg) intraabdominal pressure groups (9). The reduction of intraabdominal pressure did not reduce POP.

Logically, total volume of intraperitoneal insufflations of CO_2 during laparoscopy may be associated with pain in patients submitted to laparoscopic urologic procedures. Total amount of CO_2 insufflated during laparosopic urologic procedures was not recorded in our study. We think that it was the limitation of our study. The number of patients are limited in the study due to the large number of exclusion criteria. This is the other limitation of the study.

Vilos and colleagues reported that the intraperitoneal pressure was correlated positively with BMI (19). It was suggested the use of low pressure in patients with higher BMIs. In our study, there was no statistical difference in BMI among the groups.

In the literature, various methods have experienced to reduce POP after laparoscopic surgical procedures. The pulmonary recruitment maneuver, intraperitoneal normal saline infusion and using low pressure pneumoperitoneum were found to reduce POP (11, 12, 20, 21). Additionally, intraperitoneal administration of local anesthetics or some analgesics or combination of these; periportal local anesthetic injection; or combined periportal and intraperitoneal administration of local anesthetic were efficient in reducing POP in laparoscopic procedures (22-26). However, some studies reported that periportal, intraperitoneal or combined periportal and intraperitoneal administration of local anesthetic did not influence POP after laparoscopic surgery (27, 28). The majority of studies have been performed on patients who underwent laparoscopic cholecystectomy and laparoscopic gynecological procedures. There is no study on this issue in laparoscopic urologic surgery.

In our study, increased hemorrhage volume and reduced POP were detected in the low pressure group. We found a relationship between lower pressure pneumoperitoneum and less pain, particularly during the early postoperative period. However, there was no significant difference in the pain scores in the late postoperative period, postoperative hospital stays and duration of

surgery among the groups. On the basis of those findings, the widespread use of lower pressure should be considered for POP control and patient comfort. According to the recommendation of the European Association for Endoscopic Surgery, a rational approach could be to employ minimum pneumoperitoneum pressure that allows adequate exposure of the surgical field (5).

CONCLUSIONS

According to our study, however, lower insufflation pressure may result in more increased hemorrhage; but it is associated with less post-operative pain scores in the early postoperative period. Additionally, use of lower pneumoperitoneum pressure in laparoscopy is important for not only postoperative pain but also intraoperative and postoperative other complications of laparoscopy such as subcutaneous emphysema, acidosis, cardiac arrhythmia, gas embolism, pneumothorax. We think that employing minimum intraperitonel insufflation pressure that allows adequate exposure of the surgical field in laparoscopic urologic surgeries is seen as a logical strategy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bessell JR, Baxter P, Riddell P, Watkin S, Maddern GJ. A randomized controlled trial of laparoscopic extraperitoneal hernia repair as a day surgical procedure. Surg Endosc. 1996;10:495-500.
2. Berggren U, Gordh T, Grama D, Haglund U, Rastad J, Arvidsson D. Laparoscopic versus open cholecystectomy: hospitalization, sick leave, analgesia and trauma responses. Br J Surg. 1994;81:1362-5.
3. Baxter JN, O'Dwyer PJ. Pathophysiology of laparoscopy. Br J Surg. 1995;82:1-2.
4. Pak CH, Baik S, Kim CS. Initial experience with retroperitoneal laparoendoscopic single-site surgery for upper urinary tract surgery. Korean J Urol. 2011;52:842-6.
5. Neudecker J, Sauerland S, Neugebauer E, Bergamaschi R, Bonjer HJ, Cuschieri A, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc. 2002;16:1121-43.
6. Dexter SP, Vucevic M, Gibson J, McMahon MJ. Hemodynamic consequences of high-and low-pressure capnoperitoneum during laparoscopic cholecystectomy. Surg Endosc. 1999;13:376-81.
7. Ninomiya K, Kitano S, Yoshida T, Bandoh T, Baatar D, Matsumoto T. Comparison of pneumoperitoneum and abdominal wall lifting as to hemodynamics and surgical stress response during laparoscopic cholecystectomy. Surg Endosc. 1998;12:124-8.
8. Liapis D, de la Taille A, Ploussard G, Robert G, Bastien L, Hoznek A, et al. Analysis of complications from 600 retroperitoneoscopic procedures of the upper urinary tract during the last 10 years. World J Urol. 2008;26:523-30.
9. Perrakis E, Vezakis A, Velimezis G, Savanis G, Deverakis S, Antoniades J, et al. Randomized comparison between different insufflation pressures for laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2003;13:245-9.
10. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. Eur J Surg. 2001;167:84-96.
11. Yasir M, Mehta KS, Banday VH, Aiman A, Masood I, Iqbal B. Evaluation of post operative shoulder tip pain in low pressure versus standard pressure pneumoperitoneum during laparoscopic cholecystectomy. Surgeon. 2012;10:71-4.
12. Kojima Y, Yokota S, Ina H. Shoulder pain after gynaecological laparoscopy caused by arm abduction. Eur J Anaesthesiol. 2004;21:578-9.
13. Topçu HO, Cavkaytar S, Kokanalı K, Guzel AI, Islimye M, Doganay M. A prospective randomized trial of postoperative pain following diferente insufflation pressures during gynecologic laparoscopy. Eur J Obstet Gynecol Reprod Biol. 2014;182:81-5.
14. Bala D, Shields D, Shukri S. Prospective randomized trial of low-pressure pneumoperitoneum for reduction of shoulder-tip pain following laparoscopy (Br J Surg 2000;87:1161-5). Br J Surg. 2001;88:315.
15. Joshipura VP, Haribhakti SP, Patel NR, Naik RP, Soni HN, Patel B, et al. A prospective randomized, controlled study comparing low pressure versus high pressure pneumoperitoneum during laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2009;19:234-40.
16. Wallace DH, Serpell MG, Baxter JN, O'Dwyer PJ. Randomized trial of diferente insufflation pressures for laparoscopic cholecystectomy. Br J Surg. 1997;84:455-8.
17. Celik AS, Frat N, Celebi F, Guzey D, Kaplan R, Birol S, et al. Laparoscopic cholecystectomy and postoperative pain: is it affected by intra-abdominal pressure? Surg Laparosc Endosc Percutan Tech. 2010;20:220-2.
18. Chok KS, Yuen WK, Lau H, Fan ST. Prospective randomized trial on low-pressure versus standard-pressure pneumoperitoneum in outpatient laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2006;16:383-6.

19. Vilos AG, Vilos GA, Abu-Rafea B, Hollett-Caines J, Al-Omran M. Effect of body habitus and parity on the initial Veres intraperitoneal CO2 insufflation pressure during laparoscopic access in women. J Minim Invasive Gynecol. 2006;13:108-13.
20. Kong TW, Park H, Cheong JY, Min SK, Ryu HS. Efficacy of continuous wound infiltration of local anesthetic for pain relief after gynecologic laparoscopy. Int J Gynaecol Obstet. 2014;124:212-5.
21. Tsai HW, Chen YJ, Ho CM, Hseu SS, Chao KC, Tsai SK, et al. Maneuvers to decrease laparoscopy-induced shoulder and upper abdominal pain: a randomized controlled study. Arch Surg. 2011;146:1360-6.
22. Elhakim M, Elkott M, Ali NM, Tahoun HM. Intraperitoneal lidocaine for postoperative pain after laparoscopy. Acta Anaesthesiol Scand. 2000;44:280-4.
23. Elhakim M, Amine H, Kamel S, Saad F. Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2000;44:929-33.
24. Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. Anesth Analg. 2000;91:403-7.
25. Colbert ST, Moran K, O'Hanlon DM, Chambers F, Moriarty DC, Blunnie WP. Na assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. Anesth Analg. 2000;91:667-70.
26. Maharjan SK, Shrestha S. Intraperitoneal and periportal injection of bupivacaine for pain after laparoscopic cholecystectomy. Kathmandu Univ Med J (KUMJ). 2009;7:50-3.
27. Savaris RF, Chicar LL, Cristovam RS, Moraes GS, Miguel OA. Does bupivacaine in laparoscopic ports reduce postsurgery pain in tubal ligation by electrocoagulation? A randomized controlled trial. Contraception. 2010;81:542-6.
28. Hilvering B, Draaisma WA, van der Bilt JD, Valk RM, Kofman KE, Consten EC. Randomized clinical trial of combined preincisional infiltration and intraperitoneal instillation of levobupivacaine for postoperative pain after laparoscopic cholecystectomy. Br J Surg. 2011;98:784-9.

Correspondence address:
Ali Akkoc, MD
Department of Urology
Gazi Yasargil Training and Research Hospital
Diyarbakir, Turkey
Fax: + 90 412 258-0060
E-mail: aliakkoc@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 525-532, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0482

Anterior six arms prolene mesh for high stage vaginal prolapse: five years follow-up

Luis Gustavo M. de Toledo [1,2], André Costa-Matos [2], Susane Mey Hwang [2], Raquel Dória Ramos Richetti [2], Silvia S. Carramão [1], Antônio P. F. Auge [1]

[1] Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brasil; [2] Serviço de Uroginecologia, Maternidade Cachoeirinha, São Paulo, SP, Brasil

ABSTRACT

Introduction: In high stage vaginal prolapse, recurrence risk patients, anterior and apical defects need to be addressed in the same procedure. The pre-molded commercial mesh kits are expensive and not always available. Alternative effective and safe treatment ways, with lower costs are desirable.
Objective: To present long term follow-up of patients treated with a homemade mesh shape to correct high stage prolapses.
Materials and Methods: We describe prospectively 18 patients with anterior and apical vaginal prolapses, stages III and IV, repaired using this specific design of mesh. All patients were submitted to pre-operative clinical evaluation and urodynamics. Prolapse was classified using the pelvic organ prolapse quantification (POP-Q). Intervention: Prolapse surgery, using a six arms prolene mesh, through a single anterior vaginal incision. Outcome Measurements: POP-Q, patients satisfaction, descriptive statistical analysis.
Results: Between February 2009 and Oct 2010, 18 consecutive women underwent the above-mentioned surgery. Mean age was 68 years. At a mean follow-up of .,4 years (5 to 5.8 years), 16 (89%) patients were continent, mean Ba point came from +4.7cm to -2.5cm, mean C point from +2.8cm to -6.6cm and mean Bp point from +1.3 to -1.7cm. There were two (11%) objective failures, but all the patients were considered success subjectively. There were two cases of mesh vaginal extrusion.
Conclusions: The homemade six arms prolene mesh allows concomitant correction of anterior and apical prolapses, through a single anterior vaginal incision, being an effective, safe and affordable treatment option when mesh is needed.

ARTICLE INFO

Keywords:
Surgical Mesh; Pelvic Organ Prolapse; Surgical Procedures, Operative

Int Braz J Urol. 2017; 43: 525-32

Submitted for publication:
August 25, 2016

Accepted after revision:
November 11, 2016

Published as Ahead of Print:
February 10, 2017

INTRODUCTION

Urinary incontinence and pelvic organ prolapse are some of the most commonly treated conditions in postmenopausal women. American women have an estimated 20% lifetime risk of undergoing a surgery for urinary incontinence or pelvic organ prolapse (POP) (1). Surgical cure rates vary greatly depending on surgical technique and the type of materials used (2).

According to Whiteside et al. (3), 58% of the women who had undergone surgery for genital prolapse, presented recurrence at 1-year follow-up evaluation. Treatment failures could be attributable to the use of weak native tissues. The use of mesh in POP surgery has been discussed exten-

sively lately, but the benefit is likely when there is a combination of risk factors such as recurrent POP, deficient fascia, chronic increased abdominal pressure, advanced stage and apical-anterior defect (4).Surgery using mesh, in this situation, presents better results in correcting high grades anterior and apical vaginal prolapses (2, 5).

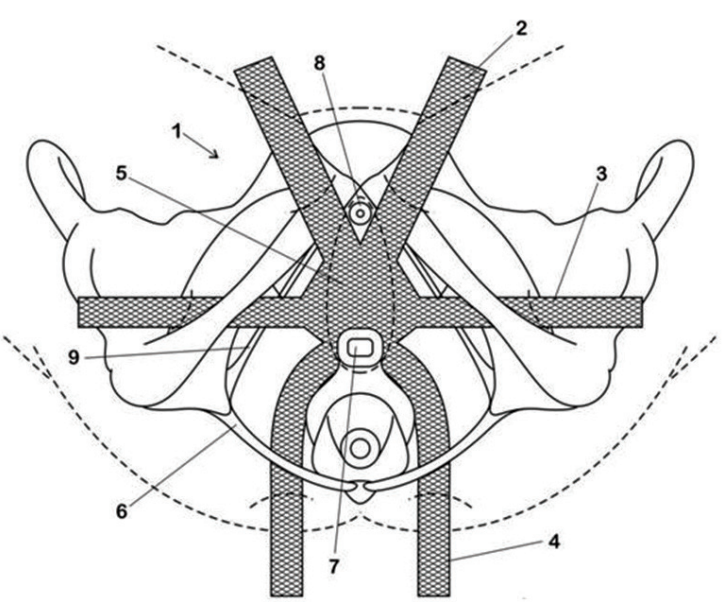
There is a high concomitance of apical and anterior prolapses in POP-Qstages III and IV. High stage anterior prolapses, those that may have benefit from mesh, are almost never just an anterior defect. Apical prolapse is frequently present and may be unnoticed. When apical prolapse is predominant, it's correction alone leads to anterior recurrence in up to 40% cases (6). Therefore, correction of these two defects, simultaneously, is required for a successful treatment. Today, abdominal sacral colpopexy using synthetic mesh over the anterior and/or posterior vaginal wall seems to be the more reliable procedure for the cure of genital prolapse with vaginal vault involvement, but the latest publications showed similar results with sacrospinous fixation that also provides good vaginal support (5, 7-9).

Previous experience has showed that synthetic material can reduce prolapse recurrence rates (10). The last generation of mesh kits were introduced addressing this practical problem, the combination of anterior and apical prolapses. Other ways of surgical management of multi-compartment prolapses are described. Feiner et al. (11) presented good results using anterior mesh associated to sacrospinous ligament sutures to treat concomitant anterior and apical defects. Mourtialon and Delorme (12) have proposed a similar mesh shape with good initial results. We propose a mesh shape to correct both anterior and apical prolapses, associated or not with stress urinary incontinence (SUI), with a single anterior vaginal incision, showing long-term results.

PATIENTS AND METHODS

Patients withanterior and/or apical stage III or IV POP and not needing hysterectomy for any uterine pathology met the inclusion criteria. All patients who met inclusion criteria and were treated surgically from February 2009 to Oct 2010, by two of the authors, in an institutional referral center of São Paulo, Brazil, were included. We describe prospectively 18 consecutive patients who were surgically treated using a specific design of mesh (Figure-1). All patients were operated by the resident physician in training and were supervised

Figure 1 - Antero apical mesh configuration: 1) the mesh;2) pre pubic arms;3) transobturator arms;4)sacrospinous ligament arms;5) body of the mesh;6) sacrospinous ligament;7) uterus cervix or vaginal vault;8) urethra;9) arcus tendineus.



and assisted by two surgeons (LGMT and ACM). The surgical steps were standardized so as to minimize variations between the two surgeons. The Institutional Review Board approved the study protocol, and a written informed consent was obtained after giving detailed explanations about the procedure. No financial assistance was received from any company or institution for the execution of this study.

All patients were submitted to a complete pre-operative evaluation including medical history, physical examination and urine culture. Urodynamic evaluation was performed when indicated by urinary symptoms (urinary incontinence, urgency or voiding disorders) or positive cough stress test (spontaneous or after prolapse reduction). Urodynamic investigation included a free flowmetry, filling cystomanometry and pressure flow studies(13). Occult SUI was assessed by prolapse reduction test with Cheron clamp, in supine and standing positions. The prolapse stage was assessed in lithotomy position while patient performed Valsalva maneuver. Prolapse was classified using Pelvic Organ Prolapse Quantification (POP-Q) (14). International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS) was used to subjective assessment of POP bother, severity, and impact on quality of life (15). Mesh complications were classified by IUGA/ICS Prosthesis/Graft Complication Classification Code (16).

A concomitant procedure was performed if necessary, including posterior vaginal repair and perineorraphy. Slings were not used as the anterior arms of the mesh were used to give a mid urethral support.

After surgery, evaluations were done at 3 weeks, 3 and 6 months and annually thereafter. Objective recurrent prolapse was defined as any anterior or posterior descent of stage II or higher (Ba or Bp≥-1cm), or apical descent of more than 1/3TVL (total vaginal length), even if asymptomatic. The post-operative assessments were performed by a third staff member (SMH).

Surgical description

This procedure was performed under spinal anesthesia. All patients were placed in the lithotomy position with thighs flexed at approximately 90º. After cleaning the entire surgical area with antiseptic, a Foley 16Fr catheter was placed. All patients had an intravenous perioperative antibiotic prophylaxis (Cefazolin 2g). We infiltrate the vaginal wall with a vasoconstrictive (epinephrine 1:200.000) solution to ease dissection and reduce bleeding. A midline longitudinal incision was made in the anterior vaginal wall from 2cm below the urethral meatus until 2cm from the uterine cervix. Sub fascial mucosal dissection was done until arcus tendineus bilaterally, pericervical ring proximally and middle urethra distally. Midline plication was done to reduce cystocele. Mesh positioning was done with aid of permanent needles, delivering two pre-pubic arms providing sub urethral support and avoiding mesh migration proximally, two transobturator (TO) arms as close as possible to the ischial spine through the arcus tendineus ligament, treating lateral defect, and two arms through the sacrospinous ligament, through trans gluteus access, 1.5 to 3cm medial to the ischial spine, to avoid injury to the pudendal nerves and vessels, rounding anteriorly the uterine cervix, to treat apical support defect. Fixation of the proximal end of the mesh to the pericervical ring used 2.0-polyglactin absorbable sutures (Vicryl, Ethicon, Somerville, NJ, USA). The vaginal incision was closed with interrupted 3.0-polycaprone sutures, before pulling the gluteal arms and prolapse reduction. One of the gluteus arms was pierced to the other side through retro anal subcutaneous path, and fixed to the other arm, with absorbable suture, to prevent loosening and early relapse. After the procedure, lubricated vaginal packing was placed for 12hs (Figure-1).

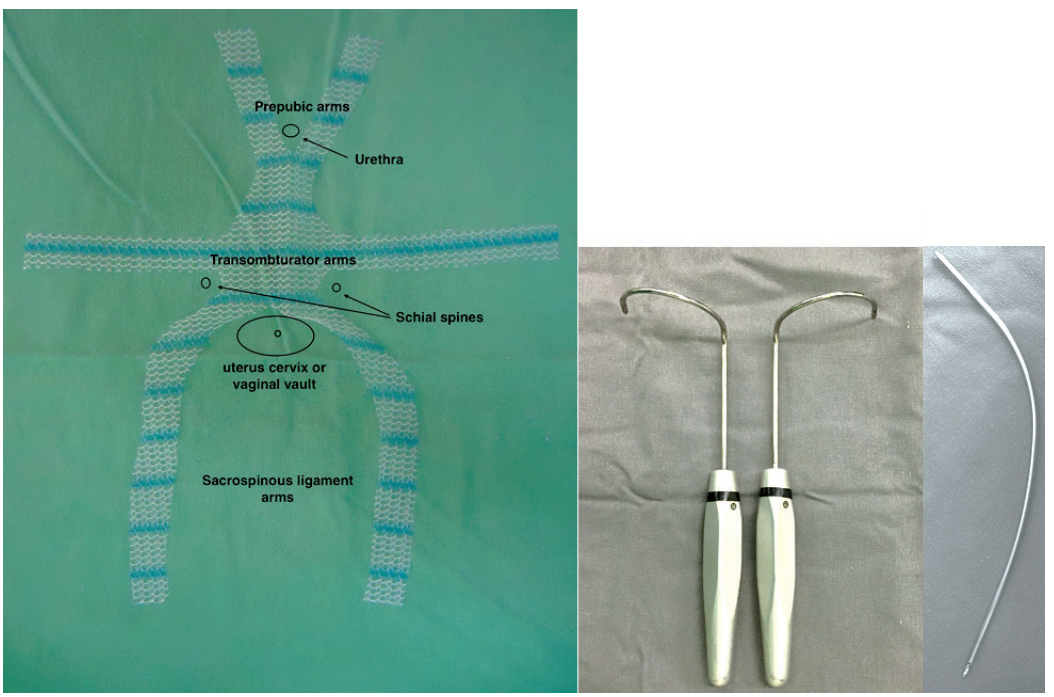
The mesh used was a non-absorbable monofilament soft polypropylene mesh (Gynecare Gynemesh™, Ethicon, Somerville, NJ, USA). Permanent retrieving needles were used to place the mesh arms (Figure-2).

Simple descriptive statistical analysis is described.

RESULTS

Nineteen patients were operated using the six arms mesh during the study period, one

Figure 2 - Molded anterior apical mesh, transobturator and trans gluteus sacrospinous retrieving needles.



of then lost follow-up and could not be reached for five years outcomes. Eighteen women had their data analysed. Mean age was 68 years. Pre-operative patient's characteristics are summarized in Table-1. Six (33%) patients had previous abdominal hysterectomy, and two had previous POP surgery. Three patients (16%) complained of SUI before surgery, seven had urgency (39%) and eight patients (44%) presented some voiding dysfunction (inability to empty the bladder, poor stream, digital maneuvers). Pre-operative clinical data are listed in Table-2.

Table 1 - Pre-operative patient's characteristics.

Characteristics	Mean (range) or n (%)
Age (years)	68 (53-81)
Parity (n)	5 (1-13)
BMI	27 (16.8-33)
Menopausal status	18 (100%)
Hormone replacement therapy	None
Previous hysterectomy	6 (33%)
Previous prolapse repair	2 (11%)
Previous surgery for SUI	2 (11%)
Sexual activity	2 (11%)
Dyspareunia	2 (11%)

BMI = Body Mass Index

Average operative time was 132min (90-180min). Posterior colporrhaphy was performed in six (33%) patients. No bladder or rectal injury was recorded. One patient had self-limited hypotension during legs repositioning. One patient had hemorrhage requiring transfusion of 3UI of blood concentrate, and presented with pelvic hematoma requiring open surgical drainage by Pfannenstiel incision. Three patients had urinary retention needing to be discharged with urinary catheter; two of them needed surgical relaxation of the pre pubic arms a week later, which could be done with local anesthesia. They regained normal voiding. The others had catheter removed after 24h. Median catheter use was one day (1-7d). Ten (55%) patients went home in the first postoperative day. Median hospital stay was oneday (1-18d). Mesh vaginal extrusion was identified in two patients, three months after surgery. They were two and three cm in diameter and occurred in the suture line. The patients presented with vaginal dis-

Table 2 - Pre-operative POP-Q stage data.

Prolapse	Anterior Vaginal Wall	Apical	Posterior Vaginal Wall
Stage 0–1	None	None	6(33.3%)
Stage 2	None	4 (22.2%)	4 (22.2%)
Stage 3	10 (55.6%)	10 (55.6%)	7(38.9%)
Stage 4	8 (44.4%)	4 (22.2%)	1 (5.6%)

POP-Q = pelvic organ prolapse quantification

Table 3 - Pre and postoperative POP-Q.

	Mean pre and post operative POP-Q			
Point	Mean pre-op (cm)	Mean post-op (cm)	Mean difference (cm)	P value
Aa	1.5	-2.5	4.0	<0.001
Ba	4.7	-2.5	7.2	<0.001
Ap	0	-1.7	1.7	NS
Bp	1.3	-1.7	3.0	0.02
C	2.8	-6.6	9.4	<0.001
D	1.4	-7.8	9.2	<0.001

POP-Q = Pelvic organ prolapse quantification

charge. Both were classified as 3BbT3S1 and were successfully treated with extirpation of the extruded mesh, with no prolapse recurrence. No organ erosion was identified.

At a mean follow-up of 5.4 years (5 to 5.8yr), 16 (89%) patients were continent, mean Ba point moved from +4.7cm preoperatively to -2.5cm postoperatively, mean C point, from +2.8cm to -6.6cm and mean Bp point, from +1.3 to -1.7cm (Table-3). All the patients were considered success subjectively. There were two objective relapses, one apical stage I and one posterior stage II, both asymptomatic, with no need of re-operation so far. The two sexual actives patients had no dyspareunia. SUI was diagnosed in three patients preoperatively and was totally controlled after surgery in two of them. Five (28%) patients complained of urgency and three (16%) of voiding symptoms postoperatively. The mean ICIQ-VS scores improved significantly postoperatively in all three domains. Vaginal symptom scored from 36.3 to 7.8; sexual matter scored from 30 to 12 (only two patients) and quality of life scored from 9 to 1.6.

DISCUSSION

With an aging population, the demand for physicians and surgeons trained in management of pelvic organ prolapse will increase. New technologies such as the development of vaginal approaches, using or not prosthetic devices, which are effective and reproducible may facilitate surgery and provide more widely better results.

The sacrocolpopexy is more widely applied for level one and high grades prolapses, with long follow-up consistent results and thus this technique is considered the gold standard(9, 17, 18). However, data of transvaginal sacrospinous colpopexy using mesh, with up to 90% objective cure and low complications rate, with relative long follow-up have also been published (19, 20). A recently published systematic review, comparing transvaginal meshes with native tissue

repair for vaginal prolapse reported that permanent meshes are associated with lower rates of subjective and objective prolapse recurrence, and prolapse reoperations. But, on the other hand, it is also associated to 8% reoperation for mesh exposure, more bladder injury and de novo stress urinary incontinence (21). We understand and reinforce that patient selection is extremely important to avoid unnecessary mesh use. We also believe that most mesh complications are due to technical mistakes, such as excess of mesh volume, focal tension, asymmetry, folding, mucosal damage and ischemia during dissection. Another practical observation is that we can lower complications maintaining the results using less and less mesh volume, prioritizing the correction of apical defect, as an anterior apical sling, pushing uterine cervix or vaginal vault towards sacrospinous ligament. We feel this is the right way of high stage POP treatment, less mesh volume addressing apical defect.

The anterior vaginal approach to the sacrospinous ligament is not a new technique, but its association to mesh molded to treat concomitantly apical and anterior vaginal prolapses, has recently been developed. By the time our patients were treated, only Elevate™ (American Medical Systems, Minnetonka, Minnesota, USA) had been marketed. The older generation of meshes kits used to treat apical defect are combined with posterior prolapse treatment, which is unnecessary since the later has no benefit from meshes, presenting similar results with conventional approach (9, 11). On the other hand, stages III and IV anterior prolapses are rarely isolated and generally associated with apical defect. So, it's rational that mesh treatment should combine anterior and apical repair and not posterior and apical as most of the mesh kits used to be designed for.

In the end of 2009, Mourtialon and Delorme (12) have published a new approach to fix cystocele and uterus or vault prolapsed with a six arms mesh that allow, as we do, only one anterior incision. However, a small difference is that we use pre-pubic arms, which prevent proximal migration, stabilizes the mesh distally preventing its folding in the longitudinal direction, and can eventually treat SUI. Importantly, thesepre-pubic arms differfrompre-pubic slings, which were abandoneddue to complicationssuch as extrusion and failures by migrating distally. In the pre-pubic sling, the force vector is toward the urethral meatus because there is no traction in the proximal direction. In other way, the anterior apical mesh is fixed proximally to the pericervical ring and to sacrospinous ligaments which prevents distal migration.

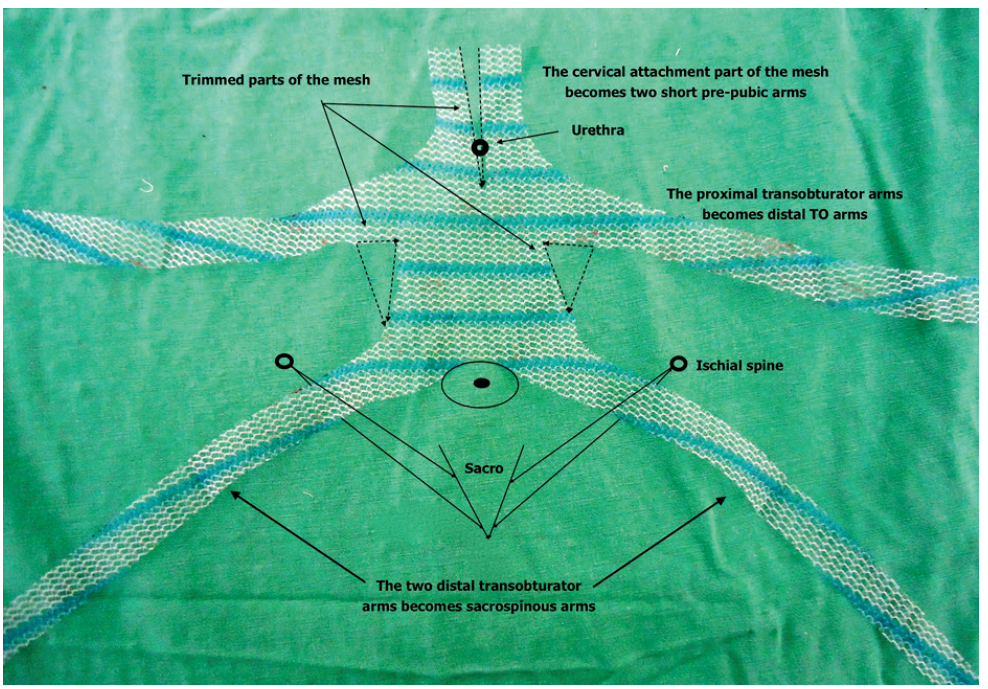
Alternative ways of treating multi-compartment prolapse are described. Feiner et al. (11) presented good results using anterior mesh associated to sacrospinous ligament sutures to treat concomitant anterior and apical defects. At the time, we also had done adaptations to treat these kinds of prolapse, one of them was, as we called it, the "Inverted Anterior Prolift". We used it upside down, so the two distal TO arms transfixed sacrospinous ligament through trans gluteal approach, the proximal TO arms becomes distal and cervical attachment part of mesh becomes two short pre--pubic arms (Figure-3).

Furthermore, the choice between a complete vaginal reconstruction of all compartments and a specific repair of only the defective areas is much debated (8). The risk of a specific repair is to provide a de novo prolapse in a compartment that previously appeared well supported. According to the prospective epidemiologic evaluation of Clark et al. (6), 60% of recurrence occurred at the same anatomic site, implying direct failure of the surgical procedure and 40% of recurrence occurred at a different site, which suggests a change in stability of the pelvic floor after surgery.

Our design of mesh allows correction of the three De Lancey´s level defects using only one incision and low volume of mesh. Therefore, anterior apical mesh seems rational and should reduce surgery time, morbidity, relapses and costs in high grade, recurrence risk prolapse patients.

Despite not removing vaginal epithelium, at the short-term follow-up, the vagina adheres to the underlying mesh, providing good functional and anatomical results while avoiding vaginal narrowing or shortening in most cases. Milani et al. (22) reported increasing dyspareunia with the anterior and posterior prolapse repair with prolene mesh. Dyspareunia increased by 20% after anterior repair and by 63% after posterior repair. Our

Figure 3 - Inverted Anterior Prolift.



findings don't suggest such results, however the majority of our patients (89%) were sexual inactive. Dwyer and O'Reilly (23) published sexual outcomes after transvaginal repair with Atrium polypropylene mesh (Hudson, New Hampshire, USA) in 67 sexually active patients. Dyspareunia was reported by 25.8% of the patients before surgery and 9.1% of the patients at 24 months post-operatively. Only three cases of de novo dyspareunia were reported in this study. The authors believe, as we do, that the removal of excess vaginal tissue is unnecessary and indeed deleterious.

Limitations of our study are the small sample size, poor LUTS assessment and the absence of a control group. However, five years follow up gives consistency to our good results and low complication rates. Some issues need to be addressed in future studies including prospective randomized comparison of anatomical and functional outcomes for mesh reinforcement versus site specific fascial repair alone and abdominal sacrocolpopexy. Another issue to be answered is if minimal (sling) apical mesh lowers complications maintaining results better than native tissue repair.

CONCLUSIONS

The six arms prolene mesh allows concomitant correction of anterior and apical high stages prolapses, through a single anterior vaginal incision, with high success and acceptable complications rates. It may be an alternative when mesh is desirable but kits are not available.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol. 2014;123:1201-6.
2. Jakus SM, Shapiro A, Hall CD. Biologic and synthetic graft use in pelvic surgery: a review. Obstet Gynecol Surv. 2008;63:253-66.
3. Whiteside JL, Weber AM, Meyn LA, Walters MD. Risk factors for prolapse recurrence after vaginal repair. Am J Obstet Gynecol. 2004;191:1533-8.

4. Davila GW, Baessler K, Cosson M, Cardozo L. Selection of patients in whom vaginal graft use may be appropriate. Consensus of the 2nd IUGA Grafts Roundtable: optimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery. Int Urogynecol J. 2012;23:S7-14.
5. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol. 2004;190:20-6.
6. Clark AL, Gregory T, Smith VJ, Edwards R. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2003;189:1261-7.
7. Gadonneix P, Ercoli A, Scambia G, Villet R. The use of laparoscopic sacrocolpopexy in the management of pelvic organ prolapse. Curr Opin Obstet Gynecol. 2005;17:376-80.
8. Benson JT, Lucente V, McClellan E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol. 1996;175:1418-21.
9. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013;4:CD004014.
10. Julian TM. The efficacy of Marlex mesh in the repair of severe, recurrent vaginal prolapse of the anterior midvaginal wall. Am J Obstet Gynecol. 1996;175:1472-5.
11. Feiner B, Gietelink L, Maher C. Anterior vaginal mesh sacrospinous hysteropexy and posterior fascial plication for anterior compartment dominated uterovaginal prolapse. Int Urogynecol J. 2010;21:203-8.
12. Mourtialon P, Delorme E. Trans-Sacrospinous in/out Tension-Free Passage: Treatment of Cystocele and Uterus or Vault Prolapse Using a 6 Arms Mesh. Journal Of Minimally Invasive Gynecology.2009; 6 (Suppl 1): S150.
13. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002;21:261-74.
14. Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996;175:10-7.
15. Tamanini JT, Almeida FG, Girotti ME, Riccetto CL, Palma PC, Rios LA. The Portuguese validation of the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS) for Brazilian women with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:1385-91.
16. Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J. 2011;22:3-15.
17. North CE, Ali-Ross NS, Smith AR, Reid FM. A prospective study of laparoscopic sacrocolpopexy for the management of pelvic organ prolapse. BJOG. 2009;116:1251-7.
18. Ostrzenski A. Laparoscopic colposuspension for total vaginal prolapse. Int J Gynaecol Obstet. 1996;55:147-52.
19. Lo TS, Ashok K. Combined anterior trans-obturator mesh and sacrospinous ligament fixation in women with severe prolapse--a case series of 30 months follow-up. Int Urogynecol J. 2011;22:299-306.
20. Dong S, Zhong Y, Chu L, Li H, Tong X, Wang J. Age-stratified analysis of long-term outcomes of transvaginal mesh repair for treatment of pelvic organ prolapse. Int J Gynaecol Obstet. 2016;135:112-6.
21. Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016;2:CD012079.
22. Milani R, Salvatore S, Soligo M, Pifarotti P, Meschia M, Cortese M. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG. 2005;112:107-11.
23. Dwyer PL, O'Reilly BA. Transvaginal repair of anterior and posterior compartment prolapse with Atrium polypropylene mesh. BJOG. 2004;111:831-6.

Correspondence address:
Luis Gustavo M. de Toledo, PhD
Rua Airosa Galvão, 168 / 92, Água Branca
São Paulo, SP, 05002-070, Brasil
Fax: +55 11 2373-5567
E-mail: drluisgtoledo@gmail.com

ORIGINAL ARTICLE

Vol. 43 (3): 533-539, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0356

Safety and short term outcomes of a new truly minimally-invasive mesh-less and dissection-less anchoring system for pelvic organ prolapse apical repair

Adi Y. Weintraub [1], Masha Ben Zvi [2], David Yohay [1], Joerg Neymeyer [3], Yonatan Reuven [4], Menahem Neuman [5,6], Alex Tsivian [2]

[1] Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheba, Israel; [2] Department of Urologic Surgery, Edith Wolfson Medical Center, Holon, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3] Department of Urology, Charitè University, Berlin, Germany; [4] Siaal Research Center for Family Medicine and Primary Care, Division of Community Health, Faculty of Health Science, Ben-Gurion University of the Negev, Beer Sheva, Israel; [5] Urogynecology, Department of Obstetrics and Gynecology, Galilee Hospital, and the Faculty of Medicine in the Galilee, Bar Ilan University, Safed, Israel; [6] Assuta Medical Centers, Tel Aviv and Rishon Le-Zion, Israel

ABSTRACT

Objective: To evaluate the safety and short term outcomes of a new, truly minimally-invasive, mesh-less and dissection-less anchoring system for pelvic floor apical repair.
Methods: A prospective study was conducted using the NeuGuide™ device system for pelvic floor apical repair. The primary effectiveness outcome was centro-apical pelvic floor prolapse by POP-Q after six months. The primary safety outcome was intra-operative, immediate (first 48 h) post-operative complications and adverse effects after six months. A standardized questionnaire (UDI-6) to assess quality of life at entry and during follow-up visits was used. Patients' six months-follow-up and evaluation are reported.
Results: The mean age of the study population (n=10) was 63.8±12.0 years. All patients had a previous prolapse surgery. Five had a previous hysterectomy and two had stress urinary incontinence symptoms. During surgery six patients had a concurrent colporrhaphy. There was no injury to the bladder, rectum, pudendal nerves, or major pelvic vessels and no febrile morbidity was recorded. At six months, no cases of centro-apical recurrence were noted. Patients were satisfied with the procedure and had favorable quality of life scores. Using the UDI-6 questionnaire an improvement, in all domains was seen. Moreover, although the sample size was small, the improvement in urge and overflow incontinence related domains were demonstrated to be statistically significant.
Conclusions: This new NeuGuide™ device allows rapid and safe introduction of a suspending suture through the sacrospinous ligament and makes sacrospinous ligament fixation easy to perform, while avoiding dissection and mesh complications.

ARTICLE INFO

Keywords:
Prolapse; Minimally Invasive Surgical Procedures; Pelvic Floor Disorders

Int Braz J Urol. 2017; 43: 533-9

Submitted for publication:
June 24, 2016

Accepted after revision:
September 20, 2016

Published as Ahead of Print:
February 02, 2017

INTRODUCTION

Pelvic organ prolapse (POP) is a common problem in women and often requires surgical correction. In the USA, about 200,000 women undergo surgery for prolapse correction every year (1). The lifetime risk of a woman to undergo a surgical procedure for the correction of pelvic floor dysfunctions (PFD) is 11%. Among these women, there is a close to 30% risk of re-operation due to failure or prolapse of another compartment (2).

Apical prolapse is defined as the descent of the apex of the vagina into the lower vagina, to or beyond the hymeneal ring. The apex can be either the uterus and cervix, cervix alone, or vaginal vault, depending upon whether the woman has undergone hysterectomy. The classification of prolapse according to the separate compartments is arbitrary, since the vagina is a continuum and prolapse of one compartment is often associated with prolapse of another (3).

Loss of apical support is usually present in women with advanced and symptomatic prolapse that extends beyond the hymen. Women may present with symptoms of anterior, posterior, central prolapse or any combination of these. Clinical manifestations include a bulge sensation or vaginal pressure, urinary, defecatory or sexual dysfunction (4). There is growing understanding that adequate vaginal apex support is essential for a durable surgical repair in women with advanced prolapse (5). Moreover, surgical correction of the anterior and posterior walls may fail unless the apex is adequately supported (6).

There is a wide variety of surgical treatments available for prolapse; this indicates that there is a lack of consensus as to the optimal surgical approach (5, 7).

Transvaginal sacrospinous ligament fixation (SSLF) was shown to have shorter operating time, less wound complications, quicker recovery to daily activities, and was cheaper than abdominal sacrocolpopexy (8). Moreover, the vaginal approach facilitates the concomitant correction of other vaginal defects as well. Because of a high risk for ureteral injury, the sacrospinous ligament (SSL) is preferred over the uterosacral ligament as the fixation point (9). However, transvaginal anchoring or placement of the fixation sutures through a deep, narrow space to the SSL is technically challenging and potentially dangerous. Indeed, numerous surgical adjuncts for SSL anchoring or suture placement have been introduced over the years with no device proven to be superior to others (10-16). These techniques all require deep vaginal dissection in order to gain safe access to the SSL. Many SSLF operations involving mesh implants were criticized by the FDA as having increased risk for severe and frequent adverse effects (17).

We have recently published our preliminary study demonstrating the biomechanical properties, feasibility and potential advantages of a new device - the NeuGuide™ (18). This new anchoring device intends to provide a truly minimally invasive, dissection-less approach for SSLF. This device enables the surgeon to perform a pelvic centro-apical support operation with no mesh implants, using just suturing materials. The aim of the current prospective pilot study is to evaluate the safety and short term outcomes of this new anchoring system for pelvic floor apical repair.

MATERIALS AND METHODS

Study design

A prospective study was conducted, following IRB approval. Surgeries were carried out by two experienced and well-trained urologic surgeons. All surgeries were performed using the same surgical technique. The primary effectiveness outcome was centro-apical pelvic floor prolapse by measuring the POP-Q point C/D after 6 months. The primary safety outcome was intraoperative complications and adverse effects after 6 months. A standardized questionnaire to assess quality of life (QoL) at entry and during follow-up visits was used.

Study population

A pilot of ten patients who presented with a diagnosis of POP-Q stage III centro-apical pelvic floor prolapse with significant symptoms were offered to enroll in the study. Informed consent was obtained after thorough information was presented. Inclusion criteria included: women aged

50-80 years, POP-Q stage III centro-apical pelvic floor prolapse, scheduled to undergo a POP surgery and had agreed to undergo it using the NeuGuide™ device, and who were willing to return for follow-up evaluation and fill questionnaires as indicated by the study protocol. Women with a diagnosis of reproductive tract anomalies, prior pelvic radiation therapy or any malignancy, women with a significant history of pelvic inflammatory disease, women with a known allergy to Nickel or Nitinol and women unable to complete written questionnaires were excluded from the study.

Data collection

Follow up assessment was carried out 4-6 weeks, three months and six months after surgery. We present the cumulative data regarding adverse outcomes at six months due to the small number of participants in this pilot study and the few events that occurred in order to avoid repetition and confusion. The UDI-6 score was provided for all follow up visits (n=8/10, n=6/10, n=9/10, respectively). Outcome measures included anatomical and functional cure rates, levels of post-operative pain and dyspareunia as well as intra and post-operative complication rates. Data was collected prospectively and included demographic features and validated PFD related quality of life (QoL) questionnaires (Urogenital Distress Inventory - UDI-6). Modified POP-Q scores (Ba, Bp, C and D) were measured preoperatively and at each post-operative visit. Stage of prolapse was defined as the most prolapsed compartment. Success of the operation was defined as a composite of no central compartment bulge symptoms and no prolapse beyond the stage I (1 cm proximal to the hymenal ring).

Device description and surgical technique

The NeuGuide™ is designed to enable centro-apical pelvic floor support for the uterine cervix or vaginal vault without need of either vaginal dissection or mesh implants in patients with a central compartment defect that need suspension. The NeuGuide™ device is comprised of two main elements: an anchor unit and a delivery system. The delivery system enables the guidance, insertion and deployment of the anchor element. The device's anchor unit is designed as a sharp needle point Nitinol harpoon enabling piercing through the vaginal layers and the ligament. The anchor is deployed and placed with the use of an applicator. The anchor incorporates a surgical suture at its distal end, which following its deployment enables fixation and the continuation of the surgical procedure as intended for the repair process. It has a thimble that is an accessory to the device and can be used as an introducer for better handling of the NeuGuide™.

The anchor penetration diameter is 2.0 mm. Once deployed (passed the SSL), the wings open to 4.0 mm. The work channel length is 120 m (this limits the anchor penetration depth beyond the ligament in order to avoid injury). The device shaft diameter is 2.5 mm and its length 285 mm. The suture length is 70 cm and the work channel is designed to fit all sizes (self-adjusting). The applicator includes two concentric hollow shafts. The outer shaft constrains the anchor wings from being deployed. Once the button is pressed, the inner shaft pushes the anchor distally and allows the wings to deploy. The applicator is equipped with a safety latch that protects the button, to avoid undesired deployment.

The steps of the surgical procedure are presented in Table-1.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, software version 22.0). Data on continuous variables with normal distribution were presented as mean±SD. Ordinal variables were presented as median and range, statistical analysis was completed using the Wilcoxon test. Categorical data were shown in counts. Two-sided p-value of <0.05 was considered significant.

RESULTS

Baseline preoperative clinical characteristics of the patients who underwent NeuGuide™ surgery are presented in Table-2. The mean age of the study population at the time of surgery was 63.8±12.0 years. All patients had a previous POP surgery, five had a previous hysterectomy and 2

Table 1 - The steps of the NeuGuide device surgical procedure.

1	The NeuGuide device is mounted on the right index finger, and introduced into the vaginal cavity
2	The right iscial spine and the SSL are palpated through the vaginal wall
3	The index finger is stabilized intimately to the mid SSL
4	The anchor is deployed, and adequate pull-out force is proven
5	A 1 cm longitudinal shallow and high mucosal incision is made at the posterior vaginal wall
6	The anchor's suture is mounted on a virgin needle
7	The suture is inserted backwards through the vaginal wall at its entering point, passed under the vaginal wall, then through the cervical istmus and out to the vaginal cavity again through the posterior colpotomy
8	The previous steps are repeated on the left side and the suture is tied appropriately
9	The small posterior vaginal incision is closed

SSL= Sacro-spinous ligament

Table 2 - Preoperative demographic and clinical characteristics of 10 patients who underwent NeuGuide™ surgery.

Characteristics	n = 10
Age	63.8±12.0
Body Mass Index	27.1±3.7
Parity	2 (1-3)
Health problems	6
SUI	2
Previous hysterectomy	5
Previous POP surgery	10
POP	10
Point C/D POPQ median (range)	3 (2-4)
Central compartment prolapse stage ≥ 3	10
Cystocele stage ≥ 2	9
Rectocele stage ≥ 2	7
Enterocele stage ≥ 2	0
Concomitant procedure	6
Anterior colporrhaphy	4
Posterior colporrhaphy	2
MUS	0

Values are presented as mean±SD, median and range or number of women
MUS = Midurethral sling; **SUI =** Stress urinary incontinence; **POP =** Pelvic organ prolapse; **POPQ =** Pelvic organ prolapse quantification system.

had stress urinary incontinence (SUI) symptoms. All patients had at least stage II prolapse in at least two compartments. Preoperative point C/D POPQ showed a median (range) of 3 [2-4]. During surgery 6 patients had a concurrent colporrhaphy and no injury to the bladder, rectum, pudendal nerves, or major pelvic vessels were noted.

Table-3 presents postoperative outcomes of patients who underwent NeuGuide™ surgery. No post-operative febrile morbidity was recorded. At the six months-follow-up, none of the patients had prolapse symptoms. Patients were found to be satisfied with the procedure with a median of 9, and favorable QoL scores were recorded with a median of 8 (on a scale of 0=not at all to 10=very much) (Table-3). All patients had significantly improved anatomical results (median point C/D POPQ score 0).

Using the UDI-6 standardized questionnaire, all domains showed an improvement in symptom related QoL. Moreover, improvement in urge and overflow incontinence related domains was demonstrated to be statistically significant (Table-4).

DISCUSSION

In this pilot study, we report our first short-term results of apical prolapse correction

Table 3 – Postoperative outcomes of patients who underwent NeuGuide™ surgery.

Characteristics	n = 10
Point C/D POPQ	-5 (-4/-7)
Hematoma formation	0
Abscess formation	0
Post-operative pelvic pain	0
Post-operative buttock pain	1
De Novo dyspareunia	0
De Novo SUI	0
De Novo urinary frequency	0
De Novo urge incontinence	1
Recurrent POP	0
Satisfaction	8 (9-7)
Quality of life	9 (9-7)

Values are presented as median and range or number of women.
SUI = Stress urinary incontinence; **POP =** Pelvic organ prolapse; **POPQ =** Pelvic organ prolapse quantification system.

after six months low complication rates were noted. None of the patients suffered from recurrent prolapse at the six months-follow-up. Satisfaction and QoL scores were high.

There is a wide variety of surgical procedures available for apical prolapse repair. This indicates that there is a lack of consensus as to the optimal surgical approach (5, 7). For years, mesh augmentation was the most common technique for apical prolapse repair. Following the FDA notification in 2011 (16), due to high occurrence of late complications with mesh as a foreign body, the current recommendation of the American College of Obstetricians and Gynecologists and the American Urogynecologic Society is for a judicious use of mesh implants that should be reserved for high risk individuals and selected patients only (19, 20).

POP is common and often requires surgical correction. The final surgical decision must be individualized. If a vaginal approach is chosen using a novel device - NeuGuide™ - a new anchoring device intended to provide a truly minimally invasive, dissection-less approach for SSLF. Our findings demonstrate that the primary effectiveness outcome, centro-apical pelvic floor prolapse at six months-follow-up, was highly successful. With regard to the primary safety outcomes, no intraoperative complications were recorded and and the patient is sexually active, then anatomic preservation of the vagina should be pursued (21). This has traditionally been accomplished with SSLF or other vaginal procedures such as uterosacral ligament suspension (USLS). USLS may be easier to perform than SSLF, with less risk of hemorrhage or infection, but does carry a higher risk of ureteral injury especially in patients with

Table 4 – Urogenital symptoms and Quality of life assessed with Urogenital Distress Inventory (UDI-6) (N=10).

UDI-6	Pre-surgery (N=10)	4-6 weeks after surgery (N=8)	Three months after surgery (N=6)	Six months after surgery (N=9)
Frequent urination	70	56*	50*	60
Urine leakage related to urgency	33	29	27	26*
Urine leakage related to physical activity	33	29	22	26
Small amounts of urine leakage (drops)	33	17	17	20*
Difficulty emptying your bladder	50	29	39	26
Pain or discomfort in the lower abdomen/ genitalia	50	28	33	30

Values are presented as percentages.
*P value <0.05

concomitant anterior colporrhaphy (22). Moreover, USLS is less practical in treating patients with post-hysterectomy vault prolapse. In our study, five patients were post hysterectomy and six had a concomitant anterior or posterior prolapse repair.

Informed decision-making about optimal surgical repair of apical prolapse with vaginal native tissue versus transvaginal mesh requires understanding the balance between the potential "harm" of mesh-related complications and the potential "benefit" of reducing prolapse recurrence. Dieter et al. (23) examined this harm/benefit balance and concluded that based on the best available evidence, there is considerable uncertainty about the harm/benefit trade-off between native tissue and transvaginal mesh for apical prolapse repair (23). In our study using the NeuGuide™ device, mesh complications were taken out of the equation.

Recurrent prolapse is also a major concern following POP surgery. In our study, at six months, all patients had significantly improved anatomical results (median point C/D POPQ score 0) and no cases of recurrence were noted. Lavelle et al. (24) reported their experience with POP recurrence after native tissue anterior vaginal suspension procedures. After a mean follow-up at 5.8±3.7 years, they reported prolapse recurrence rates of approximately 45% (isolated anterior 7.4%, isolated apical 10.7%, isolated posterior 8.3%, multiple compartments 19%) (24). Compared to their results, ours seem promising. However, a long-term follow-up will be needed in order to establish the sustainability of these results.

The primary limitations of the study include its single-arm evaluation. The lack of a control group restricts the external validity of this study. The 6-months evaluation period also may not be long enough to draw substantial conclusions. Another limitation that could restrict the external validity of this study was the fact that all surgical procedures were performed by two surgeons (MN and AT) who have extensive experience with pelvic surgery. However, since this is a new procedure it is unlikely that the surgeon's experience has affected the results. Finally, our study was too small to add meaningful data to the literature about objective and subjective outcomes of this device but it was a pilot study on human subjects and the outcomes are encouraging.

The strengths of the study include the prospective design allowing comprehensive data collection, the evaluation of self-reported patients centered outcomes and the use of validated QoL questionnaires. In addition, safety and efficacy of this new device were previously shown in a cadaver and animal study that was methodologically meticulous (18).

In conclusion, this new NeuGuide™ device allows rapid and safe introduction of a suspending suture through the SSL and makes SSLF easy to perform, while avoiding dissection and mesh complications. This procedure might be appropriate for patients with loss of apical support or elongated coli who wish to avoid mesh augmentation. Further studies are needed in order to substantiate these results and to increase the external validity of our findings.

CONFLICT OF INTEREST

Menahem Neuman is founder of POP Medical Solutions

Another Athors

None declared.

REFERENCES

1. Boyles SH, Weber AM, Meyn L. Procedures for pelvic organ prolapse in the United States, 1979-1997. Am J Obstet Gynecol. 2003;188:108-15.
2. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89:501-6.
3. Summers A, Winkel LA, Hussain HK, DeLancey JO. The relationship between anterior and apical compartment support. Am J Obstet Gynecol. 2006;194:1438-43.
4. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet. 2007;369:1027-38.
5. Barber MD, Maher C. Apical prolapse. Int Urogynecol J. 2013;24:1815-33.
6. Rooney K, Kenton K, Mueller ER, FitzGerald MP, Brubaker L. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. Am J Obstet Gynecol. 2006;195:1837-40.

7. Maher C, Feiner B, Baessler K, Adams EJ, Hagen S, Glazener CM. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2010;4:CD004014.
8. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol. 2004;190:20-6.
9. Yazdany T, Bhatia N. Uterosacral ligament vaginal vault suspension: anatomy, outcome and surgical considerations. Curr Opin Obstet Gynecol. 2008;20:484-8.
10. Miyazaki FS. Miya Hook ligature carrier for sacrospinous ligament suspension. Obstet Gynecol. 1987;70:286-8.
11. Sharp TR. Sacrospinous suspension made easy. Obstet Gynecol. 1993;82:873-5.
12. Lind LR, Choe J, Bhatia NN. An in-line suturing device to simplify sacrospinous vaginal vault suspension. Obstet Gynecol. 1997;89:129-32.
13. Chou LY, Chang DY, Sheu BC, Huang SC, Chen SY, Chang WC. Clinical outcome of transvaginal sacrospinous fixation with the Veronikis ligature carrier in genital prolapse. Eur J Obstet Gynecol Reprod Biol. 2010;152:108-10.
14. Friedman T, Neuman M, Peled Y, Krissi H. A new reusable suturing device for vaginal sacrospinous fixation: feasibility and safety study. Eur J Obstet Gynecol Reprod Biol. 2015;193:23-6.
15. Brennand EA, Bhayana D, Tang S, Birch C, Murphy M, Cenaiko D, et al. Anchor placement and subsequent movement in a mesh kit with self-fixating tips: 6-month follow-up of a prospective cohort. BJOG. 2014;121:634-40.
16. Anding R, Tabaza R, Staat M, Trenz E, Lohmann P, Klinge U, et al. Introducing a method of in vitro testing of different anchoring systems used for female incontinence and prolapse surgery. Biomed Res Int. 2013;2013:401417.
17. FDA Safety communication: Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Trans-vaginal Placement for Pelvic Organ Prolapse. July 2011. available at. http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf
18. Tsivian M, Weintraub AY, Neuman M, Tsivian A. Introducing a true minimally invasive meshless and dissectionless anchoring system for pelvic organ prolapse repair. Int Urogynecol J. 2016;27:601-6.
19. Committee on Gynecologic Practice. Vaginal placement of synthetic mesh for pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2012;18:5-9.
20. Davila GW, Baessler K, Cosson M, Cardozo L. Selection of patients in whom vaginal graft use may be appropriate. Consensus of the 2nd IUGA Grafts Roundtable: optimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery. Int Urogynecol J. 2012;23:S7-14.
21. Lovatsis D, P Drutz H. Vaginal surgical approach to vaginal vault prolapse: considerations of anatomic correction and safety. Curr Opin Obstet Gynecol. 2003;15:435-7.
22. Jackson E, Bilbao JA, Vera RW, Mulla ZD, Mallett VT, Montoya TI. Risk factors for ureteral occlusion during transvaginal uterosacral ligament suspension. Int Urogynecol J. 2015;26:1809-14.
23. Dieter AA, Willis-Gray MG, Weidner AC, Visco AG, Myers ER. Vaginal native tissue repair versus transvaginal mesh repair for apical prolapse: how utilizing different methods of analysis affects the estimated trade-off between reoperation for mesh exposure/erosion and reoperation for recurrent prolapse. Int Urogynecol J. 2015;26:721-7.
24. Lavelle RS, Christie AL, Alhalabi F, Zimmern PE. Risk of Prolapse Recurrence after Native Tissue Anterior Vaginal Suspension Procedure with Intermediate to Long-Term Followup. J Urol. 2016;195:1014-20.

Correspondence address:
Adi Y. Weintraub, MD
Department of Obstetrics and Gynecology
Soroka University Medical Center
Faculty of Health Sciences
Ben-Gurion University of the Negev
Beer Sheva, Israel
E-mail: adiyehud@bgu.ac.il

ORIGINAL ARTICLE

Vol. 43 (3): 540-548, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0405

Surgical treatment of detrusor underactivity: a short term proof of concept study

Jerry G. Blaivas [1, 2, 3], James C. Forde [1, 3], Jonathan L. Davila [2, 3], Lucas Policastro [2, 3], Michael Tyler [2, 3], Joshua Aizen [2, 3], Anand Badri [2, 3], Rajveer S. Purohit [1, 2, 3], Jeffrey P. Weiss [2, 3]

[1] Department of Urology, Weill Medical College of Cornell University, New York, NY, USA; [2] Department of Urology, SUNY Downstate Medical School, Brooklyn, NY, USA; [3] Institute for Bladder and Prostate Research, New York, NY, USA

ABSTRACT

Objectives: To compare the surgical outcomes of men with bladder outlet obstruction (BOO) due to benign prostatic obstruction (BPO) to those with detrusor underactivity (DU) or acontractile detrusor (DA).
Materials and Methods: This retrospective, IRB approved study included men who underwent BPO surgery for refractory LUTS or urinary retention. Patients were grouped based on videourodynamic (VUDS) findings: 1) men with BOO, 2) men with DU and 3) men with DA. The primary outcome measure was the Patient Global Impression of Improvement (PGII). Secondary outcome measures included uroflow (Q_{max}), post-void residual volume (PVR) and the need for clean intermittent catheterization (CIC).
Results: One hundred and nineteen patients were evaluated: 1) 34 with BOO, 2) 62 with DU and 3) 23 with DA. Subjective success rate (PGII) was highest in the BOO group (97%) and those with DU (98%), while DA patients had a PGII success of 26%, ($p<0.0001$). After surgery, patients with BOO had the lowest PVR (68.5mL). Fifty-six patients (47%) performed CIC pre-operatively (47% of BOO, 32% of DU and 87% of DA patients). None of the patients in the BOO and DU groups required CIC post operatively compared to16/23 (69%) of patients in the DA group ($p<0.0001$).
Conclusions: BPO surgery is a viable treatment option in men with presumed BOO and DU while DA is a poor prognostic sign in men who do not void spontaneously pre-operatively.

ARTICLE INFO

Keywords:
Prostatic Hyperplasia; Urinary Bladder Neck Obstruction; Prostate

Int Braz J Urol. 2017; 43: 540-8

Submitted for publication:
July 16, 2016

Accepted after revision:
October 25, 2016

Published as Ahead of Print:
February 21, 2016

INTRODUCTION

The goal of prostate surgery for bladder outlet obstruction (BOO) is to improve lower urinary tract symptoms (LUTS) in men by relieving benign prostatic obstruction (BPO). Its efficacy in men with proven BOO has been well documented (1, 2). Impaired detrusor contractility in the form of detrusor underactivity (DU) or detrusor acontractility (DA) can contribute to LUTS and confound the diagnosis of BPO. The diagnosis of DU can only be made by detrusor pressure-uroflow urodynamic studies (3). DU is defined by the International Continence Society (ICS) as, "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying, and/or failure to achieve complete bladder emptying within a normal time span" (4). This definition, though, is devoid of metrics; and does not specifically define "reduced strength," detrusor contraction "duration", and "a normal time span".

It has been reported that as many as 48% of men being assessed for LUTS display evidence of DU (5). There is much lacking in our understanding of the underlying physiologic mechanisms of DU, which is likely to be multi-factorial in nature, with both myogenic and neurogenic etiologies. It is also generally recognized that detrusor contractility diminishes with aging (4, 6, 7), but in some cases DU co-exists with BPO and can be a result of long standing untreated obstruction. Levin et al., in experimental studies in humans and rabbits have demonstrated that obstruction can lead to the development of smooth muscle hypertrophy, which is associated with significant intracellular and extracellular abnormalities in the smooth muscle cell (8, 9). Specifically, they documented changes in contractile protein expression, abnormalities of calcium signaling, impaired cell communication and mitochondrial dysfunction. Those authors postulated that these findings were responsible for both detrusor instability and impaired detrusor contractility (8, 9).

At present, there are no clear methods of diagnosing BPO in men with DU unless detrusor pressure at maximum uroflow ($pdetQ_{max}$) is > 40 cm H_20 and men with DU represent an underreported segment of the population of those with LUTS. In addition, there is much controversy in the surgical management of these cases as many urologists hesitate to consider prostate surgery in men with DU for fear that the results are suboptimal, unnecessarily subjecting them to the risk of the surgical procedure (10). In this study, we investigate this problem by comparing the outcomes of endoscopic prostate surgery in men with urodynamic evidence of BOO compared to those with either DU or DA.

MATERIALS AND METHODS

This is a retrospective, IRB approved study of men who underwent endoscopic surgery for BPO at a single institution in the form of either a monopolar Transurethral Resection of the Prostate (TURP) or Photoselective Vaporization of the Prostate (PVP) using the potassium titanyl phosphate (KTP) laser. Indications for surgery were refractory LUTS thought to be due to BPO or refractory urinary retention. A database was searched for patients who underwent either of these procedures and also underwent preoperative videourodynamics (VUDS). The patients were divided into three groups based on videourodynamic findings, 1) men with BOO (defined by a Bladder Outlet Obstruction index (BOOI) > 40) (11), 2) men with DU and 3) men with acontractile detrusor (DA). DU was defined by a Bladder Contractility Index (BCI) < 100. Acontractile detrusor (DA) was defined as the absence of a detrusor contraction on VUDS despite filling to bladder capacity. In patients with equivocal findings (BOOI between 30-39), the urodynamicist made a clinical judgment based on detrusor contraction duration and magnitude and the radiographic appearance of the urethra during voiding.

Patients who were on CIC were advised to try to void before each catheterization and their ability to do so was recorded. All subjects had pre-operative uroflow (Q_{max}), post-void residual volume (PVR) measurements, VUDS and cystoscopy. Post-operative Q_{max}, PVR, need for clean intermittent catheterization (CIC), and Patient Global Impression of Improvement (PGII) (12) score were obtained at least 3 months and up to 12 months after BPO surgery. The Patient Global Impression of Improvement (PGII) is an instrument used to assess patient satisfaction following treatment for a given condition; the seven point scale rates outcomes from 1=very much better to 7= very much worse (12). The PGII has previously been used to validate the success of patients following BPO surgery (13). The AUA symptom score (AUASS) or the lower urinary tract symptom score (LUTSS) (14) were collected before and after surgery in men who were not catheter dependent preoperatively.

When multiple values of Q_{max} and PVR were available, the highest and lowest values were used, respectively. Subjective success was defined by a PGII score of 1-3 whereas failure (no change or worsening of symptoms) was scored 4-7. All available data parameters were compared using either unpaired non-parametric two-tailed t test or Kruskal-Wallis test. All analyses were performed using Prism Graphpad 5 (CA, USA).

RESULTS

In total, 157 men were identified who underwent surgery for BPO (Figure-1). Of these, 38 were excluded because of incomplete VUDS or missing PGII data. The remaining 119 were divided as follows; 1) 34 men with BOO, 2) 62 men with DU and 3) 23 men with DA. Follow up ranged from 3-12 months (mean 9 months). Table-1 shows the breakdown between the number of TURP and PVP procedures performed for the individual groups. From the total of 119 surgeries for BPO, TURP accounted for 57 procedures (48%) while 62 PVP procedures (52%) were performed.

Table-2 shows that there was no difference in age, PVR or prostate volume between the three groups, but there was a higher pre-op Q_{max} in the BOO group (p<0.001). As expected both BCI and BOOI significantly varied between BOO and DU groups (p<0.0001).

Table-3 shows the pre and postoperative results. The subjective success rate (PGII) was highest in the BOO (97%) and DU (98%) groups, while the DA patients had a PGII success rate of only 26% (p<0.0001). Comparison of AUASS and

Figure 1 - Patient selection.

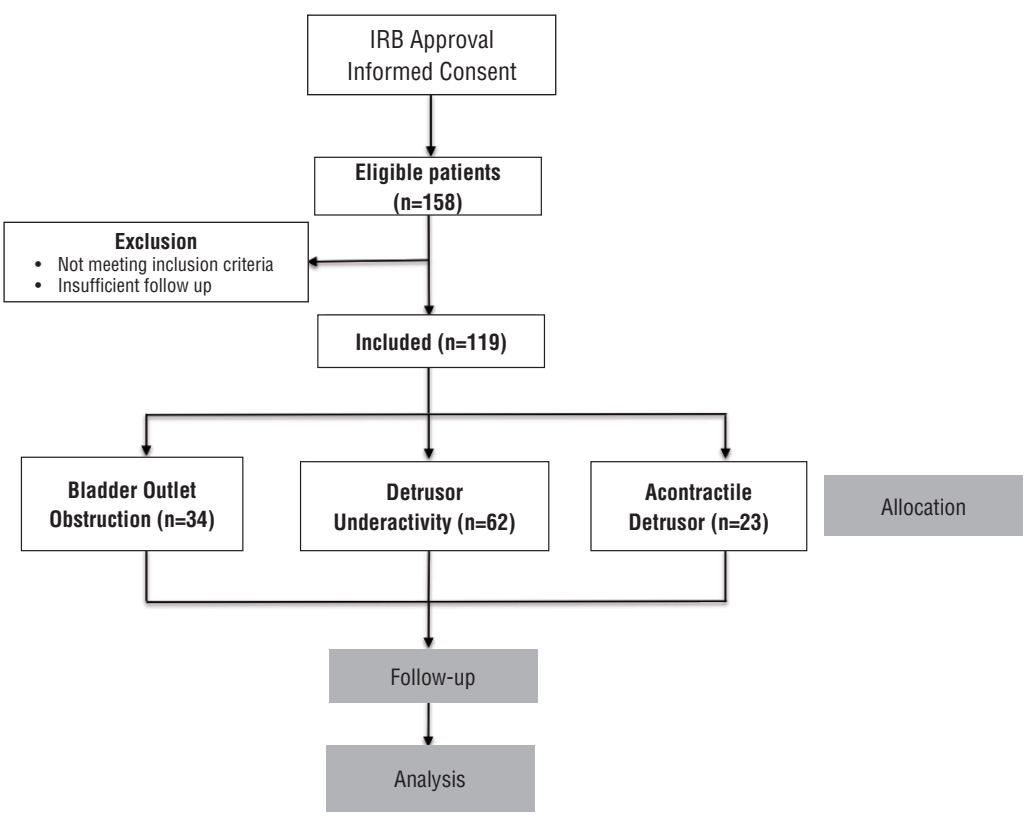


Table 1 - Type of BPO surgery performed in each group.

	BOO [n=34]	DU [n=62]	DA [n=23]
TURP (%)	11 (32%)	31 (50%)	15 (65%)
PVP (%)	23 (68%)	31 (50%)	8 (35%)

Table 2 - Preoperative data.

	BOO [n=34]	SD	DU [n=62]	SD	DA [n=23]	SD	P value
Age (in years)	67.9	12.4	68.4	11.9	71.6	11.8	0.47
BCI	124	22	54	26	--	--	<0.0001
BOOI	69	39	23	27	--	--	<0.0001
Pre-Op Qmax (mL/s)	7.8	5.2	4.4	3.7	--	--	<0.001
Pre-Op PVR (mL)	481	443	381	376	--	--	0.08
Bladder Capacity (mL)	553	302	619	392	1034	665	0.0001
Prostate volume (mL)	46	21	47	28	50	26	0.82

Table 3 - Comparison between Pre- and Post-Operative Outcomes.

Parameter	BOO [n=34]	DU [n=62]	DA [n=23]	P value
PGII success (%)	33/34 (97%)	61/62 (98%)	6/23 (26%)	<0.0001
Pre-op need for CIC (%)	16/34 (47%)	20/62 (32%)	20/23 (87%)	<0.0001
Post-op need for CIC (%)	0/34 (0%)**	0/62 (0%)**	16/23 (69%)*	<0.0001
%Δ in need for CIC	-100%	-100%	-17%	<0.0001
Pre-op Q_{max} (mL/s)	7.8	4.4	--	<0.001
Post-op Q_{max} (mL/s)	18.9**	15.9**	--	0.07
Δ Q_{max}	11.1	11.4	--	0.95
Pre-op PVR (mL/s)	481.3	380.7	--	0.08
Post-op PVR (mL/s)	68.5**	78.3**	--	0.32
Δ PVR	-393.3	-295.5	--	0.09
Pre-op AUASS	21.6	15.3	16.0	0.22
Post-op AUASS	5.5**	9.5*	9.0	0.45
Pre-op LUTSS	26.4	21.7	27.0	0.54
Post-op LUTSS	12.5**	14.3*	16.4	0.72

* indicates pre vs. post $p < 0.03$
** indicates pre vs. post $p < 0.003$
Δ = The symbol means change.

LUTSS scores before and after surgery revealed symptomatic improvements in the DU (p<0.025) and BOO (p<0.0006) groups. After BPO surgery, patients with BOO had a similar PVR to the DU group (68.5mL vs. 78.3mL, p=0.032). The change in Q_{max} after surgery was also similar between BOO and DU groups (11.1mL/s vs. 11.4mL/s, p=0.95). In both BOO and DU groups, improvements in Q_{max} and PVR after surgery were significant (p<0.0001).

Of the 119 patients, 56 (47%) were on CIC pre-operatively. This included 47% of BOO patients, 32% with DU and 87% of the patients in the DA group. Three men in the DA group were able to void spontaneously at home but unable to demonstrate this on VUDS. After surgery, a further 4 patients with DA no longer required CIC, leaving 16/23 (69%) patients in the DA group who were CIC-dependent post-operatively compared to none of the patients in the BOO and DU groups (p<0.0001). This improvement was significant in all groups (DA, p=0.01; BOO and DU, p<0.0001).

DISCUSSION

Historically, impaired or absent detrusor contractions during urodynamics has been considered a poor prognostic sign for a successful outcome after BPO surgery in men with refractory LUTS (10, 15). The data presented herein suggests that outcomes do not differ between patients with and without DU undergoing BPO surgery. Specifically, there was no difference in outcomes after BPO surgery in men with DU and BOO versus BOO alone who can generate a detrusor contraction during VUDS. Preoperatively, men with BOO had higher Q_{max}, but there was no difference between the degrees of improvement in parameters postoperatively.

Further analysis of data revealed that men with detrusor acontractility who never void spontaneously while on CIC have an overall poor prognosis. Urodynamic studies provide the physician with a snapshot of bladder function in a potentially intimidating environment, which may inhibit normal voiding function and may result in a spurious acontractile detrusor. We hypothesize that if a man is able to void between catheterizations while on CIC, he likely has retained at least some detrusor function and that BPO surgery will reduce outlet resistance and improve voiding mechanics. To wit, the data confirms a significant failure rate in patients on CIC who are never able to void spontaneously with only 26% of those patients having a successful outcome after BPO surgery.

Our literature search found a limited number of studies describing the outcomes of patients with DU after BPO surgery and, in fact, Thomas et al. in 2003 reported that they were unable to find a single relevant study when they reported their results on 22 patients with DU who had undergone TURP. Their study, with a mean follow-up of 11 years, found no clinical or urodynamic benefit from surgery (15). However, they did not report any patient reported outcomes like the PGII. Further, this study was highly selected in so far as only 22 at 284 patients with DU actually underwent TURP (15). A number of recent studies, however, showed much more encouraging results. Masumori et al. reported the long-term outcomes of a cohort of 92 men undergoing TURP (16). There were 34 patients who completed the 12-year follow-up including a subgroup of 12 patients with DU who reported a long-term benefit in terms of IPSS and QoL scores following surgery (16). Han et al. examined the effect of TURP in 25 men with weak bladder contractility compared to 46 men undergoing TURP with obstructed and/or normal bladder contractility and compared pre and post-operative IPSS, quality of life questionnaires and uroflowmetry (17). Groups were separated on a urodynamic basis using BOOI < 40 and BCI < 100 as criteria for inclusion into their DU group (17). They reported a 60% satisfaction rate among the 25 patients having poor bladder contractility with significant improvements in both voiding and storage parameters of IPSS and quality of life questionnaire (IPSS/QoL). Flow rates between groups did not differ, however, there was a significant reduction in post-operative PVR. Although patients with normal bladder contractility had significantly more improvement after TURP, outcomes were promising for those with evidence of impaired bladder contractility. Improvement in this group of patients was attributed to BOO, masked by the underlying DU, which was trea-

ted by resection, unrecognized by initial urodynamic study due to reduced detrusor pressure at the time of voiding. These findings were corroborated by van Venrooij et al. who reported that bladder outlet reduction in 34 patients with equivocally obstructed or unobstructed bladders produced a reduction in symptoms albeit to a lesser extent (70%) than 59 patients who were obstructed (18). They also document a significant 40% reduction in urethral resistance in the unobstructed group, which is a possible explanation for the improvement in those without obstruction (18).

In addition to these comparative studies, additional authors have also suggested that TURP is a viable option in patients with DU. Specifically, Ou et al. reported on their prospective cohort of 20 patients with BPH and urodynamically diagnosed detrusor "hypocontractility", revealing significant improvements in IPSS/QoL, Q_{max}, PVR and maximum P_{det} after TURP (19). Seki et al. retrospectively reviewed 190 patients with DU and assessed outcomes 12 months after TURP, concluding that only pre-operative level of storage symptoms in this group negatively impacted improvement post-operatively. However, peak urinary flow rates were positively influenced by baseline degree of bladder obstruction (20). Tanaka et al. examined the preoperative urodynamics of 92 men who underwent TURP and classified them as either BOO, DU and detrusor overactivity (DO) (21). There were 37 (40.2%) patients deemed to have weak/very weak contractility (18). They confirmed that a higher degree of bladder outlet obstruction predicts a better chance of improvement after TURP, but that presence of DU itself did not influence the likelihood of positive post-surgical outcome (21). In comparison to these published studies we included a significant number of patients with DU (62 patients or 52% of total patients involved) with a subjective success rate of 98%. The improvement in Q_{max} was comparable between both BOO and DU patients.

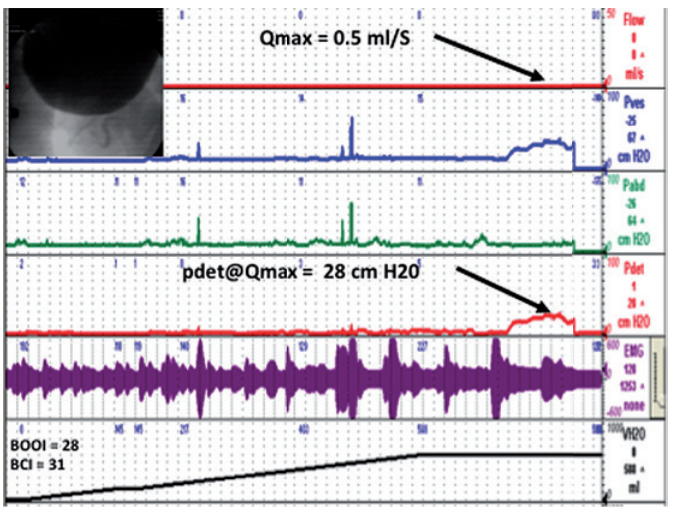
The utility of urodynamics in this setting has been called into question as it has been suggested that objective findings are generally inaccurate in predicting response to surgery (22, 23). We find urodynamics very useful in predicting the outcome of surgery, but our opinion is based largely on a qualitative assessment of the pressure flow curve and radiographic appearance of the urethra during voiding as depicted in the two videourodynamic tracings seen in Figures 2 and 3 comparing a patient with DU and BOO and a patient with BOO and normal detrusor function.

We believe that a sustained detrusor contraction and narrowed prostatic urethra portends a good outcome, but a much larger study is necessary to determine whether this is true. Some investigators have attempted to find features that can provide useful clinical information to guide those who question the efficacy of surgical intervention. Blatt et al. investigated ultrastructural features on detrusor biopsy in patients with detrusor failure after TURP and found that a combination of muscle cell size, shape, collagenosis and abnormal fascicles predicted postoperative voiding failure (24).

Although urodynamics has its limitations, it does provide useful information specifically in those who are found to have no detrusor function who never void spontaneously. Our data suggests that these patients are likely not going to benefit from surgery and should thus be considered for more conservative management (i.e. continuous or intermittent catheterization). However, the observation that occasional patients with DA do come off CIC keeps the surgical option open for this poor-prognosis group.

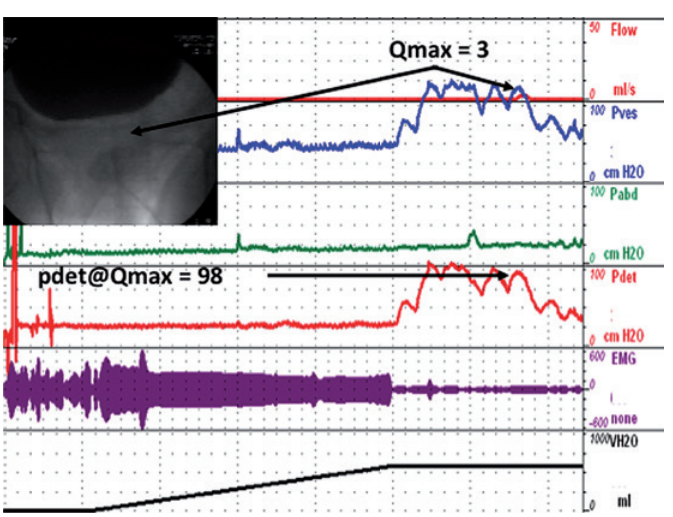
There are a number of limitations to this study. Because of its retrospective nature, it was not possible to determine how many surgical candidates were not offered or refused surgery. Further, there were different group sizes and relatively small numbers, but that is due, in part, to the fact that a smaller number of patients with impaired detrusor contractility undergo BPO surgery. The study included two different types of surgery for BPO (both TURP and PVP). Our hypothesis was to evaluate the effect of BPO surgery as an entity in patients with DU or DA compared to outcomes in those with proven BOO. We acknowledge that variations may exist in terms of technique between each procedure type. However, both standard electrosurgical TURP and PVP are well-established surgical treatments for BPO with the latter recently shown to 'exhibit efficacy and safety outcomes

Figure 2 - Sample VUDS of patient with DU.



Example of patient with urodynamic evidence of detrusor underactivity. He has a low amplitude sustained contraction occurring for roughly 60 seconds. Pdet at Q_{max} is only 28 cm of water and the Q_{max} at this point is 0.5mL per second. According to BOO index calculation, he does not have urodynamic evidence of an obstruction.

Figure 3 - Sample VUDS of patient with BOO and normal detrusor function.



Patient with a strong, high pressure bladder contraction and obvious bladder obstruction.

similar to TURP' in the recently published GOLIATH study (25).

Notwithstanding that, our cohort of DU patients is one of the largest published series to date. Follow up was limited to 3-12 months after surgery because we considered this study a proof of concept design and recognize that larger numbers and longer follow up is necessary to prove long term efficacy. Another limitation is the inherent bias generated as groups were constructed based on a clinical suspicion that there was an underlying obstruction that was not documented by urodynamics.

Despite the unstructured follow up, we believe that results of the study prove an important point, a proof of concept – that most

men with detrusor underactivity have an underlying prostatic obstruction and that surgery designed to relieve the obstruction is effective in the majority of patients. The durability of the outcome remains in question[15], though there have been reports of long-term benefit (20).

CONCLUSIONS

BPO surgery is a viable treatment option in men with presumed BOO and DU. However, acontractile detrusor is a poor prognostic sign in men who do not void spontaneously while on intermittent catheterization. Prospective studies with larger patient cohorts would be beneficial to help confirm the findings of this study.

ABBREVIATIONS

LUTS = Lower Urinary Tract Symptoms
BOO = Bladder Outlet Obstruction
BPO = Benign Prostatic Obstruction
DU = Detrusor Underactivity
DA = Acontractile Detrusor
VUDS = Videourodynamics
Q_{max} = Maximum flow rate
Pdet = Detrusor pressure
PVR = Post Void Residual volume
PGII = Patient Global Impression of Improvement (PGII)
CIC = Clean Intermittent Catheterization
ICS = International Continence Society
IRB = Institutional Review Board
TURP = Transurethral Resection of the Prostate
PVP = Photoselective Vaporization of the Prostate
KTP = Potasium Titanyl Phosphate
BOOI = Bladder Outlet Obstruction Index
BCI = Bladder Contractility Index
AUA = American Urological Association
IPSS = International Prostate Symptom Score
AUASS = AUA Symptom Score
LUTSS = Lower Urinary Tract Symptom Score
QoL = Quality of Life

CONFLICT OF INTEREST

Jeffrey P. Weiss has served as an advisor for Allergan, Astellas, Ferring, Pfizer, and Vantia. Jerry G. Blaivas is co-founder and CSO of Symptelligence Medical Informatics

Other Authors: None declared.

REFERENCES

1. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol. 2015;67:1099-109.
2. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011;185:1793-803.
3. Gammie A, Kaper M, Dorrepaal C, Kos T, Abrams P. Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies. Eur Urol. 2016;69:361-9.
4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. Standardisation Sub-committee of the International Continence Society.. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167-78.
5. Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, et al. The underactive bladder: a new clinical concept? Eur Urol. 2015;68:351-3.
6. Diokno AC, Brock BM, Brown MB, Herzog AR. Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. J Urol. 1986;136:1022-5.
7. Taylor JA 3rd, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. J Am Geriatr Soc. 2006;54:1920-32.
8. Levin RM, Haugaard N, O'Connor L, Buttyan R, Das A, Dixon JS, et al. Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: a direct comparison. Neurourol Urodyn. 2000;19:609-29.
9. Levin RM, Wein AJ, Saito M, Longhurst PA. Factors that modulate the initiation of micturition. Scand J Urol Nephrol Suppl. 1995;175:3-10.
10. Javlé P, Jenkins SA, Machin DG, Parsons KF. Grading of benign prostatic obstruction can predict the outcome of transurethral prostatectomy. J Urol. 1998;160:1713-7.
11. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int. 1999;84:14-5.
12. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol. 2003;189:98-101.

13. Hossack T, Woo H. Validation of a patient reported outcome questionnaire for assessing success of endoscopic prostatectomy. Prostate Int. 2014;2:182-7.
14. Blaivas JG, Tsui JF, Mekel G, Benedon MS, Li B, Friedman FM, et al. Validation of the lower urinary tract symptom score. Can J Urol. 2015;22:7952-8.
15. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. BJU Int. 2004;93:745-50.
16. Masumori N, Furuya R, Tanaka Y, Furuya S, Ogura H, Tsukamoto T. The 12-year symptomatic outcome of transurethral resection of the prostate for patients with lower urinary tract symptoms suggestive of benign prostatic obstruction compared to the urodynamic findings before surgery. BJU Int. 2010;105:1429-33.
17. Han DH, Jeong YS, Choo MS, Lee KS. The efficacy of transurethral resection of the prostate in the patients with weak bladder contractility index. Urology. 2008;71:657-61.
18. van Venrooij GE, van Melick HH, Boon TA. Comparison of outcomes of transurethral prostate resection in urodynamicallyobstructed versus selected urodynamicallyunobstructed or equivocal men. Urology. 2003;62:672-6.
19. Ou R, Pan C, Chen H, Wu S, Wei X, Deng X, et al. Urodynamically diagnosed detrusor hypocontractility: should transurethral resection of the prostate be contraindicated? Int Urol Nephrol. 2012;44:35-9.
20. Seki N, Kai N, Seguchi H, Takei M, Yamaguchi A, Naito S. Predictives regarding outcome after transurethral resection for prostatic adenoma associated with detrusor underactivity. Urology. 2006;67:306-10.
21. Tanaka Y, Masumori N, Itoh N, Furuya S, Ogura H, Tsukamoto T. Is the short-term outcome of transurethral resection of the prostate affected by preoperative degree of bladder outlet obstruction, status of detrusor contractility or detrusor overactivity? Int J Urol. 2006;13:1398-404.
22. Bruskewitz R, Jensen KM, Iversen P, Madsen PO. The relevance of minimum urethral resistance in prostatism. J Urol. 1983;129:769-71.
23. Djavan B, Madersbacher S, Klingler C, Marberger M. Urodynamic assessment of patients with acute urinary retention: is treatment failure after prostatectomy predictable? J Urol. 1997;158:1829-33.
24. Blatt AH, Brammah S, Tse V, Chan L. Transurethral prostate resection in patients with hypocontractile detrusor--what is the predictive value of ultrastructural detrusor changes? J Urol. 2012;188:2294-9.
25. Thomas JA, Tubaro A, Barber N, d'Ancona F, Muir G, Witzsch U, et al. A Multicenter Randomized Noninferiority Trial Comparing GreenLight-XPS Laser Vaporization of the Prostate and Transurethral Resection of the Prostate for the Treatment of Benign Prostatic Obstruction: Two-yr Outcomes of the GOLIATH Study. Eur Urol. 2016;69:94-102.

Correspondence address:
Jerry G. Blaivas, MD
Institute for Bladder and Prostate Research
445 East 77th Street, New York
NY, 10075, USA
Fax: +1 212 772-191
E-mail: jamesforde@rcsi.ie

ORIGINAL ARTICLE

Vol. 43 (3): 549-555, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0132

Urinary excretion of EGF and MCP–1 in children with vesico–ureteral reflux

Valentina Pastore [1], Fabio Bartoli [1]

[1] *Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy*

ABSTRACT

Purpose: The aim of this study was to investigate the urinary concentration of epidermal growth factor (EGF) and monocyte chemotactic protein-1 (MCP-1) as reflux nephropathy (RN) biomarkers before and after endoscopic treatment of moderate to severe vesico-ureteral reflux (VUR).

Materials and methods: A prospective study was carried out on 72 children with moderate to severe VUR. All patients underwent endoscopic treatment using Macroplastique® or Deflux®. Vesico-ureteral reflux resolution was tested by post-operative voiding cystourethrography after 3 months and 2 years. Follow-up urinary samples were collected at that time. Control samples were taken from healthy children with no clinical evidence of renal and bladder disease and no history of UTI.

Results: In VUR patients, pre-operative urinary EGF levels had a down-regulation when compared to controls. Following successful VUR repair, urinary EGF levels of VUR children progressively increased only at long term follow-up but without returning to normal levels. Urinary MCP-1 levels were highly expressed in pre-operative samples and decreased markedly during early post-operative measurements. Urinary MCP-1 levels did not further decreased in late post-operative follow-up. In fact, these levels remained significantly higher when compared to controls.

Conclusions: Urinary levels of EGF and MCP-1 may become useful markers for monitoring the response to surgical treatment in VUR patients. Although endoscopic VUR treatment is effective in reducing the inflammatory response, the persistence of significant abnormal levels of inflammatory cytokines (such as urinary MCP-1) at long term follow-up suggests that surgery alone may not completely treat the chronic renal inflammation evidenced in these children.

ARTICLE INFO

Keywords:
Urinary Tract; EGF Family of Proteins; Vesico-Ureteral Reflux

Int Braz J Urol. 2017; 43: 549-55

Submitted for publication:
March 11, 2015

Accepted after revision:
October 07, 2016

Published as Ahead of Print:
January 03, 2017

INTRODUCTION

Vesicoureteral reflux (VUR) is the most common urological disease in children, affecting nearly 1% of the general pediatric population (1). Vesicoureteral reflux is found in 25-70% of children with urinary tract infections (UTIs) (2). These children are at risk of pyelonephritis or renal scarring, which may progress to reflux nephropathy (RN) and end-stage renal damage (3, 4). The main histopathological findings of RN are tubular atrophy with prominent mononuclear inflammatory cellular infiltrate and interstitial fibrosis (5). The main biomolecular mechanisms responsible for its progression still under investigation are genetic, pro-inflammatory and pro-apoptotic. The kidney is an important site for the production of epidermal growth factor (EGF) (6) which play a major

role in renal growth modulation and turnover of tubular cells, glomerular hemodynamics, renal metabolism, tubular transport and eicosanoid synthesis (7, 8). Tissue EGF down-regulation has been reported in several chronic renal diseases (8-10), in obstructive (11) and in RN (12). Monocyte chemotactic protein-1 (MCP-1) is a powerful and specific chemotactic and activating factor for circulating monocytes (13). Infiltrating monocytes contribute to a decline in renal function following acute and chronic renal injury (14). Our group has recently shown an inverse relationship between EGF and MCP-1 (decreased EGF and increased MCP-1) tissue expression in obstructive nephropathy (11), with similar findings also reported recently in renal biopsies obtained from nephrectomies secondary to RN (12). Nevertheless, the role of EGF and MCP-1 as biomarkers of renal damage progression isn't totally elucidated and has been the subject of widespread interest in recent years. The aim of the present study was to investigate the role of EGF and MCP-1 urinary levels as biomarkers of RN before and after endoscopic treatment for VUR at long term follow-up.

MATERIALS AND METHODS

A prospective study was carried out from 2006 to 2012 on 72 children (44 boys and 28 girls) from 1 to 12 years of age (mean 4 + 2.7 years) with primary moderate to severe VUR. Vesico-ureteral reflux was graded according to the International Reflux Study Committee by voiding cystourethrography (VCUG) as moderate (grade III) or severe (grade IV-V). All patients had been started on antibiotic prophylaxis for 1 year before being referred for surgery, unless high grade VUR with recurrent UTIs resistant to prophylaxis coexisted. Informed consent was obtained for endoscopic treatment of VUR, collection of urinary samples and use of medical records for scientific purposes. All the children had been free of UTIs for at least 1 month and all inflammatory indexes (fever, white blood count, c-reactive protein) were normal at the time of treatment or sample collection. None of the children included had abnormal serum creatinine. All patients underwent endoscopic treatment with both Macroplastique® or Deflux®. Vesico-ureteral reflux resolution was tested by post-operative VCUG after 3 months and 2 years. Further follow-up studies included renal ultrasound (US) at 1, 3, 6 and 12 months. All patients continued antibiotic prophylaxis for at least 3 months after endoscopic injection. At US follow-up, 5 asymptomatic children developed transitory urinary obstruction, which was resolved spontaneously within one year in 4 cases. One patient required ureteric reimplantation due to persisting ureterovesical obstruction. Urinary samples were collected at the time of surgical procedure (pre-operative) and at 3 and 24 months after endoscopic treatment (post-operative). Control urinary samples were obtained from 15 children who were free of systemic, renal or inflammatory diseases at the time of urinary collection. Control cases were selected after having enrolled affected children to match them for age and sex. Clinical characteristics of VUR patients included in the study are reported in Table-1.

Table 1 - Clinical characteristics of vesico-ureteral reflux (VUR) patients included in the study.

Clinical Characteristics (number of pts)	Yes	No
Recurrent UTI	52	20
Bilateral VUR	25	47
Age range 12- 36 months	45	27
Severe VUR	49	23
Split Renal Function $\leq$ 40%	29	43

Enzyme-linked immunosorbent assay (ELISA)

Urinary samples were collected, with patients properly hydrated (on free fluid intake), before and at 3 and 24 months after surgery. Once collected, urinary samples were centrifuged at 10.000rpm x 10 minutes, then stored in a deep freezer at -80°C until tested. Because urinary EGF concentration is significantly higher than that of MCP-1, urinary samples were diluted by 2 and 200 before measurement of urinary concentrations of MCP-1 and EGF respectively. Quantitative measurements were obtained by using a human MCP-1 and EGF ELISA commercial kit (Quantikinine; R&D, Abingdon, UK, and Biotrak; Amersham, UK, respectively), a multiple sandwich solid-phase enzyme immunoassay that used monoclonal antibody raised against human MCP-1 and EGF. ELISA sensitivity was 5pg/mL for MCP-1 and 8pg/mL for EGF. The enzymatic reaction was detected in an automatic microplate photometer (Titertek; Flow Labs, Helsinki, Finland), with MCP-1 and EGF concentrations of unknown samples determined by interpolation into standard curve developed with known amounts of recombinant human MCP-1 and EGF. Urinary MCP-1 and EGF levels were normalized to urinary creatinine excretion and expressed as pg/mg urinary creatinine, respectively. The urinary levels of both EGF and MCP-1 were not only expressed as the ratio of cytokine to urinary creatinine as specifically advised by R&D but also by calculating the EGF/MCP-1 ratio (from now on simply referred to as Ratio). The Ratio was calculated by separately dividing the mean and SD of EGF and MCP-1, after which each result was multiplied by 100. The final results express RATIO [mean]+[SD] in Arbitrary Unit (AU).

Example:

RATIO [mean]=EGF [mean] x 100 MCP-1 [mean]

RATIO [SD]=EGF [SD] x 100 MCP-1 [SD]

Statistical analysis

Single extreme values of each group were excluded, with data expressed as mean + SD. Quantitative data were compared among groups by analysis of variance and paired t-test, as appropriate. Correlation coefficients were Pearson's r values. Differences were considered significant when $p < 0.05$. The study of patient subgroups (age, gender, laterality, grade, UTIs, scars) is not reported in this paper since the number of patients and samples were insufficient to guarantee accurate statistical analysis for these subgroups.

RESULTS

All numerical results (mean + SD) of urinary levels of EGF, MCP-1 and Ratio are reported in Table-2.

Pre-operative urinary levels of EGF, MCP-1 and Ratio (Figure-1).

Pre-operative urinary levels of VUR patients vs control patients had a significant down--regulation of EGF (uEGF CTRL vs. uEGF VUR PRE-OP, p=0.044) and up-regulation of MCP-

Table 2 - Pre-and post-operative urinary concentration of EGF, MCP-1 and Ratio in control and in vesico-ureteral reflux patients.

	EGF pre-op (pg/mL) Mean ± SD	EGF post-op 3 (pg/mL) Mean ± SD	EGF post-op 24 (pg/mL) Mean ± SD	MCP-1 pre-op (pg/mL) Mean ± SD	MCP-1 post-op 3 (pg/mL) Mean ± SD	MCP-1 post-op 24 (pg/mL) Mean ± SD	EGF/MCP-1 pre-op (AU) Mean ± SD	EGF/MCP-1 post-op 3 (AU) Mean ± SD	EGF/MCP-1 post-op 24 (AU) Mean ± SD
CTRL	790 ± 190			85 ± 57			750 ± 260		
VUR	681 ± 277	489 ± 251	587 ± 198	194 ± 128	110 ± 86	101 ± 62	410 ± 150	552 ± 190	600 ± 140
p= values	^p=0.044	^p=0.001; *p=0.012	^p=0.031; *p=0.037; °p=0.042	^ p=0.012	^p=0.047; *p=0.001	^p=0.043; *p=0.001; °p=n.s.	^p=0.001	^p=0.025; *p=0.003	^p=0.042; *p=0.0011; °p=n.s.

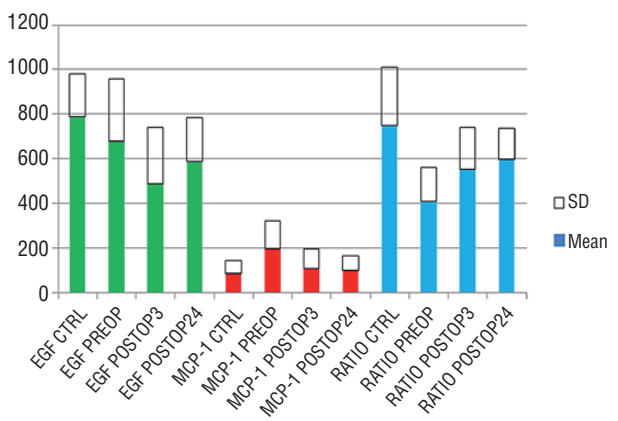
^-Statistical differences with control

*-Statistical differences between pre-operative and post-operative

°-Statistical differences between post-operative

1 (uMCP-1 CTRL vs. uMCP-1 VUR PRE-OP, p=0.012). In addition, Ratio values had a marked decrease when compared to controls (Ratio CTRL vs. Ratio PRE-OP VUR, p=0.001). These findings demonstrate a strongly inflammatory response and decreased regenerative activity in patients with severe VUR prior to surgical treatment.

Figure 1 - Pre-and post-operative urinary levels of EGF, MCP-1 and Ratio in control and in vesico-ureteral reflux patients.



Post-operative urinary levels of EGF, MCP-1 and Ratio (Figure-1).

A) EGF

Unexpectedly, 3-month post-operative urinary EGF levels had a further decrease, which was statistically significant compared to pre-operative values (uEGF VUR PRE-OP vs. uEGF VUR POST-OP-3, p=0.012). However, urinary EGF concentration at 24 months follow-up demonstrated significant recovery when compared to that at 3 months follow-up (uEGF VUR POST-OP-3 vs. uEGF VUR POST-OP-24, p=0.042), although still lower than controls and PRE-OP (uEGF VUR POST-24 vs. uEGF CTRL, p=0.031; uEGF VUR POST-24 vs. uEGF VUR PRE-OP, p=0.037).

B) MCP-1

Post-operative urinary MCP levels-1 had a marked reduction when compared to pre-operative levels (uMCP-1 VUR PRE-OP vs. uMCP-1 VUR POST-OP-3, p=0.001; uMCP-1 VUR PRE-OP vs. uMCP-1 VUR POST-OP-24, p=0.001). However, despite the initial improvement in MCP-1 concentration, urinary concentrations measured at 24 months follow-up did not differ significantly from those measured at 3 months follow-up (uMCP-1 VUR POST-3 vs. uMCP-1 VUR POST-24, p=n.s). Furthermore, post-operative MCP-1 concentrations at 24 months follow-up remained significantly higher than in controls (uMCP-1 VUR CTRL vs. uMCP-1 VUR POST-24, p=0.043).

C) Ratio

Ratio measurements at 3 and 24 months follow-up had a clear and constant increase in values (Ratio VUR PRE-OP vs. Ratio VUR POST--OP-3, p=0.003; Ratio VUR PRE-OP vs. Ratio VUR POST-OP-24, p=0.0011) when compared to pre--operative urinary Ratio levels. Although the Ratio at 24 months was significantly reduced compared to CTRL, it continued to improve compared to that measured at 3 months follow-up (Ratio VUR POST-OP-3 vs. Ratio VUR POST-OP-24, p=0.04).

Figure-1 summarizes the mean and SD of pre-and post-operative urinary levels of EGF, MCP-1 and Ratio in CTRL and VUR patients.

DISCUSSION

Post-operative results obtained from urinary samples of children with treated VUR clearly demonstrate decreased inflammatory response and a progressively better regenerative/inflammatory Ratio when compared to pre-operative results.

The histological hallmark of RN is chronic inflammation and tubular atrophy (5). The role of EGF as a renal growth factor is well documented in both animal and human studies. MCP-1, a potent and specific chemotactic agent for monocytes, has also been thoroughly investigated in experimental and clinical models of urinary tract obstruction (11). However, there is little data available regarding the changes of these cytokines in patients with RN and, to our knowledge, no reports about their changes before and after VUR endoscopic treatment. Although various studies have investigated tissue expression of EGF and MCP-1 on kidney remnants obtained from nephrectomies

of children with severe RN, indicating a significant down-regulation of EGF and upregulation of MCP-1 (12), they failed to answer two questions: 1) are urinary levels of these cytokines useful in clinical practice in the monitoring of renal damage progression in RN? and 2) does surgical treatment of VUR improve RN outcome by decreasing inflammatory response? Our previous studies in children with urinary flow impairment secondary to ureteropelvic junction obstruction demonstrate that both EGF and MCP-1 are useful biomarkers for monitoring renal damage progression before and after surgical repair (14).

The aim of this study was to monitor these biomarkers in patients with VUR who needed endoscopic VUR treatment. In the past 20 years, endoscopic treatment of VUR has become the treatment of choice for all VUR grades, at our Institute as well (15).

We were concerned that the foreign body reaction which invariably takes place in these patients after bulking agent injection could have constituted a bias (16, 17). In fact, although foreign body reaction to bulking agents is important to stabilize the implant, for the purposes of this study it may have increased the urinary concentration of MCP-1. In order to minimize this possible bias, we set the first urinary sample collection at 3 months after endoscopic injection.

Indeed, in patients with RN we observed a pre-operative down-regulation of urinary concentration of EGF when compared to CTRL although, interestingly, even this finding worsened 3 months after VUR treatment. In contrast, urinary EGF levels returned to pre-operative levels at 24 months follow-up. No patient had post-operative EGF urinary concentration returned to normal levels. Urinary MCP-1 levels seem to follow a different pattern. In fact, they are highly expressed in pre-operative samples and improved markedly during early post-operative measurement, after which they remain stable on late post-operative follow--up although still higher than those measured on CTRL samples. It is our opinion that MCP-1 increases mainly as a result of acute tubular damage secondary to VUR , while its prompt reduction following surgical VUR treatment demonstrates a positive anti-inflammatory action of VUR correction. However, children with treated VUR still have abnormal levels of MCP-1 at long term follow-up. These findings may suggest the presence of chronic renal or urinary inflammation persisting over time.

Furthermore, Ratio analysis provides a clearer view of changes occurring in these children, as this Ratio showed a marked decrease in pre-operative urinary samples and significant improvement in samples obtained at both early and late follow-up. However, post-operative Ratio levels continued to be significantly down-regulated when compared to CTRL, a result which lends further support to the opinion that some forms of poor tubular regeneration or persisting chronic inflammation still continue in these children.

Indeed, it has been demonstrated that in animal models a fibrotic process continues following treatment with progressive renal damage as a consequence of inflammatory response and renal apoptosis (18, 19). The end-point is progressive and chronic fibrosis which, in many cases, produces a hypoplastic kidney or chronic renal failure. The fibrotic response is characterized by thickening of the tubular basement membrane and widespread fiber accumulation in the tubule-interstitial compartment, defined as tubule-interstitial fibrosis (TIF) (20). The pathophysiology of TIF seems to be the response to a range of cellular stress, alteration of cellular death/proliferation and development of renal inflammation. Interleukins are secreted by injured tubular and urinary epithelium in infectious and non-infectious urinary tract conditions (21, 22). IL-6 seems to be associated with the presence of high grade VUR while IL-8 is linked to scar formation (23). Recent studies (24) point to a relationship between kidney injury molecule-1 (KIM-1), a trans-membrane protein and a marker of tubular damage, and severity of scar formation while urinary excretion of Beta 2-microglobin has been tested as a urinary marker of tubular damage and scar formation in VUR patients (25, 26). In addition, MCP-1 and macrophage colony stimulating factor (M-CSF) facilitate the homing of inflammatory cells to areas of tubular damage (27). The cellular death as a consequence of inflammatory response occurs at two levels: first, due to myeloperoxidase release

by macrophages and neutrophils which catalyzes the production of toxic pro-oxidants such as hypochlorous and nitric acids; and second, due to tumor necrosis factor alpha (TNF-alpha) and Fas Ligand originating from those cells and latterly from the arrival of T-cells. These cytokines constitute the major receptor-triggered apoptotic signals in nephrons following urinary obstruction (28, 29), with a key role also played by transforming growth factor-beta 1 (TGF-β1), regarded as the pro-fibrotic factor "par excellence".

A popular theory suggests that fibrosis occurs through a trans-differentiation process known as epithelial-to-mesenchimal trans-differentiation (EMT) and that TGF-β1 directly induces EMT (this phenomenon has been tested in cultured tubular epithelial cells) especially when EGF is added (30). Therefore, as we have demonstrated in these children, the persistence of abnormal levels of urinary MCP-1, may contribute to maintaining TIF and EMT. From a clinical point of view, our results confirm the need for some medical therapy able to further down-regulate the inflammatory response in the long term follow-up. We are still unable to suggest new drugs useful for this purpose because most of them are still under basic experimental steps. Steroids may be an option but their adverse effects are still a great problem. The main limit of this research is the small number of cases enrolled which has limited the statistical analysis of patient's subgroups. To correct this, we are planning an international multicenter study to confirm the results and to further analyze the clinical significance of our preliminary data.

CONCLUSIONS

In conclusion, we believe that, in the future, urinary levels of EGF and MCP-1 and above all their Ratio may become useful markers for monitoring response to surgical treatment in VUR patients. Additionally, a multicentric study is needed for better analysis of these urinary biomarkers in patient subgroups, particularly in relation to the presence of renal scars. Although endoscopic treatment of VUR is effective in significantly reducing the inflammatory response triggered by VUR, the persistence at long term follow-up of abnormal levels of inflammatory cytokines suggests that successful surgery alone may not completely treat the chronic renal inflammation evident in these children. The development of new, effective and minimally toxic medical therapies able to modulate the cascade of inflammatory, apoptotic and pro-fibrotic events occurring in VUR is the next challenge to be faced.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Arant BS Jr. Vesicoureteric reflux and renal injury. Am J Kidney Dis. 1991;17:491-511.
2. Cosentino M, Caffaratti J, Bujons A, Garat JM, Villavicencio H. Vesico-ureteral reflux, endoscopic management. Arch Argent Pediatr. 2013;111:349-52.
3. Silva JM, Santos Diniz JS, Marino VS, Lima EM, Cardoso LS, Vasconcelos MA, et al. Clinical course of 735 children and adolescents with primary vesicoureteral reflux. Pediatr Nephrol. 2006;21:981-8.
4. Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. J Urol. 2009;181:290-7.
5. Fillion ML, Watt CL, Gupta IR. Vesicoureteric reflux and reflux nephropathy: from mouse models to childhood disease. Pediatr Nephrol. 2014;29:757-66.
6. Singh B, Coffey RJ. Trafficking of epidermal growth factor receptor ligands in polarized epithelial cells. Annu Rev Physiol. 2014;76:275-300.
7. Harris RC. Potential physiologic roles for epidermal growth factor in the kidney. Am J Kidney Dis. 1991;17:627-30.
8. Tang J, Liu N, Zhuang S. Role of epidermal growth factor receptor in acute and chronic kidney injury. Kidney Int. 2013;83:804-10.
9. Gesualdo L, Di Paolo S, Calabró A, Milani S, Maiorano E, Ranieri E, et al. Expression of epidermal growth factor and its receptor in normal and diseased human kidney: an immunohistochemical and in situ hybridization study. Kidney Int. 1996;49:656-65.
10. Fanos V, Pizzini C, Mussap M, Benini D, Pleban M. Urinary epidermal growth factor in different renal conditions in children. Ren Fail. 2001;23:605-10.
11. Grandaliano G, Gesualdo L, Bartoli F, Ranieri E, Monno R, Leggio A, et al. MCP-1 and EGF renal expression and urine excretion in human congenital obstructive nephropathy. Kidney Int. 2000;58:182-92.

12. Chertin B, Farkas A, Puri P. Epidermal growth factor and monocyte chemotactic peptide-1 expression in reflux nephropathy. Eur Urol. 2003;44:144-9.
13. Viedt C, Orth SR. Monocyte chemoattractant protein-1 (MCP-1) in the kidney: does it more than simply attract monocytes? Nephrol Dial Transplant. 2002;17:2043-7.
14. Bartoli F, Penza R, Aceto G, Niglio F, D'Addato O, Pastore V, et al. Urinary epidermal growth factor, monocyte chemotactic protein-1, and β2-microglobulin in children with ureteropelvic junction obstruction. J Pediatr Surg. 2011;46:530-6.
15. Baek M, Kim KD. Current surgical management of vesicoureteral reflux. Korean J Urol. 2013;54:732-7.
16. Stenberg A, Larsson E, Läckgren G. Endoscopic treatment with dextranomer-hyaluronic acid for vesicoureteral reflux: histological findings. J Urol. 2003;169:1109-13.
17. Arena S, Fazzari C, Implatini A, Torre S, Villari D, Arena F, et al. Dextranomer/hyaluronic Acid copolymer implant for vesicoureteral reflux: role of myofibroblast differentiation. J Urol. 2009;181:2695-701.
18. Chan W, Krieg RJ Jr, Ward K, Santos F Jr, Lin KC, Chan JC. Progression after release of obstructive nephropathy. Pediatr Nephrol. 2001;16:238-44.
19. Ito K, Chen J, El Chaar M, Stern JM, Seshan SV, Khodadadian JJ, et al. Renal damage progresses despite improvement of renal function after relief of unilateral ureteral obstruction in adult rats. Am J Physiol Renal Physiol. 2004;287:F1283-93.
20. Kaneto H, Ohtani H, Fukuzaki A, Ishidoya S, Takeda A, Ogata Y, et al. Increased expression of TGF-beta1 but not of its receptors contributes to human obstructive nephropathy. Kidney Int. 1999;56:2137-46.
21. Galanakis E, Bitsori M, Dimitriou H, Giannakopoulou C, Karkavitsas NS, Kalmanti M. Serum and urine interleukin-6 and transforming growth factor-beta1 in young infants with pyelonephritis. Int Urol Nephrol. 2007;39:581-5.
22. Bitsori M, Karatzi M, Dimitriou H, Christakou E, Savvidou A, Galanakis E. Urine IL-8 concentrations in infectious and non-infectious urinary tract conditions. Pediatr Nephrol. 2011;26:2003-7.
23. Gokce I, Alpay H, Biyikli N, Unluguzel G, Dede F, Topuzoglu A. Urinary levels of interleukin-6 and interleukin-8 in patients with vesicoureteral reflux and renal parenchymal scar. Pediatr Nephrol. 2010;25:905-12.
24. Toker A, Ziypak T, Orsal E, Laloglu E, Bedir F, Aksoy Y. Is urinary kidney injury molecule-1 a noninvasive marker for renal scarring in children with vesicoureteral reflux? Urology. 2013;81:168-72.
25. Assadi FK. Urinary beta 2-microglobulin as a marker for vesicoureteral reflux. Pediatr Nephrol. 1996;10:642-4.
26. Sharifian M, Karimi A, Mohkam M, et al. Urinary Beta 2-Microglobulin as a prognostic marker in children with pyelonephritis. Archives of Pediatric Infectious Diseases 2012; 1:18-22.
27. Weisbart RH, Golde DW, Clark SC, Wong GG, Gasson JC. Human granulocyte-macrophage colony-stimulating factor is a neutrophil activator. Nature. 1985;314:361-3.
28. Donnahoo KK, Shames BD, Harken AH, Meldrum DR. Review article: the role of tumor necrosis factor in renal ischemia-reperfusion injury. J Urol. 1999;162:196-203.
29. Schelling JR, Nkemere N, Kopp JB, Cleveland RP. Fas-dependent fratricidal apoptosis is a mechanism of tubular epithelial cell deletion in chronic renal failure. Lab Invest. 1998;78:813-24.
30. Zavadil J, Böttinger EP. TGF-beta and epithelial-to-mesenchymal transitions. Oncogene. 2005;24:5764-74.

Correspondence address:
Valentina Pastore, MD
Department of Medical and Surgical Sciences
University of Foggia, Foggia, Italy
Viale Pinto 1, Foggia 71122, Italy
Fax: + 39 088 173-2541
E-mail: valentinapastore1427@gmail.com

Vol. 43 (3): 556-560, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2016.0164

Unusual intravesical foreign body in young female migrated from vagina due to autoerotism

Ankur Bansal [1], Manoj Kumar [1], Gautam Kanodia [1], Ruchir Aeron [1], Sunny Goel [1]

[1] *King George Medical University, Lucknow, Uttar Pradesh, India*

Keywords: Urinary Bladder; Vagina; Urogenital System

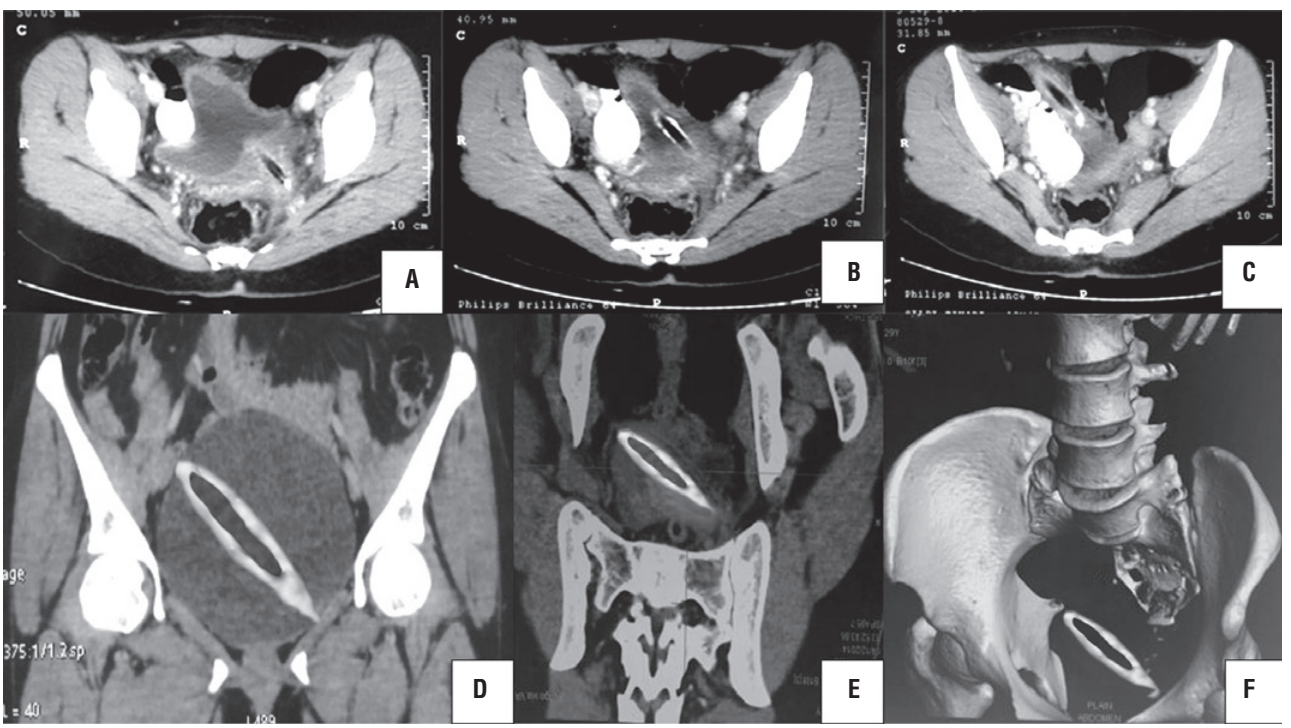
INTRODUCTION

Foreign bodies are rarely found in genitourinary system and pose a challenge to the practitioner. The usual causes for insertion of foreign bodies in genitourinary system include sexual curiosity, autoerotic stimulation, or during invasive procedures (1). These patients may remain asymptomatic or have minimal discomfort but usually patient presents with urinary tract infection, severe pain and hematuria (2). Foreign bodies should be removed completely and procedures used should be simple and minimally traumatic to the genitourinary tract (1). Herein, we present a case and management of self-inserted foreign body in the vagina of a young girl for erotic stimulation.

CASE PRESENTATION

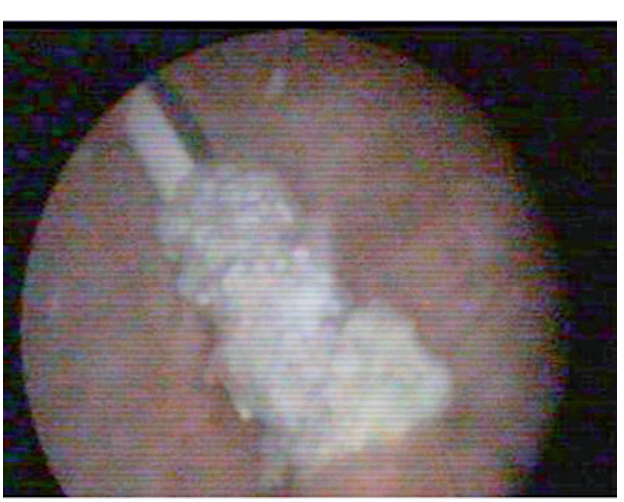
An 18-year old unmarried illiterate girl presented with dysuria, increased frequency of micturition and occasional mild hematuria. The patient had history of insertion of plastic pen through vagina 6 months earlier for sexual gratification. There was no history of continuous leakage of urine per vagina. She informed history of normal menstruation. There was no associated psychiatric illness. Laboratory investigations such as electrolyte profile and blood count were normal but routine urine analysis showed pyuria and microscopic hematuria. General physical examination revealed no abnormality. On per vaginal and speculum examination, a pointed object was felt at anterior vaginal wall with no continuous leakage of urine from vagina. The digital rectal examination was normal. Plain X-ray pelvis was normal. Contrast enhanced computed tomography showed a 10.2 x 1.2cm hypodense linear object piercing the anterior vaginal wall and left posterior bladder wall with majority of its part lying inside the bladder. The tip of the foreign body pierced right to anterior bladder wall and reached the abdominal wall (Figure-1) with normal upper tracts, uterus and ovaries. Cystoscopy showed encrusted plastic pen inside the bladder extending from right anterior bladder wall up to the left posterior bladder wall (Figure-2) with a small portion of pen (approximately 3mm) protruding through anterior vaginal wall visualized on vaginoscopy. Patient refused psychiatric evaluation. Foreign body was broken into two parts by transurethral cystolithopaxy using stone punch under regional anesthesia and was removed under cystoscopic guidance (Figure-3). Following its removal, repeat cystoscopy and vaginoscopy revealed a 3 x 3mm supratrigonal vesicovaginal fistula with inflamed vaginal mucosa. Foley catheter (16Fr) was inserted per urethra and the patient was discharged on postoperative day 3 with an advice to follow-up after 3 weeks. She did not complain of continuous leakage of urine per vagina in the post-operative period. Foley catheter was removed at 3 weeks and voiding cystourethrogram was performed which revealed intact bladder and complete emptying of

Figure 1 - Computed tomography scan [axial section (A-C) and coronal section (D-F)] showing hypodense linear foreign body (10.2 x 1.2cm) piercing the anterior vaginal wall and left posterior bladder wall with majority of its part lying inside the bladder. The tip of foreign body pierced right to anterior bladder wall and reached the abdominal wall.



bladder in post void film with no dye in vagina (Figure-4). The patient was fully continent with no urine leakage per vagina. Patient was doing well at 6 months follow-up.

Figure 2 - Cystoscopy showed encrusted plastic pen inside the bladder extending from right anterior bladder wall up to left posterior bladder wall.



DISCUSSION

Various intravesical foreign bodies reported include surgical gauze, pieces of Foley balloon catheter, intrauterine device, metal wire, carrot, lead pencil, ball pen, needle, household batteries, screw, pessaries and broken parts of endoscopic instruments etc. (3, 4). Multiple routes of entry of intravesical foreign bodies include self-insertion, iatrogenic, migration from adjacent organs, via urethra or traumatic route. Psychological circumstances which leads to self-insertion of such foreign bodies includes mental illness, sexual curiosity and borderline personality disorder (5). In our case, the reason of self-insertion was erotic stimulation and the route of insertion was traumatic migration from adjacent organ (vagina). Although the route of insertion mentioned and pointed out by the patient was vagina and not urethra, but as the patient was illiterate, it may not be accurate. Foreign bodies from adjacent

Figure 3 (A-C) - Foreign body (encrusted pen) was broken into two parts by transurethral cystolithopaxy using stone punch and was removed under cystoscopic guidance.

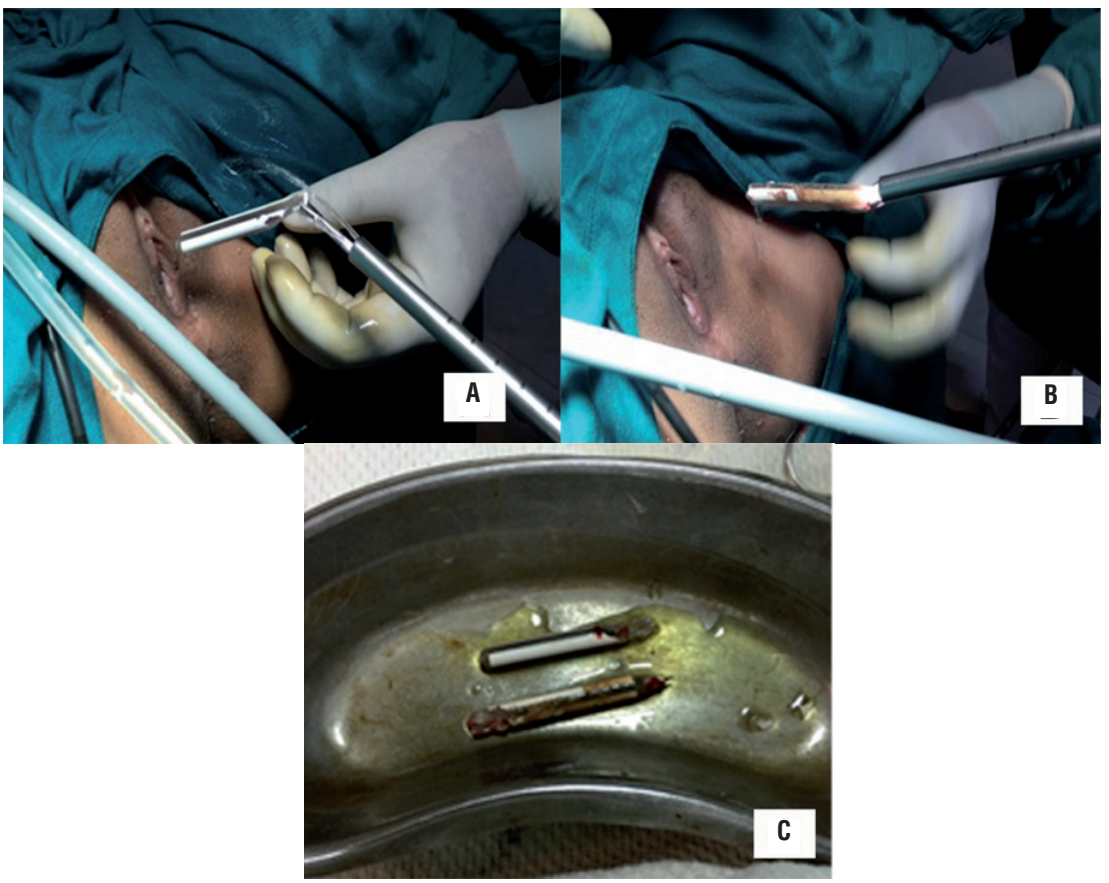
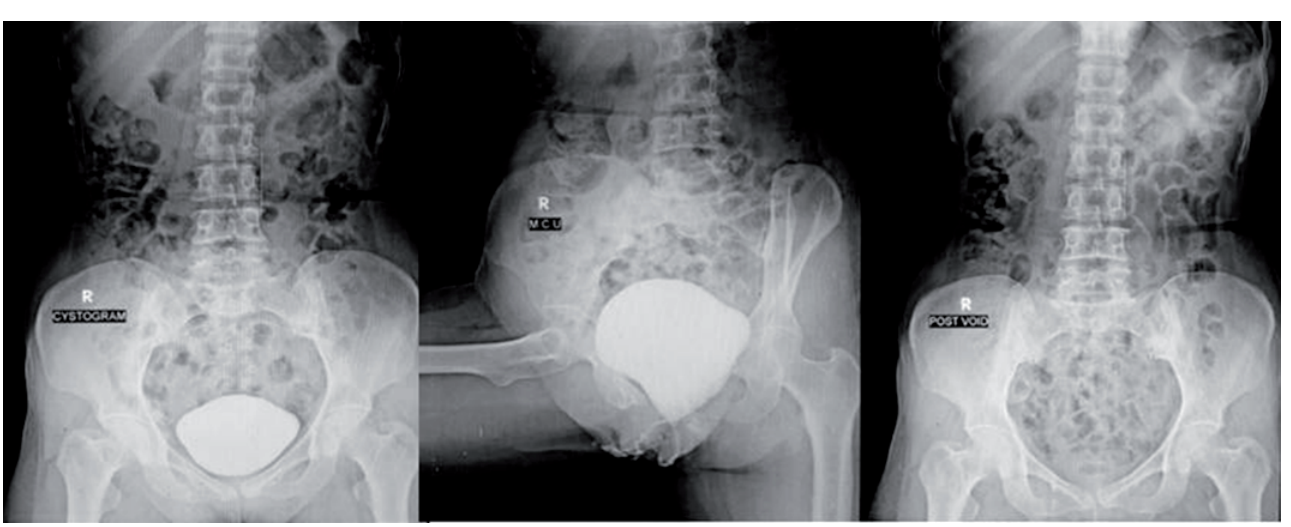


Figure 4 - Voiding cystourethrogram revealed intact bladder and complete emptying of bladder in post void film with no dye in vagina.



viscera such as gastrointestinal tract and female genitourinary tract migrating traumatically into urinary bladder are extremely rare. In a study done by Rafique et al. (3), 5 such cases of foreign bodies migrating into bladder from genitourinary tract (intrauterine copper device in 4 females) and gastrointestinal tract (3-inch copper wire being swallowed by young boy) were reported. Our case was very interesting and is probably the first case report in which the pen inserted in vagina for sexual gratification almost completely migrated into bladder.

Usually patient remains asymptomatic or may present with symptoms related to irritation of the lower urinary tract such as frequency, dysuria, microscopic or gross haematuria, lower abdominal pain, urethral discharge, strangury and acute urinary retention (2, 3). During sexual history or urogenital examination if the patient becomes anxious, high suspicion for self-insertion of foreign bodies should always be kept in mind (3).

Radiologic evaluation helps in determining the exact size, location and number of the foreign bodies (1). Confirmation can easily be done in cases of radiopaque foreign bodies with plain kidney urinary bladder (KUB) radiograph and for radiolucent foreign bodies with ultrasound and computed tomography (CT) (6). However, urethrocystoscopy remains the most accurate method for diagnosis of intravesical foreign bodies.

Nowadays, endoscopic procedures are preferred treatment modalities as they minimize the lower urinary tract injuries. However, open procedures like suprapubic cystostomy are still recommended in few cases to reduce the risk of urethral and bladder injury (1). As female bladder can be easily accessed via urethra, foreign bodies can safely be removed endoscopically (4). Due to high incidence of psychiatric disease, dementia and mental retardation in these patients, routine psychiatric evaluation is recommended (7). Although it is not universally accepted, this will prevent further incidence of insertion of foreign bodies in genitourinary tract.

Urogenital fistula can be a complication of foreign body insertion in genitourinary tract. Management of urogenital fistulas depends on size and location of the defect. Spontaneous healing can occur with bladder drainage alone if the fistula size is small. Davits et al. (8) reported a series of four patients in whom fistula developed after vaginal and abdominal hysterectomy, and treated successfully with prolonged bladder drainage (19-54 days). Spontaneous closure of the fistula is unlikely if healing does not occur within 4 weeks (9).

Conclusion: In young patients presenting with chronic lower urinary tract symptoms, foreign bodies should always be kept in mind as a differential diagnosis. Detailed history and clinical examination can detect the presence of a foreign body, however imaging modalities like X-ray pelvis, CT whole abdomen and endoscopy (cystoscopy/vaginoscopy) may be required. With advancement in endoscopic techniques, majority of cases can be treated successfully with minimally invasive techniques. Small vesicovaginal fistulas are likely to heal spontaneously with prolonged catheterization.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Johnin K, Kushima M, Koizumi S, Okada Y. Percutaneous transvesical retrieval of foreign bodies penetrating the urethra. J Urol. 1999;161:915-6.
2. van Ophoven A, deKernion JB. Clinical management of foreign bodies of the genitourinary tract. J Urol. 2000;164:274-87.
3. Rafique M. Intravesical foreign bodies: review and current management strategies. Urol J. 2008;5:223-31.
4. Kochakarn W, Pummanagura W. Foreign bodies in the female urinary bladder: 20-year experience in Ramathibodi Hospital. Asian J Surg. 2008;31:130-3.
5. Rahman NU, Elliott SP, McAninch JW. Self-inflicted male urethral foreign body insertion: endoscopic management and complications. BJU Int. 2004;94:1051-3.
6. Trehan RK, Haroon A, Memon S, Turner D. Successful removal of a telefone cable, a foreign body through the urethra into the bladder: a case report. J Med Case Rep. 2007;1:153.

7. Kenney RD. Adolescent males who insert genitourinary foreign bodies: is psychiatric referral required? Urology. 1988;32:127-9.
8. Davits RJ, Miranda SI. Conservative treatment of vesicovaginal fistulas by bladder drainage alone. Br J Urol. 1991;68:155-6.
9. Gerber GS, Schoenberg HW. Female urinary tract fistulas. J Urol. 1993;149:229-36.

Correspondence address:
Ankur Bansal, MD
Department of Urology
King George Medical College
Lucknow, Uttar Pradesh, India
Telephone: +91 885 380-7160
E-mail: ankurbansaldmc@gmail.com

ARTICLE INFO

Int Braz J Urol. 2017; 43: 556-60

Submitted for publication:
March 14, 2016

Accepted after revision:
April 24, 2016

Published as Ahead of Print:
September 20, 2016

RADIOLOGY PAGE

Vol. 43 (3): 561-562, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0420

A rare case of supernumerary fused and malrotated kidney

Volkan Sen [1], Ibrahim Halil Bozkurt [1], Tarik Yonguc [1], Ozgu Aydogdu [1], Ismail Basmaci [1]

[1] *Izmir Bozyaka Training and Research Hospital – Urology, Izmir, Turkey*

MANUSCRIPT

The supernumerary kidney is an accessory organ with its own blood supply and collecting system. It is a very rare type of congenital renal anomaly with fewer than 100 cases reported since firstly described at 1656 (1). Embryological basis of supernumerary kidney is connected to the abnormal division of the nephrogenic cord into two metanephric blastemas which will form two kidneys (2). It may be either completely separate or only loosely attached to the major kidney on the ipsilateral side. This anomaly is usually asymptomatic but may rarely become symptomatic in early adulthood (3). The mean age at diagnosis is 36 years. The most common presenting symptoms are pain, fever and a palpable abdominal mass. Ultrasonography, CT and MR urography may be needed to identify the anomaly.

We aimed to present a rare case of supernumerary fused and malrotated kidney. Thirty--seven year-old woman was admitted to our clinic with left flank pain. CT scan demonstrated multiple calculi in the left kidney and supernumerary fused kidney (Figures 1 and 2). The third kidney was below the right kidney, malrotated and had its own blood supply (Figure-3).

Grieshammer and colleagues showed that mutant mice lacking either SLIT2 or its receptor ROBO2 develop supernumerary ureteric buds that are correlated with abnormal maintenance of Gdnf expression in anterior metanephric mesenchyme (4). The SLIT2/ROBO2 intercellular signaling system restricts, directly or indirectly, in extent of the Gdnf expression and plays a critical role in

Figure 1 - Computed tomography scan with multiple calculus in left kidney.

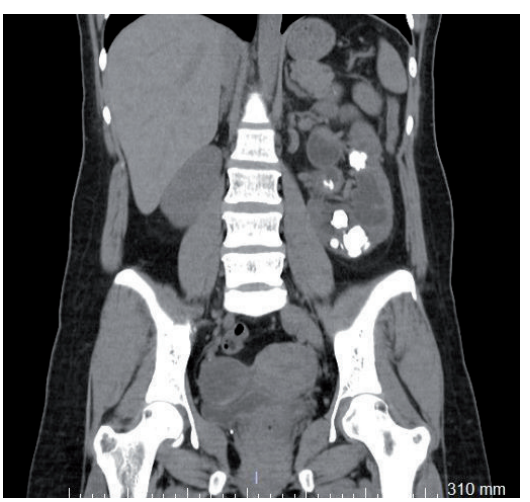


Figure 2 - Computed tomography scan of right kidney.

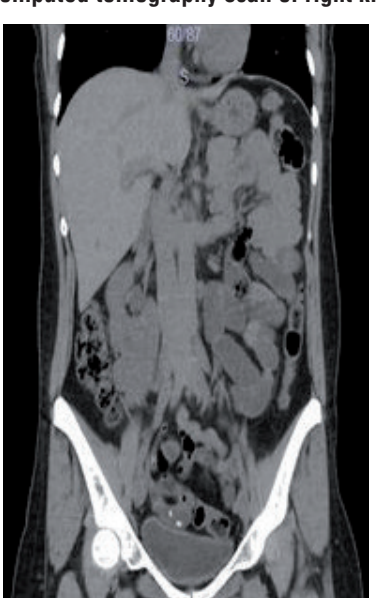
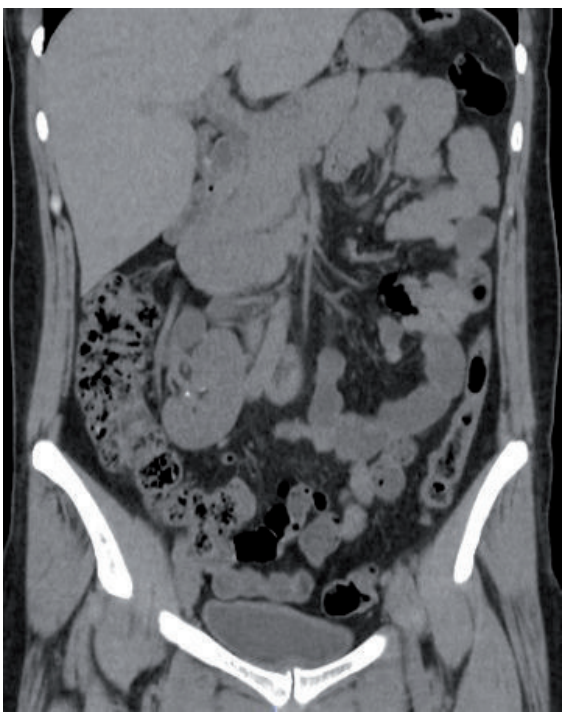


Figure 3 - Computed tomography scan of supernumerary kidney with its own blood supply and collecting system.



precisely positioning the side of kidney induction. The rare location and malrotation of supernumerary kidney of our case could be explained by this hypothesis. Percutaneous nephrolithotomy was performed to the left kidney and no problem was observed in follow-up.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sureka B, Mittal MK, Mittal A, Sinha M, Thukral BB. Supernumerary kidneys—a rare anatomic variant. Surg Radiol Anat. 2014;36:199-202.
2. Tada Y, Kokado Y, Hashinaka Y, Kadowaki T, Takasugi Y, Shin T, et al. Free supernumerary kidney: a case report and review. J Urol. 1981;126:231-2.
3. CARLSON HE. Supernumerary kidney: a summary of 51 reported cases. J Urol. 1950;64:224-9.
4. Grieshammer U, Le Ma, Plump AS, Wang F, Tessier-Lavigne M, Martin GR. SLIT2-mediated ROBO2 signaling restricts kidney induction to a single site. Dev Cell. 2004;6:709-17.

ARTICLE INFO

Int Braz J Urol. 2017; 43: 561-2

Submitted for publication:
July 25, 2015

Accepted after revision:
March 25, 2016

Published as Ahead of Print:
November 02, 2016

Correspondence address:
Volkan Sen, MD
Department of Urology
Dokuz Eylul University School of Medicine – Urology
Izmir, 35340, Turkey
Telephone: + 90 553 389-6859
E-mail: sen_volkan@yahoo.com

RADIOLOGY PAGE

Vol. 43 (3): 563-565, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0300

Metanephric Adenofibroma in a young adult

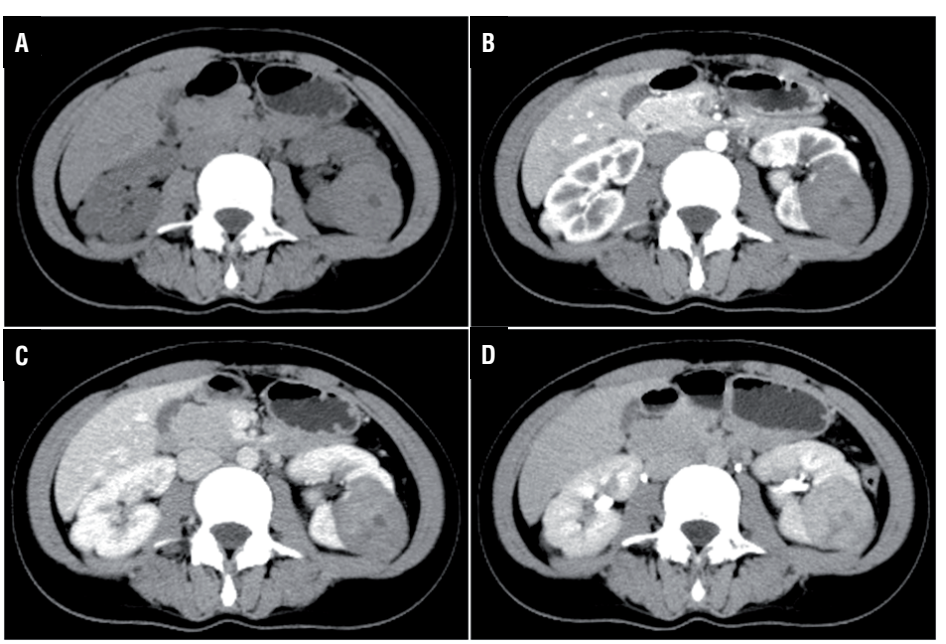
Feiya Yang [1], Canfeng Zhang [1], Mingshuai Wang [1], Xiquan Tian [1], Wenlong Wang [2], Nianzeng Xing [1]

[1] Department of Urology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, P.R. China;
[2] Department of Orthopedics, Beijing Chaoyang Hospital, Capital Medical University, Beijing, P.R. China

CASE

A 29-year-old female patient was admitted after a computed tomography (CT) scan showing a neoplasm measuring 4.5×4.0×4.5cm located in the middle and dorsal part of the left kidney (Figure-1). In the CT plain scan phase, the neoplasm had almost equal density with the normal kidney, and the CT unit was 45. It had a clear boundary, and part of the neoplasm extruded the renal contour. A multiple patchy low density area could be seen in the neoplasm that had a CT unit of 10. The renal sinus and calyx were slightly squeezed (Figure-1A). In the arterial phase, the neoplasm was slightly homogenously enhanced, and the CT unit was 57.2. The boundary was clear, and no obvious enhancement was manifested in the low density area. No other enhanced or abnormal low density foci were observed in the remaining renal parenchyma (Figure-1B). In the venous phase, the neoplasm was continuously enhanced and the CT unit was 68.9 (Figure-1C). In the excretory

Figure 1 - Enhanced computed tomography scan (CT) demonstrated a 4.5×4.0×4.5cm neoplasm in the middle and dorsal part of left kidney (CT unit: 45). It had a clear boundary and part of the neoplasm extruded the renal contour. Multiple patchy low density area could be seen in the neoplasm (CT unit: 10). The neoplasm was lightly enhanced in the arterial phase (CT unit: 57.2), and it was continuously enhanced in the venous (CT unit: 68.9) and excretory phase (CT unit: 88.8). The low density area did not show any enhancement.



A = CT plain scan. B = The arterial phase. **C** = The venous phase. **D** = The excretory phase.

phase, the neoplasm was persistly enhanced, and the CT unit was 88.8. The low density area did not show obvious enhancement, and there was no change in compression or obvious destruction in the renal sinus and calyx. The perirenal fatty gap was clear (Figure-1D). All of the manifestations were different from that of renal malignant tumors. A laparoscopic partial nephrectomy under general anesthesia was performed to completely resect the lesion. Gross examination indicated a red-white cystic solid tumor mass measuring 5×4cm (Figure-2). There was liquefaction and necrosis in the center of this neoplasm. Postoperative histopathologic examination verified that it was metanephric adenofibroma (Figure-3). The patient was discharged on postoperative day 5, and no recurrence or metastasis was observed during the 8 months of postoperative follow-up.

MAF (metanephric adenofibroma), initially reported in 1992 (1), is a rare metanephric renal tumor that occurs primarily in children and young adults (2). Histopathologic examination reveals

Figure 2 - Gross pathologic features of the resected specimen. The cut section indicated a red-white cystic solid tumor mass measuring 5×4cm (A). The lesion was completely resected and accompanied with some fat covering the outer surface (B).

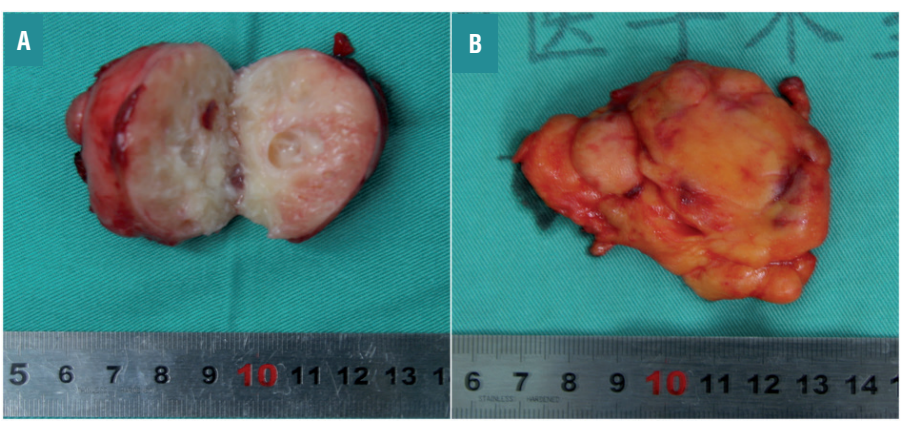
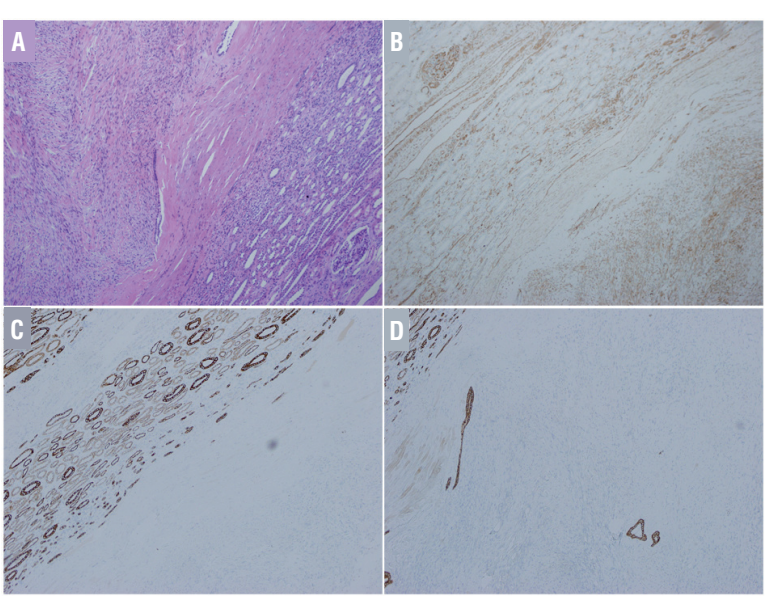


Figure 3 - Postoperative pathological examination verified metanephric adenofibroma (×100). (A) Spindle cells proliferate and the cell size is consistent with a few acini and tubular structures scattering among them and some are cystic expansion. The lined epithelial cells did not show atypia. Immunohistochemical results show that vimentin is positive for tumor (B) and CK is positive for small tube and negative for tumor (C, D).



MAF to be a benign tumor that is composed of varying proportions of epithelial-stromal elements and immunohistochemistry can differentiate it from Wilms tumor and papillary renal cell carcinoma mainly using CK, vimentin, CD34 and cytokeratin 7 (3). Galluzzo ML (4) reported a case with simultaneous MAF, Wilms tumor and clear cell carcinoma, indicating a relationship between these tumors.

Herein, we describe the CT manifestations of MAF to help make the accurate preoperative diagnosis of MAF, the diagnostic methods of which have not been sufficiently reported. Currently, its confirmed diagnosis mainly depends on postoperative pathology. As for the best treatment modality, surgery is preferred, among which laparoscopic partial nephrectomy is ideal when conditions permit. Although no postoperative recurrence is reported, long-term follow-up is still needed. More clinical cases are required to facilitate formulations of standard treatment and follow-up for MAF.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hennigar RA, Beckwith JB. Nephrogenic adenofibroma. A novel kidney tumor of young people. Am J Surg Pathol. 1992;16:325-34.
2. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. Eur Urol. 2006;49:798-805.
3. Arroyo MR, Green DM, Perlman EJ, Beckwith JB, Argani P. The spectrum of metanephric adenofibroma and related lesions: clinicopathologic study of 25 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol. 2001;25:433-44.
4. Galluzzo ML, Garcia de Davila MT, Vujanić GM. A composite renal tumor: metanephric adenofibroma, Wilms tumor, and renal cell carcinoma: a missing link? Pediatr Dev Pathol. 2012;15:65-70.

Correspondence address:
Nianzeng Xing, MD
Department of Urology
Beijing Chaoyang Hospital
Capital Medical University
No.8 Gongren Tiyuchang Nanlu
Beijing, 100020, P.R. China
Telephone: +86 010 6593-5241
E-mail: xingnianzeng@hotmail.com

ARTICLE INFO

Int Braz J Urol. 2017; 43: 564-5

Submitted for publication:
June 04, 2015

Accepted after revision:
November 30, 2015

Published as Ahead of Print:
November 02, 2016

VIDEO SECTION

Vol. 43 (3): 566-566, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0091

Laparoscopic resection of prescral and obturator fossa schwannoma

Marcos Tobias-Machado [1], Alexandre Kiyoshi Hidaka [1], Letícia Lumy Kanawa Sato [1], Igor Nunes Silva [1], Pablo Aloisio Lima Mattos [1], Antonio Carlos Lima Pompeo [1]

[1] *Departamento de Urologia, Faculdade de Medicina do ABC, Santo André, São Paulo, Brasil*

ABSTRACT

Introduction: Pelvic Schwannoma is an extremely rare event. Laparoscopic approach for radical resection on pelvic region already has been described in the literature. However, with better image quality provided by optic in the laparoscopy we can assure an improvement in this kind of approach for tumor resection.
Objective: Our goal is to describe and evaluate the results of one laparoscopic resection of presacral and obturator fossa tumor.
Materials and Methods: We present a case of a 60-year-old man with progressive congestion in the right inferior member and CT scan revealing a mass with miscellaneous content located behind of the right iliac vessels and right obturator nerve. Exploratory transperitoneal laparoscopy was indicated. During laparoscopy it was possible to see the mass between the spermatic cord and external iliac artery. We made the identification and preservation of iliac vessels and obturator nerve. Resection of the tumor was performed carefully, allowing the safe removal of the specimen with complete preservation of the iliac vessels and obturator nerve.
Results: Mean operative time of 150 minutes. No perioperative complications occurred. Two days of hospital stay. Posterior histopathological exam confirmed that the mass was a Schwannoma.
Conclusion: The maximization of the image in the laparoscopic surgery offers dexterity and capacity of dissection required for complex mass dissection on pelvic region.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Available at: http://www.intbrazjurol.com.br/video-section/20150091-tobias-machado_et_al/

Int Braz J Urol. 2017; 43 (Video #8): 566-6

Submitted for publication:
February 18, 2015

Accepted after revision:
November 06, 2015

Published as Ahead of Print:
September 20, 2016

Correspondence address:
Alexandre Kiyoshi Hidaka, MD
Departamento de Urologia
Faculdade de Medicina do ABC
Avenida: Principe de Gales 821
Santo André, SP, 09060-650, Brasil
Fax: + 55 11 4993-5400
E-mail: kiyoshihidaka01@gmail.com

VIDEO SECTION

Vol. 43 (3): 567-567, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2015.0648

Laparoscopic partial nephrectomy for multiple (four) tumors

Lessandro Curcio [1], Bruno Salama [1], Daniel Luis Pinto [1], Antonio Claudio Ahouagi [1]

[1] *Hospital Federal Ipanema, RJ, Brasil*

ABSTRACT

Background: Nephron sparing surgery (NSS) is well established as the standard of care for most surgical small renal tumors when technically feasible. While the majority of sporadic renal tumors are solitary, multifocal tumors have been reported in 5.4% to 25% of patients with tumors smaller than 5cm. We present a video where we approach, through laparoscopy, four tumors on the same kidney.
Case study: Male, 58y, went through a routine abdominal ultrasound which showed a 5cm left kidney nodule. His MRI pointed a total of 4 nodules on his left kidney. The aspect suggested a papillary cancer due to high cellularity and low vascularization. The patient was submitted to partial nephrectomy under ischemia to remove the two largest tumors (inferior pole) and a resection without clamping of the other two ipsilateral tumors.
Result: We performed the surgery in 2 stages. In the first one, we approached the 2 tumors located on the inferior pole inducing warm ischemia, whereas in the second stage we resected the 2 remaining tumors using the technique without clamping. The surgery lasted 220 minutes, with 800mL of blood loss, not requiring blood transfusion. Ischemia time was 35 minutes. The histopathological analysis confirmed that the 4 tumors were papillary cancer, with free margins.
Conclusion: NSS can be performed and should be tried in patients with multiple kidney tumors, preferably through laparoscopy or assisted by robot. It can be made either using or not clamping of the pedicle, depending on the RENAL score.

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Available at: http://www.intbrazjurol.com.br/video-section/20150648-curcio_et_al/
Int Braz J Urol. 2017; 43 (Video #9): 567-7

Submitted for publication:
November 12, 2015

Accepted after revision:
January 26, 2016

Published as Ahead of Print:
October 20, 2016

Correspondence address:
Lessandro Curcio Gonçalves, MD
Américas Avenue 13554, Bl 02 Ap 805
Barra da Tijuca, RJ, 22790-702, Brasil
E-mail: urocurcio@gmail.com.br

LETTER TO THE EDITOR

Vol. 43 (3): 568-570, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2017.0074

Re: Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015

José Carlos Truzzi [1], Carlos Alberto Ricetto Sacomani [1], José Antônio Prezzoti [1]

[1] *Departamento de Uroneurologia, Sociedade Brasileira de Urologia, Rio de Janeiro, RJ, Brasil*

To the editor,

The article entitled "Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015" (1), presents results which interpretation deserves some remarks. This retrospective study was performed at Belo Horizonte (Minas Gerais, Brazil) involving a 11 year-period (2004-2015) in 15 different hospitals, being the procedure performed by 28 different surgeons. A simple mathematic analysis shows that there were less than eight procedures per year (7, 8/year), and that each doctor implanted a median of three sphincters in that period, corresponding in absolute numbers to 0.27 implants per year per physician. This value does not allow a correct learning curve for a complex procedure that demands technical expertise, wide knowledge of voiding dysfunctions and physiology of male urinary incontinence. Also, previous clinical data of included implanted patients were not presented. Parameters such as severity of post-prostatectomy incontinence, presence (or not) or detrusor hyperactivity, impaired bladder complacency, detrusor hypocontractility, urethral stenosis or stenosis of urethro-vesical anastomosis, ureteral reflux, diabetes mellitus, were not provided. When all patients are considered as a whole without consideration of the above mentioned parameters, there is a risk of interpretation of results of a heterogenous group of patients. Analysis was based in an administrative data bank of a health insurance company. There was no collection of data from the patient's charts. Questions related to indication, evolution and results regarding the used technique were not available.

In relation to complications, it is possible to question if those mentioned as due to sphincter implantation were really related, among which urethral stenosis and spermatic cord torsion. Urethral stenosis and stenosis of urethro-vesical anastomosis may occur due to radical prostatectomy and not necessarily due to the sphincter implant. The mentioned testicular torsion (spermatic cord torsion) is not a complication of artificial sphincter implant. The candidate to artificial sphincter must be evaluated thoroughly before the surgical act. It is essential to understand the basic mechanisms of the functioning of artificial sphincter in order to operate it correctly.

Also, among the listed complications, even if graded as Clavien-Dindo III, transitory acute urinary retention usually occurs due to urethral edema related to urethral manipulation during surgery with high resolution success with bladder catheterization in less than 48 hours.

According to presented data, four (16.7%) of artificial sphincters showed mechanical problems. However, the authors stated that eight patients (33.3%) needed change of cuff due to malfunction and three (12.5%) had to change the regulator balloon. All these are usually caused by

mechanical failure. There is an incompatibility of presented data: were there four or eleven failed sphincters?

When such complications are addressed altogether, without correct evaluation of patients (using only data obtained from charts) it is possible to criticize negatively an internationally accepted procedure, considered as gold-standard in the treatment of male urinary incontinence, used for more than 30 years and more that 100.000 documented implants. It is important to stress that artificial sphincter implant does not guarantee full continence recovery, but it is a treatment option for severe urinary incontinence, that improves quality of life of patients with involuntary urinary leakage. In that study, it was reported that 15.3% of patients remained incontinent following the sphincter implant. However, it is difficult to interpret this data, since there was no description of pre-operatory status, or if there was reduction of incontinence episodes or lowering of number of used pads following sphincter implant.

A recent review included 1.082 patients submitted to implantation of AMS-800 artificial sphincter, 78% following radical prostatectomy and 27% after pelvic radiation, with a median follow-up of more than five years. Primary implanted sphincter survival was 74% after 5 years and 41% at 15 years of follow-up (2). Other studies showed similar survival rates in shorter follow-ups periods, and more modest late survival rates (3, 4). But when it was applied the subjective satisfaction index, 73% of patients were satisfied or very satisfied with their continence (5). In a systematic review of literature concerning surgical treatment of post-radical prostatectomy urinary incontinence, conducted recently by Crivellaro et al., artificial sphincter presented the better positive results, but with wide variability margin (20% to 89%), followed by slings and urethral compressor model pro-ACT (3). In that same systematic review, urethral erosion was the most frequent complication of artificial sphincter implant, with an incidence of 3% to 7.4%; general infection rate after implant was up to 10% (3).

Previous exposure to radiation is classically considered a risk factor for complications, mainly erosion and local infection (6). However, Rivera et al. did not show any statistical difference in the number of removals of artificial sphincters, survival and rate of infection or erosion among 323 radiated patients from a total of 872 submitted to AMS-800 implant (7).

The authors stated that there are no Brazilian studies on the subject of artificial sphincters and they are wrong: Trigo Rocha et al. published at Urology journal (8) the results of 40 patients submitted to sphincter implant following post-radical prostatectomy incontinence followed-up to a medium of 53 months.

In conclusion, the article presented results contrary to the majority of national and international studies on the theme, and raises doubts on probable causes, such as local problems or the analyzed patient's sample. It is interesting that the authors stablish which factors caused such unsatisfactory results. Also, it should have been stated in the "Conflict of Interests" (although mentioned in the authors identification) that the authors are members of a technical group associated to a private health institution.

REFERENCES

1. Santos AC Junior, Rodrigues LO, Azevedo DC, Carvalho LM, Fernandes MR, Avelar SO, Horta MG, Kelles SM. Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015. Int Braz J Urol. 2017;43:150-4.
2. Linder BJ, Rivera ME, Ziegelmann MJ, Elliott DS. Long-term Outcomes Following Artificial Urinary Sphincter Placement: An Analysis of 1082 Cases at Mayo Clinic. Urology. 2015;86:602-7.
3. Crivellaro S, Morlacco A, Bodo G, Agro' EF, Gozzi C, Pistolesi D, et al. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. Neurourol Urodyn. 2016;35:875-881.
4. Van Bruwaene S, De Ridder D, Van der Aa F. The use of sling vs sphincter in post-prostatectomy urinary incontinence. BJU Int. 2015;116:330-42.
5. Montague DK, Angermeier KW, Paolone DR. Long-term continence and patient satisfaction after artificial sphincter implantation for urinary incontinence after prostatectomy. J Urol. 2001;166:547-9.
6. Bates AS, Martin RM, Terry TR. Complications following artificial urinary sphincter placement after radical prostatectomy and radiotherapy: a meta-analysis. BJU Int. 2015;116:623-33.
7. Rivera ME, Linder BJ, Ziegelmann MJ, Viers BR, Rangel LJ, Elliott DS. The Impact of Prior Radiation Therapy on Artificial Urinary Sphincter Device Survival. J Urol. 2016;195:1033-7.
8. Trigo Rocha F, Gomes CM, Mitre AI, Arap S, Srougi M. A prospective study evaluating the efficacy of the artificial sphincter AMS 800 for the treatment of postradical prostatectomy urinary incontinence and the correlation between preoperative urodynamic and surgical outcomes. Urology. 2008;71:85-9.

ARTICLE INFO

Int Braz J Urol. 2017; 43: 568-70

Submitted for publication:
February 08, 2017

Accepted after revision:
February 10, 2017

Published as Ahead of Print:
March 15, 2017

Correspondence address:
Jose Carlos Truzzi, MD
UNIFESP
Rua Dr. Oscar Monteiro de Barros, 617/141
São Paulo, SP, 05641-010, Brasil
E-mail: jctruzzi@hotmail.com

LETTER TO THE EDITOR

Vol. 43 (3): 571-571, May - June, 2017
doi: 10.1590/S1677-5538.IBJU.2017.0074.1

REPLY BY THE AUTHORS: Re: Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015

Augusto Cesar Soares dos Santos Junior [1,2], Luíza de Oliveira Rodrigues [1,2], Daniela Castelo Azevedo [1,2], Lélia Maria de Almeida Carvalho [1,2], Mariana Ribeiro Fernandes [1,2], Sandra de Oliveira Sapori Avelar [1,2], Maria da Glória Cruvinel Horta [1,2], Silvana Márcia Bruschi Kelles [1,2]

[1] Grupo de Avaliação de Tecnologia em Saúde, Unimed BH, MG, Brasil; [2] Núcleo de Avaliação de Tecnologia em Saúde, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), MG, Brasil

To the editor,

We appreciated the comments made on our article entitled "Re: Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015" (1, 2) as we believe that discussions regarding the artificial urinary sphincter (AUS) in Brazil are scarce and should be encouraged. Other authors, aligned with our results and from different international locations, have recently also reported concern with the AUS because of its high revision and explantation rates due to mechanical failure, urethral atrophy, infection, erosion, etc (3, 4).

A report of a Consensus Conference (5), based on the most recent data available in literature as well as expert opinions, was recently published outlining a wide array of challenges. The Consensus highlights the need to inform patients about expected rates of mechanical failure, erosion and infection which would result in a re-operation rates ranging from 14.8% to 44.8%. According to this publication, radiated patients are at high risk for increased adverse outcomes and complications, such as cuff erosion as well as re-operation, and should be informed about that. This same Consensus Conference have also outlined that currently the means to report the outcomes post-AUS are variable and need to become standardized.

The affiliation of the authors, the limitations of our observational study and the source of the data are clearly stated in the paper. Despite these limitations, the complication rate observed after AUS implantation should not be overlooked. In the absence of national clinical registries in Brazil, we understand that this study, based on an administrative data collection, is a source of "real-world" healthcare data on a large population of unselected patients. Although AUS implants are recommended as the gold-standard treatment for severe persistent urinary incontinence after prostatectomy, there are still several challenges regarding its indications, management, and follow-up to be overcome and discussed

REFERENCES

1. Truzzi JC, Sacomani CA, Prezzoti JA. Re: Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015. Int Braz J Urol. 2017;43: [Epub ahead of print].
2. Santos AC Junior, Rodrigues LO, Azevedo DC, Carvalho LM, Fernandes MR, Avelar SO, et al. Artificial urinary sphincter for urinary incontinence after radical prostatectomy: a historical cohort from 2004 to 2015. Int Braz J Urol. 2017;43:150-4.
3. Wang R, McGuire EJ, He C, Faerber GJ, Latini JM. Long-term outcomes after primary failures of artificial urinary sphincter implantation. Urology. 2012;79:922-8.
4. Farag F, van der Doelen M, van Breda J, D'Hauwers K, Heesakkers J. Decline in artificial urinary sphincter survival in modern practice-Do we treat a different patient? Neurourol Urodyn. 2016;31. doi: 10.1002/nau.23110. [Epub ahead of print]
5. Biardeau X, Aharony S; AUS Consensus Group., Campeau L, Corcos J. Artificial Urinary Sphincter: Report of the 2015 Consensus Conference. Neurourol Urodyn. 2016;35(Suppl 2):S8-24.

Correspondence address:
Augusto Cesar Soares dos Santos Junior, MD, PhD
Rua Dos Inconfidentes 44, 10º andar
Belo Horizonte, 30140-120, Brasil
Telephone: +55 31 3229-6666
E-mail: acssjr@gmail.com

INTERNATIONAL
BRAZ J UROL

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Sidney Glina, M.D, PhD
Editor, International Braz J Urol

by e-mail with attached text files and figures to:
submission@brazjurol.com.br

Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Urol.**

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: www.icmje.org.

In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The **International Braz J Urol** contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology Page**

and **Video Section**. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine **(http://www.nlm.nih.gov/mesh/meshhome.html)**. One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases. *Structure of the articles*

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
4) IMPORTANT - Avoid - Do Not

a) **DO NOT** embed the images in the text; save them as a separate file
b) **DO NOT** supply artwork as a native file. Most illustration packages now give the option to "save as" or export as EPS, TIFF or JPG.
c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of **all authors** must be included; when exist more than six authors, list the first six authors followed **by et al.** The **initial** and the **final** pages of the reference should be provided:

Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

INTERNATIONAL
BRAZ J UROL

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- **Conflict of Interest** – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- **Check that each figure is cited in the text. The illustrations are not merged in the text.**
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not **embed in Word or PowerPoint.**
- A list of abbreviations is provided.