ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 41, NUMBER 2, MARCH - APRIL, 2015

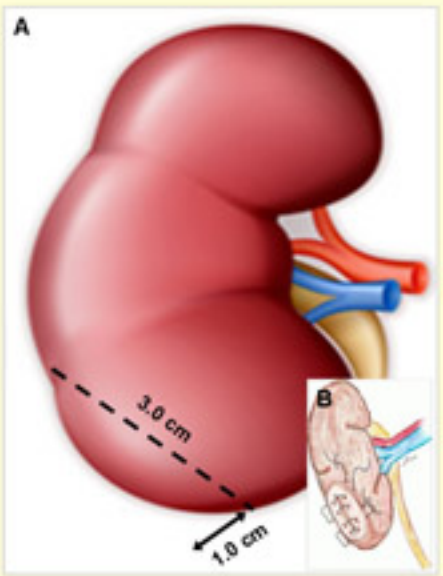

Figure 2 - Partial nephrectomy: A. Lower pole resected. B. "U" suture was done.

XXXV Brazilian Congress of Urology
October 31 - November 4, 2015 - Rio de Janeiro - RJ - Brazil

INTERNATIONAL

BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY - SBU

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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
DRQ Gráfica e Editora Ltd.

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.

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EDITORIAL
IN THIS ISSUE

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doi: 10.1590/S1677-5538.IBJU.2015.02.01

The importance of Renal Anatomy in Endourologic Procedures

The March-April 2015 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Infertility, neuro-urology, BPH, Prostate Cancer, Renal Cancer, Tuberculosis, Genital trauma and basic research. The papers come from many different countries such as Brazil, USA, China, Turkey, Iran, Portugal, Egypt, Japan and Korea and as usual the editor´s comment highlights some papers. We decided to comment 2 papers about Endourology.

Doctor Koyuncu and collegues, from Turkey performed on page 245 an interesting study about the treatment of lower pole stones. The authors compared the efficacy of intra-renal surgery and Percutaneous Nephrolithotomy (PNL) in lower pole stones ≥2 cm in 109 patients retrospectively and they concluded that intra-renal surgery could be an effective treatment alternative to PNL in lower pole stones larger than 2 cm, especially in selected patients. Further, multi-centric comparative studies with larger study population are needed to confirm these results.

Inferior pole stones can be treated with ESWL, flexible ureteroscopy and percutaneous nephrolitotripsy (1). Anatomical aspects of the inferior renal pole, especially calice distribution, angle between the lower infundibulum and renal pelvis (LIP), infundibular length and calice width, are determinant for the success of each treatment modality (2, 3). The size of calculi is one of most important factors for decision on the best treatment method (4). Stones wider than 20 mm are better treated with percutaneous surgery, while stones smaller than 10 mm show good results when treated by flexible ureteroscopy (FUR) or extracorporeal shockwave lithotripsy (ESWL), and stones between 10 and 20 mm are treated with FUR with good results (4). The spatial anatomy of the lower pole group of calices influences the success rate of FUR (5, 6). Patients with unfavorable parameters show lower stone free rates when FUR was the method of choice (5, 6). In this paper the authors analyzed only the size of the stones and do not analyzed the anatomic factors of the lower pole, one of the most important factors to decide the treatment in this kind of cases.

Doctor Balasar and collegues from Turkey performed on page 274 an interesting study about Incidence of retro-renal colon during percutaneous nephrolithotomy. They studied the number of retro-renal colon presence in the CT images taken before PNL applications in 394 patients retrospectively. The authors found that 27 patients (6.9%) had retro-renal colon with 18 (4.6%) on the left and 4 (1.0%) on the right side. The other 5 (1.3%) patients had bilateral retro-renal colons and concluded that retro-renal colon is more frequently found on the left side and on the lower pole of the kidney. Therefore, when accessing the lower pole of the kidney, especially on the left side, the risk of colonic injuries should be considered during PNL.

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The knowledge of kidney and retroperitoneum anatomy is very important to make the PNL. The procedure could be performed in prone or supine position and one of the most terrible complication of this procedure is the colon perforation. In a very recent and important radiologic paper (7) performed in 700 patients (350 made CT in prone position and 350 in supine position) the authors observed that 6.8% of patients in prone position had retro-renal colon and 2% of patients in supine position had retro--renal colon.

With the study of these 2 important papers we concluded that kidney and intra--renal anatomy are very important for all kind of endourologic procedures.

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doi: 10.1590/S1677-5538.IBJU.2015.02.02

How Dangerous is Testosterone Supplementation?

Recently, significant media attention has been focused on testosterone supplementation therapy (TST) and increased cardiovascular (CV) risk. Treatment for testosterone deficiency syndrome (TDS) has been on the rise in the past several years. US Food & Drug Administration (FDA) drug utilization data showed sales increased 65% between 2009 and 2013 (1). The true prevalence of TDS varies based on the source, definition of the condition and age of population studied, however, it is believed to range from 2-39% (2, 3). Patients suffering from TDS are at an irrefutably increased risk for bone density loss, development of type 2 diabetes (T2DM), anemia, sarcopenia, cognitive deficits, and premature death (4). Shores et al, have shown increased mortality rates in men with low testosterone (mortality rates with normal, equivocal, and low testosterone levels were 20%, 25%, 35% respectively) (5).

Patients should be made aware of possible adverse events associated with TST in particular as polycythemia and hyperestrogenism (6). Polycythemia is believed to be a dose-dependent effect and hematocrit levels should be maintained below 54% to prevent hyperviscosity-related events. Hyperestrogenism is a response of testosterone conversion to estrogen via aromatase in adipose tissue and may be associated with gynecomastia. Two recent meta-analyses have shown that prostate related events (rates of prostate cancer, PSA >4 ng/mL, prostate biopsies) were not statistically significantly higher in the testosterone supplementation group compared to the placebo group (6, 7). Also these meta-analyses demonstrated no significant elevation in CV risk. In a meta--analysis by Aruajo et al., the authors reported that testosterone levels ≥2.18 standard deviations below normal range were associated with 35% and 25% elevated risk in all--cause mortality and CV disease mortality, respectively (8). However, the authors note that their analysis showed considerable between-study heterogeneity limiting the clinical extrapolation of the data.

Some of the difficulty addressing research in TST relates to the methodological challenges related to studying patients with TDS, including: population heterogeneity, circadian rhythm of testosterone secretion, use of total vs. free testosterone, number of pre-treatment testosterone levels, covariate analysis, duration and follow-up of TST. There is often significant heterogeneity in the populations being studied therefore limiting the validity of comparative analyses. Ideally, populations should be matched in patient demographics, and baseline TDS parameters (symptoms and severity). Trial design should account for testosterone level variance based on circadian rhythm and consistently use total (by LCMS analysis) or free testosterone (by equilibrium dialysis) level measurement. Also, important for trial design are standardized minimum number of pre-treatment testosterone levels, standardized duration of treatment and follow-up

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protocols. Statistical analyses should be appropriate (routinely used and interpretable by the average scientific reader) and validated for the type of study.

There have been three articles popularized by the media in the last couple years. Basaria et al. published in the New England Journal of Medicine a randomized, double-blinded, placebo-controlled trial in men with TDS (total testosterone [TT]100-350 ng/dL) older than 65 years of age with the primary end-point of assessing frailty (mobility) data (in particular quadriceps strength) (9). Patients were treated for 6 months (T gel vs. placebo) and had TT levels maintained between 500-1000 ng/dL. Once again, neither primary nor secondary endpoints were CV events. The CV and atherosclerotic events were recorded via self-report or medical record review or physician assessment. In all, 209 patients were randomized and 176 completed the 6 month treatment period. Of note, there was a higher rate of prior CV morbidities in the T supplementation group at baseline. The authors reported more CV events in the testosterone group compared to placebo (23 vs. 5 subjects), indeed the study was ceased prematurely because of this signal. However, some of the symptoms defined as CV in nature would not put a patient at increased risk of significant morbidity or mortality (peripheral edema, systolic hypertension, atrial tachyarrythmias). It is unclear whether any significant difference would have been demonstrated between the groups if myocardial infarction (MI) and cerebrovascular accident (CVA) had been used to define CV events.

In another such article, Vigen et al. published in JAMA a retrospective review of men with low TT (<300 ng/dL) who underwent coronary angiography (CA) in the Veterans Affairs (VA) hospital system (10). Men who were on TST prior to CA were excluded from the study. Only the TT level closest to the CA was used. It was assumed that patients adhered to TST the entire study period based on filling an initial prescription from the VA pharmacy. Primary end-points were time to all-cause mortality and time to hospitalization for MI or CVA. They used Cox proportional hazards models with a rarely utilized statistical test known as 'stabilized inverse probability of treatment weighting' to control for over 50 different variables to assess the relationship between TST and the primary endpoints. There was no control used for time of day in TT testing. There were 8709 patients included in the study and of these 1223 (14%) initiated TST a median of 531 days after the angiography. However, after publication the authors adjusted their reported data and changed the number of patients excluded due to starting TST after MI or stroke from 128 to 1132, all of whom, we believe, should have been included in the non-TST group within the study. Only 60% of TST patients had a follow-up TT level checked while on therapy and 18% of the TST group only filled one prescription. The outcomes were as follows: death - non-TST 9%, TST 12%; MI - non-TST 6%, TST 2%; CVA - non-TST 6%, TST 3%. Yet, through obtuse statistical analysis weighting for 50 confounders, many of which are not classically associated with TDS, the authors suggested CV event were three times more likely in the TST group. The major limitations to this study included: convoluted and complex statistical analysis, data errors within the original paper, erroneous exclusion criteria, flawed laboratory testing (time not factored in TT), inadequate documentation of TST, insufficient follow-up of TST patients.

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More recently, Finkle et al. published in PLoS ONE a retrospective cohort study using an insurance claims registry database. The study was conducted by a private firm in conjunction with the NIH. They used the insurance database to access diagnosis, prescriptions, and procedures but they had no data on TT levels or indications for treatment. The study group included patients who filled a prescription for testosterone (n=55,593) and the control group were patients who filled a prescription for a phosphodiesterase type-5 inhibitor (PDE5i) (n=167,279). Patients were followed for 90 days post-prescription and covariates were determined from data drawn from 12 months pre-prescription. They had no data on medication use compliance. The primary endpoint was non-fatal MI within 90 days of filling the prescription. They analyzed MI rates pre and post testosterone prescription. They found that men on TST over 65 years of age (RR= 2.19 vs. 1.15) and men under 65 years with prior history of heart disease (RR= 2.9 vs. 1.4) had higher relative risks (RR) of non-fatal MI when compared to their PDE5i counterparts. The major limitations of this study included: the fact that all data were based on prescription data, questionable control group, short follow-up (90 days), and questionable conflict of interest with authors (one of the authors was owner of the private group analyzing the data). It is being increasingly appreciated that PDE5i may be cardioprotective, thus using them as a control group in a study assessing MI events is flawed and essentially invalidates the data (11).

Overall, these three papers claiming increased CV risks in patient using TST are all inherently flawed and limit the interpretation of the data and the clinical applicability is questionable. Especially when more than two decades of good science and the Araujo meta-analysis have found quite the opposite, that TDS is associated with a higher incidence of CV events. Finally, more recently, Corona et al show in a large meta-analysis no association between TST and increased CV risk (12). In September 2014, a US Food and Drug Administration advisory panel met and determined more studies are needed to identify the true CV risk with TST and they recommended changing labeling to stress use only in those patients with a diagnosis of hypogonadism (1). In December 2014, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee determined there was no consistent evidence of an increased CV risk with the use of TST (13). With this, the media attention surrounding TST has declined and most importantly, our clinical practice regarding TST prescribing and what we tell patients has not changed.

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DIFFERENCE OF OPINION

Vol. 41 (1): 199-202, January - February, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.03

In the era of flexible ureteroscopy is there still a place for Shock-wave lithotripsy?

Opinion: YES

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Keywords: Kidney Calculi; Lithotripsy; Ureteroscopy

INTRODUCTION

The prevalence of urolithiasis has increased to 8.8% in the United States of America, due to diet and lifestyle changes and associated increasing diabetes and obesity (1). Urinary stones represent a significant economic burden both directly (treatment associated costs) and indirectly (e.g. time off work) (2). The emergence of a non-invasive intervention in 1980, shock wave lithotripsy (SWL), revolutionised the treatment or urinary calculi (3).

Miniaturisation and refinements to endourologists' armamentarium over the past two decades have increased the efficacy and application of endoscopic stone management. The lower renal pole calyces can now be accessed with "near certainty" using modern flexible ureteroscopes (4). However, innovation and refinement to the technology and technique used for SWL have also improved its efficacy and reduced associated side-effects in recent decade (5). The optimal treatment modality for renal and ureteric calculi is therefore controversial (6).

EFFICACY

Small (<10 mm) renal stones respond well to SWL, with stone free rates (SFR) up to 91.5% reported by randomised controlled trials (RCTs) (6, 7). For medium sized (10-20 mm) middle or upper calyceal stones a large retrospective analysis found no difference between URS and SWL (92% vs. 87%; p>0.05): no randomised studies are available (8). Medium sized lower pole stones respond less well to lithotripsy as fragments clear less well from this dependent location: a recent meta-analysis showed a risk ratio (RR) of 1.50 (95% CI 1.20-1.87; p=0.0003) in favour of URS (SFR were 85-86% vs. 54-60%) (9). However, the benefit for URS was clinically insignificant for small lower pole renal stones in the same meta-analysis (RR 1.1 95%CI 1.03-1.19), although this remained statistically significant (p=0.004).

Distal ureteric calculi, although often more difficult to access with SWL, responded as effectively to SWL and URS for ≤20 mm radio-opaque stones (SFR 92.7% vs. 94.9%, p>0.05) in the only large RCT which used modern equipment (10). A large RCT examining the treatment of ≤10 mm proximal ureteric calculi found no significant difference in the SFR following SWL or URS (SFR 80% {46/58 patients} vs. 100% {52/52}, p>0.05) (11). However, SWL was less effective than URS for >10mm proximal ureteric stones (88% vs. 60%, p<0.05) in the same RCT (12).

The efficacy and safety of SWL have been improved by using shock wave sources with larger focal zones and improved coupling mechanisms. Further improvements have been gained with modified techniques including pulse rate, ramping strategies, improved localisation with real-time monitoring (e.g. using colour duplex ultrasonography) and analgesics (limiting patient movement) (6, 13). Finally, adjuvant therapy following SWL might improve SFR as many as 1.77 fold, such as: medical expulsive therapy (14), potassium citrate (15), thiazide diuretics (16) and percussion, diuresis and inversion (PDI) therapy for lower pole stones (17). However, these adjuvants have yet to be included in randomised trials comparing SWL with adjuvant vs. endourological interventions.

Secondary outcomes: beyond stone free rates

Judgements regarding the relative benefits and harms of SWL and endourological techniques in the treatment of urolithiasis go beyond SFR. URS may have higher complication and re-treatment rates (6,12). A Cochrane review of RCTs comparing URS and SWL for ureteric stones found SWL has a lower auxiliary treatment rate and a shorter hospital stay (12). A recent systematic review of RCTs on lower pole renal stones found no difference in re-treatment or unplanned procedure rates between SWL and URS, although the quality of evidence (GRADE) was low or very low and incidence rates were low for both interventions (9).

For patients the most important outcome may be the effect of each treatment on their health related quality of life (QoL) including time off work and pain. Time till return to normal activities (including driving, non-strenuous activity and work) and post-operative analgesic requirements were shorter in two RCTs following a single session of SWL vs. URS for renal stones (18, 19). An RCT comparing URS and SWL for ureteric calculi similarly demonstrated less pain and a quicker convalescence for SWL (20). However, there are currently no validated questionnaires to robustly assess QoL in the treatment of urolithiasis and as such the evidence for QoL outcomes is lacking.

Pearle et al. asked patients with ≤10 mm lower pole stones whether they would undergo the same treatment again after URS and SWL: patients favoured SWL: 63% vs. 90%; p=0.031 (18). However when patients underwent multiple SWL sessions for larger lower pole stones the same results were not replicated (19). Pearle et al., in a separate RCT, found a higher satisfaction following SWL vs. URS for ureteric calculi, although statistical significance was not reached (94% vs. 87%; p>0.05) (20).

Ureteric stenting is more frequently required with URS than SWL, typically for 1-2weeks (6). Stent related symptoms including suprapubic pain, frequency and dysuria are commonly bothersome (21). One RCT reported 46% of patients required anticholinergics for stent related symptoms following URS (19). SWL is now typically conducted without general anaesthesia, which is typically required for URS and may necessitate an overnight hospital stay and/or present significant risks in co-morbid patients. Finally, renal scarring induced by SWL has been linked with renal impairment and diastolic hypertension (22). However, no prospective study with long-term follow-up has proven this association (23).

CONCLUSIONS

SWL produces acceptable SFR in the treatment of small and medium sized renal and ureteric calculi. URS may be more effective in terms of stone clearance, from a single session, particularly for larger lower pole renal stones. However, SWL is less invasive and has a lower complication rate than URS for renal stones. SWL is associated with a shorter hospital stay and quicker return to normal activities. SWL typically avoids stent insertion (with its associated bothersome symptoms) and general anaesthesia. Patients report a higher satisfaction rate with a single session of SWL than URS. Further technological and technique modifications will further improve the safety, efficacy and acceptability of SWL in the future.

ABBREVIATIONS

SWL = Shock wave lithotripsy
URS = Ureteroscopy

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DIFFERENCE OF OPINION

Vol. 41 (1): 203-206, January - February, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.04

In the era of flexible ureteroscopy is there still a place for Shock-wave lithotripsy?

Opinion: NO

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Keywords: Kidney Calculi; Lithotripsy; Ureteroscopy

Flexible ureteroscopy will replace almost completely ESWL for the treatment of renal stones in few years, even in developing countries. This process is already ongoing and probably is irreversible. Let´s try to understand how and why this phenomenon is happening.

Since the development of the External Shockwave Lithotripsy (ESWL) in the late 70's (1), it has been the standard treatment for small renal stones (2). However, recent years have seen a significant shift towards endoscopic therapies (3). This can be attributed to the evolving surgical experience in the use of these techniques, but even more to major improvement in the technical equipment. The question of if the flexible ureteroscopy will substitute ESWL as the choice therapy for renal stones is controversial. First of all, they are not totally comparable, since ESWL is a non-invasive method. If ESWL is not an option no more, we lose a noninvasive method of treatment of renal stones. Otherwise, a non-invasive method doesn't means that it is not harmful, because its association with late development of diabetes and hypertension is still controversial, while a link between ESWL and phosphate calcium stones is possible (4). However, as flexible ureteroscopy has higher success rates, it can be justified, since the complications rates are low. Regarding the cost, in some services the flexible ureteroscopy is cost effective compared to ESWL (5).

If we see this issue from a current point of view only, it sounds almost absurd to state that ESWL will disappear. Almost 60% of renal stones today are treatment by ESWL, at low cost and low complications rates. No one should close an ESWL service that is established and working properly. The urological guidelines support the use of ESWL for renal and ureteral stones (2, 6). However, we are discussing the future of renal stones treatment, what includes search for better treatments, with lower costs, higher success rates and low complications rates, with a high acceptance and satisfaction of the patients.

What we observe worldwide and in Brazil currently is an increase in the use of flexible and a decrease in the ESWL (3, 7, 8).

Herein, we describe some reasons for this change that we have observed:

1. Flexible ureteroscopy has been taught for many years in residency programs, congresses and specific courses for that. So, more urologists are able to perform an adequate flexible ureteroscopy.
2. The flexible ureteroscope has suffering tremendous advances and nowadays it is more durable, with small caliber and with improved vision with the digital system. With adequate care, a flexible ureteroscope can last for a hundred procedures or more, what diminishes the total cost of the procedure (9, 10).
3. The cost of the flexible ureteroscopy has decreasing and is much more affordable today than it was a few years ago. Conversely, the cost of a new ESWL machine is still high and we do not observe a decrease in prices with the new equipment and there is considerable maintenance cost (11, 12).
4. The new ESWL machines fails in demonstrate better results than the old models. None modern ESWL equipment showed to be better than the Dornier HM-3, the first equipment developed (13).
5. New disposables devices have been introduced almost daily, as ureteral sheaths, baskets, laser fibers, what can improve the outcomes (14).
6. There is an undeniable commercial and marketing appeal on flexible, a fact that is less observed with the ESWL machines.
7. Residents and young urologists prefer to do a flexible rather than an ESWL (15).
8. Reimbursement for flexible ureteroscopy is usually higher than for ESWL.
9. Outcomes of flexible ureteroscopy are superior than ESWL in a single session (6).

Normally, ESWL equipment occupies a considerable physical space in the hospital, many times inside a surgical center, with a post-operative room for the patients. That room is expensive, because usually it is underused during the day and stays closed during the night and weekends. It could have others use, more rentable for the Hospital.

Movable lithotripsy services were proposed in the North America and Europe in order to solve this problem. A truck was built with an ESWL machine inside and went to the hospitals to treat the patients. Nevertheless, the success rates published recently are about 50% (16). These poor results can compromise seriously the life of these mobile ESWL.

If you or your Institution have an ESWL service, keep using it, because you are offering a good and recommended treatment for the patients and the acquisition cost of the machine must be paid. However, in a strict administrative point of view (and administrators that make purchases for the hospitals), who is going to buy a new ESWL machine today, that is expensive, has a considerable maintenance cost, is each time less indicated for the urologists, occupies a relatively big and expensive space in the Hospital, if you can buy 2 or 3 flexibles ureteroscopes that will have a lower total cost for the institution, treat the patients more efficiently and is required by the urologists?

So, ESWL will die?

In my view, will not, and nor should die. But certainly it use will decrease a lot, until stabilize around 10 to 20% of all stone treatments. One possible solution is to create regional reference centers that will drain the cases of a determined region, with good

machines (17) and a dedicate team focused in apply all the recommended techniques to improve the outcomes, including a good selection of the patients based on the CT scan analysis (18), performing an adequate procedure, under sedation or general anesthesia, with good gel coupling, with frequency between 60 and 90 Hz (19), progressive increase of potency, and use of alpha-blockers after the procedure, mainly for stones bigger than 10 mm (20). This can give an extra life for the ESWL, making justice with one of the most incredible advances of the urology history.

But, as stated in the beginning of this article, flexible ureteroscopy will probably replace almost completely the use of ESWL in the clinical practice in few years, even in developing countries, unless arising another non-invasive technology that is cheaper and with high success rates (21).

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REVIEW ARTICLE

Vol. 41 (2): 207-219, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.05

OnabotulinumtoxinA for neurogenic detrusor overactivity and dose differences: a systematic review

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ABSTRACT

Purpose: To evaluate the efficacy and safety of onabotulinumtoxinA for patients with neurogenic detrusor overactivity (NDO).

Materials and Methods: We searched the Cochrane Library, PUBMED, EMBASE, Chinese Bio-medicine database, China Journal Full-text Database, VIP database, Wanfang database for randomized controlled trials (from inception to September 2012). Two authors independently selected studies, extracted data and assessed the methodological and evidence quality using the Cochrane Risk of Bias Table and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) respectively. Data analysis was performed by RevMan 5.1 and descriptive analysis was employed if necessary.

Results: Eight studies were selected (n=1879 participants). OnabotulinumtoxinA was more related to urinary tract infection (UTI) (200U: OR 1.72, CI: 1.18-2.52; 300U: OR 1.88, CI: 1.31-2.69) versus placebo. Also, OnabotulinumtoxinA was superior to placebo in improving maximum cystometric capacity (MCC) (200U: OR 138.80, CI: 112.45-165.15; 300U: OR 152.09, CI: 125.25-178.93) and decreasing maximum detrusor pressure (MDP) (200U: MD -29.61, CI: -36.52--22.69; 300U: MD-28.92, CI: -39.59--18.25). However, there were no statistical differences between 200U and 300U onabotulinumtoxinA in UTI (OR 0.84, CI: 0.58-1.22), MCC (OR-12.72, CI: -43.36-17.92) and MDP (MD 2.21, CI: -6.80-11.22).

Conclusions: OnabotulinumtoxinA may provide superior clinical and urodynamic benefit for populations with NDO. High-quality studies are required for evaluating the optimal dose, long-term application and when to perform repeated injections.

ARTICLE INFO

Key words:
onabotulinumtoxinA [Supplementary Concept]; Randomized Controlled Trials as Topic; Meta-Analysis [Publication Type]; Review Literature as Topic

Int Braz J Urol. 2015; 41: 207-19

Submitted for publication:
March 19, 2014

Accepted after revision:
June 08, 2014

INTRODUCTION

Overactive bladder syndrome (OAB) is described as the urgency-frequency syndrome, with or without urgent urinary incontinence (1). One type is neurogenic detrusor overactivity (NDO), secondary to spinal cord injury and multiple sclerosis (2). Subjects with NDO are characterized by involuntary bladder contractions at low volumes, low bladder capacity and incontinence, and often

have high transient bladder pressures. NDO negatively affects the quality of life (QoL) and causes complications within this population like depression, poor sleep, urinary tract infections, skin infections and disturbances of sexual lives (3).

Current treatment options mainly consist of medications (antimuscarinic drugs), behavior adjustments (timing training, bladder retraining, pelvic floor training), surgeries and interventional therapies. Although symptoms can be improved, unsatisfactory effects still exist in many cases. For example, antimuscarinics, the first-line medication (4), can have troublesome side effects, such as dry mouth, constipation as well as blurred vision (5).

FDA approved onabotulinumtoxinA for the treatment of NDO in August 2011. OnabotulinumtoxinA has exerted a positive impact on the urodynamic parameters, urinary continence and QoL (6, 7) by preventing the release of acetylcholine at the neuromuscular junction in the afferent and efferent (8) pathways of the bladder wall, urothelium or lamina propria, to inhibit detrusor contraction. Positioned between oral anticholinergic treatment that was ineffective or not tolerated and invasive surgery, this therapy is a minimally invasive treatment option (9). Economically, onabotulinumtoxinA causes a significant reduction in the morbidity as well as in the costs associated with necessary medications (10).

Currently, to our knowledge, there is no consensus regarding the clinical effect of onabotulinumtoxinA on the NDO and different doses, though plenty of relevant articles have been published. Additionally, no articles have been subjected to grade the quality of the overall evidence. Systematic review is of great importance to summarize evidence accurately and reliably. We aim to provide more insight into these topics based on recent randomized controlled trials.

MATERIALS AND METHODS

Only randomized controlled trials were included.

Types of participants

Participants diagnosed with NDO that are defined by the International Continence Society (ICS) (1) regardless of race, age, gender, course of disease and the origin of studies were included.

Types of interventions

OnabotulinumtoxinA was in the treatment group. The control group included any other interventions.

Types of outcome measures

Primary outcomes: Quality of life [scores of the QOL by means of the Incontinence QOL questionnaire, I-QOL (11); King's Health Questionnaire, KHQ (12)]. The most frequent adverse events: urinary tract infection (13).

Secondary outcomes: The frequency of urinary incontinence episodes; Two key urodynamic parameters: MCC (maximum cystometric capacity) and MDP (maximum detrusor pressure).

Search methods for identifiation of studies

A comprehensive search was performed of the Cochrane Library (2012, 9 issue), PUBMED (1966 to September 2012), EMBASE (1974 to September 2012), Chinese Bio-medicine database (1978 to September 2012), China Journal Full-text Database (1979 to September 2012), VIP database (1989 to September 2012), Wanfang database without language restrictions.

The main keywords were: urinary bladder diseases, bladder overactivity, detrusor overactivity, onabotulinumtoxina, clostridium botulinum toxins. Part of the databases applied subject headings. Search strategies were adjusted adhering to characteristics of different databases. The search strategy for PUBMED is presented in supplementary information.

DATA COLLECTION AND ANALYSIS

Selection of Studies

Two researchers independently scanned titles and abstracts consistent with predetermined criteria. Next, they read full texts and determined whether they were eligible. Disagreements were mediated and discussed with a third person. Contact with the authors by e-mail was carried out if any information was not available.

Assessment of risk of bias

The risks of bias of the included studies were independently assessed by two reviewers correlating with methods recommended by The Cochrane Collaboration. It was judged by the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. These criteria were judged as: 'Yes' (low risk of bias), 'No' (high risk of bias), or 'Unclear' (unclear or unknown risk of bias).

QUALITY ASSESSMENT OF THE EVIDENCE

The overall quality of evidence was assessed for every outcome using GRADE (14) by one reviewer and was validated by a second person with the GRADE pro Version 3.6 software. Five study limitations (Limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision and reporting bias) were assessed. The confidence of our estimated effect size was reflected through high, moderate, low or very low quality.

Statistical analysis

Statistical analysis was performed using the Review Manager software 5.1. Relative risk (RR) or odd ratio (OR), along with 95% confidence interval (CI) was calculated for dichotomous data. Mean difference (MD) with 95% confidence interval (CI) was calculated for continuous data. Heterogeneity between different studies was assessed by χ^2 test with $p<0.10$ used to indicate statistical significance and measure the quantity of heterogeneity, with $I^2>50\%$ indicating significant heterogeneity. The meta-analysis was conducted using the fixed-effect model if there was no statistically significant heterogeneity ($p\geq0.10$, $I2\leq50\%$). Otherwise, we initially analyzed the reasons of heterogeneity and pooled the data with random--effect models. Descriptive analysis was applied if the data could not be extracted for meta-analysis.

RESULTS

Description of studies

Our search included eight eligible studies (15-22) (Table-1). The flow of literature was shown in the PRISMA flow chart (Figure-1).

Risk of bias in included studies and quality of evidence.

The methodology for the individual trial and summary of findings for the main comparisons are delineated in Tables 2 and 3, respectively. We sent e-mails to the authors for unclear information, but no responses were received.

Effects of interventions scores for QoL

Four studies (16, 17, 21, 22) evaluated the impact of onabotulinumtoxinA 200U and 300U on QOL showing robust improvements in the mean change from baseline, which was significantly superior to the effect of placebo. Of these, one study (16) recorded I-QOL total scores ($p<0.05$) at week 2, 6, 12 and 24. The remaining three studies (17, 21, 22) recorded it at weeks 6 and 12 ($p<0.001$).

Two studies (18, 19) separately compared onabotulinumtoxinA 300U (18) and 500U (19) to placebo according to I-QOL total QOL scores (18) and the Qualiveen questionnaire (19), both showing greater improvement from baseline.

The frequency of urinary incontinence episodes

Compared to placebo, significant reduction of the frequency of urinary incontinence episodes in onabotulinumtoxinA group was seen in seven studies (15, 17-22).

Four studies (15, 17, 21, 22) compared onabotulinumtoxinA 200U and 300U groups to placebo. One study (15) revealed the decrease at weeks 12 and 18 in the 200 U onabotulinumtoxinA group. One study (21) reported the reduction at week 6 (-21.8 and-19.4 for the 200 and 300 U groups, respectively, vs.-13.2 for placebo; $P<0.01$). Cruz et al. (17) (200U: $p<0.001$, $p<0.01$, $p<0.01$; 300U: $p<0.01$, $p<0.01$, $p<0.001$) and Ginsberg et al. (22) ($p\leq0.008$) showed the efficacy at weeks 2, 6, and 12. Furthermore, three studies (15, 17-22) found that there were no clinically relevant differences between the onabotulinumtoxinA dose groups.

Two studies (18, 19) separately compared onabotulinumtoxinA 300U (18) and 500U (19) to placebo at weeks 6 ($p<0.0001$), 24($p=0.0007$), 36($p=0.0112$) (18) and at 0-6weeks ($p<0.001$), 7-12weeks ($p=0.002$), 13-26 weeks ($p=0.010$) (19). OnabotulinumtoxinA was compared with RTX in one study (20) at months 6, 12, 18 ($p<0.05$).

Table 1 - Characteristics of included studies.

Study	year	T /C	Gender (M/F)	No. of patient (T/C)	Age, mean (SD), years	Way of anesthesia	Diseases that causes NDO	The duration of Follow up
Schurch et al. (15)	2005	300U 200U placebo	36/23	19 19 21	41(20-72)	general, spinal, local or no anesthesia	spinal cord injury and multiple sclerosis	2, 6, 12, 18 and 24 weeks
Schurch et al. (16)	2007	300U 200U placebo	59	-	21-73	-	-	2, 6, 12, 18 and 24 weeks
Cruz et al. (17)	2011	300U 200U placebo	39/52 38/54 43/49	91 92 92	44.4±13.9 46.0±13.1 46.9±13.4	general, local or no anesthesia	spinal cord injury and multiple sclerosis	2, 6, 12 and 52 weeks
Herschorn et al. (18)	2011	300U placebo	15/13 19/10	28 29	42.0±13.3 43.7±14.3	general or local anesthesia	spinal cord injury and multiple sclerosis	1, 3 4, 6, 24 and 36 weeks
Ehren et al. (19)	2007	500U placebo	17/14	17 14	36(21-66)	general or local anesthesia	spinal cord injury, multiple sclerosis, myelomeningocele, trauma at birth and myelitis	26 weeks
Giannantoni et al. (20)	2004	300U RTX	18/7	12 13	38.4±12.5	spinal anesthesia and sedation	chronic spinal cord injury	14.2±3.9 months, 14.8±3 months
Sussman et al.(21)	2012	300U 200U placebo	39/52 39/53 43/49	91 92 92	44.4 (13.9) 46.0 (13.1) 46.9 (13.4)	-	multiple sclerosis and spinal cord injury	6 and 12 weeks
Ginsberg et al. (22)	2012	300U 200U placebo	43/89 55/80 73/76	132 135 149	47±12 46±14 46±13	no anesthesia, local anesthetic instillation without or with sedation, or general anesthesia	multiple sclerosis and spinal cord injury	2, 6 and 12 weeks

T = The treatment group; **C =** The control group.

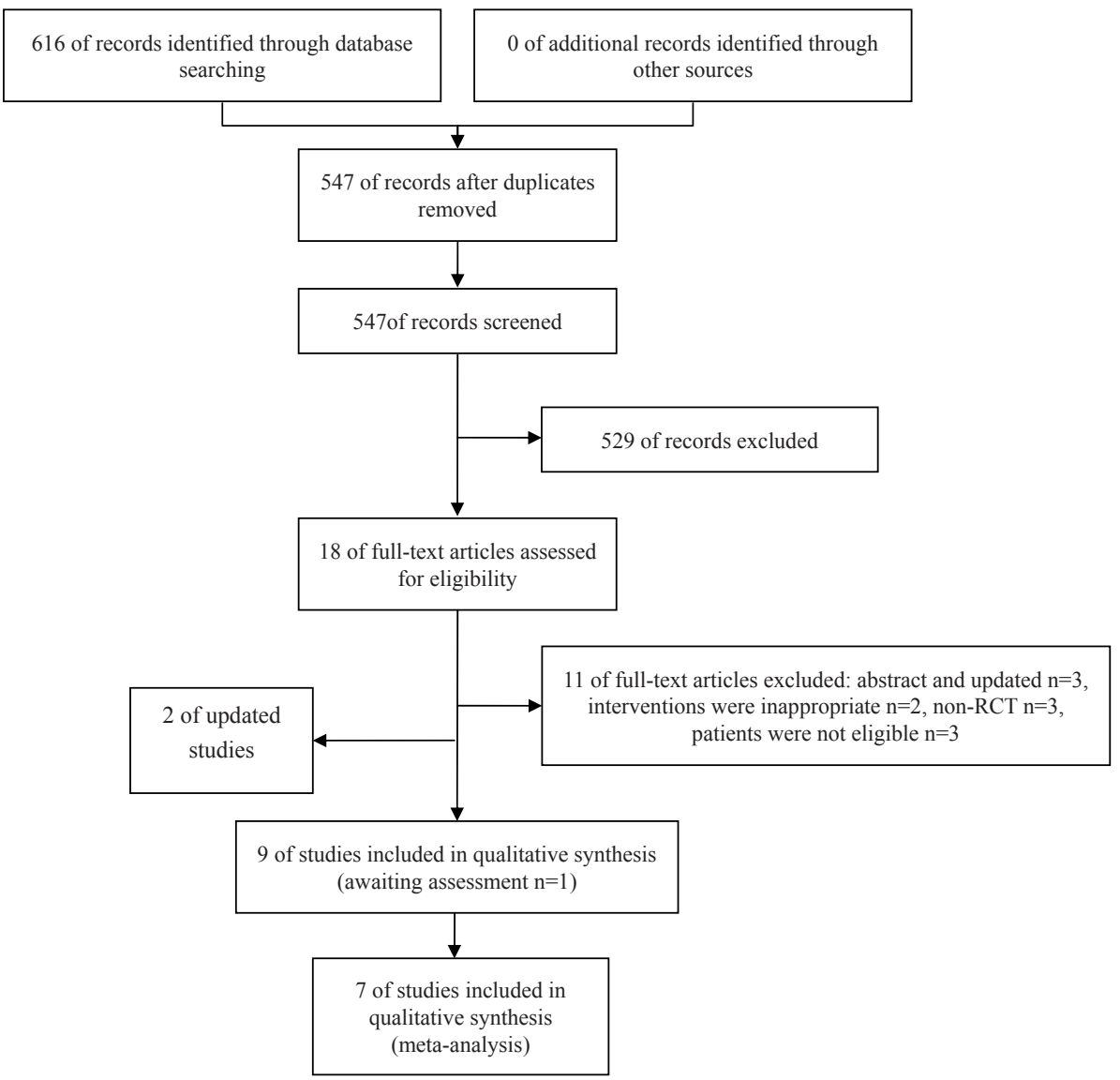
Adverse events

All studies reported adverse events. Of these, four studies (15, 17, 18, 22) reported the rate of UTI. There was no statistical heterogeneity between subgroup studies (200U: p=0.59, I2=0%; 300U: p=0.72, I2=0%; 200U versus 300U: p=0.35, I2=5%), and the pooled data showed that the rate in onabotulinumtoxinA 200U (OR 1.72, CI: 1. 18–2.52) (15, 17, 22) and 300U(OR 1.88, CI: 1.31–2.69) (15, 17, 18, 22) (Figure-2) group was both significantly higher than that in placebo. Also, there was no statistical heterogeneity between the two treatment groups (OR 0.84, CI: 0.58–1.22) (15, 17, 22).

MCC and MDP

Six studies were identified and all reported the outcomes at week 6. Therefore, we po-

Figure 1 - The flowchart of literature screening.



oled the data of week 6 for MCC and MDP, and described the data for other weeks.

Week 6: For MCC, there was no statistical heterogeneity between subgroup studies (200U: p=0.81, I^2=0%; 300U: p=0.95, I^2=0%; 200U versus 300U: p=0.81, I^2=0%). The result showed that MCC in 200U (15, 17, 22) and 300U onabotulinumtoxinA (15, 17, 22) groups was both significantly bigger than that in placebo (200U: OR 138.80, CI: 112.45–165.15; 300U: OR 152.09, CI: 125.25–178.93) (Figure-3). For MDP, there was statistically significant heterogeneity between trials (300U: p=0.09, I^2=59%) (15, 17, 22). Considering that there was statistical heterogeneity but no significantly clinical heterogeneity among studies, we pooled data with random-effect mode. The result showed that MDP in 200U (15, 17, 22) and 300U onabotulinumtoxinA (15, 17, 22) group was significantly smaller than that in the placebo group (200U: MD-29.61, CI: -36.52- -22.69;

300U: MD-28.92, CI: -39.59- -18.25) (Figure-4). Additionally, there were both no statistical differences between 200U and 300U onabotulinumtoxinA in MCC (OR-12.72, CI: -43.36–17.92) (Figure-3) and MDP (MD 2.21, CI: -6.80–11.22) (Figure-4).

Other weeks: One study (15) revealed significant increases and decreases from baseline in MCC ($p \leq 0.020$) and MDP ($p \leq 0.023$) in each onabotulinumtoxinA treatment group at all post--treatment time points. One study (18) described the outcome by the use of median showing improvement in urodynamic parameters of onabotulinumtoxinA group (MCC was improved at week 24(P=0.031); MDP was reduced at week 24 (P=0.0006), 36(P=0.0011). Similar findings existed in one study (19) (MCC was improved at 12 weeks (p=0.026); MDP was reduced ($p<0.01$) throughout the whole study period). One study (20) detected an improvement in MCC and MDP ($p<0.01$) in onabotulinumtoxinA group compared with RTX at 6, 12 and 18-month.

DISCUSSION

This research was designed in order to evaluate onabotulinumtoxinA for patients with NDO. Five outcomes were monitored: quality of life, urinary incontinence episodes, adverse events, MCC and MDP. Totaling three outcomes (UTI, MCC, MDP) were applied GRADE to assess the quality of evidence. Regrettably, no high quality of evidence was found to favor the effect of onabotulinumtoxinA on them illustrating that the confidence for our conclusion was not very strong. We solely analyzed two key urodynamic parameters (MCC and MDP) due to the paucity of other well-reported parameters in most studies. Similarly, we only performed a meta-analysis for UTI, but not for other adverse events, such as dysreflexia or muscular weakness. Six studies commented on the duration of clinical effect (15-19, 22). The duration was maintained for 24 weeks (15, 16), 42.1 weeks (17), 26 weeks (19), and 254-256 days (22). And improvements were evident at week 6 and persisted to weeks 24 to 36 (18). The clinical effect of the therapy was transient and dose related, whereas solely three studies (17, 20, 22) mentioned repeated injection. Intervals between reinjections were 6.8 ± 1.5 months (20) and 295-337 days (22). Moreover, repeat efficacies (reduced weekly UI episodes and maximum detrusor pressure, increased MCC and I-QOL total summary score) were observed (17, 20). Considering the inconsistent results reporting, our review was not designed specifically to assess duration of the clinical effect, reinjection effect, interval between reinjections, or other symptoms as urgency. The antimuscarinic co-treatment

Table 2 - Risk of bias in included studies.

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Schurch et al. (15)	Yes*	Unclear	Yes||	Yes	Unclear	Unclear
Schurch et al. (16)	Unclear	Unclear	Yes||	Unclear	Unclear	Unclear
Cruz et al. (17)	Yes†	Unclear	Yes||	Yes	Unclear	Unclear
Herschorn et al. (18)	Yes‡	Unclear	Yes||	Yes	Unclear	Unclear
Ehren et al. (19)	Unclear	Unclear	Yes||	Yes	Unclear	Unclear
Giannantoni et al. (20)	Yes§	Unclear	Unclear	Yes	Unclear	Unclear
Sussman et al.(21)	Yes†	Unclear	Yes||	Yes	Unclear	Unclear
Ginsberg et al. (22)	Unclear	Unclear	Yes||	Yes	Unclear	Unclear

* = unique randomization number; † = an automated interactive voice or web response system; ‡ = sequential treatment assignment numbers; § = commercially available software; || = 'double-blind', but the objective of blinding wasn't mentioned

Table 3 - Summary of findings for the main comparisons

OnabotulinumtoxinA versus Placebo for NDO
Patient or population: patients with NDO
Settings:
Intervention: OnabotulinumtoxinA versus Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**OnabotulinumtoxinA versus Placebo**				
The rate of UTI - 200U BOTOX versus Control	**Study population**		**OR 1.72** (1.18 to 2.52)	501 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	281 per 1000	**402 per 1000** (316 to 496)				
	Moderate					
	222 per 1000	**329 per 1000 (**252 to 418)				
The rate of UTI - 300U BOTOX versus Control	**Study population**		**OR 1.88** (1.31 to 2.69)	548 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	309 per 1000	**456 per 1000** (369 to 546)				
	Moderate					
	280 per 1000	**422 per 1000** (338 to 511)				
The rate of UTI - 200U BOTOX versus 300U BOTOX	**Study population**		**OR 0.84** (0.58 to 1.22)	480 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	434 per 1000	**392 per 1000** (308 to 483)				
	Moderate					
	382 per 1000	**342 per 1000** (264 to 430)				
MCC - 200U BOTOX versus Control (the 6th week)		The mean mcc - 200u botox versus control (the 6th week) in the intervention groups was **138.8 higher** (112.45 to 165.15 higher)		508 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
MCC - 300U BOTOX versus Control (the 6th week)		The mean mcc - 300u botox versus control (the 6th week) in the intervention groups was **152.09 higher** (125.25 to 178.93 higher)		504 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	

MCC - 200U BOTOX versus 300U BOTOX	The mean mcc - 200u botox versus 300u botox in the intervention groups was **12.72 lower** (43.36 lower to 17.92 higher)	488 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
MDP - 200U BOTOX versus Control (the 6th week)	The mean mdp - 200u botox versus control (the 6th week) in the intervention groups was **29.61 lower** (36.52 to 22.69 lower)	508 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
MDP - 300U BOTOX versus Control (the 6th week)	The mean mdp - 300u botox versus control (the 6th week) in the intervention groups was **28.92 lower** (39.59 to 18.25 lower)	504 (3 studies)	⊕⊕⊖⊖ **low**[1,2]
MDP - 200U BOTOX versus 300U BOTOX	The mean mdp - 200u botox versus 300u botox in the intervention groups was **2.21 higher** (6.8 lower to 11.22 higher)	488 (3 studies)	⊕⊕⊕⊖ **moderate**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence

High quality = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

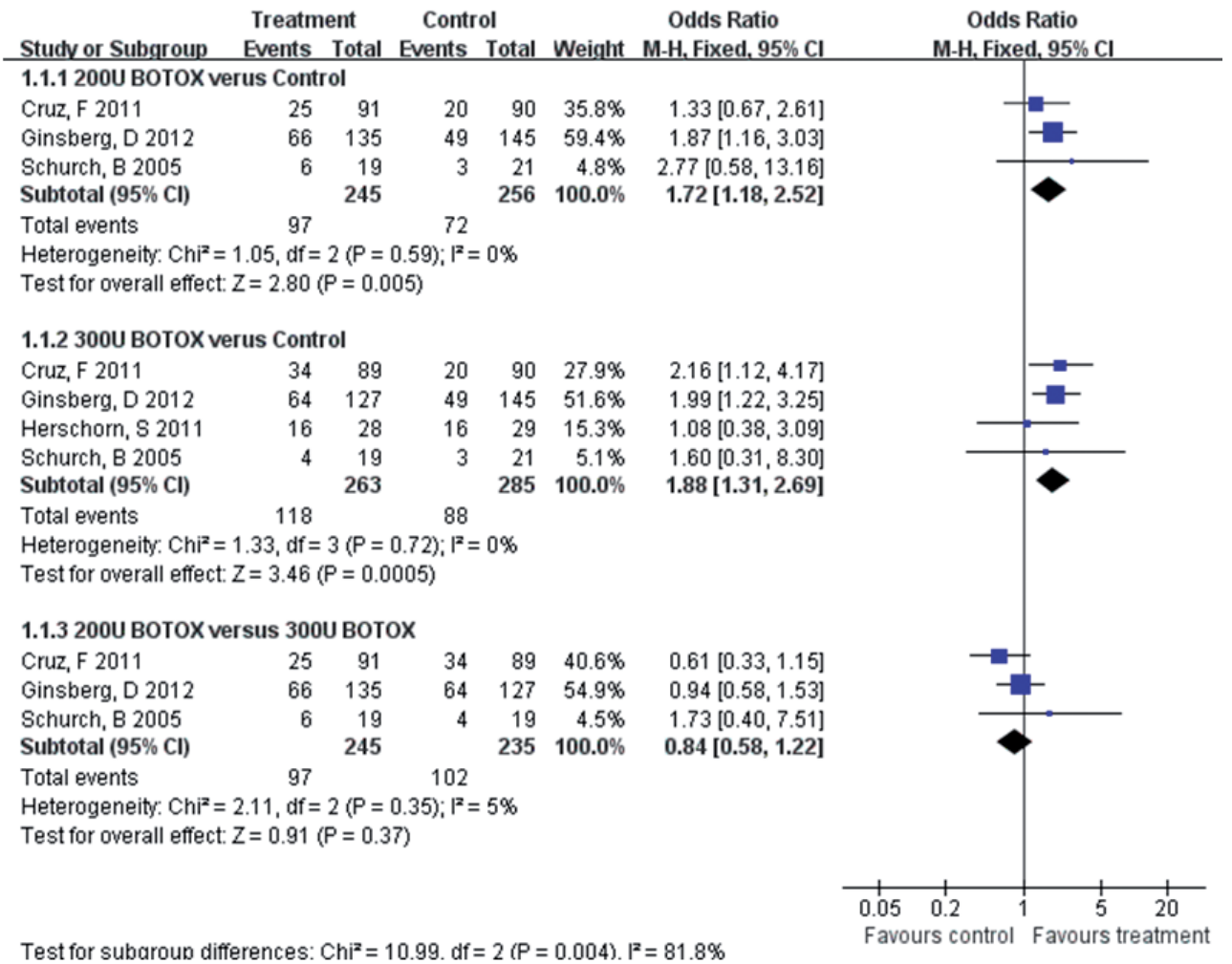
Low quality = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality = We are very uncertain about the estimate.

[1] From the result of risk of bias, sequence generation, allocation concealment and blinding of some studies were assessed as "unclear".

[2] I^2>50%.

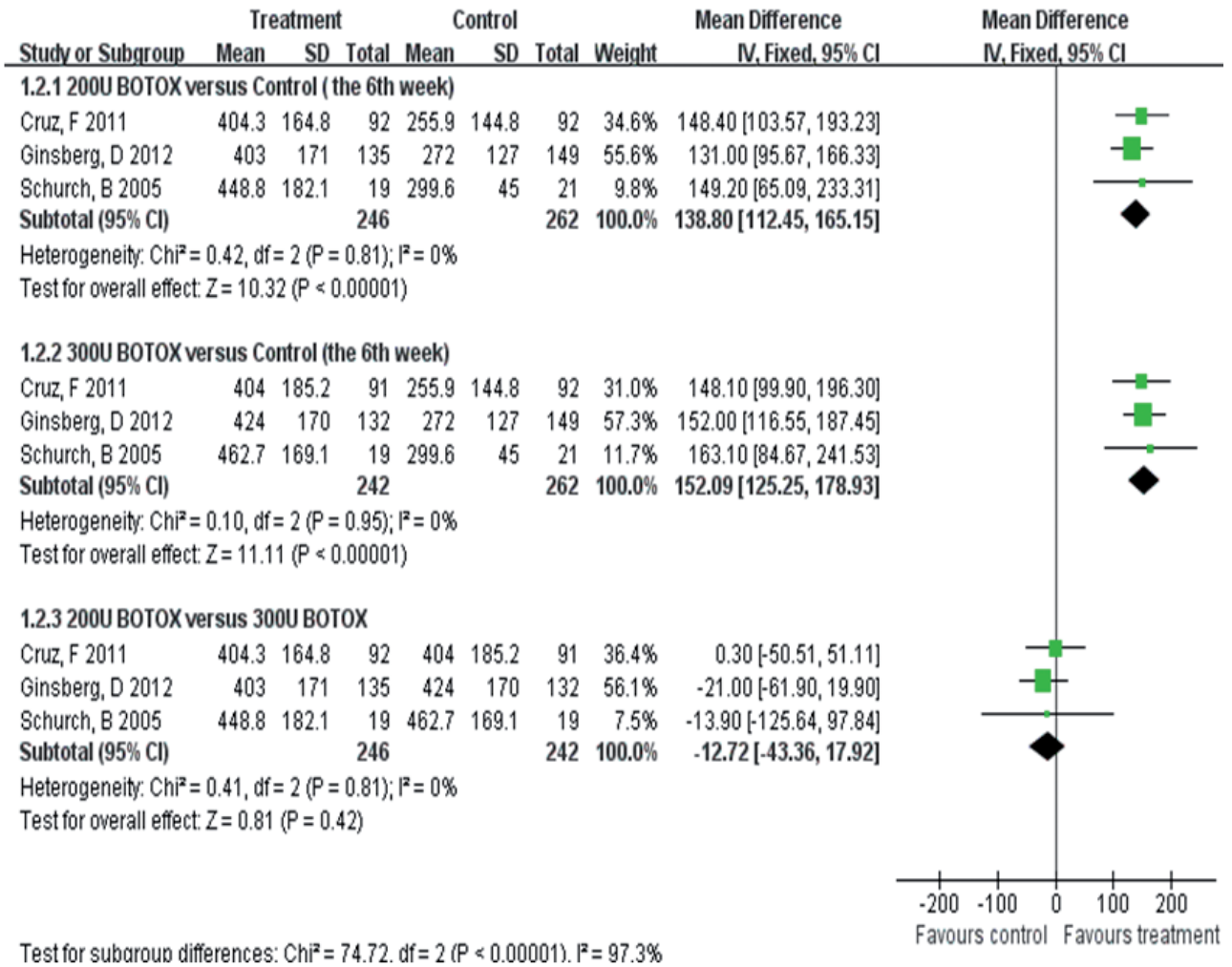
Figure 2 - Forest plot for the outcome of the rate of urinary tract infection (UTI).



was a major bias on results, and was performed in seven studies (15, 17, 18-22). However, only three studies (18-20) revealed that patients treated with onabotulinumtoxinA could use a smaller amount of antimuscarinics; therefore, its potential impact on the efficacy of Botox cannot be definitely appraised. Meanwhile, effective and well tolerated monotherapy effect of BoNTA in patients with NDO has also been reported by Grise et al. (23).

There were clinical studies and systematic reviews (23, 24) concerning onabotulinumtoxinA for NDO. The Cochrane Review (24) was published on the same subject as our review but with some differences in design, such as types of studies and participants. Additionally, their conclusions have some other points that contrast with ours: 1. The Cochrane Review revealed that lower doses of botulinum toxin (100 to 150 U) appeared to have beneficial effects, but larger doses (300 U) may have been more effective and longer lasting, but with more side effects. However, our review did not find clear dose differences (200 VS 300 U); 2. The Cochrane Review revealed that suburothelial injection had comparable efficacy to intradetrusor injection. However, our review did not compare different site injections because all included studies that applied intradetrusor injection. 3. The Cochrane Review indicated that the

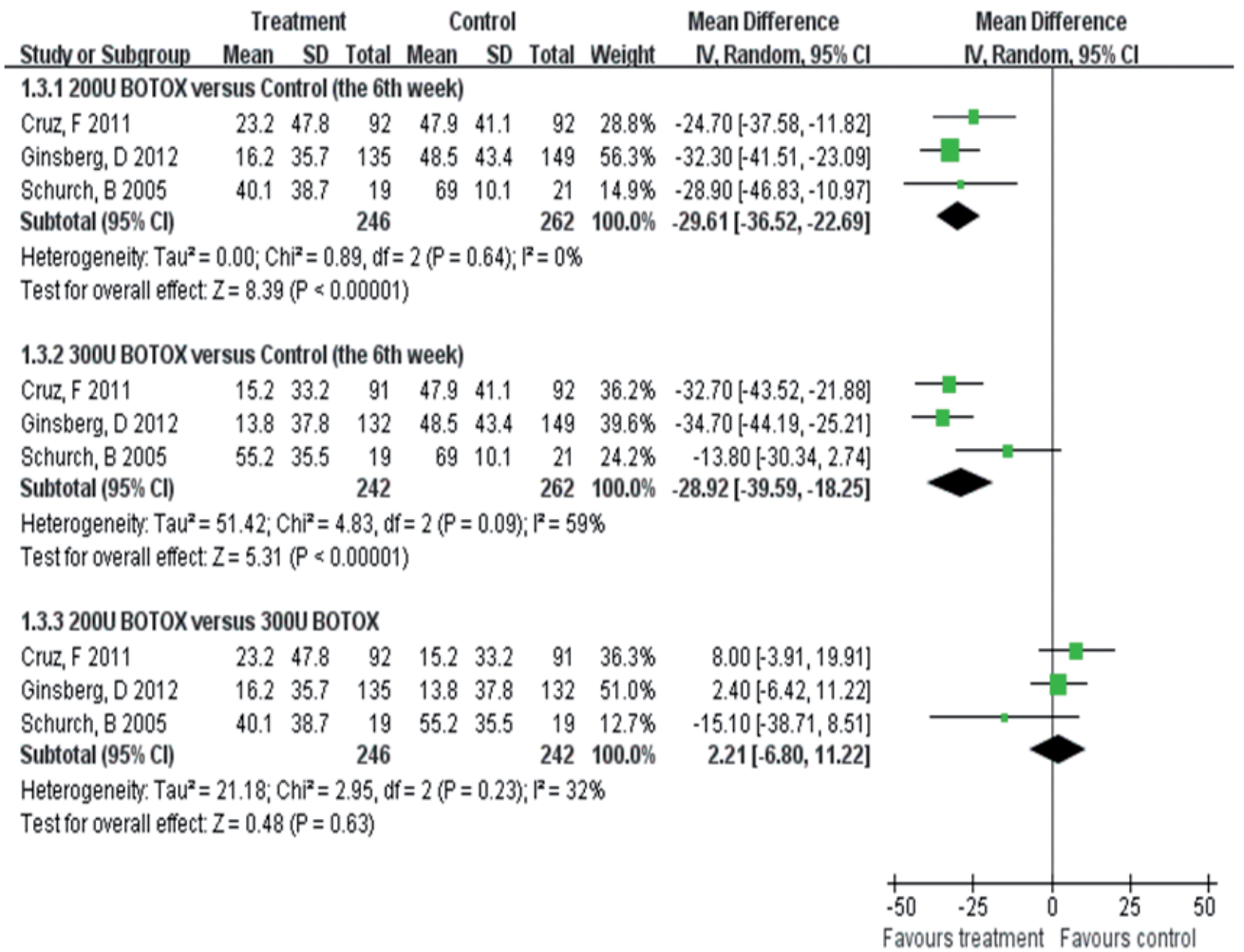
Figure 3 - Forest plot for the outcome of maximum cystometric capacity (MCC).



effect of botulinum toxin may last for a number of months and is dependent upon dose and type of toxin used. However, our review was not designed specifically to assess duration of the clinical effect duo to inconsistent report of results. Moreover, our research was mainly about onabotulinumtoxinA for NDO due to the dearth of studies about onabotulinumtoxinB. Regrettably, in spite of some similar conclusions, long term outcomes, safety, and optimal dose of botulinum toxin for OAB all remain still unanswered. To our acknowledge, our systematic review is the first to highlight a dose difference in terms of clinical effect and grade the quality of evidence in accordance with GRADE to reflect the confidence of our estimated effect size. However, it is still unknown whether higher or lower doses are more beneficial for patients due to the failure of finding clear difference between 200U and 300U. More studies should be initiated to determine the optimal dosage.

Methodological deficiency makes it difficult to reach more valid and reliable decisions. Six trials reported adequate randomization and one trial performed the exact allocation concealment. However, the remaining failed to mention the information above, which indicates the existence of selection bias. Seven trials performed blinding choice and most were double-blinded. Mostly, we considered objectives as patients and doctors. For subjective measurement, the score of QoL, was susceptible to

Figure 4 - Forest plot for the outcome of maximum detrusor pressure (MDP).



performance bias and detection bias. One trial failed to implement the blinding implying the possibility of performance bias.

During treatment, some failed to perform anesthesia before injection, while others required general, local and spinal anesthesia (Table-1). We should also pay close attention to those patients who have a failure or intolerance to onabotulinumtoxinA to ensure its safety. The possible plausible explanation for this may be the emergence of an antibody or variation of axolemma receptor's structures and tissues (25).

Some limitations for our systematic review should be acknowledged. First, published results were hindered by small sample size, and vague description about the allocation concealment in findings. Second, it is sufficient to raise doubts about long-term application owing to the short-term studies, with only one with duration up to 18 months. Third, our research was mainly about onabotulinumtoxinA for NDO due to the dearth of studies about onabotulinumtoxinB. We hope high quality of RCTs in this field will be implemented in the future. Forth, one concern we have is that the conclusion of having more UTI after onobotulinumtoxin cannot be accurately answered without a uniform definition of a UTI due to the significant difference between laboratory infections and clinical infections. Finally, it is also worth noting that GRADE's approach to assess risk of bias shares some fundamental limi-

tations with the very large number of alternative approaches. For example, empirical evidence supporting the criteria is limited and attempts to show systematic difference between studies that meet or do not meet specific criteria shows inconsistent results. Furthermore, the relative weight one should put on the criteria remains uncertain.

CONCLUSIONS

OnabotulinumtoxinA appears to be a cost--effective intervention for populations with NDO; however, the findings are not strongly definitive based on limited trials. In addition, we fail to find any dose differences.

Search Strategy for PUBMED

#1 Botulinum Toxin* OR botuli* OR Botulinu* toxin* OR "Clostridium botulinum Toxins" OR "Clostridium botulinum" OR onobotulinumtoxin
#2 "Botulinum Toxins"[Mesh]
#3 #1 OR #2
#4 "bladder overactivity" OR "detrusor overactivity" OR "overactive urinary bladder" OR "overactive bladder symptoms" OR "detrusor hyperreflexia" OR "urinary urgency" OR "urinary incontinence" OR "Urinary Bladder Diseases" OR "bladder dysfunction"
#5 "Urinary Bladder Diseases" (Mesh)
#6 #4 OR #5
#7 "Randomized Controlled Trial" (Publication Type)
#8 "Randomized Controlled Trials as Topic"(Mesh)
#9 "Controlled Clinical Trial" (Publication Type)
#10 "Controlled Clinical Trials as Topic"(Mesh)
#11 randomized (Title/Abstract)
#12 placebo (Title/Abstract)
#13 drug therapy (MeSH Subheading)
#14 randomly (Title/Abstract)
#15 trial (Title/Abstract)
#16 groups (Title/Abstract)
#17 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 "Animals" (Mesh)
#19 "Humans" (Mesh)
#20 #18 NOT #19#21 #17 NOT #20
#22 #3 AND #6 AND #21

ACKNOWLEDGMENTS

The authors thank Tracy, Stacie, Bing Bai, Jinqiu Yuan and YuanjunTeng that provided assistance with comments on revising the final manuscript. No financial or research funding are disclosed.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

Vol. 41 (2): 220-229, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.06

Comparison between the retropubic and transobturator approaches in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications

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ABSTRACT

Objective: This study aimed to compare the effectiveness and complications between the retropubic and transobturator approaches for the treatment of female stress urinary incontinence (SUI) by conducting a systematic review.
Materials and Methods: We selected all randomized controlled trials (RCTs) that compared retropubic and transobturator sling placements for treatment of SUI. We estimated pooled odds ratios and 95% confidence intervals for intraoperative and postoperative outcomes and complications.
Results: Six hundred twelve studies that compared retropubic and transobturator approaches to midurethral sling placement were identified, of which 16 were included in our research. Our study was based on results from 2646 women. We performed a subgroup analysis to compare outcomes and complications between the two approaches. The evidence to support the superior approach that leads to better objective/subjective cure rate was insufficient. The transobturator approach was associated with lower risks of bladder perforation (odds ratio (OR) 0.17, 95% confidence interval (CI) 0.09-0.32), retropubic/vaginal hematoma (OR 0.32, 95% CI 0.16-0.63), and long-term voiding dysfunction (OR 0.32, 95% CI 0.17-0.61). However, the risk of thigh/groin pain seemed higher in the transobturator group (OR 2.53, 95% CI 1.72-3.72). We found no statistically significant differences in the risks of other complications between the two approaches.
Conclusions: This meta-analysis shows analogical objective and subjective cure rates between the retropubic and transobturator approaches to midurethral sling placement. The transobturator approach was associated with lower risks of several complications. However, good-quality studies with long-term follow-ups are warranted for further research.

ARTICLE INFO

Key words:
stress urinary incontinence; retropubic tape; transobturator tape; meta-analysis; systematic review

Int Braz J Urol. 2015; 41: 220-9

Submitted for publication:
May 06, 2014

Accepted after revision:
July 28, 2014

INTRODUCTION

Stress urinary incontinence (SUI) is a major health problem that affects millions of women throughout the world. It is estimated to affect 15% to 35% of women in the general population (1).

Since it was first described by Ulmsten et al. (2) in 1996, the tension-free vaginal tape (TVT) has been considered as the first-line approach for the treatment of SUI. Although the TVT procedure was shown to have a high and stable cure rate in the medium and long terms (3, 4), complications such as bladder perforation, retropubic hematoma related to the passage of the sling through the retropubic space (5), and voiding dysfunction (6) have been reported. To minimize these complications, in 2001,

Delorme (7) described a new route of inserting the tape, which the author called transobturator taping (TOT), in which the tape was inserted through the obturator foramina.

In 2003, de Leval (8) introduced a modified technique called TVT-O, in which the tape is inserted in a reverse route, in through a vaginal incision and out through the obturator foramen (inside out).

Both the TOT and TVT-O procedures proved to have high success rates in short and medium term follow-ups and to be associated with few perioperative complications (9, 10). However, the use of transobturator slings is associated with specific complications such as thigh pain (11). Furthermore, whether the TOTs (both TOT and TVT-O) are equal to the TVT in effectiveness for the treatment of SUI is controversial. Some studies showed that the TOTs were as effective as the TVT (12, 13), but some trials proved that the TVT was superior than the TOT in terms of outcomes (14).

However, current researches were often driven by local norms and individual surgeon preferences instead of evidence-based medicine. Proper comparisons of effectiveness and associated complications between TVT and TOTs are currently limited.

The objectives of this systematic review were to determine and compare effectiveness between the TOTs and TVT in randomized controlled trials (RCTs) and to explore complication rates.

MATERIALS AND METHODS

A prospective protocol for this systematic review was developed. The study inclusion and exclusion criteria, statistical method, approach to estimating study quality, and outcomes are described in the sections that follow. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Cangzhou People Hospital. Written informed consent was obtained from all participants.

Sources

All RCTs that compared retropubic and transobturator midurethral sling placement in the treatment of SUI were collected. We searched literatures from 2001 to 2011 using the following online databases: PubMed, Springer, OVID, EBSCO, SAGE Journals, and Web of Science. We also found meeting abstracts from 2001 to 2011 on the Web sites of the International Continence Society, the American Urogynecologic Society, and Society for Urodynamics and Female Urology.

Our search strategy included the Medical Subject Heading term "urinary incontinence" and other "free" keywords such as "retropubic," "transobturator," "tension-free vaginal tape," "TVT," "TVT-O," "TOT," "Monarc," "SPARC," and "midurethral sling." These search terms were used singly and in combination. There were no language restrictions on our searches. Two reviewers collaboratively performed our literature research. The corresponding author of each RCT included in the analysis was contacted.

Inclusion/Exclusion Criteria

All prospective RCTs that compared TOTs (TOT or TVT-O) and TVT in the treatment of urodynamically proven SUI were included. The following inclusion criteria were used: (i) prospective randomized studies that compared between the retropubic and transobturator approaches to tension-free midurethral polypropylene sling placement for SUI; (ii) clearly defined objective and/or subjective outcome measures; and (iii) clearly defined follow-up periods. Studies were excluded on the basis of the following criteria: (i) duplicate reports, in which case the report containing the most complete data was included; (ii) patients who had previously undergone anti-incontinence surgery; (iii) the rate of loss to follow-up was higher than 15% in general; (iv) fewer than 40 included cases; (v) the operation method included TVT-secure; and (vi) animal experiments.

Data Abstraction

The quality of the research studies and data abstraction were evaluated independently by two reviewers (Feng S and Qinglu S) according to Cochrane guidelines 4.2.2 and the quality-control standards set by Jada et al. (15). In case of any dissents between the two reviewers, a third member (Hongbo Z) participated in a discussion

to reach a consensus. We collected the following information: (i) the quality of the trials (allocation concealment, randomization method, blinding, power calculation, and intention-to-treat analysis); (ii) the participants' characteristics (number, type of sling used, and type of SUI, either isolated or mixed); (iii) follow-up duration and number of patients lost to follow-up; (iv) outcomes, namely subjective and/or objective cure; (v) intraoperative (bladder perforation and retropubic/vaginal hematoma) and postoperative complications (thigh/groin pain, de novo urgency or urge incontinence, transient voiding dysfunction, long-term voiding dysfunction, and tape erosion).

Statistical analysis

Statistical analysis was performed using the RevMan 5.0.24 software. For the dichotomous data in our review, we assessed statistical heterogeneity using the following criteria: "P≤0.05 or I2≥50%" was considered to represent statistically significant heterogeneity, and the Mantel-Haenszel random effects model was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). The Peto fixed effects model was used if "P>0.05 and I2<50%."

We assessed publication bias using funnel plots. Subgroups were established prior to the analysis of the objective/subjective outcomes, according to two perspectives as follows: (i) women with isolated and mixed incontinence and women with isolated incontinence, and (ii) "TVT vs. TOT" and "TVT vs. TVT-O." The subgroups established prior to the analysis of the complications included only "TVT vs. TOT" and "TVT vs. TVT-O."

RESULTS

Characteristics of the studies

Our search identified 612 reports, of which 588 were excluded on the basis of their titles/abstracts because of several shortcomings, including the following: lack of a comparative study design, a retrospective design, midurethral slings made of autogenous materials, non-randomized study design, association with other pelvic operations, and fewer than 40 study subjects. The remaining trials were assessed in detail. Three were excluded because neither the objective nor subjective cure criteria were defined (16-18). One was excluded because of lack of a clear explanation of the randomization method (19). Another was excluded because of a high rate of loss to follow-up (20). Three were excluded because of duplicate reports (21-23). Sixteen prospective randomized studies (24-39) were included in the review. The included studies used different objective cure criteria, singly or in combination, such as negative cough stress test result in the urodynamic testing (24-27, 29-39), and 1-hour pad test <1 g (28,29,34), <2 g (32,38), and <3 g (30). Twelve trials reported subjective cure rates (24-30, 32-35, 39). Different subjective measures such as the visual analogue scale, Incontinence Impact Questionnaire, Urogenital Distress Inventory, and other validated questionnaires were also used. Patient satisfaction of the subjective cure was described as "satisfied," "very satisfied," or "dry."

We randomized 2646 women to undergo midurethral sling placement for SUI using either TOTs (TOT/TVT-O) or TVT. Nine trials included women with either isolated or mixed SUI (25-27, 30-32, 34, 35, 39). Seven trials included women with isolated SUI only (24, 28, 29, 33, 36-38). Ten trials compared between TVT-O and TVT (24-26, 29, 34-39); 5 trials compared between TOT and TVT (27, 28, 31-33); and 1 trial included both TOT and TVT-O (30). Perioperative cystoscopy was performed for all the patients in 7 trials (25-28, 30, 31, 38); cystoscopy was used only for the TVT group in the remaining trials. Five of the trials reported allocation concealment (26, 28, 32, 33, 38). Thirteen trials had computer-generated randomization (24-28, 30-37), whereas the other trials used quasi-randomization. Only one trial had a single-blind design (24). Power calculation was performed in 10 trials (25-28, 31, 33, 34-36, 38); intention-to-treat (ITT) analysis was performed in only 1 trial (25). In all the trials, the general rates of loss to follow-up were not higher than 15%. The mean follow-up periods ranged from 6 to 36 months. The details of the included trials are shown in Table-1.

Effectiveness

We performed the first subgroup analysis according to different types of SUI ("isolated and

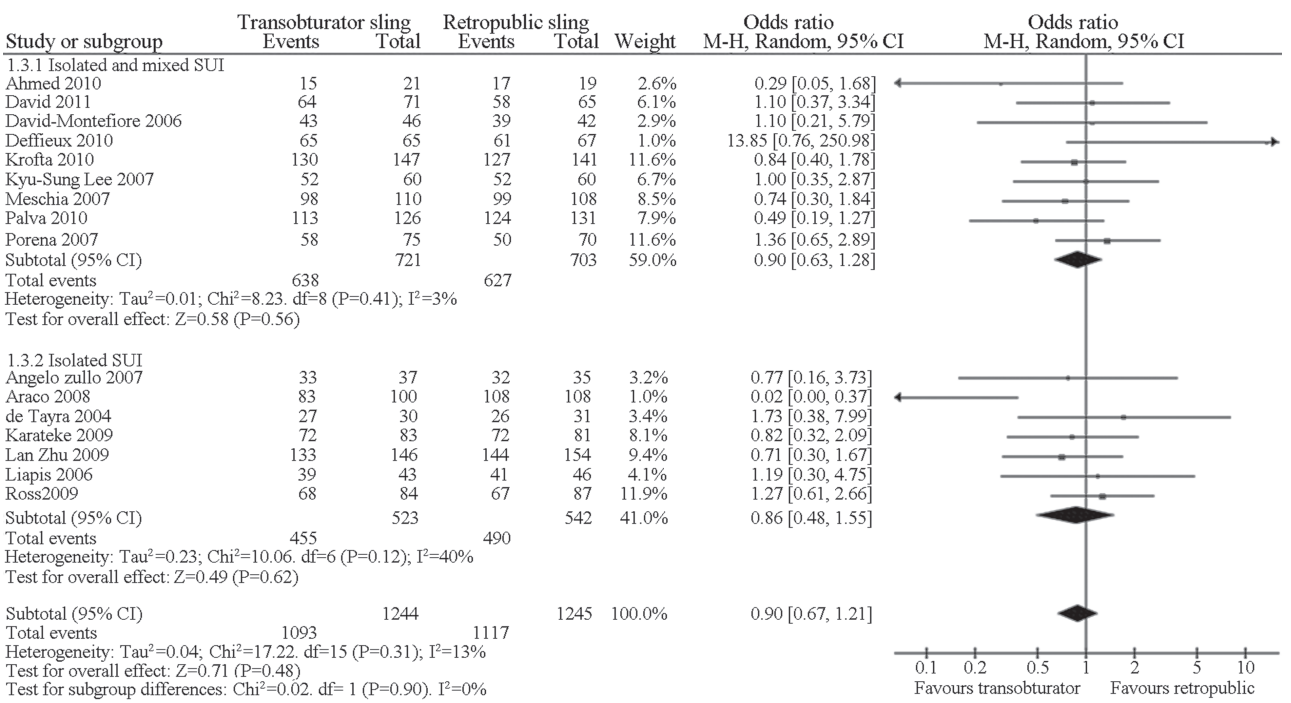
Table 1 - Basic data of research from literatures.

Author	Year	Country	Follow-up duration (month)	Research quality	Retropubic group	Transobturator group
Zhu et al	2008	China	14.5	A	35 (TVT)	34 (TVT-O)
Karateke et al	2009	Turkey	14	A	83 (TVT)	84 (TVT-O)
Palva et al	2010	Finland	36	B	136 (TVT)	131 (TVT-O)
Deffieux et al	2010	France	24	B	67 (TVT)	67 (TVT-O)
Porena et al	2007	Italy	31	B	70 (TVT)	75 (TOT)
Ross et al	2009	Canada	12	B	105 (TVT)	94 (TVT-O)
Liapis et al	2006	Greece	12	B	46 (TVT)	43 (TVT-O)
Wang et al	2011	China	12	B	32 (TVT)	36 (TVT-O)
David et al	2011	Switzerland	12	B	65 (TVT)	70 (TVT-O/TOT)
Lee et al	2006	Republic of Korea	13	B	60 (TVT)	60 (TVT-O)
David-Montefiore et al	2006	France	24	B	42 (TVT)	46 (TOT)
Ahmed et al	2010	Egypt	20	B	19 (TVT)	21 (TVT-O)
de Tayrac et al	2004	France	12	B	31 (TVT)	30 (TVT-O)
Krofta et al	2010	Czech	12	B	149 (TVT)	151 (TVT-O)
Meschia et al	2007	Italy	6	B	114 (TVT)	117 (TVT-O)
Angelo et al	2007	Italy	12	B	35 (TVT)	37 (TVT-O)
Zhu et al	2009	China	6	B	160 (TVT)	155 (TVT-O)
Araco et al	2008	Britain, Italy	12	B	120 (TVT)	120 (TVT-O)
Total					1369	1371

mixed SUI" and "isolated SUI"). When compared with the TVT group, the objective cure rate in the transobturator group was equivalent to that of the "isolated and mixed SUI" subgroup (OR 0.90, 95% CI 0.63-1.28), as well as that of the "isolated SUI" subgroup (OR 0.86, 95% CI 0.48-1.55). The differences in combined objective cure rate were not statistically significant (OR 0.90, 95% CI 0.67-1.21). When the transobturator and TVT groups were compared in terms of subjective cure, the "isolated and mixed SUI" (OR 0.91, 95% CI 0.68-1.23) and "isolated SUI" subgroups had equivalent results (OR 1.17, 95% CI 0.71-1.93), while differences in combined subjective cure were not statistically significant (OR 0.97, 95% CI 0.76-1.26). Figure-1 provides the objective cure rates of the transobturator group (TVT-O and TOT) in comparison with those of the TVT group in the first subgroup analysis.

We performed another subgroup analysis based on different anti-incontinence approaches ("TVT-O vs. TVT" and "TOT vs. TVT"). One study (30) was excluded in the meta-analysis because of the use of combined TVT-O and TOT in the transobturator group. When compared with TVT, the objective cure of SUI was equivalent between the TVT-O (OR 0.77, 95% CI 0.51-1.15) and TOT groups (OR 1.07, 95% CI 0.68-1.68), and the combined objective cure was not statistically significant (OR 0.86, 95% CI (0.63-1.16). The subjective cure in the transobturator group (TVT-O and TOT) in comparison with that in the TVT group

Figure 1 - Meta-analysis of objective cure of SUI between transobturator and TVT approaches in the first subgroup analysis.



was also not statistically significant (TVT-O vs. TVT: OR 0.97, 95% CI 0.71-1.33; TOT vs. TVT: OR 1.05, 95% CI 0.37-2.99, and total: OR 1.02, 95% CI 0.77-1.34). Figure-2 provides the objective cure rates of the two approaches (TVT-O and TOT) in comparison with that of the TVT in the subgroup analysis. The funnel plots indicated symmetrical distribution of the studies, indicating a low likelihood of publication or reporting bias (Figure-3).

COMPLICATIONS

We excluded one study (30) in the analysis of complications because it used the combination of TVT-O and TOT in the transobturator group.

All the trials provided data on bladder perforation. In comparison with TVT, TVT-O and TOT were associated with statistically significantly lower risk of bladder perforation as follows: TVT--O group (OR 0.18, 95% CI 0.08-0.38), TOT group (OR 0.17, 95% CI 0.06-0.49), combined TVT-O and TOT (OR 0.17, 95% CI 0.09-0.32).

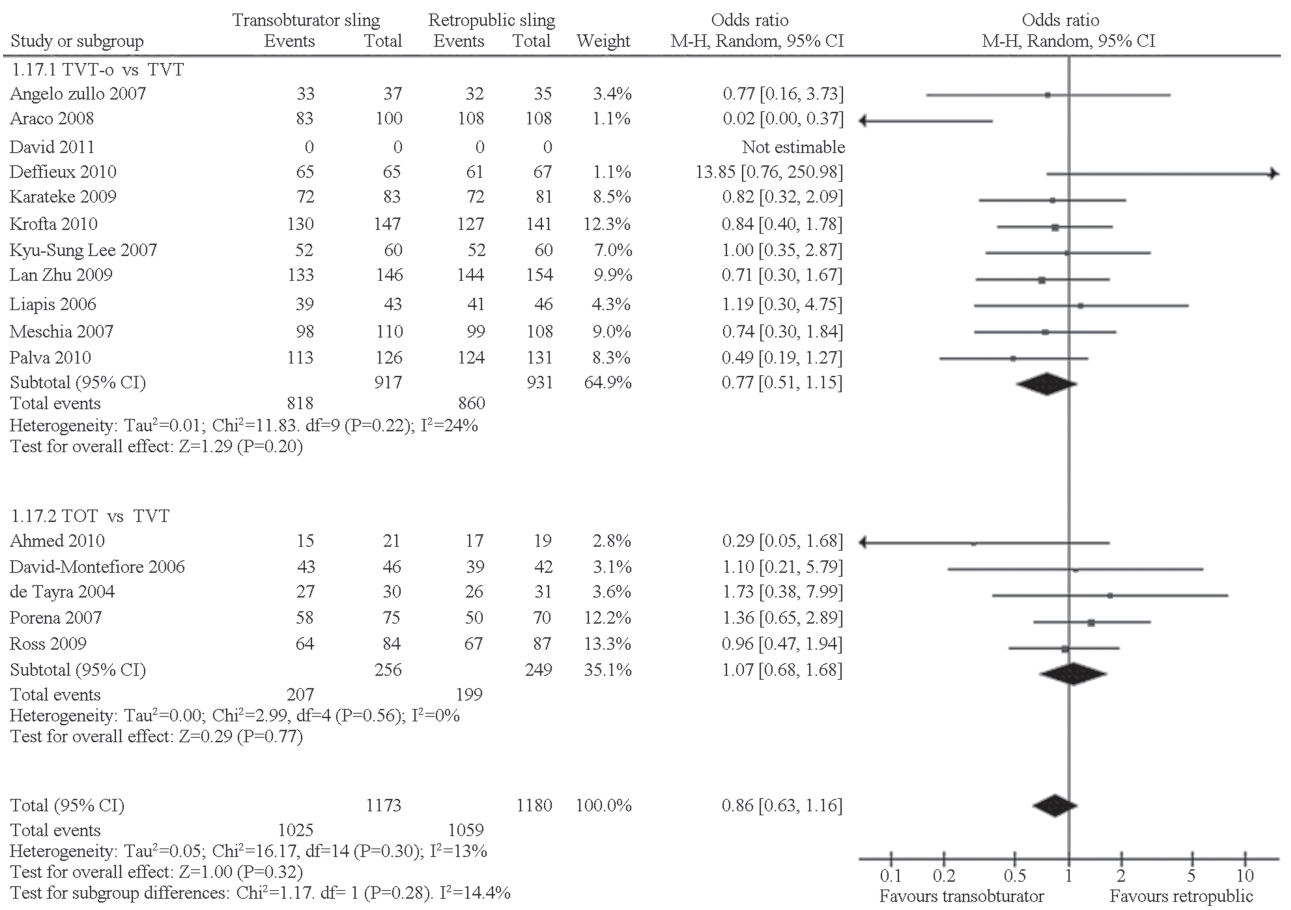
All trials reported data on retropubic/vaginal hematoma. In the subgroup analysis, the risk of hematoma was lower in both the TVT-O (OR 0.42, 95% CI 0.19-0.93) and TOT groups (OR 0.13, 95% CI 0.03-0.53) than in the TVT group.

Eleven trials (25-28, 31, 32, 34-37, 39) represented data on thigh/groin pain. The description and criteria of pain in each trial were not accordant. The TVT-O group seemed to be associated with a higher risk of pain than the TVT group (OR 2.8, 95% CI 1.81-4.45). However, no statistically significant difference was found between the TOT and TVT subgroups (OR 1.85, 95% CI 0.88-3.90). The risk of thigh/groin pain was higher for the combined TVT-O and TOT group (OR 2.53, 95% CI 1.72-3.72).

Thirteen trials (24-27, 29, 31, 33, 34-39) provided data on transient voiding dysfunction. The risks of transient voiding dysfunction were equivalent (TVT-O vs. TVT: OR 1.26, 95% CI 0.89-1.77 and TOT vs. TVT: OR 0.73, 95% CI 0.29-1.86).

Eleven studies (25-29, 31, 33, 34, 36, 38, 39) provided data on long-term voiding dysfunction. In the subgroup analysis, the risk of long--term voiding dysfunction was lower in the TVT-O group (OR 0.23, 95% CI 0.10-0.52) and equivalent

Figure 2 - Meta-analysis of the objective cure of the two approaches (TVT-O and TOT) in comparison with TVT.



between the TOT (OR 0.54, 95% CI 0.19-1.49) and TVT groups.

Eleven studies (24, 25, 28, 29, 31, 33, 34, 36-39) described postoperative symptoms of de novo urgency/urge incontinence. The risks were equivalent between the transobturator and retropubic groups (TVT-O vs. TVT: OR 0.96, 95% CI 0.56-1.65 and TOT vs. TVT: OR 1.03, 95% CI 0.41-2.60).

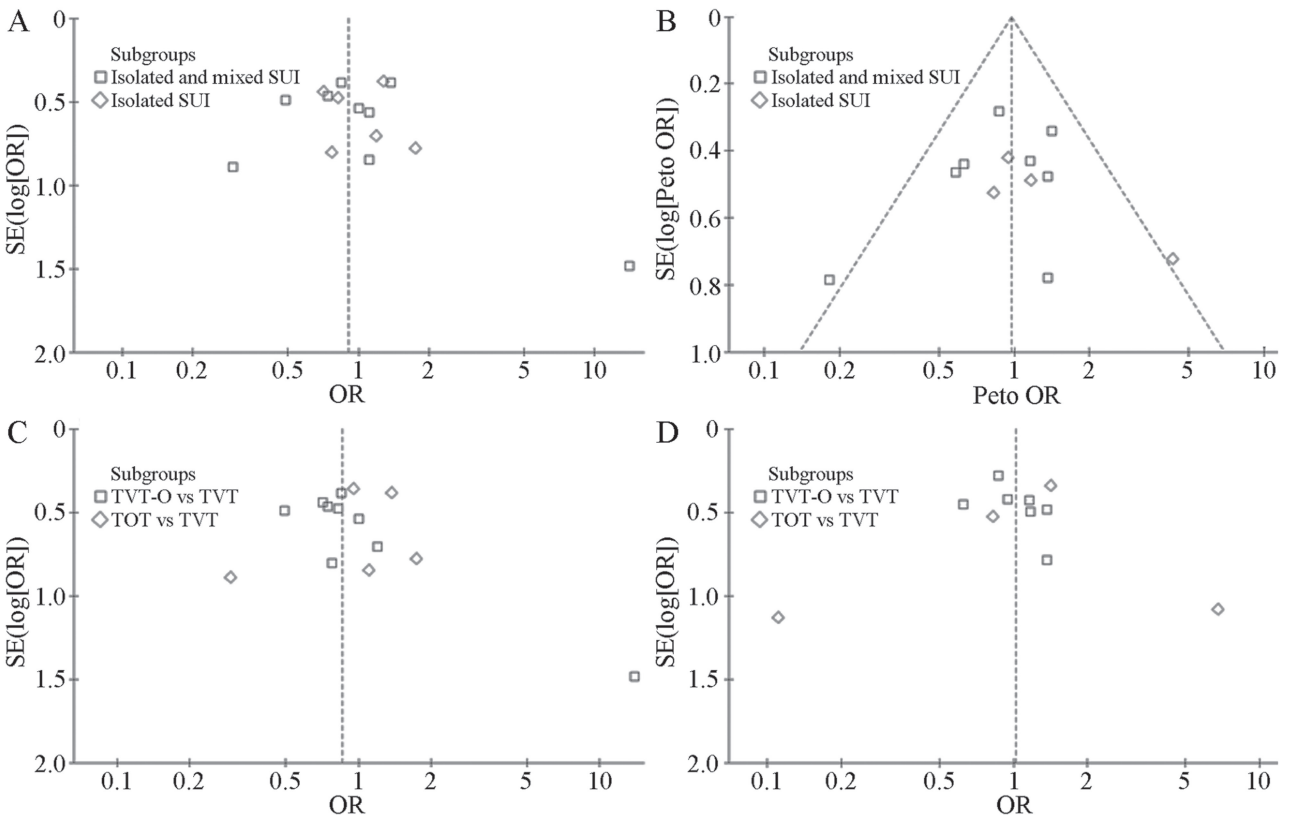
All the trials reported data on tape erosion. The risks of tape erosion were equivalent (TVT-O vs. TVT: OR 0.95, 95% CI 0.45–1.98 and TOT vs. TVT: OR 2.40, 95% CI 0.54-10.62).

Figure-4 provides a summary of the complications associated with the two tapes (TVT-O and TOT) in comparison with the TVT.

DISCUSSION

This systematic review has several superiorities. To ensure the accordance of baseline participant characteristics, we included only prospective and RCTs trials. To minimize the likelihood of publication or reporting bias, we set no language restrictions on our searches and sought both published and unpublished studies. Two reviewers independently estimated the quality of the studies according to Cochrane guidelines 4.2.2 and quality-control standards set by Jada et al. To obtain the most accurate results possible, we performed a subgroup analysis from two angles, namely (1) “isolated and mixed SUI” and “isolated SUI,” and (2) “TVT-O vs. TVT” and “TOT versus TVT.”

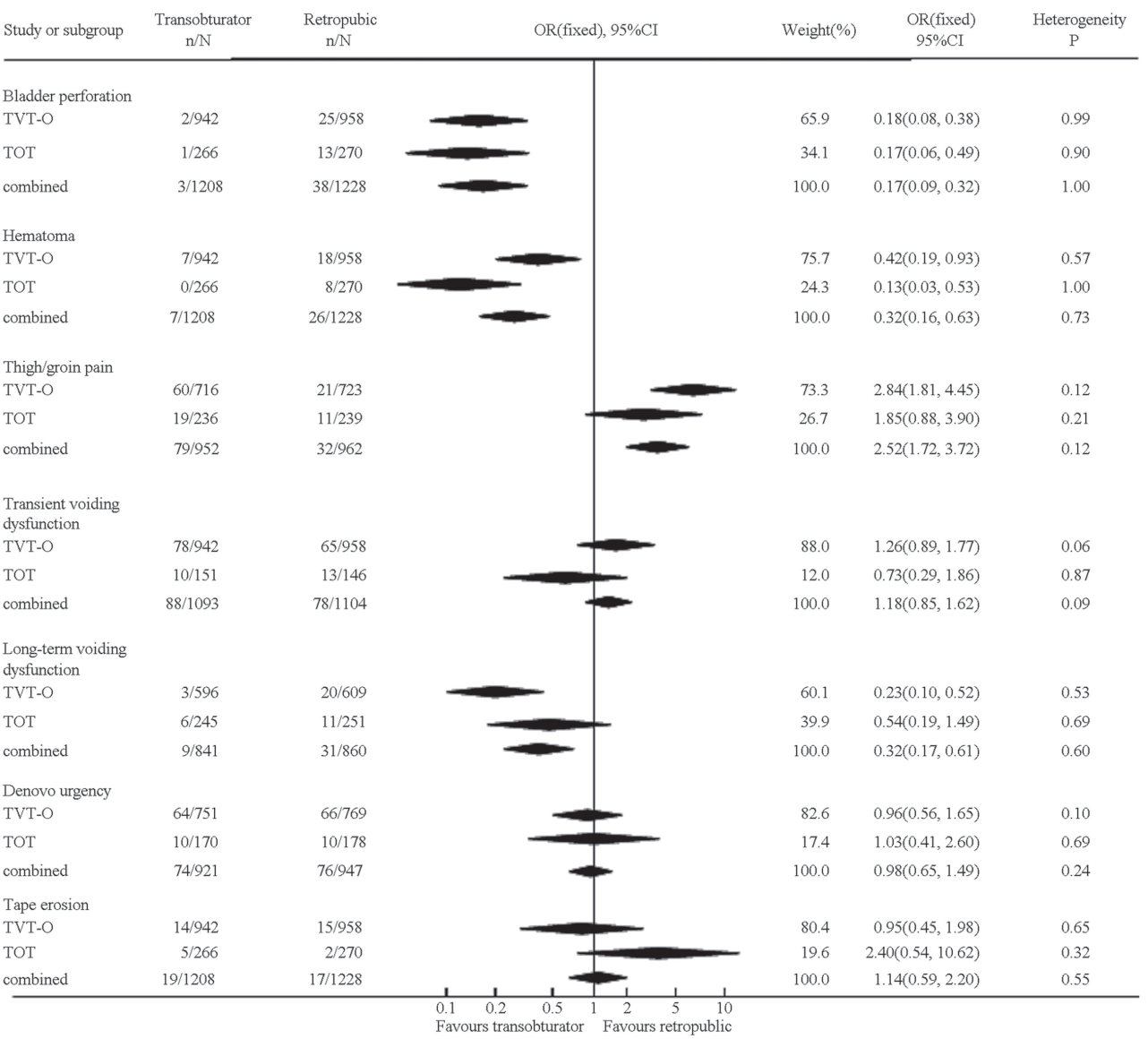
Figure 3 - A and B: Funnel plot of included trials to study the objective/subjective cure of SUI between transobturator and retropubic procedures in the first subgroup analysis C and D: Funnel plot of included trials to study the objective/subjective cure of SUI with procedures by TVT-O/TOT versus TVT.



We found no statistically significant difference in either objective or subjective cure between the transobturator and retropubic approaches for the treatment of female SUI. The funnel plots of the outcomes in the two subgroup analyses were evenly distributed, indicating a less likelihood of publication bias and higher confidence in the results. These results are consistent with those of most of the included trials (24-31, 33-37, 39). However, these findings cannot demonstrate the equivalent effectiveness of the two approaches. Although we compared between the transobturator and retropubic approaches in the "isolated and mixed SUI" and "isolated SUI" subgroups, the comparison between the two approaches in women with intrinsic sphincter deficiency (ISD) was ignored because of the lack of sufficient relative trials. In fact, several studies (14, 40) proved that the transobturator approach was inferior to the retropubic approach in the treatment of ISD in women. Thus, further research in this field is warranted.

Both the TVT-O and TOT approaches are recognized as associated with lower risks of bladder perforation and retropubic hematoma than the TVT. This review confirms the above-mentioned standpoint. However, some RCTs avoided the systematic use of cystoscopy with transobturator procedures (24, 29, 32-37, 39), and all the 3 cases of bladder perforation during the transobturator procedure were reported by the trials in which perioperative cystoscopy was routinely used for all the patients (26, 27). Thus, the real bladder perforation rate during transobturator procedures may be a little higher. Although previous research (41) suggests that systematic use of cystoscopy was

Figure 4 - Complications of the two procedures (TVTO and TOT) in comparison with TVT.



not necessary for transobturator approach, surgeons must be aware of the risk of bladder perforation, even with the transobturator procedure.

We found that the transobturator approach, especially the TVT-O procedure, was associated with a lower risk of long-term voiding dysfunction than the TVT. This result may be explained by the following, as reported by Juma (42) and Morey (43): the orientation of the transobturator tension-free midurethral sling was more similar to the natural hammock shape, as compared with the TVT procedure. As a result of lower shearing force to the urethra, the transobturator tape is more appropriate for women with slow urine flow rate.

Although we concluded that the risk of thigh/groin pain was higher in the transobturator group, the result was not persuasive owing to the lack of unified definition and description of the duration of pain. Some authors have reported that the hammock nature of the transobturator procedure decreases the risk of de novo urgency or urge incontinence (42). However, we found only insufficient evidence to sup-

port that claim, or that one approach leads to a lower risk of tape erosion.

Our study has potential limitations. First, the quality of the included trials was not good enough. For example, only one of the 16 trials had a single--blind design (24) and intention-to-treat analysis was performed only in one study (25). That may be a source of heterogeneity. Second, the criteria of objective and subjective cure, and complications such as pain were not consistent. These negative factors may cause bias and heterogeneity. Among our trials, the last one had the longest follow-up period of 36 months. The follow-up periods were too short to appropriately reflect long-term outcomes and complications.

In conclusion, the transobturator and retropubic approaches were equally effective for the treatment of SUI. In particular, the transobturator approach was associated with a decreased risk of complications. However, good-quality studies with long-term follow-up are warranted for further research.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 230-238, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.07

The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double blind placebo controlled clinical trial

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ABSTRACT

Varicocele is one of the most common causes of male infertility and spontaneous pregnancy rate after varicocelectomy is only about 30%. The most important seminal antioxidant is vitamin C but recent studies about the effects of vitamin C on spermatogenesis are controversial; therefore, we decided to evaluate its role after varicocelectomy. In a double blind randomized controlled clinical trial, 115 men with infertility and clinical varicocele with abnormal semen analyses were recruited. After surgery, the intervention group received vitamin C (250 mg bid) and the control group received placebo for three months. Mean sperm count, motility, and morphology index of two semen analyses (before and after surgery) were compared between the two groups. Univariate general linear model and stepwise linear regression were used in analysis. The mean age (±SD) of participants was 27.6±5.3 years. Vitamin C group had statistically significant better normal motility (20.8 vs. 12.6, P=0.041) and morphology (23.2 vs. 10.5, P<0.001) than placebo group. Considering the values prior to surgery as covariate, vitamin C was not effective on sperm count (P=0.091); but it improved sperm motility (P=0.016) and morphology (P<0.001) even after excluding the confounding effect of age (P=0.044 and P=0.001, respectively). Vitamin C was also an independent factor in predicting motility and normal morphology after surgery. Ascorbic acid can play a role as adjuvant treatment after varicocelectomy in infertile men.

ARTICLE INFO

Key words:
Ascorbic Acid; Varicocele; Infertility, Male; Semen Analysis

Int Braz J Urol. 2015; 41: 230-8

Submitted for publication:
January 04, 2014

Accepted after revision:
May 22, 2014

INTRODUCTION

The overall prevalence of infertility is up to 15% of couples and in half of the cases male factor is involved. Infertility has had an increasing trend during recent decades in Iran (1). In addition, the quality of semen in men has declined during the past few decades (2) and impaired sperm function has been considered as the most common cause of infertility (3).

Infertility is an important issue for couples with sometimes severe consequences. The treatment of infertility requires a multi-faceted therapeutic approach, consisting of improvements in environmental and occupational risk factors, nutritional imbalances, antioxidants, medical therapies, surgeries, and assisted reproductive technology (ART).

Selvakumar E et al. established the effect of lipoic acid (an antioxidant like substance) in

improvement of semen quality and reducing the oxidative stress and DNA damage induced by cyclophosphamide in rats (4). Other antioxidants like vitamin C (ascorbic acid) and vitamin E have been proved to ameliorate the oxidative stress and sperm toxicity induced by endosulfan in rats (5). One before-after study evaluated the effects of vitamins C and E (each one 500 mg/day) and demonstrated no efficacy of these antioxidants on DNA peroxidation in fertile and subfertile dogs; but, this controversial result could have been due to the very low sample size (6). The protective effects of ascorbic acid on p-dimethylaminoazobenzene induced genotoxicity and cytotoxicity have also been confirmed in mice (7).

Another study with a low sample size (eight healthy volunteers with azoospermia) illustrated that administration of testosterone propionate over a four-week period did not change the level of ascorbic acid in human semen even after 12 injections (8).

A recent review showed that vitamin C has controversial effects on sperm parameters and pregnancy rate in subfertile males with idiopathic oligoasthenoteratozoospermia (9).

Because the effect of vitamin C in spermatogenesis is still controversial and the proof for its clinical use challenging, we decided to evaluate its role as a supplement (as an antioxidant nutrient) after varicocele surgery (known as improving a definite cause of infertility). Previous population-based study on Iranian couples showed varicocele as a main risk factor for infertility (1).

Varicocele is one of the most common causes of male infertility and although its surgical repair results in improved spermatogenesis in 70% of patients, spontaneous pregnancy rate is only about 30% after varicocele repair without other treatments (10). Regarding the high prevalence of varicocele and suboptimal results of its surgical repair in improvement of pregnancy rates, additional treatment modalities are necessary. Recently, oxidative stress has been proposed to be an important factor in the pathophysiology of varicocele-induced infertility. The most important seminal antioxidant is ascorbic acid (vitamin C) which comprises 65% (11, 12) of antioxidant capacity of semen and is currently used in-vitro to improve sperm quality in infertility clinics. Therefore, we decided to evaluate the effects of supplemental vitamin C medical therapy after varicocelectomy for its probable improvement of infertility.

In this double-blind placebo controlled clinical trial, we assessed the effects of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile Iranian men.

MATERIALS AND METHODS

In this double blind randomized controlled clinical trial, we recruited infertile males who had palpable varicocele (grades 2 and 3) from February 2010 to May 2011. In the presence of a palpable varicocele in physical examination and accompanying abnormalities in count, motility, or morphology of sperm in two separate semen analyses, they became candidates for surgery.

Other inclusion criteria were: age range between 18 and 50, weight between 50 and 100 kilograms, and being married; the negative inclusion criteria were: absence of azoospermia, diabetes mellitus, hormonal disorders (according to medical history and clinical examination), tobacco smoking, opium or recreational drugs addiction, regular usage of vitamins or nutritional supplements, active or chronic genitourinary infection (based on medical history, physical examination, semen and urine analysis), history of peptic ulcer, and previous reaction to or intolerance to vitamin C. Exclusion criteria were missed follow-up, incorrect usage of the capsules, demonstrating side effects due to vitamin C, and commencement of smoking or opium addiction during the follow-up period, and delayed complications of varicocelectomy such as: hydrocele, recurrence of varicocele, and testicular atrophy.

In this study, infertility was defined as the inability to achieve a pregnancy after one year of unprotected regular intercourse. Normal semen sample was considered as defined by WHO (1999) (13): volume more than or equal to 2.0 mL, sperm count greater than or equal to 20 million per mL, motility (movement of the sperm) value greater than or equal to 50% with forward progression (grades “a+b”), or greater than or equal to 25% with rapid progression (grade “a”) within 60 mi-

nutes of ejaculation, morphology greater than or equal to 30% with normal forms, and white blood cell count less than 1 million per mL. All semen samples were obtained by masturbation in the lab and were analyzed in a reference laboratory (Sina Laboratory of Arak) by an experienced specialist in pathology and clinical laboratory medicine. Sperm counts were measured by the hemocytometer method using a Neubauer sperm counting chamber after immobilization of spermatozoa with neutral formalin. Sperm motility was calculated by scanning several fields under high-dry objective, until a total of at least 200 spermatozoa were registered. Morphology was assessed by differential counts of morphologically normal and abnormal spermatozoa types on Pap-stained slides.

The surgical approach was open inguinal method (Ivanissevich) which does not need special equipment and is still the most prevalent approach in Iran. All patients in both groups had varicocelectomy without image magnification. Our secondary complications were rare and they were excluded from the study and only those with clinically cured varicocele were selected for the final analysis. If there was any other unaccounted factor from Ivanissevich method that could affect the results, since both groups had the same type of operation, it would be balanced in the two groups.

Randomization

After including 115 eligible patients that had surgery, we randomly allocated these patients into vitamin C (intervention) or placebo group according to simple randomization method using Excel 2010 software (Microsoft Corporation, Washington, USA) by "RANDBETWEEN(0;1000000)" function. The allocation sequence was produced by our statistician and was delivered to our pharmacist. Participants were enrolled by the two executive urologists who were unaware of the results of the allocation table. Then based on the numbers in the sequence being odd or even each new patient after varicocele surgery was assigned to intervention or placebo group by our pharmacist who supplied the drugs. The ratio of placebo to intervention group was 1.5. Therefore, 46 cases were allocated to vitamin C and 69 cases to placebo group. Lost to follow-up patients were substituted with matching new cases. The intervention group received capsules containing 250 mg of vitamin C (OSVAH Pharmaceutical Co. Tehran, Iran) in two daily doses, one in the morning and one in the evening. Controls received starch-filled capsules (Osveh Co., Tehran, Iran) as placebo. Both groups received capsules for three months after surgery.

Then, two separate semen analyses were obtained, each after 3 days of abstinence. Samples were collected inside the laboratory by masturbation into sterile containers and allowed to liquefy at 37°C for 30 min. Mean sperm count, motility, and morphology index of each of the two semen analyses (before and after surgery) were compared between two groups as our primary outcomes.Moreover, complications of surgery, varicocele grade, age and weight were determined.

Motility was defined as mean percent of good motility (type A plus type B) divided by all motility types (Type A+Type B+Type C+Type D). These types are defined as: Fast progressive (Type A), Slow progressive (Type B), Non-progressive (Type C), Immotile (Type D).

Statistical analysis

Descriptive indices like percent, mean, standard deviation (SD) were employed in this study. We also used chi-square for evaluating association between categorical variables, repeated measure ANOVA for evaluating the simultaneous effect of both treatments (vitamin C or placebo) and time (before and after surgery). Student-t test was used for comparing quantitative variables in different groups. We used univariate general linear model for comparing the status of quantitative indices of semen analysis after varicocelectomy considering baseline values as covariates (omitting their confounding effect on post-surgery values) and stepwise linear regression for predicting post-surgery semen indices. P-value less than 0.05 was considered statistically significant. All statistical analyses were executed by SPSS 20 (SPSS Inc., Chicago, Illinois, USA).

Ethics

We explained the aim and method of the study for the patients. All cases were aware of and accepted that they will receive vitamin C or placebo; however, they did not know which drug (intervention or placebo) they would receive. All cases signed an informed written consent form before entering the study and they were informed that they could terminate their cooperation with use whenever they wanted without any consequences.

The trial is registered in Iranian Registry of Clinical Trials (IRCT) site (www.irct.ir), with the code number "IRCT201103042134N2".

RESULTS

Mean age (±SD) of the participants was 27.6±5.3 years. Five patients from the intervention group and eight patients from controls did not show-up for the follow-up visits and were substituted with matched new cases. We performed the intention to treat analysis in all parts of the study. The grades of varicocele were 2 and 3 in 9 (19.6%) and 37 (80.4%) of cases in vitamin C group and 10 (14.5%) and 59 (85.5%) cases in placebo group, respectively. The grade of varicocele was not statistically different between vitamin C and placebo groups (P=0.473). Totally, in both groups, in 35 (30.4%) cases the sperm count worsened after the intervention. Also, in 22 (19.1%) and 14 (12.2%) cases the motility or normal morphology declined, respectively.

Basic characteristics of the two groups are presented in Table-1. As it shows, the intervention group was younger; but semen analysis indices were not significantly different between the two groups.

Evaluating the simultaneous effect of treatment and time by repeated ANOVA showed that vitamin C group had statistically significantly better status than the placebo group except for the sperm count which although was higher in the intervention group, the difference was not statistically significant (Table-2). Similarly, we compared the mean difference of values of different indices of semen analysis (for example: mean of differences of sperm count before and after surgery in each intervention or placebo group) between the two groups using student t--test (Table-3). Again, motility and morphology, but not sperm count, were significantly better in vitamin C as compared to the placebo group.

Using univariate general linear model, we considered the values of before surgery as covariate and evaluated the effects of vitamin C in comparison with placebo on sperm indices. According to this analysis, vitamin C was not effective on sperm count (P=0.091), even after excluding the confounding effect of age (P=0.151). But, vitamin C was effective on sperm motility (P=0.016) and morphology (P<0.001) even after excluding the confounding effect of age (P=0.044 and P=0.001, respectively).

Table 1 - Basic characteristics of the intervention and placebo groups before treatment*

	Group		Sig.
	Vitamin C	Placebo	
Age, year	26.3±4.9	28.5±5.5	0.025
Count, million/mL	42.5±28.4	37.5±28.1	0.362
Motility, %	33.8±15.5	32.4±14.3	0.618
Morphology, %	52.2±16.1	57±18.2	0.147
Oligozoospermia, %	30.4	26.1	0.610
Asthenozoospermia, %	89.1	91.3	0.698
Teratozoospermia, %	4.3	7.2	0.524

* = All variables refer to the condition of patients before surgery, values are presented as mean±SD

Table 2 - Comparison of the results of the surgery between the intervention and placebo group*

	Group		Sig.
	Vitamin C	Placebo	
Mean count, million/mL	58.4±24.3	48.7±27.8	0.328
Mean normal motility**, %	54.5±18.3	44.9±21.4	**0.041**
Mean normal morphology, %	75.3±13.1	67.5±16.4	**<0.001**
Normal count, %	95.7%	81.2%	**0.025**
Normal motility, %	67.4%	44.9%	0.066
Normal morphology, %	100.0%	98.6%	0.033

* = Values are presented as mean±SD; ** = Sum of (a+b) motility type

Table 3 - Comparing the mean differences of indices before and after surgery status between the intervention and placebo groups*

	Group		Sig.
	Vitamin C	Placebo	
Count[a], million/mL	15.9±25.3	11.1±26.2	0.328
Motility[b], %	20.8±21.3	12.6±20.5	0.041
Morphology[c], %	23.2±18.7	10.5±15.8	<0.001

* = all values are presented as mean±SD

a = (mean count after surgery - mean count before surgery); b = (mean motility after surgery - mean motility before surgery); c = (mean normal morphology after surgery - mean normal morphology before surgery)

Stepwise linear regression showed that sperm count before intervention could significantly predict post-intervention sperm count (Table-4). The regression formula for count after surgery without vitamin C was:

Sperm count after surgery = (0.53 × sperm count before intervention) + 31.6

It shows that varicocelectomy by itself can increase the sperm count from 10 to 36.9 million/mL irrespective of administration of vitamin C supplementation.

Motility after surgery was also predictable by motility and morphology before intervention and vitamin C or placebo (Table-4). The regression formula was:

Sperm motility after surgery = (0.425 × motility before intervention) + (10.154 × D#) + (0.238 × morphology before intervention) + 17.6

D="1" if the intervention was vitamin C and "zero" if it was placebo

The value of normal morphology after surgery was only dependent on morphology before intervention (Table-4). Its regression model was:

Sperm morphology after surgery = (0.404 × morphology before intervention) + (9.758 × D#) + 44.5

D="1" if the intervention was vitamin C and "zero" if it was placebo

Adjusted R-squares of these models were 0.307, 0.170 and 0.248 for count, motility and morphology, respectively. It shows that the models for predicting count and morphology had higher accuracy, respectively, irrespective of the number of independent variables included in the model. In each model, higher standardized beta

Table 4 – Stepwise linear regression model of post-surgical indices of semen analysis.

Dependent variable	Independent variable	Unstandardized Coefficients		Standardized Beta	Sig.	Model	
		Beta	SE of Beta			R-square	Sig.
Count	Sperm count before intervention	0.53	0.074	0.56	<0.001	0.31	<0.001
Motility	Motility before intervention	0.425	0.120	0.303	0.001	0.192	<0.001
	Giving vitamin C	10.154	3.630	0.241	0.006		
	Normal morphology before intervention	0.238	0.102	0.201	0.022		
Morphology	Normal morphology before intervention	0.404	0.073	0.452	<0.001	0.261	<0.001
	Giving vitamin C	9.758	2.604	0.307	<0.001		

showed the more important predictors of the value of dependent variables.

DISCUSSION

Totally, in 30.4%, 19.1% and 12.2% of cases the sperm count, motility and normal morphology worsened after the intervention, respectively. Vitamin C was not effective on sperm count; but effective on sperm motility and morphology even after excluding the confounding effect of the age. Despite the statistically different age between vitamin C and placebo groups, the age difference of 2.2 years does not seem clinically important and based on the mean semen parameters before the surgery the two groups were comparable.

All our analyses in this study showed that vitamin C supplementation had significant positive effects on sperm motility and morphology; but not in sperm count in infertile young adult males with low quality sperm. It means that ascorbic acid could positively affect qualitative and not quantitative characteristics of sperm analysis.

It is obvious that better sperm quantity or quality before surgery resulted in better situation after surgery for most patients (totally and not individually because the model predicts the mean indices for all patients and not for each individual). However, the aim of our study was to answer whether vitamin C had an additive role for improvement of semen parameters after varicocelectomy, since our regression models showed vitamin C could increase post-operative motility and normal morphology but not sperm count. These findings confirmed the results of our univariate analyses.

One Egyptian study has shown that smoking significantly decreases seminal plasma ascorbic acid and it is also associated with reduced semen parameters which can worsen male fertilization potential (14). Subsequently, we excluded smokers and drug addicts from our study to restrict the confounding effect of smoking and related habits.

Colagar AH and Marzony ET showed that fertile smoker men have lower concentrations of seminal ascorbic acid than fertile non-smokers. This study also illustrated that infertile smokers have lower vitamin C level than fertile smoker men (12).

One observational study on healthy non--smoking American volunteers established that higher intake of antioxidants consisting of vitamin C by normal diet or supplement usage is associated with higher sperm count and motility (15). Our study was a randomized controlled clinical trial (RCT) and included cases after varicocele surgery, thus these differences make these two studies non-comparable. However, both results support the same issue which is effectiveness of vitamin C on fertility indices of the semen.

The evaluation of the effects of different dosages of vitamin C on infertility needs more sophisticated studies; however, one study has shown that an increase in vitamin C dosage from 200 to 1000 mg per day significantly improved sperm quality (16).

Before surgery, most of our cases had poor sperm motility but over two-thirds had normal sperm counts. Thus, the improvement in semen indices with vitamin C cannot be generalize to all patients and more studies in different populations with different pre-surgery patterns of sperm analysis especially in those with more severe oligozoospermia, are needed.

Varicocelectomy is not a definite treatment for infertility in cases who have varicocele (17) and in some of our cases sperm analysis even worsened after surgery. Since none of our patients had testis atrophy, vascular damage during surgery could not be a culprit and progressive degeneration of spermatogenesis as the natural course of varicocele should have been the cause.

One study on 30 subfertile men showed that varicocelectomy decreased oxidative damage in sperm DNA and improved the quality of sperm (18). Another study on 13 infertile patients demonstrated similar results to our study; but, due to small sample size their findings were not statistically significant (19).

Pesticides produce sperm toxicity and one animal study on mice showed that vitamin C can prevent these effects. This study proved that higher doses of vitamin C resulted in more significant amelioration of sperm count and morphology after administration of pesticides (20).

Audet I et al. demonstrated that water soluble vitamins improved semen production and motile sperm counts in boars (21).

Another study on rainbow trouts showed that sperm concentration and motility (fertility) decreases in fishes with ascorbic acid deficiency and vitamin C is important for male fish reproduction (22).

On the other hand, Donoghue AM and Donoghue DJ demonstrated that vitamin C had no effect on sperm viability, membrane integrity, or sperm motility index in turkeys at any concentration or time period tested (23). Moreover, in one RCT on 31 infertile men with asthenozoospermia, administration of high-dose oral vitamin C (1000 mg) and E (800 mg) for 56 days did not show any effect on semen parameters or pregnancies during the treatment period (24). It should be noted that these patients' infertility was due to causes other than varicocele and the only treatment they received were vitamin supplements; therefore, this study could not be compared to ours.

A recent study has shown that vitamin C partially reduced semen oxidative stress level and number of abnormal sperms; but, did not improve sperm motility in hyperglycemic rats (25).

One study in Spain illustrated that 1 g vitamin C and 1 g vitamin E daily for two months in 38 cases with elevated percentage of DNA-fragmented spermatozoa decreased fragmentation in 76% of cases. This study showed no effect on fertilization and cleavage rates or on embryo morphology after ICSI; however, clinical pregnancy and implantation rates improved (26).

At present, a large proportion of the Iranian population ingests insufficient amounts of antioxidants like vitamin C. According to a recent study, vitamin C intake was lower than the recommended daily allowance (RDA) in 28% of urban men and 55% of men living in rural areas of Iran. In 6% of urban men and 13% of rural men, the daily intake of vitamin C was lower than the lowest threshold intake (LTI) (27).

In 2010, the mean intake of fruit and vegetable servings per day was 1.74 ± 1.16 in 102 elderly Iranian men (28) which is far from the minimum recommended five servings of fruits and vegetables per day in 2002 (Centers for Disease Control and Prevention (CDC)) (29). Our findings suggest that a healthy diet with sufficient supplements might be an inexpensive and safe way to improve semen quality and fertility.

There have not been many studies concerning the role of vitamin C in the treatment of male infertility and still controversies exist due to different basic characteristics of the study samples, cause of infertility, small sample sizes, comorbidities, hormonal status, and other co-variables that potentially influence the results in such clinical studies.

Since vitamin C is a safe and cheap supplement with possible therapeutic effects in some cases of male infertility, further studies are necessary.

Limitations

We did not assess the levels of ascorbic acid in serum or semen of the patients and demonstration of the relation of seminal vitamin C levels with improvement in sperm indices could have supported our findings.

We used conventional semen analysis which is not an accurate predictor of fertility as Purvis K. and Christiansen E have shown that many cases with below normal values of sperm are able to impregnate their partners (30). The best outcome for evaluation of improvement in infertility is pregnancy rate which needs long term follow-ups.

Strengths

Because of variations between multiple samples from the same person, we obtained two separate samples from each case and mean values of all indices were used in all analyzes. Our inclusion and exclusion criteria have limited the reproducibility of our results to nonsmoker young infertile males with clinical varicocele, while it increased the accuracy of the study by removing many confounders which might have distorted the results.

Thirty six percent of couples with low sperm counts are able to achieve natural conception without any therapy. Thus, studies about the effectiveness of different therapies in male infertility without control groups have doubtful results (17). As a result, we included placebo as control group in our study.

Most of the mentioned studies concerning the effects of vitamin C on male infertility in human subjects had small sample sizes. However, our larger sample size helped in obtaining statistically significant results.

CONCLUSIONS

Despite the controversies about the effects of ascorbic acid on spermatogenesis, most studies suggest a positive effect. The present study showed that vitamin C can play a role as adjuvant treatment after varicocelectomy in infertile men specifically on quality and not quantity of sperm.

ACKNOWLEDGEMENTS

Authors express our special thanks from all patients participated in this study and all colleagues that helped us in running the study and data collection. We would also like to thank Sina Laboratory of Arak for their help.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 239-244, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.08

Outcome of Transurethral Plasmakinetic Vaporization for Benign Prostatic Hyperplasia

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ABSTRACT

Purpose: To assess the outcome of transurethral plasmakinetic vaporization (PKVP) in the management of benign prostatic hyperplasia (BPH).

Patients and methods: From August 2010 to May 2012, 60 patients with obstructive LUTS due to BPH were included in the study. All patients were evaluated by International Prostate Symptom Score (IPSS), general examination, digital rectal examination, PSA, routine laboratory examinations, pelvi-abdominal ultrasound, trans-rectal ultrasound, and uroflowmetry. Patients with Qmax of <10 mL/sec., an IPSS of >8 and a prostate volume of >40 mL underwent transurethral PKVP.

Results: Mean age of the patients was 66.8±4.5 years. The mean times of the operation, post-operative bladder irrigation, and post-operative catheterization were 63.8±13.9 minutes, 15.2±5.7 hours, and 23.9±5.2 hours, respectively. At 3 months of follow-up, there were significant reductions in the mean IPSS from 23.4±3.5 to 9.2±3.7 (P=0.4), mean PSA from 3.03±2.2 ng/mL to 1.2±1.04 ng/mL (P value=0.02), mean post voiding residual urine from 149.8±59.5 mL to 46.9±24.1 mL (P value <0.01), and mean prostate volume from 72.8±10.3 mL to 22.7±6.1 mL (P value <0.01).

Also, there was a statistically significant increase in the mean Q max. from 8.7±2.4 mL/s to 19.5±3.5 mL/s (P value <0.01).

Conclusion: PKVP is an effective and safe treatment option in the management of symptomatic BPH.

ARTICLE INFO

Key words:
Prostatic Hyperplasia; Transurethral Resection of Prostate; Prostatectomy

Int Braz J Urol. 2015; 41: 239-44

Submitted for publication:
August 11, 2013

Accepted after revision:
June 23, 2014

INTRODUCTION

Benign prostatic enlargement represents a significant health problem in aged males due to its negative impact on the health related quality of life; medical therapy of the prostate improved patients' symptoms but yielded the presentation of large-sized prostates (1).

The conventional standard monopolar transurethral resection of the prostate (TURP) is still the first-line treatment option for surgical management of BPH sized from 30 to 80 mL and this modality still have 18% morbidity and 0.2% mortality rate (2).

With the advancement in the bipolar technology, the popularity of transurethral electro-vaporization of the prostate has been increased, especially after the development of the Gyrus® PlasmaKinetic® Tissue Management System (Gyrus Medical Ltd, Bucks, UK) (3). In 2009 the European Association of Urology recommended transurethral plasmakinetic vaporization of the prostate (PKVP) as an alternative to the conventional monopolar TURP with promising initial reports of lower morbidity and similar efficacy and durability (4). In the current study, the technique of PKVP was evaluated regarding its efficacy, safety, and morbidity.

MATERIALS AND METHODS

From August 2010 till May 2012, 60 patients with obstructive LUTS due to BPH were enrolled in the study. All patients were evaluated by International Prostate Symptom Score (IPSS), general examination, digital rectal examination (DRE), PSA, serum biochemistry, coagulation profile, urine culture and sensitivity, pelvi-abdominal ultrasound, trans-rectal ultrasound (TRUS) ,and uroflowmetry. The inclusion criteria were recurrent urinary retention in spite of medical treatment, maximum flow rate (Q max.) of <10 mL/second, IPSS of >20. Patients with previous prostate or urethral surgery, prostate cancer, or neurogenic bladder were excluded from the study.

The procedure with its benefits and all possible complications was explained to the patients and a written consent was signed by all patients, and the study was approved by the Local Ethics and Research Committee.

TECHNIQUE

Several prostatic fragments were resected first by standard TURP for pathological examination. Transurethral plasmakinetic vaporization of the prostate (PKVP) was carried out using the Olympus SurgMaster (Tokyo,Japan) bipolar high frequency generator, with special 'mushroom' shape vapo-resection electrode and isotonic 0.9% sodium chloride (saline) as an irrigating fluid.

The spherical shape of the new type of electrode displaying a plasma corona on its surface was gradually moved into direct contact with the BPH tissue (the 'hovering' technique), thus producing a virtually bloodless vaporization in 280-320 W.

The procedure was performed like a TURP, starting at the bladder neck (Figure-1), then continuing to the lateral lobes (Figure-2) and finally to the apical portion of the prostate. After finishing at the level of the capsular fibers, a transurethral resection like cavity was obtained (Figure-3). Coagulation of any hemorrhagic sources was practically concomitant. In all cases, a 20 F Foley's catheter was placed at the end of the procedure. Continuous bladder irrigation was necessary until hematuria sufficiently resolved.

Figure 1 - Initiation of the transurethral PKVP.

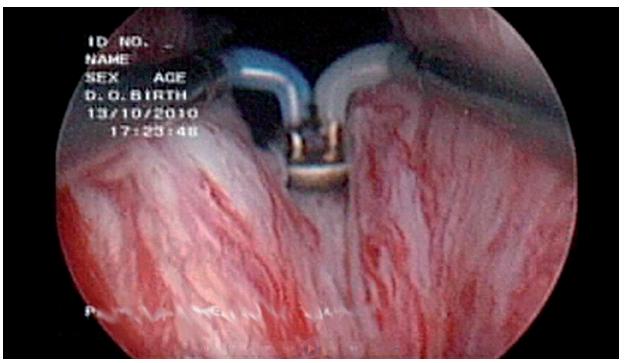

Figure 2 - Transurethral PKVP of the right lobe of the prostate.

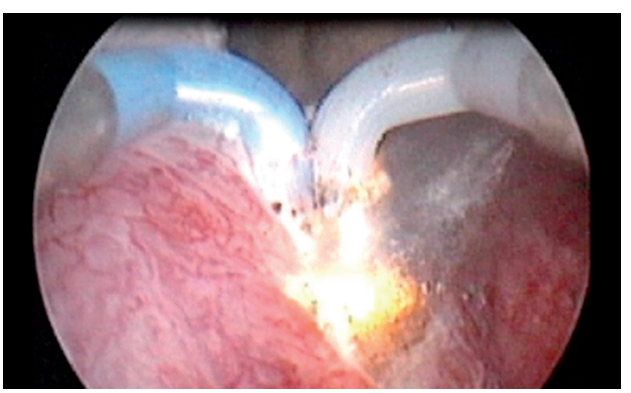

Figure 3 - At the end of the procedure and cavity formation.

Intra-operative, immediate post-operative data and complications were recorded. After 3 months, all patients were assessed by the PSA level, IPSS, uroflowmetry, post-voiding residual urine volume estimation, and prostate size estimation by TRUS. All data were tabulated and statistically

analyzed using SPSS ver. 16 software, P values were estimated and considered statistically significant if <0.05.

RESULTS

In the current study, the mean age of the patients was 66.8±4.5 years. The mean pre-operative serum PSA level was 3.03±2.2 ng/mL. In 12 patients (20%), the serum PSA levels were more than 4 ngl/mL, and all of them showed a negative result for malignancy in TRUS prostatic biopsy before inclusion in the study.

The mean operative time was 63.8±13.9 minutes, the mean post-operative bladder irrigation time was 15.2±5.7 hours, and the mean post-operative catheterization time was 23.9±5.2 hours.

The operative and postoperative data are shown in Table-1.

Immediate post-operative period showed no significant changes between the mean pre--operative hemoglobin (12.7±1.06 g/dL) and serum Na (139.7±3.5 mmol/l) and the post-operative values (11.8±0.9 g/dL and (139.1±5.5 mmol/L), respectively. At 3 months of follow-up, there was a decrease in the mean IPSS from 23.4±3.5 pre-operatively to 9.2±3.7, however, this decrease was statistically non-significant (*P* value=0.4). There was statistically significant decrease in the mean PSA from 3.03±2.2 ng/mL to 1.2±1.04 ng/mL (P value=0.02), mean post voiding residual urine from 149.8±59.5 mL to 46.9±24.1 mL (*P* value=0.01), and mean prostate volume from 72.8±10.3 mL to 22.7±6.1 mL (*P* value=0.01). Also, there was a statistically significant increase in the mean Qmax from 8.7±2.4 mL/s to 19.5±3.5 mL/s (*P* value=0.01).

The post-operative complications are shown in Table-2. There was persistent hematuria developed in two patients (3.3%) that resolved spontaneously on the first postoperative month. Transient mild to moderate dysuria was reported in 6 patients (10%), and resolved with medications within 2 weeks. Urinary tract infection with positive urine culture occurred in 20% of cases, treated with proper antimicrobial drugs. Seven patients (11.7%) presented with severe obstructive LUTS within 10 days post surgical which were dealt with catheterization for one week then catheter removed and all patients voided normally.

No patients developed acute urine retention or secondary hemorrhage. Blood transfusion was not needed and no postoperative clot retention was reported. No reoperation was required and no incontinence or TUR syndrome appeared.

DISCUSSION

Currently, the classic TURP is still the gold standard minimally invasive treatment for BPH,

Table 1 - Pre-operative and post-operative data of the patients.

	Pre-operative data	Post-operative data	P-value
Immediate post-operative			
Mean Hb (g/dL)	12.7±1.06	11.8±0.9	0.15
Mean Na (mmol/L)	139.7±3.5	139.1±5.5	0.52
3 month post-operative			
Mean IPSS	23.4±3.5	9.2±3.7	0.4
Mean PSA (ng/mL)	3.03±2.2	1.2±1.04	0.02
Mean prostate vol.(mL)	72.8±10.3	22.7±6.1	0.01
Mean residual urine (mL)	149.8±59.5	46.9±24.1	0.01
Mean Qmax. (mL/sec.)	8.7±2.4	19.5±3.5	0.01

Table 2 - Complications.

Item	N = 60
Hematuria: No. (%)	2 (3.3)
Irritative symptoms: No. (%)	6 (10)
UTI: No. (%)	12 (20)
Obstructive urinary symptoms: No. (%)	7 (11.7)
Clot retention: No. (%)	0 (0)
Secondary hemorrhage: No. (%)	0 (0)
Re-operation: No. (%)	0 (0)
TUR syndrome: No. (%)	0 (0)

however many alternative treatment modalities have been developed recently aiming to reduce the 18% early post-operative morbidity and the 0.2% intra-operative mortality (2). Plasmakinetic technology in resection is one of the recent minimally invasive treatment options for BPH with an efficiency similar to that of TURP (5).

During PKVP there is a significant reduction in the stages of the conventional TURP due to concomitant vaporization and hemostasis, and quick evacuation of the few resected tissue fragments so there is less operative time than in TURP (3).

In the study of Engeler et al., the mean duration of surgery was 50 minutes (6), and in the studies of Zhang et al. (7), and Ahyai et al. (8), the operative time was 39±15.5 minutes and 36 minutes, respectively. The relatively longer operative time in the current study (63.8±13.9 minutes) might be due to the stepwise learning curve, as the mean operative time in the first thirty patients was 71.5±14.02 minutes and in the second half of patients was 56±8.7 minutes.

As regard to catheter removal, our results were comparable to the results of Reich et al., where the mean catheterization time was 41 hours (9), and in the study of Ahyai et al., the catheter was removed after a mean of 1.3 days after bipolar vaporization (8).

In the current study there was no statistically significant difference between the pre-operative and post-operative mean hemoglobin values, there was a minimal drop in the mean hemoglobin value of nearly 0.9 g/dL. This was comparable to many recent studies that found that the mean reduction in hemoglobin was 0.6 g/dL (3), 0.3 g/dL (6) and 0.8 gm/dL in the study of Hon et al. (10). Gilling and associates added that due to the excellent haemostasis of vaporization, this technique could be specially if not solely indicated for patients at high risk of bleeding and those receiving oral anticoagulants (11).

TUR syndrome is the most important complications of TURP that may develop in 2% of patients submitted to TURP (2) as a result of hyponatremia with the use of glycine solution that enters the vascular circulation due to open vessels or periprostatic extravasation (12). This risk was eliminated with bipolar plasmakinetic technology, because of usage of isotonic saline solution for irrigation (4-8). In our study, the immediate decrease in postoperative serum Na level was statistically insignificant (P=0.52), so TUR syndrome was not an issue in the present study; this was in agree with many previously published studies (4-8).

In the current study, the mean size of the prostate was statistically significantly decreased when measured by TRUS after 3 month from PKVP (P=0.01).These results were consistent with many recent studies. In the study of Geavlete et al. (3) the mean preoperative prostate volume was 56.2 mL that reduced to 16.8 mL, when estimated at 6 months postoperative. In the study of Nuhoglu et al. (13) mean preoperative prostate volume was 47±7.7 mL that was significantly reduced to 22±6.8 mL after one year, and in the study of Liu et al. (14) mean preoperative prostate volume was 67.7+12 gm (range 35 to 256) and the mean resected volume was 42.8+7.7 gm (range 23 to 219) using plasmakinetic technology.

Generally, there is significant decrease of the pre-operative serum PSA levels at 3 months after the conventional TURP and open prostatectomy (15),and in the current study, the decrease in the mean PSA level at 3 months follow-up was statistically significant (P=0.02). This is in agree with the result of Geavlete et al. (3), as they reported a significant decrease of the mean pre-operative PSA from 1.82 ng/mL to a mean of 1.1 ng/mL,

0.93 ng/mL, and 0.74 ng/mL at 1,3,and 6 months follow-up, respectively.

In the current study there was statistically significant increase in the mean Qmax (P=0.01), and another statistically significant decrease in the mean post voiding residual urine (P=0.01) at 3 months follow-up. We founded also improvement in the mean IPSS at 3 months follow-up, however it was statistically not significant (P=0.4).

There are many studies supporting the significant improvement in the previous parameters after PKVP. Talic et al. found improvement in IPSS from 24.9 to 4±3.4 and Qmax from 7.5 to 19±6.5 mL/sec.(16), and Nuhoglu et al. (13) reported improvements in IPSS from 17.6±6.1 to 4.8±3.4, Q max of 6.9±2.8 mL/s to 17.6±4.3 mL/s, and decrease in the mean post voiding residual urine from 96±27 mL to 27±17 mL at 1 month follow-up.

In the present study, persistent hematuria developed in two patients (3.3%) that recovered in the first postoperative month without the need of any treatment.

Blood transfusion was not needed and no post-operative clot retention occurred. No reoperation was required in our short term follow-up while in the study of Karaman et al., they reported 12% incidence of reoperation but after 3 years of follow-up (17). No incontinence or meatal stenosis appeared despite the use of a 27-Fr. resectoscope.

Dysuria and frequency as post-operative irritative symptoms were reported in10% of cases and responded well to antimuscarinic treatment; this relative high rate was probably as a result of oedema secondary to higher current with lower frequency exerted on the tissues as claimed by Tefekli et al. (18); however, Singh and his colleagues reported that postoperative dysuria was less intense with bipolar TURP that could be attributed to the greater thermal damage and formation of granulation tissue with monopolar current (19). Ahyai and associates reported a fairly high rate of transient dysuria 8.3% which looks like a characteristic adverse event after bipolar vaporization (8). There were 7 patients (11.7%) presented with severe obstructive LUTS with significant high post voiding residual urine in the first 10 post-operative days which were dealt with by catheterization for one week ,then all patients voided normally after catheter removal. This higher recatherization rate with the bipolar device was also described in a randomized study of Dunsmuir et al. (12) ,and in a study of Reich et al.: 13% of patients were recatheterized temporarily in less than 24 hours after initial catheter removal (9).

CONCLUSIONS

The initial short-term results of PKVP shows good efficacy, reduced morbidity and fast recovery, early postoperative urethral catheter removal, a shorter hospital stay and the absence of TUR syndrome risk. Despite these very promising initial short-term results, long-term studies assessing the durability are mandatory to confirm the superiority of PKVP over TURP as a primary treatment option in BPH.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 245-251, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.09

Intrarenal Surgery vs Percutaneous Nephrolithotomy in the Management of Lower Pole Stones Greater than 2 cm

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ABSTRACT

Purpose: To compare the efficacy of RIRS and PNL in lower pole stones ≥2 cm.
Materials and and Methods: A total of 109 patients who underwent PNL or RIRS for solitary lower pole stone between April 2009 and December 2012, were retrospectively analyzed. Lower pole stone was diagnosed with CT scan. Stone size was assessed as the longest axis of the stone. All patients were informed about the advantages, disadvantages and probable complications of both PNL and RIRS before the selection of the procedure. Patients decided the surgery type by themselves without being under any influences and written informed consent was obtained from all patients prior to the surgery. Patients were divided into two groups according to the patients' preference of surgery type. Group 1 consisted of 77 patients who underwent PNL and Group 2 consisted of 32 patients treated with RIRS. Stone free statuses, postoperative complications, operative time and hospitalization time were compared in both groups.
Results: There was no statistical significance between the two groups in mean age, stone size, stone laterality, mean follow-up periods and mean operative times. In PNL group, stone-free rate was 96.1% at first session and 100% after the additional procedure. In Group 2, stone-free rate was 90.6% at the first procedure and 100% after the additional procedure. The final stone-free rates and operative times were similar in both groups.
Conclusions: RIRS should be an effective treatment alternative to PNL in lower pole stones larger than 2 cm, especially in selected patients.

ARTICLE INFO

Key words:
Calculi; Nephrostomy, Percutaneous; Surgical Procedures, Operative; Retrograde Obturation

Int Braz J Urol. 2015; 41: 245-51

Submitted for publication:
April 30, 2014

Accepted after revision:
May 22, 2014

INTRODUCTION

Kidney stones greater than 2 cm have long been treated with percutaneous nephrolithotomy (PNL) (1, 2). PNL is also recommended as a primary treatment in the management of renal stones ≥2 cm by European Association of Urology (EAU) guidelines (3). Although PNL has stone-free rates higher than 90% regardless of stone size and location, PNL has several disadvantages such as invasiveness, bleeding, adjacent organ injury, partial renal loss, urinary extravasation and long hospitalization (4, 5). In addition, in patients with significant morbidities such as morbid obesity and bleeding diatheses, PNL may not be the best choice. These limitations of PNL have forced urologists to spend more attention on non-invasive procedures like retrograde intrarenal surgery (RIRS) in the management of large lower pole stones.

RIRS has become popular in the last decade with the technical advancements in endourologic equipments and increased surgeon experience. Today, in the management of renal stones, RIRS provides an alternative way to PNL by minimizing the risks related to PNL. Recent studies reported stone-free rates from 77% to >90% for RIRS of renal stones and 62% to 85% for the management of lower pole stones (2, 6-9). Furthermore, several studies have reported significant success rates with RIRS in the management of large renal stones (10). Recently, studies reporting the efficacy of RIRS in lower pole stones have increased (5). In addition, the complication rates of RIRS are lower and the only disadvantage of this technique is the possible need for repetition. To our knowledge, there is no study comparing the efficacy of RIRS and PNL in lower pole stones greater than 2 cm. In this study, our aim is to compare the efficacy of RIRS and PNL in lower pole stones ≥2 cm.

MATERIALS AND METHODS

A total of 109 patients who underwent PNL or RIRS for solitary lower pole stone between April 2009 and December 2012 were retrospectively analyzed. Data were obtained from the patients' files which were recorded with electronic data management system. Patient assessment included detailed medical history, physical examination and laboratory tests including urinalysis, urine culture, complete blood count, and serum biochemistry. Lower pole stone was diagnosed with computed tomography (CT) (including axial, sagittal and transverse sections). Stone size was assessed as the longest axis of the stone on CT scan. All patients were informed with the same diagrams and photos about the advantages, disadvantages and probable complications of both PNL and RIRS before the selection of the procedure. Patients decided the surgery type by themselves without being under any influences and written informed consent was obtained from all patients prior to the surgery. Patients with the history of previous urinary stone surgery or urinary anomaly were excluded. Patients were divided into two groups according to the patients' preference of surgery type. Group 1 consisted of 77 patients who underwent PNL and Group 2 consisted of 32 patients treated with RIRS. All patients were evaluated with serum biochemistry and blood count at the day after surgery. In addition, all patients underwent CT for the stone clearance, at the first postoperative month. Treatment success was defined as stone-free status or clinically insignificant residual fragments ≤2 mm. Patients were followed up every 3 months with urinalysis, urine culture and ultrasonography.

Stone-free status, postoperative complications, operative time and hospitalization time were compared in both groups. Chi-square and t--test were used for statistical analysis and statistical significance was defined as p value <0.05 at 95% confidence interval.

PNL Technique

All procedures were performed under general anesthesia. All patients received a third generation cephalosporin at the induction of anesthesia. A 6F ureteral catheter was placed within the cystoscope and the bladder was drained with a 16F urethral Foley catheter. After ureteral catheterization, patients were placed in the prone position, and percutaneous access was achieved under fluoroscopic guidance with the use of an 18-gauge needle and a guide wire. Tract dilation was accomplished by using Amplatz dilators up to 30F. Pneumatic lithotripter was used for fragmentation and stone removal was accomplished with retrieval graspers through a rigid 22F nephroscope. The operations were completed when residual fragments were not detected on fluoroscopic imaging. After completion, a 16F re-entry catheter was inserted into the kidney and ureteral passage was controlled with antegrade pyelography. The re-entry catheter was removed on postoperative days 1 or 2 after removing the ureteral catheter and performing an antegrade pyelography confirming the ureteral passage. Then the patient was discharged on the next day.

RIRS Technique

All procedures were performed by 7.5-Fr (Karl Storz, FLEX-X2, Tuttlingen, Germany) flexible ureteroscope. All patients received a third generation cephalosporin at the induction of

anesthesia. Under general anesthesia, patients were placed in the lithotomy position on a fluoro--endoscopic table. Rigid ureteroscopy was routinely performed before flexible ureteroscopy in all patients for dilatation of the ureter and to place a hydrophilic guidewire into the renal pelvis. After passing a 0.038-inch safety guidewire into the renal pelvis, a ureteral access sheath (9.5/11.5 or 12/14Fr) was placed to allow for optimal visualization, to maintain low intrarenal pressure, and to facilitate extraction of stone fragments. For the cases in which the 12/14Fr ureteral access sheath could not progress regularly under the fluoroscopic control, 9.5/11.5Fr sheath was used. The stones were fragmented by a holmium: YAG laser (Lisa; Sphinx 30 W, Katlenburg University, Germany) (272µ caliber fiber) until they were deemed small enough to pass spontaneously. At the beginning of the laser lithotripsy, the laser functioning parameters were 1.5 Joule/11 Hertz and when the stone sizes decreased to 10 mm the parameters were changed to 10 J/12 H in order to avoid the pneumatic effect of the laser, which could migrate the stone to other poles. Basket extraction of residual fragments was not routinely performed; however, some residual fragments were removed by tipless nitinol baskets for stone analysis. At the end of the procedure, a double-J stent was placed routinely in all patients. JJ stents of the patients were removed at the postoperative first month.

RESULTS

Stone caracteristics and demographic data of the patients in both groups are presented in Table-1. There was no statistical significance between the two groups in mean age of patients (p=0.947), stone size (p=0.142) and stone laterality (p=0.820). The mean follow-up period was 13.5±4.71 months (range 3 to 22 months) in Group 1 and 12.5±5.26 months (range 3 to 19 months) in Group 2, respectively. No statistical significance was observed in mean follow-up periods in both groups (p=0.270). Mean operative time in both groups were similar; 62.5±20.67 minutes (range 38 to 107 min) in Group 1 and 67.5±22.34 (range 42 to 110 min) min in group 2 (p=0.671).

In Group 1, all procedures were performed by a single access procedure. Stone-free rate was 96.1% (74/77) at first session. Since the three patients had more than 3 residual fragments, they underwent an additional procedure (ESWL) and stone free rate increased to 100%. Thirty five (45.5%) patients were discharged at the postoperative 2nd day and 45 (54.5%) in 3rd day after confirming the ureteral passage with antegrade pyelography. Mean hospital stay was 2.4±0.49 days. One patient (0.9%) needed conservative management because of the persistent fever (Clavien grade I). Four patients (5.1%) needed blood transfusion because of hemorrhage (Clavien grade II) and one of them with significant bleeding (Clavien grade III) was treated with open surgical techniques (nephrolithotomy and primary renal parenchymal suturing). In Group 1, mean hemoglobin drop was 1.98±1.26 g/dL (range 0.3 to 8 g/dL). A JJ stent was placed into one patient (having persistent lumbar pain) (0.9%) because of the ureteral obstruction and removed at the 7th postoperative day. There was no urinary leakage, no adjacent organ

Table 1 - Stone Characteristics and Demographic Data of Patients.

	PNL Group (n=77)	RIRS Group (n=32)	p value
Mean age±SD	38.7±13.6	40.7±15.8	0.947
Male/Female	45/32	20/12	0.902
Mean stone size±SD (mm)	2.5±1.2 mm	2.3±1.2 mm	0.142
Lower pole localization (anterior/posterior)	12/65	4/28	0.236
Side (Right/Left)	50/27	21/11	0.820

injury, no kidney loss or deaths. Chemical composition of stones in Group 1 were calcium oxalate dehydrate (54/77, 70.1%), mixed (calcium oxalate dehydrate and monohydrate) (16/77, 20.7%), uric acid (5/77, 6.4%) and cystine stones (2/77, 2.5%).

In Group 2, stone-free rate was 90.6% (29/32) at the first procedure and 100% after the additional procedure (ureteroscopy). Three patients (3.2%) needed an additional procedure because of more than 3 residual fragments (three residual fragments in two patients and four in one patient, sized approximately 2 mm, in the kidney), at the first month control. In the course of removing the JJ stents of these three patients, flexible ureteroscopy was performed and all residual fragments were removed by tipless nitinol basket with no use of access sheath or holmium laser. Three patients (3.2%) with lumbar pain and persistent hematuria (Clavien grade I) were managed conservatively and discharged at the postoperative 2nd day. Recent patients (29/32, 90.6%) in RIRS group were discharged at the postoperative 1st day. In Group 2, mean hemoglobin drop was 0.18±0.18 g/dL (range 0 to 0.8 g/dL) and mean hospital stay was 1.09±0.29 days. No intraoperative complications such as ureteral perforation and no ureteral stricture at follow up period were observed. Stone analysis revealed calcium oxalate dehydrate in 23 patients (71.8%), mixed in 7 (21.8%) and uric acid in 2 (6.2%).

The treatment results of both groups are summarized in Table-2. The final stone-free rates and operative times (p=0.671) were similar in both groups. Hospitalization time (p=0.038) and hemorrhage (p<0.01) was higher in Group 1, however minor complications were similar in both groups (p=0.51).

DISCUSSION

Renal stones greater than 2 cm have traditionally been treated with PNL (1, 2). PNL is also recommended as a first line treatment option in the management of renal stones ≥2 cm in EAU and American Urological Association guidelines (3, 11). Several studies concerning about the treatment of larger renal stones, have reported stone free rates of PNL up to 95% (4, 12). PNL has also proved to be highly effective in lower pole stones. In a study, the stone-free rate of PNL was reported as 92% and 86 % for lower pole stones 1 to 2 cm and more than 2 cm, respectively (4). In a comparative study, PNL was the most effective approach for the management of lower pole stones between 1 to 2 cm, compared with RIRS and shock wave lithotripsy (13). Similar success rate was confirmed in another comparative study with a stone--free rate of 83% in lower pole stones between 1.5 to 2 cm (14). Despite the reported stone-free rates, ranging from 85% to 95%, several complications of PNL constitute a concern. The incidence of probable complications of PNL are reported in significant rates, including bleeding requiring blood transfusion 11.2% to 17.5%, fever 21% to 32.1%, sepsis 0.25% to 1.5%, pneumothorax 0% to 4% and colonic injury <1%. In consideration of other complications such as arteriovenous fistula, hypothermia, volume overload, colo-cutaneous fis-

Table 2 - Treatment Results in Both Groups.

	PNL group	RIRS group	p value
Initial stone free rate (%)	96.1% (74/77)	90.6% (29/32)	0.26
Final stone free rate (%)	100%	100%	-
Mean operative time	62.5±20.67	67.5±22.34	0.671
Hospital stay (day)	2.4±0.49	1.09±0.29	0.038
Transfusion rate (%)	5.1% (4/77)	0%	<0.01
Minor complication(%)	5/77 (6.4%)	3/32 (9.3%)	0.51

tula, electrolyte imbalance, pulmonary embolism and death, complication rate of PNL ranges from 0.03% to 10% in general (2, 10, 15). Additionally, in patients with significant comorbidities such as morbid obesity and bleeding diathesis, PNL is contraindicated due to the higher incidence of complications (11, 16). Finally, placement of the patient in a prone position increases the anesthetic risk because of the contractions of extremities and difficult airway.

Today, RIRS is an excellent minimally invasive treatment alternative for intrarenal stones smaller than 2 cm and reported stones-free rates are higher at this stone size (8, 17, 18). Increased experiences of the urologists and developments in the technology have created the substructure of this success. Development of new generation (bidirectional 270° flexion capacity, small caliber shaft and improved optics) flexible ureteroscopes, improved flexibility of holmium laser fibers, different and small diameter stone retrieval devices with the capability of facilitating intrarenal maneuvers have resulted in increased treatment success and decreased procedure related morbidity, in the management of renal stones (19-21). In addition, ureteral access sheaths provided lower intrarenal pressure during prolonged procedures and facilitated the retrieval of multiple stone fragments (22, 23). All these innovations and especially increased experience in RIRS aroused the urologists' interest to the success of this procedure in larger and lower calyceal renal stones.

Several studies reported their success rates of RIRS in the management of large renal stones. Grasso et al. reported an overall stone free rate of 91% for 66 renal stones >2 cm in 55 renal units. They reported that one third of patients have required second procedure (8). Breda et al. achieved a 93.3% success rate after an average of 2.3 procedures, in 15 patients with a single renal stone sized between 20 and 25 mm (24). In another study, authors showed an 87.5% stone free rate for renal stones between 2 and 3 cm with 43% of patients requiring second procedure (25). In a study including 22 patients with renal stones larger than 2.5 cm, authors reported a 91.6% stone free rate with an average 1.9 procedures (18). Similarly, the success rate of RIRS was evaluated in a study including 90 patients with different sized (<10mm ≥20 mm) lower pole stones. They concluded an 82% final stone free rate for lower pole stones >2 cm, after a second procedure (9). Accordingly, recent studies report up to 85% stone free rates of RIRS for the management of lower pole stones (8, 17). With these similar results, all of these studies have showed that RIRS should be an efficient treatment modality for larger renal stones as PNL which is more invasive. Nevertheless, to our knowledge, there is no study comparing the success rates of RIRS and PNL in lower pole stones >2 cm. In the management of lower pole stones greater than 2 cm, we have demonstrated a final 100% stone-free rate of RIRS with similar stone free rates of PNL. We suggest that this higher success rate in RIRS group may be related with the increased experience and the predominance of posterior localized lower pole stones in the kidney.

Furthermore, the association of longer operative time and endoscopic management of large renal stones were emphasized in the literature. However, recent reports demonstrated a rational operative time for ureteroscopy. Mariani et al. reported a mean operative time of 64 minutes (range 30 to 240 min) for the RIRS of renal stones between 2 and 4 cm (26). We also reported similar mean operative times in both groups, RIRS and PNL.

RIRS is known to have less complications compared to PNL (18). Major complications secondary to RIRS are less common and decrease in time. Today, with the decreasing size of instruments, significant complications such as ureteral avulsion are extremely rare. In addition, RIRS has been provided safe in patients with high risk and co-morbidities such as pregnant woman, morbid obesity, bleeding diathesis and in whom PNL may be contraindicated (27, 28) In a study, with a decreased ureteroscope size, a significant decrease in complications (from 6.6% to 1.5%) was reported. (29). Likewise, in our study, similar results regarding minor complication rates were demonstrated in PNL and RIRS groups. However, intraoperative bleeding needed intervention or transfusion was significantly higher in PNL group. Also, mean hospitalization time in PNL group was longer than RIRS group.

On the other hand, several limitations of our study must be addressed: 1. the number of patients included is rather low (especially in Group 2) therefore, further multicentric series with larger and equal number of study population have to be performed; 2. This study was a retrospective analysis. We suggest that a prospective study will exactly clarify the efficacy of RIRS in large lower pole stones.

CONCLUSIONS

RIRS can be an effective treatment alternative to PNL in lower pole stones larger than 2 cm, especially in selected patients. Further, multicentric comparative studies with larger study population are needed to confirm these results.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 252-257, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.10

Use of biological Glue (Bioglue®) in laparoscopic partial nephrectomy: a study in pigs

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ABSTRACT

Introduction: Partial nephrectomy is the standard of care for localized renal tumors. However, bleeding and warm ischemia time are still controversial when laparoscopic surgeries are carried out. Herein, we aim to compare the outcomes from laparoscopic partial nephrectomy with and without the use of biological glue with purified bovine albumin and glutaraldehyde (BioGlue®).

Materials and Methods: Twenty-four kidneys of 12 pigs were used in this study. A pre-determined lower pole segment was resected (3 cm x 1 cm) and one of two different hemostatic techniques was performed. In one kidney, hemostatic "U suture" (poliglecaprone 3.0) was performed and in the contra-lateral kidney, only the biological glue was applied. Data recorded was comprised of warm ischemia time (seconds) and estimated blood loss (mL) for each procedure. In cases of bleeding after glue administration, a complementary suture was done.

Results: Mean warm ischemia time was 492.9±113.1 (351-665) seconds and 746±185.3 (409-1125) seconds for biological glue and suture groups, respectively. There was a positive significant difference in terms of warm ischemia favoring the biological glue group over the suture group (p<0.001). Mean blood loss was 39.4 (0-115) mL for the biological glue group and 39.1 (5-120) mL for the suture group (p=0.62).

Conclusion: Biological glue is an important tool for laparoscopic partial nephrectomies. It is effective for hemostatic control in selected cases, and it can be used in combination with the traditional suture techniques.

ARTICLE INFO

Key words:
Bio-glue [Supplementary Concept]; Kidney; Nephrectomy; Laparoscopy

Int Braz J Urol. 2015; 41: 252-7

Submitted for publication:
January 06, 2014

Accepted after revision:
May 03, 2014

INTRODUCTION

During the last few decades, ultrasound and computed tomography have increased the detection of renal masses smaller than 4 cm. Because of the high incidence of small renal masses and based on the fact that studies have shown that partial resection has the same oncological efficacy as radical surgery, partial nephrectomy has been increasingly used for the treatment of these patients (1). Several studies evaluating laparoscopic surgery showed overall and cancer-specific survival rates, as well as complication rates, comparable to those of open partial nephrectomy (2, 3).

When performing a laparoscopic partial nephrectomy, it is almost always necessary to keep the kidney in warm ischemia, depending on size and location of the tumor (3, 4). There is a great discussion over the maximum warm ischemia time, and most authors consider 30 minutes

as the upper limit (3, 5). The major concerns with the laparoscopic partial nephrectomy technique are the difficulty to perform kidney cooling (cold ischemia) and the longer time required to perform the parenchyma suture after the resection of the tumor. Therefore, measures should be taken so that the clamping time can be as short as possible in order to preserve as much glomerular function as possible. The shorter the ischemia time, the greater the number of nephrons spared after the procedure in both short and long term outcomes (6).

In order to improve homeostasis and reduce warm ischemia time, several tissue sealants have been developed (7-11). Here we evaluate the potential role of glutaraldehyde glue with purified bovine serum albumin (Bioglue ® - Cryolife inc. Nennesaw, GA, USA) in the homeostasis on renal surface, comparing it to traditional laparoscopic suturing. Estimated blood loss and warm ischemia time of the kidney were used to assess this comparison.

MATERIALS AND METHODS

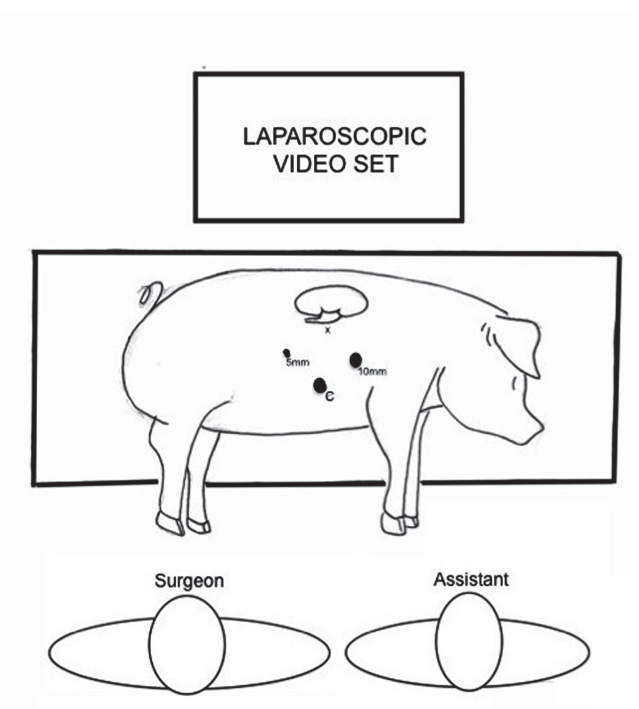
Study design: Twenty-four kidneys from 12 swine (minipig BR) were used for the comparison. All animals were acquired from the same facility and all surgeries were performed in the Institute of Education and Research of the Sirio-Libanês Hospital in São Paulo, after approval from the ethics committee.

Pigs underwent general anesthesia with endotracheal intubation. Anesthesia was induced with intramuscular ketamine (5 mg/kg), intramuscular midazolam (0.5 mg/kg), and maintained with continuous intravenous propofol (8mg/kg) and inhalatory Isoflurane (2%). For analgesia, continuous infusion of intravenous fentanyl (30µg/kg/h) was taken. At the end of the procedures, all animals were euthanized.

Each procedure was initiated with the creation of pneumoperitoneum using Veress needle (Ethicon inc. Somerville, NJ, USA), followed by trocar insertion according to Figure-1. Then, laparoscopic dissection and clamping of renal hilum (both renal artery and renal vein) were performed, followed by partial resection of a pre-determined lower pole segment of kidney (3 cm in longer diameter and 1 cm deep, Figure-2). The 1-cm deep resection was enough to extract the parenchyma segment without injuring the collecting system. Both surgeons confirmed it visually and in none of the cases, the collecting system was opened. In all procedures, we pre-established a double "U" poliglecaprone 3.0 suture using a 1 cm Hem'o'lok clip (Weck Surgical Instruments, Teleflex Medical, Durham, NC, USA) in each end of each thread as the standard. A third "U" suture was used in case of persistent bleeding. When using biological glue, the renal pedicle was unclamped two minutes after the end of application of the material (according to the company´s instructions). According to the ethics committee protocol, a poliglecaprone 3.0 suture should be added to control eventual residual bleeding after the use of biological glue.

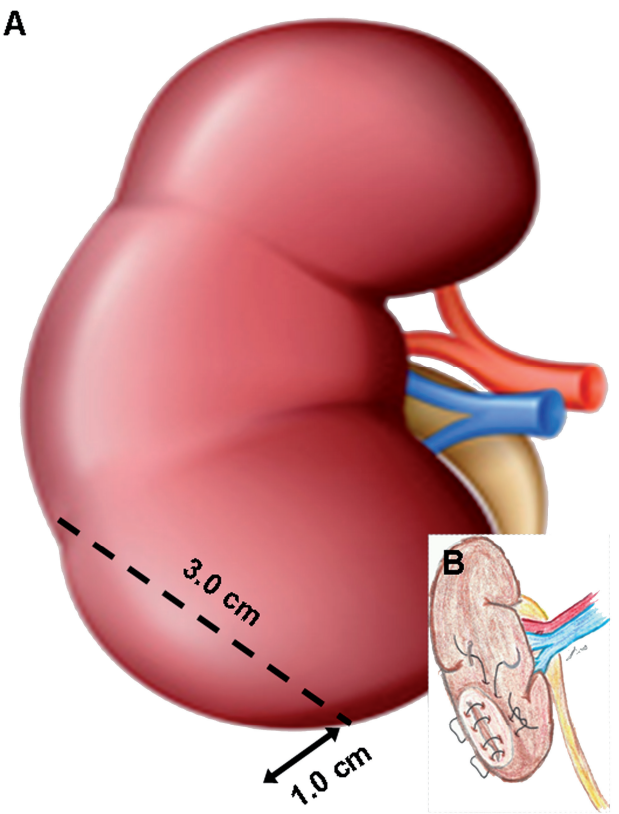
We chose to test biological glue in one kidney and suture in the contralateral side, in order to avoid selection bias. After the first side was completed, all the blood was aspirated, the cavity

Figure 1 - Trocar placement - 3 ports were placed and a small puncture ("X") was performed for the passage of the cannula for the glue application.



C = camera port.

Figure 2 - Partial nephrectomy: A. Lower pole resected. B. "U" suture was done.



was reviewed and all the trocar incision were closed using 2.0 poligalactine simple sutures. For the following side, the animal was repositioned, the pneumoperitoneum was re-gained and the trocars were placed in same fashion, however in the contralateral side.

Warm ischemia time (in seconds) and estimated blood loss (in milliliters) were recorded for each procedure. Warm ischemia time was measured from the clamp placement in the renal vessels to its removal. Extra care was taken in order to have all the blood out of the cavity after the first side was completed, avoiding inaccuracy in the contralateral measurement. All procedures were performed by two surgeons (LF and GM) with similar intermediate laparoscopic experience, presenting the same level of knowledge and practice. Both of them were participants of the Minimally Invasive Urologic Surgery Post-Graduation Annual Course. Each surgeon performed exactly the same procedures in terms of number, side and type (using either the glue or the suture).

Statistical analysis

Results were described as mean, standard deviation and range values. Mann-Whitney U test was used to compare continuous variables between the groups. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL) and the level of significance was set at $p<0.05$.

RESULTS

The results are shown in the table-1. The mean warm ischemia time was 492.9±113.1 (351-665) seconds and 746±185.3 (409-1125) seconds for bioglue and suture groups, respectively ($p<0.001$). The mean estimated blood loss was 39.4 (0-115) mL for the group using only the biological glue and 39.1 (5-120) mL for the group that used the suture. In the biological glue group, 6 cases required one "U" suture for strict control of bleeding and one case required two additional sutures. There were no intra-operative complications, there were no collecting system injuries, and all procedures were successfully finished according to the protocol. There was no significant difference between surgeons LF and GM regarding their respective outcomes: mean warm ischemia time using the biological glue (523±98 vs. 495±116, $p=0.68$); mean warm ischemia time using the suture (733±179 vs. 758±206, $p=0.74$); estimated blood loss using the biological glue (38.1±41.8 vs. 27±25.4, $p=0.93$); estimated blood loss using the suture (33.3±43.6 vs. 45.0±48.8, $p=0.68$).

DISCUSSION

Open partial nephrectomy was considered the standard of care for renal tumors smaller than 4 cm. However, recent publications have shown that laparoscopy can be used to tackle small renal masses (12). Indeed, laparoscopic partial nephrectomy has been increasingly used for this type of lesions, despite being a challenging procedure. Hemostasis control and collecting system suturing are the most difficult parts during a laparos-

Table 1 - Warm ischemia time (WIT) and estimated blood loss (EBL) for the use of bioglue and suture.

Case	Bioglue WIT (sec)	Suture WIT (sec)	p value	Bioglue EBL (mL)	Suture EBL (mL)	p value
1	552[A]	596[B]		50	120	
2	363[B]	748[A]		0	5	
3	474[A]	773[B]		27	5	
4*	351[A]	828[A]		32	15	
5*	592[A]	841[B]		115	35	
6*	567[B]	873[A]		10	20	
7	627[A]	584[B]	p<0.001	5	15	p=0.62
8*	449[B]	884[A]		63	100	
9*	542[B]	1125[B]		52	115	
10	348[A]	660[A]		0	10	
11	665[B]	633[B]		10	15	
12*	385[B]	409[A]		30	15	
Mean (stdev**)	492.9 (113.1)	746 (185.3)		39.4 (33.4)	39.1 (44.6)	

* = the use of glue required complementary; **"U"** suture; **stdev= standard deviation; [A] = operated by LF /[B] = operated by GM.

copic procedure, increasing warm ischemia time. For best outcomes with nephron sparing surgery, several tissue sealants were developed to be associated with, or even replace sutures of the renal parenchyma (7-11). The BioGlue ® is a mixture of bovine serum albumin (45% wt / vol) and glutaraldehyde (10% wt / vol) in a 4:1 ratio. To avoid any contamination, the bovine serum is purified by precipitation heat, gamma irradiation and chromatography.

Our study showed a significant shorter warm ischemia time for the biological glue group. Although we were able to remove the laparoscopic clamp in a significantly shorter period of time when using only the biological glue, in half of times we were not satisfied with the achieved hemostasis. Thus, in 50% of our procedures, an extra suture was taken in order to stop any sort of active bleeding. For this reason, we highlight here that biological glue can be helpful in bleeding control, but it still cannot be considered a replacement for renal sutures, especially because extra sutures of renal parenchyma are frequently necessary despite its use.

Nadler et al (9) showed a significantly lower blood loss in partial nephrectomies for renal tumors with biological glue (BioGlue ®) as a complementary armamentarium. The authors described it as highly effective in stopping surgical oozing. Moreover, they highlighted that due to its initially liquid consistency, biological glue can be easily maneuvered along the resected area or over a Surgicel bolster. In their series, they demonstrated the safety and efficacy of the BioGlue, when used to form a protective covering that can stabilize the bolster, after laparoscopic partial nephrectomy.

It is important to remember that the glue cannot enter the urinary tract because it may cause adhesions in the collecting system or over vessels with relevant active bleeding because adhe-

sion efficacy is reduced in such situation (11). In order to avoid the contact of the glue with the collecting system, we pre-determined a deep length of 1cm of the resected segment. This was an important maneuver, due to the possibility of local occlusion by the serum albumin glutaraldehyde, as it was previously described (13).

Our study has some limitations that should be pointed. We have a small number of cases in each arm. However, even with such numbers, we were able to report a significant shorter warm ischemia time in the bioglue group. Second, our study was made in a porcine model of partial nephrectomy, which is known to be an easier procedure when compared to partial nephrectomies in humans. The position of the kidney and easier visualization of the renal pedicle make the procedure less complex. Although our results may not be the same in humans due to these differences, the porcine model facilitated standardization of the procedure, therefore allowing our results to be better controlled. Third, as an acute experiment, some other important outcomes, including postoperative bleeding, rate of urinary extravasation, and the postoperative kidney function could not be assessed. Lastly, we did not evaluate costs. However, Dalpiaz et al (14) reported in a review that the use of sealants in the renal parenchyma may decrease the rate of bleeding during and after surgery, resulting in reduced costs for blood transfusions and blood products in perioperative time and also reducing costs with complications, operative time, length of hospital stay and intensive care unit indications.

CONCLUSIONS

The biological glue is an important tool in laparoscopic partial nephrectomies. In our series, the group that used the glue sealant had a significant shorter warm ischemia time, allowing an earlier unclamping. However complementary suture were required in half of cases.

Human clinical trials with larger numbers are needed to confirm our results in patients with small renal tumors that could lead us to better outcomes, by decreasing warm ischemia time and bleeding, when performing minimally invasive partial nephrectomy.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 258-264, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.11

Prostate-Specific Antigen fluctuation: what does it mean in diagnosis of prostate cancer?

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ABSTRACT

Objective: To investigate whether prostate-specific antigen (PSA) fluctuation correlates with a prostate cancer and to assess whether PSA fluctuation could be used for diagnosis of prostate cancer.
Materials and Methods: Our study included 229 patients who were performed a prostate biopsy (non-cancer group, 177; prostate cancer group, 52). Enrolled patients were provided twice PSA tests within 6 months. PSA fluctuation (%/month) was defined as a change rate of PSA per a month. Independent t test was used to compare between two groups. Receiver operator characteristic curve was used to assess the availability as a differential diagnostic tool and the correlation. Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSA density, and prostate volume.
Results: There were significant differences in PSA, PSA density, percentage of free PSA, and PSA fluctuation between two groups. PSA fluctuation was significantly greater in non-cancer group than prostate cancer group (19.95±23.34%/month vs 9.63±8.57%/month, P=0.004). The most optimal cut-off value of PSA fluctuation was defined as 8.48%/month (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004). In a simple linear regression model, only PSA level was significantly correlated with PSA fluctuation.
Conclusion: Patients with wide PSA fluctuations, although baseline PSA levels are high, might have a low risk of diagnosis with prostate cancer. Thus, serial PSA measurements could be an option in patients with an elevated PSA level.

ARTICLE INFO

Key words:
Prostatic Neoplasms;
Prostate-Specific Antigen;
Diagnosis

Int Braz J Urol. 2015; 41: 258-64

Submitted for publication:
October 07, 2013

Accepted after revision:
June 08, 2014

INTRODUCTION

Prostate-specific antigen (PSA) measurement in patients with serum PSA level above 4.0 ng/mL has a sensitivity of about 20%, and the specificity of PSA measurements is approximately 60% to 70% at this cut-off (1). If patients with PSA levels below 10 ng/mL were submitted to prostate biopsy, 20–40% would be diagnosed with prostate cancer and 60–80% should undergo unnecessary biopsy without detecting prostate cancer (2). Benign prostatic hyperplasia, urethral or prostatic trauma, and prostatitis, as well as prostate cancer, can all be associated with elevated serum PSA levels. Ejaculation and digital rectal examinations have been reported to increase PSA levels but studies have shown the effects to be variable or insignificant (3). These non-malignant conditions which were associated with elevation of a serum PSA would decrease the accuracy of a serum PSA. To improve low sensitivity of PSA, age-adjusted PSA, PSA density (PSAD), PSA velocity (PSAV),

or percentage of free PSA (%Free-PSA) has been introduced and used (4-8). In the last two decades, individual fluctuation in serial PSA measurements has been reported to characterize the normal biological variability in PSA among men without prostate cancer (9-13). The aims of this study were to investigate whether PSA fluctuation correlates with a prostate cancer and to assess Whether PSA fluctuation could be used for diagnosis of a prostate cancer.

MATERIALS AND METHODS

Patients and Study design

This was a retrospective cohort study in the department of urology of Chonnam National University Hospital (Gwangju, Korea) between January, 2012 and March, 2013. This study included 229 patients who were submitted to a transrectal ultrasonography (TRUS) guided prostate biopsy (177 in non-cancer group, 52 in prostate cancer group). TRUS-guided prostate biopsy was performed in at least 8 cores or more of tissue targeting the peripheral zone at the apex, mid gland, and base on each side of the prostate. Enrolled patients were provided twice PSA measurements within 6 months (baseline PSA, PSA_1; secondary PSA, PSA_2), and PSA_2 was measured at the day before prostate biopsy. Patients with urinary tract infection and who were receiving a 5-alpha reductase inhibitor were excluded from the study. The research attained ethical approval from the institutional review board of Connam National University Hospital (IRB No. 210-05-082). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed.

Definition and Measurements

PSA fluctuation (%/mo) was defined as a change rate of PSA ((PSA_2-PSA_1)/PSA1) per a month. PSAD (ng/mL/g) was defined as a PSA_2 divided by prostate volume. Prostate volume (g) was measured according to the prostate ellipsoid formula, multiplying the largest anteroposterior (height, H), transverse (width, W), and cephalocaudal (length, L) prostate diameters by 0.524 ($H \times W \times L \times \pi/6$) by using TRUS. An automated immunoassay analyzer (ARCHITECT i2000SR®, Abbott Diagnostics, Abbott Park, IL, USA) was used for all PSA measurements, and TRUS-guided prostate biopsy was recommended for a PSA level > 3.0 ng/mL or suspicious digital rectal examination.

Statistical analysis

Whitney U test was used to compare between two groups. Receiver operator characteristic (ROC) curve was used to assess the availability as a differential diagnostic tool and the correlation. Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSAD, and prostate volume. Statistical significance was set at $P<0.05$. All statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

The patients' baseline characteristics are shown in Table-1. Mean PSA_1 and PSA_2 levels were 5.93 ng/mL and 4.90 ng/mL. PSA fluctuation ranged from 0.12%/month to 122.6%/month, PSAD

Table 1 - Baseline characteristics of patients.

Variables	Mean (range)
Age (year)	66.91 (41-85)
PSA_1 (ng/mL)	5.93 (0.23-24.62)
PSA_2 (ng/mL)	4.90 (0.20-9.96)
Interval of PSA tests (month)	1.93 (1-6)
PSA fluctuation (%/month)	17.61 (0.12-122.60)
PSAD (ng/mL/g)	0.15 (0.01-0.58)
Prostate volume (g)	37.61 (8.90-160)
%Free-PSA (%)	20.22 (3.79-61.50)
No. biopsy results (%)	
Non-cancer	177 (77.3)
Prostate cancer	52 (22.7)

PSA = prostate-specific antigen, **PSA^1** = baseline PSA, **PSA^2 =** secondary PSA, **PSAD =** PSA density, **%Free-PSA =** percentage of free PSA.

from 0.01 ng/mL/g to 0.58 ng/mL/g, and prostate volume from 8.9 g to 160 g. Patients diagnosed with prostate cancer were 52 (22.7%), and patients with non-cancer were 177 (77.3%). Patients with non-cancer presented benign prostatic hyperplasia (155, 67.7%), chronic prostatitis (16, 7.0%), and atypical small acinar proliferation (6, 2.6%).

Comparison between Non-cancer group and Prostate cancer group

PSA_2 and PSAD were significantly lower in non-cancer group than prostate cancer group (4.68±2.18 vs 5.61±1.76 ng/mL, P=0.002; 0.132±0.796 vs 0.227±0.124 ng/mL/g, P<0.001). PSA fluctuation and %Free-PSA was significantly greater in non-cancer group than prostate cancer group (19.95±23.34 vs 9.63±8.57%/month, P=0.004; 21.53±9.74 vs 15.75±7.96%, P<0.001). There was significant difference in prostate volume between the two groups (40.12±19.93 vs 29.05±12.05 g, P<0.001) (Table-2).

ROC curve analyses of PSA, PSAD, %Free-PSA, and PSA fluctuation

PSA_2, PSAD, % Free-PSA, and PSA fluctuation was statistically significant as a differential diagnostic tool. The optimal cut-off values for detecting prostate cancer of PSA and PSAD were defined as 4.92 ng/mL (sensitivity, 65.4%; specificity, 56.5%; area under curve (AUC), 0.64; P=0.002) and 0.155 ng/mL/g (sensitivity, 73.1%; specificity, 71.2%; AUC, 0.762; P<0.001). The appropriate cut-off values of %Free-PSA and PSA fluctuation were defined as 17.31% (sensitivity, 63.3%; specificity, 63.5%; AUC, 0.688; P<0.001) and 8.48%/month (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004), respectively (Figure-1).

Correlation Analysis between PSA fluctuation and other variables

Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSAD, and prostate volume. PSA_1 and PSA_2 levels were significantly correlated with PSA fluctuation in a simple linear regression model (coefficient B, 3.404, P<0.001 in PSA_1; coefficient B, -3.978, P<0.001 in PSA_2). Age, %Free-PSA, PSAD, and prostate volume did not affect on PSA fluctuation (Table-3).

DISCUSSION

After the recent reports of highly anticipated data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC), the benefit of PSA screening remains controversial (14, 15). Twenty--five percent of men with PSA levels from 4 to

Table 2 - Comparison between non-cancer and prostate cancer group.

	Non-cancer group (n=177)	Prostate cancer group (n=52)	P value
Age (year)	66.36±8.45	68.78±7.61	0.103
PSA_1 (ng/mL)	6.00±3.75	5.70±1.70	0.300
PSA_2 (ng/mL)	4.68±2.18	5.61±1.76	0.002
Interval of PSA tests (month)	1.88±1.19	2.07±1.36	0.330
PSA fluctuation (%/month)	19.95±23.34	9.63±8.57	0.004
%Free-PSA (%)	21.53±9.74	15.75±7.96	<0.001
PSAD (ng/mL/g)	0.132±0.796	0.227±0.124	<0.001
Prostate volume (g)	40.12±19.93	29.05±12.05	<0.001

PSA = prostate-specific antigen, **PSA_1 =** baseline PSA, **PSA_2 =** secondary PSA, **%Free-PSA =** percentage of free PSA, **PSAD =** PSA density.

Figure 1 - Receiver operator characteristic curves analyses of secondary prostate-specific antigen (PSA_2), prostate-specific antigen density (PSAD), percentage of free prostate-specific antigen (%Free-PSA), and prostate-specific antigen (PSA) fluctuation. The optimal cut-off values for detecting prostate cancer were defined as 4.92 ng/mL in PSA_2 (sensitivity, 65.4%; specificity, 56.5%; area under curve (AUC), 0.64; P=0.002), 0.155 ng/mL/g in PSAD (sensitivity, 73.1%; specificity, 71.2%; AUC, 0.762; P<0.001), 17.31% in %Free-PSA (sensitivity, 63.3%; specificity, 63.5%; AUC, 0.688; P<0.001), and 8.48 %/month in PSA fluctuation (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004), respectively.

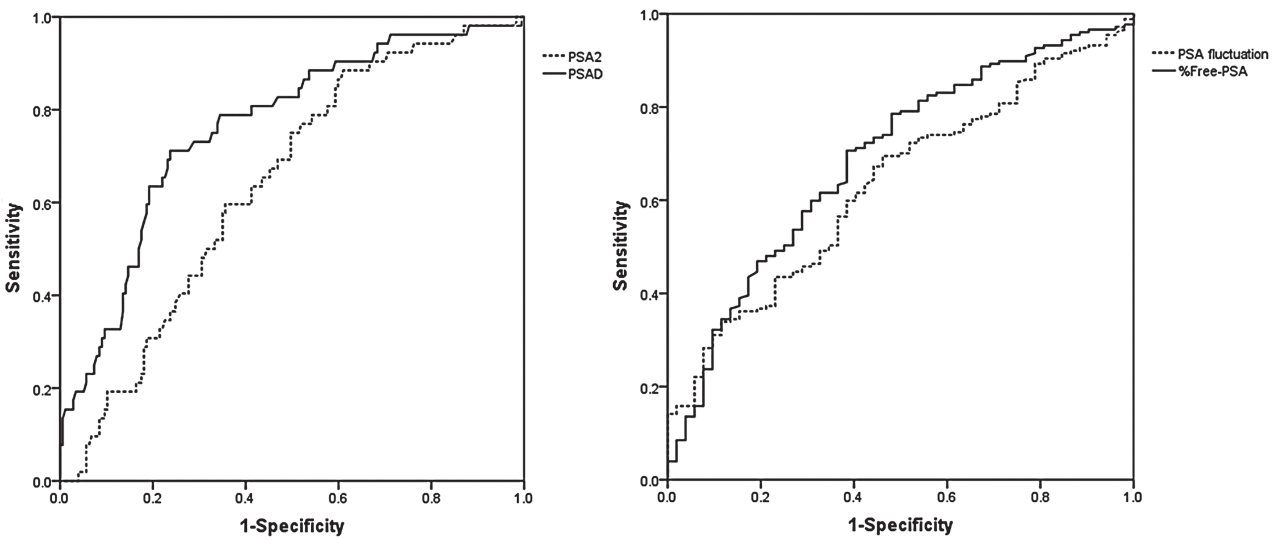

Table 3 - Simple linear regression analyses of prostate-specific antigen fluctuation and clinical parameters.

Variables	Coefficient B	SE	P value
Age (year)	-0.059	0.170	0.728
PSA_1 (ng/mL)	3.404	0.392	<0.001
PSA_2 (ng/mL)	-3.978	0.625	<0.001
%Free-PSA (%)	0.163	0.165	0.325
PSAD (ng/mL/g)	-20.061	16.029	0.212
Prostate volume (g)	-0.029	0.075	0.696

PSA = prostate-specific antigen, **PSA_1 =** baseline PSA, **PSA_2** = secondary PSA, **%Free-PSA =** percentage of free PSA, **PSAD =** PSA density.

10 ng/mL have a biopsy-proven prostate cancer, but 75% undergo unnecessary prostate biopsies, potentially leading to anxiety, discomfort, and significant additional health care cost (16). To improve the low sensitivity of PSA, age-adjusted PSA, PSAD, PSAV, and %Free-PSA have been introduced and used (4-8). In our study, the sensitivity and specificity of PSA was not high (65.4%; 56.5%; AUC, 0.64; P=0.002) in a ROC curve. Similarly with previous reports, both PSAD and %Free-PSA were the available parameters to improve the low sensitivity of PSA (sensitivity, 73.1%, 63.3%; specificity, 71.2%, 63.5%; AUC, 0.762, 0.688). In addition to PSAD and %Free-PSA, we found that PSA fluctuation is associated with the presence of a prostate cancer. Although low sensitivity and specificity, PSA fluctuation could be valuable by using with other PSA indices such as PSAD and %Free-PSA.

In several studies, biological fluctuations in PSA levels have been previously reported to cha-

racterize the normal biological variability in PSA levels among men without prostate cancer (9-13). These reports suggest that PSA fluctuation was unrelated to age (9,10). Roehrborn et al. reported a significant fluctuation between two serum PSA measurements obtained within a short-time interval of less than 90 days, and authors suggested not a single PSA measurement but repeated PSA tests (9). In our study, mean interval of twice PSA measurements was 1.93 months (approximately 57.9 days), and there was no difference in PSA_1 but significant difference in PSA_2 between two groups within a more shorter-time interval. John et al. studied to assess the relationship between prostate volume and PSA fluctuation, and found that PSA fluctuation was not correlated with PSA volume but correlated with baseline PSA levels (11). In our study, PSA fluctuation was correlated with baseline PSA levels, and not correlated with age, PSAD, %Free-PSA, and prostate volume. Thus, we suggest that PSA fluctuation could be used for the differential diagnosis regardless with age and prostate volume. Nixon et al. evaluated daily biological variations of PSA levels by obtaining 10 serum samples from 24 patients during a 2-week (12). They concluded that the degree of biological fluctuation differs among patients, and the difference between serial PSA measurements that is less than 20% to 46% may be due to biological and analytical variation alone. The reports mentioned above targeted to patients without prostate cancer, and focused on the biologic fluctuation itself. The hypothesis of our study was that degree of PSA fluctuation might differ according to the presence or absence of prostate cancer, and we found the characteristic of PSA fluctuation that patients with prostate cancer had a narrow range of fluctuation in serial PSA measurements. In addition, these results are as practically useful as other indices related to PSA such as a PSAD or %Free-PSA.

It is important to clarify that the PSA fluctuation should not be confused with PSAV as described by Carter et al. (17, 18). PSAV represent the rate of change of PSA over time that optimally requires three consecutive PSA measurements over a 2-year period, as described by Carter et al. (17, 18). PSA fluctuation is simply a mathematical estimate of the absolute monthly changes in PSA (ng/mL per a month) between two measurements that can be separated by less than 1 year. In our study, the mechanism of PSA fluctuation could not be investigated; however, PSA fluctuation might include the possibility of physiologic changes in serial PSA measurements, in contrast with the PSAV to consider a disease-progression.

In our study, when patients with prostate cancer (n = 52) were divided by a Gleason score, PSA fluctuation was greater in patients with Gleason score ≤6 (n=22) than Gleason score ≥7 (n=30), although not significantly (10.50±9.45 vs 8.99±7.97 %/month, P=0.535; data are not shown in tables). However, this result might not have sufficient statistical power, due to small sample size. We carefully suppose that there might be differences in the PSA fluctuation between low--risk and high-risk prostate cancer. A study based on larger population is necessary for further conclusive data.

The present study has several limitations. The major limitation is its retrospective design, and thus the present results may be vulnerable to confounding errors and bias. Second, intervals of PSA measurements were not regular. We enrolled patients that measured two times PSA levels within 6 months to minimize the confounding by irregular intervals. Third, there was significant difference in the prostate volume between two groups. However, we could have concluded about the difference of PSA fluctuation between two groups, because PSA fluctuation was not correlated with prostate volume in a simple linear regression model. Finally, this study may not have had sufficient statistical power, due to the relatively small sample size. Future research should include increased sample size to increase the statistical power. A prospective study based on a larger population is necessary for further conclusive data.

CONCLUSIONS

PSA fluctuation is significantly greater in patients without cancer than patients with prostate cancer, and is positively correlated with baseline PSA level. Thus, clinicians should consider that patients with wide PSA fluctuations, although ba-

seline PSA levels are high, might have a low risk of diagnosis with prostate cancer, and that serial PSA measurements could be an option in patients with an elevated PSA level.

ABBREVIATIONS

PSA = prostate-specific antigen
PSA_1 = baseline prostate-specific antigen
PSA_2 = secondary prostate-specific antigen
PSAD = prostate-specific antigen density
PSAV = prostate-specific antigen velocity
%Free-PSA = percentage of free prostate-specific antigen
TRUS = transrectal ultrasonography
ROC = receiver operator characteristic

ACKNOWLEDGEMENTS

This study was financially supported by a grant (CRI 120061-31) Chonnam National University Hospital Research Institute of Clinical Medicine and Chonnam National University (2009-1088).

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 265-273, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.12

Preoperative erectile function and the pathologic features of prostate cancer

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ABSTRACT

Purpose: We evaluated whether preoperative erectile function is associated with pathologic features in the patients who underwent radical prostatectomy (RP).

Materials and Methods: We reviewed medical records of 1,743 men who underwent RP from November 2003 through May 2012. Of these, 50 patients who had prior hormone therapy and 272 patients who had lacking data of International Index of Erectile Function-5 (IIEF-5) were excluded. Men whose IIEF-5 was in the lower 25 percentile were assigned as Low Erectile Function group and the others were assigned as Control group. We compared pathologic features using univariable and multivariable logistic regression analysis between two groups.

Results: A total of 1,421 patients were included in the analysis. Patients' age was 65.8 ± 6.7 years and prostate-specific antigen (PSA) was 12.8±16.1 ng/mL. Median and low 25 percentile of IIEF-5 were 14 and 8, respectively. Low Erectile Function group (IIEF-5<8) had higher risk to have high Gleason score (≥7(4+3), odds ratio (OR) 1.642, p<0.001) and large tumor volume (≥5 mL, OR 1.292, p=0.042). Even after adjusting age, year of surgery, body mass index, Charlson comorbidity index, PSA, clinical stage and biopsy Gleason score, Low Erectile Function group still had higher risk of high Gleason score (OR 1.910, p<0.001) and large tumor volume (OR 1.390, p=0.04) by multivariable logistic regressions.

Conclusions: Lower erectile function before RP was associated with higher Gleason's score and larger tumor volume in final pathology. Thus, erectile function could be a surrogate barometer for prostate cancer aggressiveness.

ARTICLE INFO

Key words:
Prostatic neoplasms, erectile function, pathology

Int Braz J Urol. 2015; 41: 265-73

Submitted for publication:
December 19, 2013

Accepted after revision:
June 08, 2014

INTRODUCTION

Prostate cancer (PC) is the second common cancer diagnosed and represents the sixth leading cause of death in male cancer patients worldwide (1). PC incidence rates increase in nearly all countries except in a few high-income regions. At present, any kind of radical prostatectomy (RP) is the most commonly used treatment modality for localized PC. However, there is concern about adverse pathologic outcome after RP because of heterogeneous nature of PC. With proper estimation of final pathology, some patients can choose active surveillance or radiation therapy instead of RP (2). Some patients can expect adjuvant or salvage treatment after RP (3).

Erectile dysfunction (ED) is one of the most common side effects and major reason of decrea-

sed quality of life during and after various types of treatment for PC (4-6). Preoperative erectile function is a very important predictor after PC treatment (4). Preoperative ED is also associated with various medical conditions such as obesity, hyperlipidemia, diabetes mellitus (DM), and metabolic syndrome (7, 8). ED is a multifactorial phenomenon associated with these medical conditions. Thus degree of ED may correlate with affected number and degree of these medical conditions. Furthermore, there have been some reports that many of these medical conditions are related to adverse pathologic features of PC (9-11). Consequently, decreased erectile function before RP could serve as a barometer for adverse pathologic outcomes. However, this correlation is not fully understood. Thus, we evaluated whether preoperative erectile function is associated with pathologic features in patients who underwent RP.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (Seongnam, Republic of Korea). The IRB number is B-1301/186-105.

PATIENTS

We collected the data from a prospectively registered database of an RP cohort in our institution. A total of 1,743 consecutive patients who underwent RP from November 2003 through May 2012 were evaluated. Among them, 50 patients who had prior hormone therapy and 272 patients who lacked data for the International Index of Erectile Function-5 (IIEF-5) were excluded. Thus, a total of 1,421 cases were included in the analysis. Men whose IIEF-5 was in the lower 25th percentile were assigned to the Low Erectile Function (LEF) group, and the others were assigned to the Control group. The 25th percentile was the predetermined discrimination point before analysis to evade bias.

PATHOLOGIC EXAMINATION

One experienced genitourinary pathologist (G. C) processed and examined all surgical specimens. Specimen handling and reporting followed the internationally standardized protocols (12, 13). The pathologic stage was evaluated based on the sixth edition of the American Joint Cancer Committee Cancer staging criteria. The prostate was sectioned into 4-mm slices as the protocol. The positive surgical margin was recorded if cancer was involved at the inked surface. Tumor volume was routinely measured using the grid method.

Statistical analysis

Clinicopathologic variables, including pathologic stage, Gleason's score and tumor volume, were compared between LEF and Control group using either Student t-test or chi-square test. Clinical factors including erectile function group were evaluated to associate with adverse pathologic features by means of univariate and multivariate logistic regression analyses. Tested adverse pathologic outcomes were high Gleason's score (≥7 (4+3) and tumor volume (>5 mL). Evaluated clinical factors were age, body mass index (BMI), year of surgery, Charlson comorbidity index (CCI; 0 vs. 1 vs. ≥2), pre-biopsy prostate-specific antigen (PSA), clinical stage (T1 vs. T2 vs. T3), biopsy Gleason' score (≤ 6 vs. 7 vs. ≥8), as well as erectile function group (Control vs. LEF group). All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY). For all statistical comparisons, a p value <0.05 (2-sided) was considered significant.

RESULTS

The basic characteristics of the 1,421 patients stratified by erectile function are presented in Table-1. The patients' age was 65.8±6.7 years, and the PSA was 12.8±16.1 ng/mL. The median and lower 25th percentile of the IIEF-5 were 14 and 8, respectively. A total of 346 (24.3%) patients were assigned to the LEF group (IIEF-5<8), and the remaining 1075 (75.5%) were assigned to the Control group (IIEF-5≥8). As expected, the LEF group showed an older age (p<0.001), higher prevalence of DM (p<0.001), and higher CCI (p<0.001) (Table-1). The clinicopathologic features of the LEF group more often included poorly differentiated pathology in both the pre-surgical (p<0.001) and

Table-1 - Patient demographics and clinical characteristics stratified by erectile function (<25 percentile, IIEF-5<8 vs. ≥25 percentile, IIEF-5≥8).

Variables	Low Erectile Function group (n=346)	Control group (n=1075)	p value
Age (years)	69.16±5.18	64.69±6.80	<0.001
Body mass index (kg/m^2)	24.09±2.74	24.42±2.57	0.820
Diabetes mellitus (%)	74 (21.4)	138 (12.8)	<0.001
Charson comorbidity index (%)			<0.001
0	240 (69.4)	893 (83.1)	
1	96 (27.7)	172 (16.0)	
≥2	10 (2.9)	10 (0.9)	
PSA (ng/mL)	12.31±12.65	12.94±17.07	0.780
Clinical stage (%)			0.703
≤T1c	227 (65.6)	688 (64.0)	
≥T2a	119 (34.6)	387 (36.0)	
Gleason's score, biopsy (%)			<0.001
≤6	166 (48.1)	535 (50.4)	
7	126 (36.5)	381 (35.9)	
≥8	53 (15.4)	146 (13.7)	
Prostate volume (mL)	38.07±16.66	38.02±15.79	0.900
Operation time (min)	151.88±43.05	157.59±45.95	0.550
EBL (mL)	331.72±356.19	362.25±417.59	0.223
Pathologic stage (%)			0.277
≤T2c	225 (65.1)	740 (68.9)	
≥T3a	121 (34.9)	335 (31.1)	
Gleason's score, pathologic (%)			0.007
≤6	42 (12.1)	199 (18.5)	
7	256 (74.0)	768 (71.4)	
≥8	48 (13.9)	108 (10.0)	
Tumor volume (mL)	12.52±112.85	6.57±17.94	0.048

final pathologies (p=0.007) compared to the Control group. Furthermore, the LEF group had a larger tumor volume than the Control group (p=0.048).

The LEF group had a higher risk of a high Gleason score (≥7 (4+3), odds ratio (OR) 1.642, 95% confidence interval (CI) 1.281-2.106, p<0.001) and large tumor volume (≥5 mL, OR 1.292, 95% CI 1.010–1.654, p=0.042). Even after adjusting for age, year of surgery, BMI, CCI, PSA, clinical stage, and biopsy Gleason score, the LEF group still had

a higher risk of a high Gleason score (OR 1.910, 95% CI 1.348–2.705, p<0.001) and large tumor volume (OR 1.390,95% CI 1.015 – 1.900, p=0.04) by multivariate logistic regression (Tables 2 and 3).

DISCUSSION

ED is a common disorder that affects men older than 40 years of age (8). Like a PC statistics, prevalence of ED increases exponentially by age after 50 years of age, even though worldwide basis shows a wide variation. ED increases to 20-40% in men aged between 60 to 69 years, 50-100% in men in their 70s and 80s (14). In case of the United States white men, the latent PC was found in 37%, 44%, 65% and 83% of the autopsy cases in the fifth, sixth, seventh, and eighth decades of age, respectively (15). Furthermore, the proportion of significant PC also exponentially increased with age after 60s and thereafter (16).

The etiology of ED could be classified as psychogenic, organic, or their combination. The organic causes are neurogenic, hormonal, arterial, cavernosal, and etc. ED is also associated with various medical conditions such as diabetes mellitus, hyperlipidemia, higher BMI or obesity, and consequently metabolic syndrome (8). Cardiovascular disease, in particular coronary artery disease is a strong risk factor for ED, too. ED was confirmed to be associated with significant increase in future cardiac events (17, 18). The evidence indicates that the etiology of ED is multifactorial, and ED is also associated with many systemic diseases.

However, some systemic conditions associated with ED have been revealed having correlation with negative oncologic outcome in PC. Higher BMI was associated with an increased tumor volume (9), higher Gleason grade, positive surgical margins, and early biochemical progression after RP (19). Our group also studied the association between obesity and pathological outcomes after RP in Korean men (11). We found that higher BMI was significantly associated with extraprostatic extension (p=0.014) and positive surgical margin

Table-2 - Univariate and multivariate logistic regression analysis to predict high Gleason's score (≥7 [4+3]).

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
IIEF-5<8	1.642 (1.281–2.106)	<0.001	1.910 (1.348–2.705)	<0.001
Age (years)	1.046 (1.028–1.064)	<0.001	1.016 (0.992-1.040)	0.195
Body mass index (kg/m^2)	1.026 (0.984– .070)	0.226	1.055 (0.997–1.115)	0.064
Year of surgery	1.155 (1.098–1.215)	<0.001	1.156 (1.082–1.236)	<0.001
Charlson comorbidity index		0.652		0.932
1 vs. 0	1.124 (0.852–1.484)	0.407	1.057 (0.727-1.536)	0.771
≥2 vs. 0	0.836 (0.319–2.192)	0.716	1.184 (0.329–4.260)	0.796
LogPSA (ng/mL)	17.208 (11.469–25.820)	<0.001	6.212 (3.811–10.127)	<0.001
Clinical Stage		<0.001		0.065
T2 vs. T1	2.133 (1.699–2.678)	<0.001	1.444 (1.062–1.966)	0.019
T3 vs. T1	>100	-	>100	-
Biopsy Gleason's score		<0.001		<0.001
7 vs≤6	8.387 (6.156–11.426)	<0.001	6.768 (4.865–9.414)	<0.001
≥8 vs.≤6	98.390 (56.907–170.112)	<0.001	71.329 (40.049–127.039)	<0.001

Table-3 - Univariate and multivariate logistic regression analysis to larger tumor volume (>5 mL).

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
IIEF-5<8	1.292 (1.010–1.654)	0.042	1.390 (1.015–1.900)	0.040
Age (years)	1.029 (1.013–1.046)	0.001	1.015 (0.993–1.036)	0.177
Body mass index (kg/m^2)	1.038 (0.996–1.082)	0.073	1.066 (1.014–1.122)	0.012
Year of surgery	0.942 (0.898–0.988)	0.014	0.858 (0.809–0.910)	<0.001
Charlson comorbidity index		0.233		0.844
1 vs. 0	0.922 (0.699–1.214)	0.562	0.930 (0.664–1.301)	0.930
≥2 vs. 0	0.400 (0.133–1.203)	0.103	0.765 (0.222–2.630)	0.765
LogPSA (ng/mL)	47.590 (29.778–76.057)	<0.001	31.068 (18.842–51.228)	<0.001
Clinical Stage		<0.001		0.040
T2 vs. T1	2.156 (1.723–2.697)	<0.001	1.420 (1.081–1.865)	0.012
T3 vs. T1	8.797 (0.979–79.059)	0.052	1.838 (0.074–45.930)	0.711
Biopsy Gleason's score		<0.001		<0.001
7 vs. ≤6	3.197 (2.488–4.108)	<0.001	2.040 (1.534–2.711)	<0.001
≥8 vs. ≤6	8.855 (6.210–12.626)	<0.001	4.437 (2.945–6.685)	<0.001

(p=0.019) only after multivariate-adjusting not in univariate analysis. In the present study, BMI was shown to have positive trend in higher Gleason's score and larger tumor volume without significance. When adjusting other variable, BMI was significantly associated with larger tumor volume (OR 1.066, 95% CI 1.014-1.122, p=0.012). Compared with observations from a Western cohort, this association might not be prominent. We suggest that this disparity may be due to Korean men being generally leaner than their Western counterparts. Mean BMI of our cohort was 24.3 kg/m^2 and obese men (BMI≥30 kg/m^2) only accounted for 2.2% (31/1,421).

Interestingly, several pieces of evidence have indicated that patients with DM are at decreased risk for the development of PC, which is contrary to other malignancies (20). A meta-analysis of 19 cohort or case-control study showed protective effect of DM for developing PC (relative risk (RR) 0.84, 95% CI 0.76–0.93, p<0.01) (21). A recent nationwide Swedish study incorporating more than 0.2 million men confirmed this reverse association (OR 0.80, 95% CI 0.76–0.85) (22). Meanwhile, our group demonstrated that DM was associated with higher odds of detection of overall PC (OR 1.46, 95% CI 1.06–2.01) more specifically high grade PC (OR 1.54, 95% CI 1.03–2.29) via contemporary multi-core (≥12) biopsy (23). Furthermore, our group reported that diabetics classified hemoglobin A1c less than 6.5% had significantly higher rate of extraprostatic extension of tumor and high pathologic Gleason's score (10). Our recent study indicated that diabetics had short PSA doubling time after RP than non-diabetics during follow-up (24). A pooled analysis for long--term overall mortality showed DM is associated with higher risk (HR 1.57, 95% CI 1.12–2.20) (25). Thus, we can plausibly predict that DM may have a protective effect against the development of PC, whereas pre-existing DM may lead to poor pathologic and oncologic outcomes. (26).

Thus, DM could be one explanation for patients with low erectile function having adverse pathologic features in our study.

Metabolic syndrome, a cluster of risk factors of cardiovascular disease and DM, is a common medical condition in the United States and is present in one quarter of the population, with an incidence that increases with age (26). Although the definition may vary, metabolic syndrome typically consists of DM or impaired glucose tolerance, hypertension, dyslipidemia, and obesity, which generally overlap with the medical conditions discussed above. A population-based study in Finnish men demonstrated that metabolic syndrome was related to a higher risk of having PC (RR 1.9, 95% CI 1.1–3.5) (27). Furthermore, a large matched case-control study reported from Vattikuti Urology Institute showed that metabolic syndrome men had higher Gleason grade ($p<0.001$), higher pathologic stage ($p<0.001$), and greater upgrading of Gleason grade ($p<0.001$) (28).

As discussed earlier, many systemic conditions associated with ED also associateswith an aggressive PC biology. Thus, we hypothesize that these medical conditions have a common pathway of PC development or aggressive transformation. At the least, erectile function itself could be a surrogate barometer for PC aggressiveness. In the present study, we confirmed that patients who had severe ED (IIEF-5<8) had larger tumors and higher Gleason's scores even after adjusting for other factors. As mentioned, the etiology of ED itself is multifactorial and complicated, and thus, we cannot fully understand the exact mechanism of this phenomenon. However, it could be related to an altered hormonal milieu, such as testosterone or sex hormone-binding globulin (SHBG). Low testosterone which could lower erectile function was suggested to have poor prognostic factors and higher tumor volume (29). Low testosterone was also associated with extroprostatic disease (30).

Hypogonadism may make PC more aggressive; however, the reverse is also plausible. Several studies demonstrated that serum levels of total and free testosterone were significantly elevated after radical prostatectomy (31, 32). Thus aggressive PC could be the possible cause of severe ED by inhibiting hypothalamic-pituitary axis. Our group previously reported the association between serum SHBG level with extraprostatic disease and higher Gleason score in clinically localized PC patients (33). Stimulation of cyclic adenosine monophosphate by the prostate was suggested as a possible mechanism. Significant role of SHBG in stem-like properties of PC has recently been demonstrated by cell lines study (34). SHBG was co-upregulated with related factors such as CD44, CD90, Oct3/4 and Nanog during progression. Furthermore, blocking SHBG gene rendered down regulation of theses stemness related factors. Higher SBHG expression in human PC specimens examined by immunohistochemistry is significantly associated with aggressive pathologic features (34). Thus, SHBG may involve with direct mechanism of cancer progression. Regarding obesity, adipose tissue itself has been regarded as an endocrine organ because it regulates multiple hormones via aromatase. Testosterone could be converted to estradiol by adipocytes and PC (35). This is strongly regarded as one mechanism of prostate carcinogenesis and tumor progression. Many adipokines such as leptin, interleukin-6, and adiponectin have been proved to have strong association with aggressive PC (36). The insulin/insulin-like growth factor-1 (IGF-1) axis is another commonly proposed mechanism. Poor glycemic control and hyperinsulinemia could lead to tumor aggressiveness. Chronically elevated glucose levels would lead to compensatory hyperinsulinemia. Insulin itself and IGF-1, which is regulated by insulin, promote proliferation and inhibit apoptosis in PC (37, 38). The DM-related micro-environment could be responsible for transformation to aggressive PC. Long-standing DM may cause vascular damage in both the prostate and corpus cavernosum, which is a contributing factor in the pathogenesis of benign prostatic hyperplasia and ED (39). Impaired circulation of the prostate also could induce tumor hypoxia, which may result in a more clinically aggressive tumor phenotype (40). Shared genetic susceptibility between obesity and diabetes mellitus with PC is also worth consideration. Genome wide studies showed at least 17 common

obesity loci and 18 type 2 diabetes loci (41). PC related gene could overlap with these loci. Regarding dyslipidemia related mechanism, low high-density lipoprotein and high triglyceride levels also might be associated with high-grade PC (42). In vitro, triglycerides induce the proliferation of androgen-independent PC-3 cells.

The major limitation of the present study might be its retrospective nature in a single-center cohort. Furthermore, it may be subject to inherent biases during patient selection since 16% (272/1743) of the patients were excluded due to missing IIEF-5 results. Other limitations are the lacks of information about sex-hormone level, the cause of ED, and long-term follow-up outcomes. Nevertheless, our results provide new insight into the association between erectile function and PC pathophysiology. We believe our hypothesis deserves to be evaluated in a larger, multicenter cohort or in a prospective manner. We suggest that the future study should collect more specific information such as sex-hormone level or penile Doppler.

CONCLUSIONS

Lower erectile function before RP was significantly associated with some adverse pathologic outcomes, such as a higher Gleason score and larger tumor volume, even after adjusting for other variables. Thus, decreased erectile function could be a surrogate barometer for aggressive features of PC.

ABBREVIATIONS

BMI = body mass index
CI = confidence interval
ED = erectile dysfunction
DM = diabetes mellitus
HR = hazard ratio
IIEF-5 = the international index of erectile function-5
LEF = the low erectile function
OR = odds ratio
PC = prostate cancer
RP = radical prostatectomy
SEARCH = Shared Equal Access Regional Cancer Hospital

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 274-278, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.13

Incidence of retrorenal colon during percutaneous nephrolithotomy

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ABSTRACT

Objective: The aim of this study was to investigate retrorenal colon incidence in percutaneous nephrolithotomy (PNL) interventions made in our clinic.
Materials and Methods: Clinical data of 804 PNL patients, accumulated over a 7 year period (2006-2012), was surveyed. The patient files were reviewed retrospectively, and only those who had abdominal computed tomography (CT) images before PNL intervention were included in the study. In the CT images, the position of both the ascending and descending colon in relation to the right and left kidneys were evaluated.
Results: According to our hospital reports, 394 patients with CT images were included in the present study 27 patients (6.9%) had retrorenal colon, of which 18 (4.6%) were on the left side, 4 (1.0%) on the right side and 5 (1.3%) had bilateral retrorenal colons. Colonic perforation complication was seen only in two patients and the colonic perforation rate was 0.3%. These two cases had no CT images.
Conclusions: PNL, in the process of becoming the standard treatment modality, is a safe and reliable technique for renal stone treatment. Colonic injury should be taken into consideration during PNL interventions of the lower pole of the kidney (especially on the left side) due to the location of retrorenal colon.

ARTICLE INFO

Key words:
Colon; Tomography, X-Ray Computed; Nephrostomy, Percutaneous

Int Braz J Urol. 2015; 41: 274-8

Submitted for publication:
January 24, 2014

Accepted after revision:
June 08, 2014

INTRODUCTION

Percutaneous Nephrolithotomy (PNL) is a common treatment option for patients with renal stones. PNL applications are mostly safe and associated with a low but specific complication rate. These emerge during initial puncture and lead to injuries in the surrounding organs (e.g., colon, pleural cavity, lung, spleen, liver, and duodenum) (1). The most distressing one among these complications are colonic perforations. Though very rare, they may lead to morbidity in the form of septicemia, peritonitis, abscess formation, and nephrocolic or colocutaneous fistula. Hence, knowing the position of the retrorenal colon to prevent surgical complications during PNL and other surgical modalities is a priority. In the present manuscript, we studied the number of retrorenal colon presence in the CT images taken before PNL applications.

MATERIALS AND METHODS

The medical records of 804 patients who underwent PNL in our clinic from 2006 to 2012 were reviewed retrospectively. PNL was conducted in the prone position and under fluoroscopic guidance. Patients' CT images taken before PNL were studied for the position of both the ascending and descending colon in relation to the right and left kidneys respectively.

Patients without CT images and patients with severe musculoskeletal defects, abdominal masses, previous surgery, renal abnormalities (large renal cysts, ectopic kidney, and horseshoe kidney) and ascites were excluded from the study. Hence, CT images of only 394 cases were included in our study. All CT images taken in supine position were evaluated by the same radiologist for retrorenal colon presence.

CT images were as previously identified (2); to the horizontal plane a parallel line was drawn through the posterior edge of each kidney (posterior renal line) at three renal levels: upper pole, middle pole and lower pole. The number of cases with partial colon extension posterior to the posterior renal line was determined. These were further separated to see if any part of the colon extended directly behind the lower pole (Figures 1-4), middle pole and upper pole of the kidney.

RESULTS

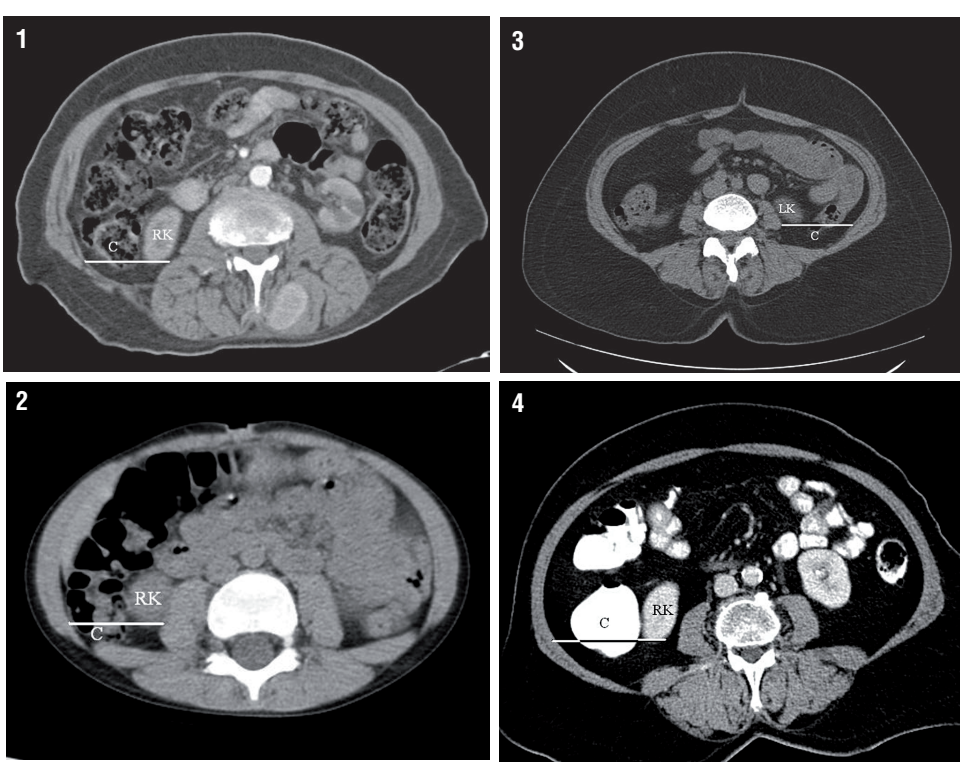
Of the 394 patients included in the present study, 178 were female and 216 were male with a mean age of 42.2 years. 27 patients (6.9%) had retrorenal colon with 18 (4.6%) on the left and 4 (1.0%) on the right side. The other 5 (1.3%) patients had bilateral retrorenal colons (Table-1). In comparison to kidney location, the retrorenal colons of all patients were at the lower poles.

During the studied period, colonic perforation was observed in only 2 cases (0.3%) that did not had CT scans taken before PNL intervention.

DISCUSSION

PNL was first described in 1976 and has become in the last 30 years almost the standard treatment modality for renal stones (3). Despite

Figures 1-4 - Anatomical variations of colon related to the kidney: Colon extended directly behind the lower pole.



RK = Right Kidney, **LK =** Left Kidney, **C =** Colon

Table 1 - Distribution of retrorenal colon according to kidney level.

Level	Left	Right	Bilateral	Total
Upper	0	0	0	0
Middle	0	0	0	0
Lower	18	4	5	27
Total	18	4	5	27

the high success rates, it is still an invasive procedure associated with significant morbidity that involves life-threatening complications.

PNL outcome depends heavily on planning and successful execution of initial kidney access as it may carry an increased risk of damage to surrounding organs. In order to gain access to the desired renal calyx with minimal complications it is necessary to evaluate renal anatomy and the surrounding organs.

An essential part of PNL tract planning is radiological imaging. Intravenous urography (IVU) has historically been the main preoperative imaging technique for PNL. The spread and increasing presence of multiphase CT scanners has made it the main imaging preference in many centers. IVU however still remains valuable for the preoperative planning and evaluation of kidney stones due to its ability to demonstrate fine details in the collecting system anatomy of the kidney. But a poorly performed IVU may have limit valuable information required before PNL application. Therefore, dynamic CT has recently become the gold standard in urolithiasis diagnosis and evaluation (4). CT used for the diagnosis of renal stones, also delineates the extent, orientation, and location of the stones within the kidney and thus enable the most suitable PNL tract selection. Moreover, by showing the relationship of the kidney and stone to the surrounding structures enables to minimize the risks of injury to the spleen, liver, or to an unsuspected retrorenal colon.

Pre and post PNL related complications rate up to 83%, including extravasation, transfusion, and fever; yet, major complications such as septicemia and colonic or pleural injury are rare (5). One of the most distressing complication ofn PNL is colonic perforation.

Colonic perforation, a rare complication of PNL, is reported in less than 1% of cases (6). During PNL, the age of the patient, existence of horse shoe kidney, previous kidney surgery, left kidney inferior location access, lateral posterior axillary line access, hypermobile kidney, and the existence of retrorenal colon are among the factors that predispose to colon perforation (5, 7).

A retrorenal colon is more frequently found on the left side and is most likely to be situated near the inferior kidney pole (8). Retrorenal colon is found in approximatively 0.6% of the general population according to the Hadar-Gadot and Sherman et al. study (9, 10). In another study with 333 participants, CT images showed that the left colon was posterior in 16.1% of cases, and the right colon was posterior in 9% of cases at the level of the lower pole (11). Total ratio of retrorenal colon was 1.7%, with 1.2% on the left side, 0.3% on the right side and 0.2% bilateral in the Atar et al. study (2). Hopper et al. reported in their study based on 500 abdomen CT scans that the overall frequency of retrorenal colon was 1.9% if the images were taken in supine position. When 90 patients were studied in the prone position, retrorenal colon was found in 10% (12). In the present study, retrorenal colon in PNL patients was found in 27 cases, (6.9%) of which 18 (4.6%) were on the left side, 4 (1.0%) on the right side, and 5 (1.3%) bilateral.

All CT scans in the present study were performed in supine position. However, in the literature the prevalence of retrorenal colon varies according to the patients' position. Hopper et. al. study, analyzing a series of 500 supine and 90 prone abdominal CT scans, determined the colon positioned posterior to the kidney in 1.9% and 10% of cases, respectively. They found that there is a high risk of colon perforation during PNL in the prone position (13). If supine and prone positioned patient images are to be compared, the prone position seems to be associated with a significantly shorter nephrostomy tract length and a greater number of potential puncture sites. A shorter tract length may ease percutaneous access and nephroscope mobility within the collecting

system and thus improve stone-free rate and decrease hematuria risk. A greater range of potential access angles may result in decreased risk of visceral injury (14). In the CROES PNL study group 1079 PNL applications were conducted in prone and 232 in supine positions without revealing a difference in complication rates (15).

PNL was applied a short time ago mainly in endourology clinics; yet, PNL related complications were generally documented by authors and departments whose main interest is PNL. However, nowadays PNL has become a routine practice in all urology clinics and the reported complications may differ from the actual ones. In the present study, the retrorenal colon rate of 6.9% of patients who underwent PNL shows actually how close the urologists are to intervene to a retrorenal colon perforation.

Unfortunately, in the two retrorenal colon perforation cases, no CT images were taken before PNL intervention and thus our ability to evaluate colon perforation risk proactively was nullified. On the other hand, no colon perforations occurred in any of the cases who had CT images obtained before PNL intervention. In order to prevent colon perforation during PNL, alternative imaging techniques are available. However, a precise and reliable standardization of imaging techniques seems currently not possible. Thus, ultrasound or CT guided puncture to the kidney calyx, in cases with previously reported anatomic variations without inflicting harm to other organs, might be used. Moreover, 3D CT can provide excellent representation of kidney anatomy and be used while planning a PNL intervention; however, it does not show the relationship between the calices and different organs, such as the colon in particular and kidney motion (16).

CONCLUSIONS

CT is the most commonly used diagnostic method for identifying retrorenal colon location variation. Retrorenal colon is more frequently found on the left side and on the lower pole of the kidney. Therefore, when accessing the lower pole of the kidney, especially on the left side, the risk of colonic injuries should be considered during PNL.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 279-287, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.14

Beneficial effects montelukast, cysteinyl-leukotriene receptor antagonist, on renal damage after unilateral ureteral obstruction in rats

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ABSTRACT

Introduction: Ureteral obstruction is a common pathology and caused kidney fibrosis and dysfunction at late period. In this present, we investigated the antifibrotic and antiinflammatory effects of montelukast which is cysteinyl leukotriene receptor antagonist, on kidney damage after unilateral ureteral obstruction(UUO) in rats.

Materials and Methods: 32 rats divided four groups. Group 1 was control, group 2 was sham, group 3 was rats with UUO and group 4 was rats with UUO which were given montelukast sodium (oral 10 mg/kg/day). After 14 days, rats were killed and their kidneys were taken and blood analysis was performed. Tubular necrosis, mononuclear cell infiltration and interstitial fibrosis scoring were determined histopathologically in a part of kidneys; nitric oxide(NO), malondialdehyde(MDA) and reduced glutathione(GSH) levels were determined in the other part of kidneys. Urea-creatinine levels were investigated at blood analysis. Statistical analyses were made by the Chi-square test and one-way analysis of variance (ANOVA).

Results: There was no difference significantly for urea-creatinine levels between groups. Pathologically, there was serious tubular necrosis and fibrosis in group 3 and there was significantly decreasing for tubular necrosis and fibrosis in group 4($p<0.005$). Also, there was significantly increasing for NO and MDA levels; decreasing for GSH levels in group 3 compared the other groups($p<0.005$).

Conclusion: We can say that montelukast prevent kidney damage with antioxidant effect, independently of NO.

ARTICLE INFO

Key words:
montelukast [Supplementary Concept]; cysteinyl-leukotriene [Supplementary Concept]; Renal Insufficiency; Ureteral Obstruction

Int Braz J Urol. 2015; 41: 279-87

Submitted for publication:
May 14, 2014

Accepted after revision:
July 27, 2014

INTRODUCTION

Chronic kidney diseases, which lead to end-stage kidney failure, are associated with changes in kidney structure and fibrosis regardless of the underlying cause. Urinary tract obstruction is characterized by tubular atrophy or dilation, tubular cell death by apoptosis and necrosis, interstitial

leukocyte infiltration, and increased interstitial matrix deposition (1). The acute phase of obstructed kidney in unilateral ureteral obstruction (UUO) is characterized by dramatic changes in glomerular filtration rate, renal blood flow, and interstitial edema (2, 3).

Such an obstruction might be observed after benign prostatic hyperplasia; renal, ureteral, or bladder calculi; urethral stricture; and neoplasm of the bladder, prostate, or urethra (1). The hydrostatic pressure, which is the result of the blockage, initiates renal injuries. The injuries are characterized by tubular dilatation or atrophy, inflammatory infiltration of leucocytes, fibroblast activation, proliferation, increase in matrix proteins, and progressive interstitial fibrosis with the loss of renal parenchyma. Unilateral ureteral obstruction (UUO) is an experimental rat model of renal injury that imitates the process of obstructive nephropathy in an accelerated manner(1).

Reactive oxygen species (ROS) are a recently recognized mechanism in the pathogenesis of UUO in experimental studies. Increased lipid peroxidation has been reported in renal cortexes of UUO animals. It has been shown that oxidative stress in UUO contributes to the development of tubulointerstitial lesions and renal fibrosis. Various factors with complex cellular and molecular interactions have also been proposed as possible causes that lead to tubulointerstitial lesions and renal fibrosis (4-7).

Nitric oxide (NO) acts as an intercellular messenger and regulates cellular functions such as vasorelaxation and inflammation. NO has an important role in the elimination of pathogens and tumor cells; however, overproduced NO is oxidized to ROS, resulting in the disruption of cell signaling and uncontrolled systemic inflammation (8, 9). Malondialdehyde (MDA) is one of the important markers of lipid peroxidation (10). Excessive MDA produced as a result of tissue injury and DNA damage could combine with free amino groups of proteins, resulting in the formation of MDA-modified protein adducts. Glutathione (GSH) is the major intracellular antioxidant with multiple biological functions, including the maintenance of the thiol moieties of proteins and the reduced from of many other biologically active molecules (11).

Leukotrienes, the products generated by the 5-lipoxygenase pathway are particularly important in inflammation; indeed, leukotrienes increase microvascular permeability and are potent chemotactic agents (12). Moreover, inhibition of 5-lipoxygenase indirectly reduces the expression of TNF-alpha (a cytokine that plays a key role in inflammation), and there are a number of studies demonstrating the role of leukotrienes as mediators of the gastric damage induced by ethanol and some other noxious substances(13, 14). Cysteinyl leukotrienes(CysLT), leukotrienes C4, D4, and E4 (LTC4, LTD4, LTE4) are secreted mainly by eosinophils, mast cells, monocytes and macrophages, and they exert a variety of actions which emphasize their importance as pathogenic elements in inflammatory states(15, 16).

Montelukast (MK-0476), a selective reversible cys-leukotriene-1 receptor (LTD4 receptor) antagonist is used in the treatment of asthma and is reported to reduce airway eosinophilic inflammation in this disease (17-19). CysLT1 receptor antagonists or biosynthesis inhibitors have been reported to ameliorate ethanol-induced gastric mucosal damage and experimental colitis (13, 20, 21).

Based on these findings, we investigated the antifibrotic and antiinflammatory effects of montelukast on kidney damage after UUO in rats by measuring MDA, NO and GSH levels and the myeloperoxidase activity.

MATERIAL AND METHODS

ANIMALS

Male Wistar Albino rats, weighing 200 to 250 g and 6 to 7 weeks old, were housed in clean plastic cages in a temperature and humidity controlled facility under a constant 12-hour light/12--hour dark photoperiods with free access to food and water. The Institutional Animal Care and Use Committee approved the use of animals and the experimental protocol, and animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals of Research Council.

TREATMENT AND EXPERIMENTAL PROTOCOLS

One week after acclimatization, UUO was induced. Briefly after induction of general anesthesia by intraperitoneal injection of thiopental (100 mg/kg), the abdominal cavity was exposed via midline incision and the left ureter was ligated at 2 points with 3-0 silk. The sham-operated rats had their ureters manipulated but not ligated. All rats were given amikacin sulfate (6 mg/kg, intramuscularly route) before operation. The rats were randomly divided into four groups, each consisting of eight animals. Rats with no operation (Group-1) received no treatment and served as controls. Rats in group 2 underwent unilateral ureteral ligation and received no treatment. Group 3 rats underwent sham operation and received no treatment with montelukast sodium (ML). Rats in Group-4 were subjected to unilateral ureteral ligation and received ML (p.o. 10mg/kg/day) (22).

At 14 days after UUO, all rats were sacrificed by high-dose ketamine. Kidneys were reached with an abdominal midline incision. Left kidney was immediately excised and separated from the surrounding tissues, washed twice with cold saline, and stored at -80°C to determine the levels of renal malondialdehyde (MDA), GSH, and NO. A portion of the left renal tissue was stored in formol solution for the histopathologic examinations. Paraffinized tissue samples were examined for leukocyte infiltration and renal fibrosis. Urea-creatinine levels were investigated at blood analysis. Renal impairment was assessed by serum urea and creatinine levels, as well as by the kidney histology. Serum urea and creatinine levels were determined with an autoanalyzer (Syncron LX20, Ireland) by using commercial Becman Coulter diagnostic kits.

MEASUREMENT OF TISSUE LIPID PEROXIDATION LEVEL

Frozen kidney samples were homogenized in Teflon-glass homogenizer with a buffer containing 1.5% potassium chloride to obtain 1:10 (w/v) whole homogenate. MDA, which is formed as an end product of the lipid peroxidation, served as an index of the intensity of oxidative stress. MDA, referred to as thiobarbituric acid reactive substance, was measured with thiobarbituric acid at 532 nm in a spectrophotometer, as described previously (23). The MDA level was expressed as mmol/g wet tissue.

MEASUREMENT OF TISSUE GSH LEVEL

Reduced GSH was estimated by the method of Moron et al. (24), where the color developed was read at 412 nm. Protein concentrations in all samples were measured using the method of Lowry et al. (25). Results were reported as mmol/g wet tissue.

MEASUREMENT OF TISSUE NO LEVEL

Total nitrite was quantified by the Griess reaction after incubating the supernatant with Escherichia coli nitrate reductase to convert NO^3 to NO^2. Griess reagent (1 mL 1% sulfanilamide, 0.1% naphthyl-ethylenediamine hydrochloride, and 2.5% phosphoric acid; Sigma Chemicals) was then added to 1 mL of supernatant (26). The absorbance was read at 545nm after 30-minute incubation. The absorbance was compared with the standard graph of $NaNO^2$, obtained from the reduction of $NaNO^3$ (1-100 mmol/L). The accuracy of the assay was checked in two ways; the inter- and intraassay coefficients of variation were 7.52% and 4.61%, respectively. To check conversion of nitrate to nitrite (recovery rate), predetermined amounts of nitrate were added to control plasma samples; these samples were deproteinized and reduced as above.

HISTOPATHOLOGICAL EXAMINATION

Histopathological evaluation was performed on kidney tissues. Paraffin-embedded specimens were cut into 6-µm thickness sections and stained with hematoxylin & eosin for examination under the light microscope using a conventional protocol (27) (BH-2; Olympus, Tokyo, Japan). A semi-quantitative evaluation of renal tissues was accomplished by scoring the degree of severity according to previously published criteria (28). All sections of kidney samples were examined for

tubular necrosis. Briefly, a minimum of 50 proximal tubules associated with 50 glomeruli were examined for each slide and an average score was obtained. Severity of lesion was graded from 0 to 3 according to the percentage of tubular involvement. Slides were examined and assigned for severity of changes using scores on scale in which (0) denotes no change; grade (1) changes affecting <25% tubular damage (mild); grade (2) changes affecting 25-50% of tubules (moderate); grade (3) changes affecting >50% of tubules (severe).

Histopathological evaluation was performed on left kidney tissues. Paraffin-embedded specimens were cut into 5-mm thick sections and stained with hematoxylin & eosin and Masson's trichrome for examination under the light microscope (BH-2; Olympus, Tokyo, Japan).

To evaluate leukocyte infiltration, the widening of interstitial spaces with focal leukocyte infiltration was assessed in five randomly chosen sections prepared from each kidney sample. For each section, the average number of leukocytes per 0.28 mm^2 was calculated from these leukocyte-infiltrated foci using a high-power microscopic field (x400).

In order to estimate the grade of interstitial fibrosis, the interstitial area that stained green with Masson's trichrome was evaluated as a percentage of the total examined area in five randomly chosen sections prepared from each kidney sample using an image analyzer (Leica; Leica Micros Imaging Solutions, Cambridge, UK). For each section, interstitial space widening with focal leukocyte infiltration and interstitial fibrosis was assessed in high-power fields (x400) to quantify the results. The Banff classification of kidney pathology was used for scoring the degree of mononuclear cell infiltration and interstitial fibrosis. The score was graded from 0 to 3, depending on the severity of histological characteristics (29).

Statistical analyses

Results of all groups were shown as mean values±standard deviation (SD). Statistical analyses of the histopathologic evaluation of the groups were carried out by the Chi-square test and biochemical data were analyzed by the one-way analysis of variance (ANOVA). The significance between two groups was determined by the Dunnett's multiple comparison test, and $P<0.05$ was accepted as statistically significant value.

RESULTS

There was no significant difference for urea-creatinine levels between groups (Table-1).

Tissue MDA levels significantly increased in Group-2 compared with Groups-1, 3, and 4 ($p<0.001$). Rats with ML administration (Group-4) showed reduced levels of lipid peroxidation as measured by MDA levels (Table-2). UUO also induced a significant increase in the tissue NO levels that have been prevented by ML (Table-2). The unilateral ureteral ligation was accompanied by a marked reduction in GSH level in the kidney tissues of rats ($p<0.001$), and treatment with ML partially elevated the GSH levels (Table-2).

Histopathologic examination was normal in rats with only sham operation (Group-3) and in rats with no operation (Group-1) (Figures 1A and B). In rats with UUO, there were mild and severe tubular necrosis in the proximal tubules compared control and sham groups (Figure-1C). In rats treated with UUO+ML, despite the presence of mild

Table 1 - Effects of UO alone and its combination with ML on plasma urea, creatinine levels in rats.

Parameters	Control	Sham	UO	UO+ML
Urea (mg/dL)	34±8.1	35.5±8.6	37.5±10.6	36.1±8.1
Creatinine (mg/dL)	0.44±0.1	0.47±0.2	0.51±0.2	0.48±0.1

Values are expressed as mean±SD for eight rats in each group.

tubular degeneration and less severe tubular necrosis, glomeruli maintained a better morphology when compared with UUO group (Figure-1D). Severe leukocyte infiltration was observed in the periglomerular and peritubular interstitium of the kidneys of the rats in group-2 with UUO (Figures 2A and B).

Quantitative analysis of the focal leukocyte infiltration area in the interstitium showed that leukocyte infiltration was significantly reduced in rats that received UUO+ML (Group-4) (Figure-2C). UUO caused a significant interstitial fibrosis in rats that received no treatment (Group-2), and the percentage area of interstitial fibrosis in the kidney of rats with UUO that received no treatment was significantly greater than that of rats with UUO that received ML (Group-4) (Figures 3A, B and C). These changes are summarized in Table-3.

Table 2 - Effect of ML on the Levels of Malondialdehyde, Glutathione, and Nitric Oxide in Each Rat Group.

Parameters	Kontrol	Sham	UO	UO + MLS
NO (nmol/g wet tissue)	30.3±9.3	30.3±10.2	63.2±15.2[a]	36.3±9.3[b]
MDA (nmol/g wet tissue)	2.6±0.7	2.7±0.7	5.1±1.2[a]	2.9±0.9 [b]
GSH (umol/g wet tissue)	2.3±0.8	2.2±0.7	1.1±0.5[c]	2.1±0.7[d]

Values are expressed as mean ± SD for eight rats in each group.

[a] Significantly different from sham ($p<0.001$); [b] Significantly different from UO group ($p<0.001$); [c] Significantly different from sham ($p<0.05$);

[d] Significantly different from UO group ($p<0.05$).

Abbreviations: **NO =** nitric oxide; **MDA =** malondialdehyde; **GSH =** reduced glutathione.

Figure 1 – A = normal tubulus and glomerules in kidney kortex H&Ex100 (control group). B = normal tubulus and glomerules in kidney kortex H&Ex100 (sham group). C = severe tubular necrosis, tubular degeneration and epithelial vacuolization in the proximal tubules H&Ex100(UUO group). D = mild epithelial vacuolization in the proximal tubules and normal glomerules H&Ex100 (UUO+ML treated group).

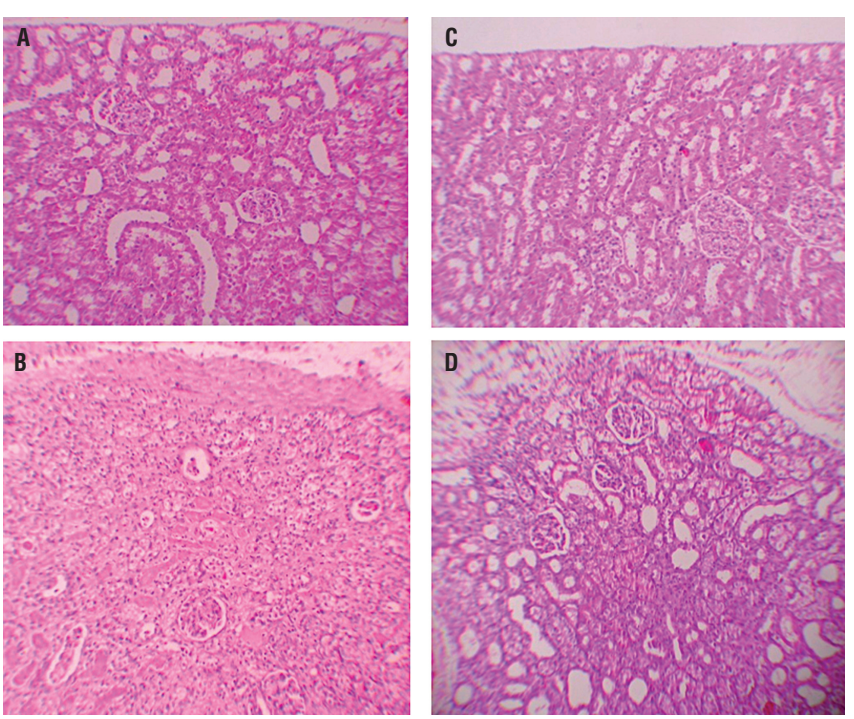

Figure 2 – A = Normal kidney morphology in a sham group. B = Leukocyte infiltration was observed in the peritubular interstitium of the UUO. C = Leukocyte infiltration was reduced in the ML-treated group (hematoxylin & eosin,*400).

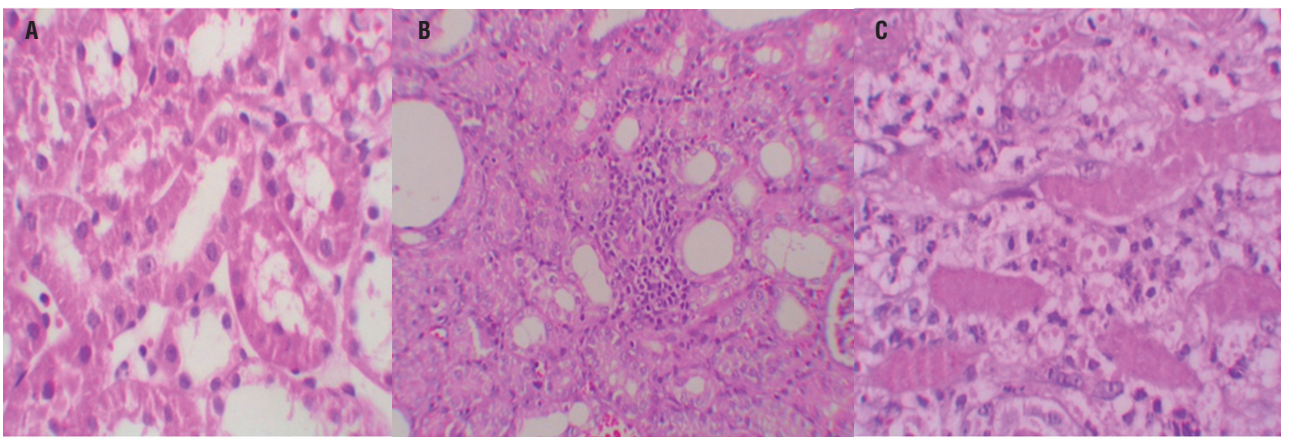

Figure 3 – A = Normal kidney morphology in a sham group. B = severe fibrosis was observed in the peritubular interstitium of the UUO. C = mild fibrosis was reduced in the ML-treated group (masson & trichrome,*400).

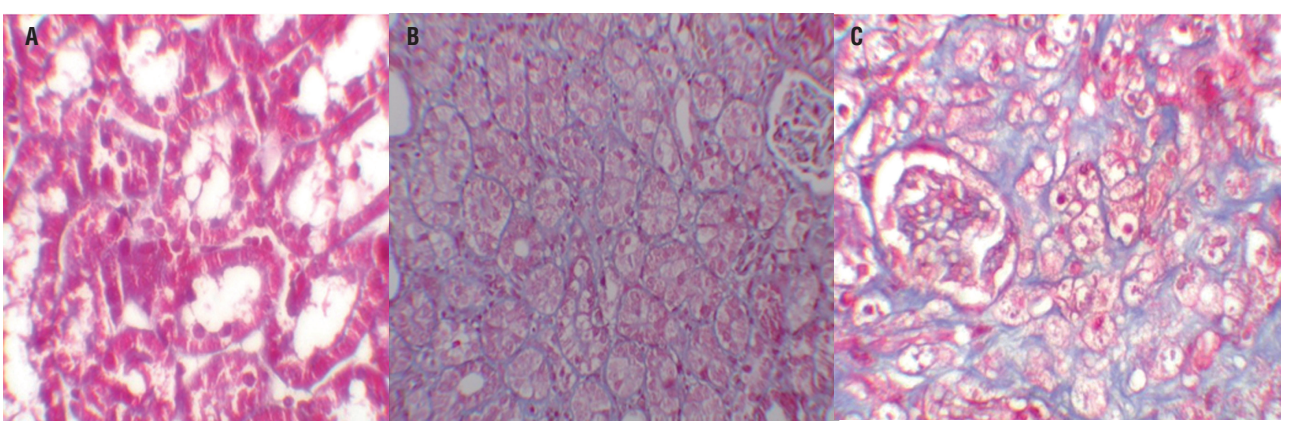

Table 3 - Semiquantitative analysis of tubular necrosis, interstitial fibrosis, mononuclear cell infiltration in control, Sham, UO, and UO+ML treated rats.

	Tubular necrosis					Interstitial fibrosis				Mononuclear cell infiltration			
	n	0	1	2	3	0	1	2	3	0	1	2	3
Control	8	8	0	0	0	8	0	0	0	7	1	0	0
Sham	8	8	0	0	0	8	0	0	0	7	1	0	0
UO[a]	8	0	1	4	3	0	2	3	3	0	2	2	4
UO+ML[b]	8	1	5	1	1	2	5	1	0	1	6	1	0

Score 0 = no degeneration, 1 = mild degeneration, 2 = moderate degeneration, and 3 = severe degeneration

[a] Statistical significant difference from the Sham group

[b] Statistical significant difference from the UO group and $P < 0.05$

DISCUSSION

The present study confirmed through a quantitative survey the protective role of ML on renal tissue damage after the induction of UUO in rats. Our results showed that the obstructed kidney had significantly higher tissue MDA, NO levels, and lower GSH levels along with more fibrosis. The current data demonstrate UUO structural and functional alterations in the kidney with a concomitant increase in proinflammatory cytokines in the blood. The CysLT1 receptor antagonist montelukast, on the other hand, reduced the severity of injury, depressed the concentration of these cytokines and increased the antioxidative capacity.

Montelukast, one of the selective reversible CysLT1 receptor antagonists, is used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies(30). It is reported that montelukast can reduce eosinophilic inflammation in the airways (31-33).

Besides, CysLT1 receptor antagonists or biosynthesis inhibitors ameliorate ethanol-induced gastric mucosal damage (13, 34), experimental colitis (35), and wound healing (36, 37).

Recently, Sener et al. (22) have reported that montelukast has protective effects on chronic renal failure-induced multiple organ injury. They attributed this to montelukast's ability to inhibit neutrophil infiltration and apoptosis. They also suggested that montelukast balances the oxidant–antioxidant status and regulates the generation of proinflammatory mediators. In a different study, it has been shown that montelukast reversed ischemia reperfusion-induced oxidant responses and improved microscopic damage and renal functions (31).

Apoptotic cell death has been reported to play an important role in UUO-induced renal damages (38). The lack of investigation on whether ML has affected the apoptotic cell death because of UUO may be a limitation of this study. However, in a recent study, curcumin and melatonine which is an antioxidant and antiinflammatory agent like ML, has been reported to prevent UUO-mediated apoptotic cell death and reduce the UUO related renal damage. While we believe that ML can reduce the UUO-induced renal damage by a similar mechanism that prevents apoptosis-related cell death, there is a need for further study on that subject for verifications.

The pathogenesis of renal fibrosis caused by UUO involves infiltration of the kidney by inflammatory cells including monocytes, activation and possible transformation of intrinsic renal cells, and interactions between infiltrating and resident cells. NF-kB is activated during renal obstruction, and inhibition of NF-kB activity has been demonstrated to prevent renal fibrosis induced by obstruction (39, 40). In the present study, in agreement with these findings, ML treatment prevented renal fibrosis in UUO rats.

In obstructive nephropathy, it is known that particularly by treatment of UUO, some functions of the kidney can be regained. However, by recovery from the ureteral obstruction, reperfusion damage may occur in the renal tissue as a result of the elevated renal blood flow.

Ischemia-reperfusion (IR) injury is one of the underlying causes of acute renal failure and ROS along with NO, and it plays important roles in mediating cell damage during IR injury (41, 42). Inflammatory cells, neutrophils, are potent cells for production of ROS that are highly produced during IR injury. Renal IR causes tissue injury by way of oxygen radicals and disturbs balance between oxidants and antioxidants in tissue (43). Rodriguez-Reynoso et al. found that exogenous melatonine (MLT) preserved renal function, increased GSH levels, reduced lipid peroxidation, and prevented the rise in NO levels induced by renal IR (44).

They also indicated that MLT treatment reduced histological kidney injury. In accordance with the increase in toxic oxygen metabolites, the renal MDA level was also significantly increased, indicating the presence of enhanced lipid peroxidation due to IR injury, while the levels of tissue glutathione were declined, demonstrating the depletion of the antioxidant pool.

Several studies have demonstrated that IR in the kidney is associated with lipid peroxidation, which is an autocatalytic mechanism leading to oxidative destruction of cellular membranes (45-47). As montelukast reduced the oxidative injury on cellular structures, the level of the intracellu-

lar antioxidant glutathione, which is otherwise oxidized when inactivating free radicals, was not changed. Thus, it appears that the anti-oxidative effect of montelukast on lipid peroxidation does not involve the expenditure of tissue GSH stores, but the antioxidant pool is further supported by the action of montelukast. Moreover, IR-induced reduction in total antioxidant capacity was also reversed by montelukast treatment (31).

As shown in our study, ML has a protective role against both renal damage arising because of UUO and the reperfusion damage occurring as a result of the treatment of obstruction that gives way to elevated renal blood flow.

In conclusion, the results reported here indicate that ML exerts a preventive effect on UUO-induced kidney damage in rats by reducing oxidative stress. We therefore propose that ML supplementation therapy can be used for kidney protection in patients with UUO, such as ureteral stones. Hovewer, further animal and clinical studies are needed to confirm our suggestion.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 288-295, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.15

Assessment of survival of patients with metastatic clear cell renal cell carcinoma after radical cytoreductive nephrectomy versus no surgery: a SEER analysis

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ABSTRACT

Purposes: To examine the factors related to the choice of cytoreductive nephrectomy (CN) for patients with metastatic clear cell renal cell carcinoma (mCCRCC), and compare the population-based survival rates of patients treated with or without surgery in the modern targeted therapy era.
Materials and Methods: From 2006 to 2009, patients with mCCRCC were identified from SEER database. The factors that affected patients to be submitted to CN were examined and propensity scores for each patient were calculated. Then patients were matched based upon propensity scores. Univariable and multivariable cox regression models were used to compare survival rates of patients treated with or without surgery. Finally, sensitivity analysis for the cox model on a hazard ratio scale was performed.
Results: Age, race, tumor size, T stage and N stage were associated with nephrectomy univariablely. After the match based upon propensity scores, the 1-, 2-, and 3-year cancer-specific survival rate estimates were 45.1%, 27.9%, and 21.7% for the no-surgery group vs 70.6%, 52.2%, and 41.7% for the surgery group, respectively (hazard ratio 0.42, 95%CI: 0.35-0.52, log-rank P<0.001). In multivariable Cox proportional hazard regression model, race, T stage, N stage and median household income were significantly associated with survival. Sensitivity analysis on a hazard ratio scale indicated that the hazard ratio might be above 1.00 only when the unknown factor had an opposite effect on survival which was 3-fold than CN.
Conclusion: The results of our study showed that CN significantly improves the survival of patients with metastatic CCRCC even in the targeted therapy era.

ARTICLE INFO

Key words:
Carcinoma, Renal Cell; Nephrectomy; SEER Program; Propensity Score; Molecular Targeted Therapy

Int Braz J Urol. 2015; 41: 288-95

Submitted for publication:
November 02, 2013

Accepted after revision:
June 06, 2014

INTRODUCTION

Renal cell carcinoma (RCC) is a common malignancy, and represents more than 3% of adult solid malignant tumors (1). Most RCCs are diagnosed in early-stage disease, but approximately 25% of RCC patients have systemic metastases at initial diagnosis (2, 3). Two randomized controlled trials have confirmed the benefit of cytoreductive nephrectomy (CN) on metastatic RCC (mRCC) in the pretargeted therapy era (4-6). The use of CN had been steadily increasing after 2001, and was generally viewed as a treatment standard (7, 8). In 2005, the Food and Drug Administration (FDA) approved the use of vascular endothelial growth factor receptor

tyrosine kinase inhibitors (VEGFR-TKIs) in renal carcinoma. The unprecedented antitumor activity and relatively favorable toxicity profile of the modern targeted therapies resulted in a shift of the standard systemic therapy for mRCC (9-11). So, in the era of VEGFR-TKIs, it is uncertain the appropriate role of CN. The present study will explore factors associated with CN and evaluate its role in modern day practice within a large North American population-based dataset.

MATERIALSN AND METHODS

Data for the current analysis were derived from the Surveillance, Epidemiology, and End Results (SEER) registry. The SEER has collected clinical and pathological data in 19 specified geographic areas of the United States (US) since 1973, including the Atlanta, Detroit, San Francisco-Oakland, Seattle-Puget Sound metropolitan areas and the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah. These data are highly representative of the demographic makeup of the United States, especially in terms of geography, socioeconomic status, race/ethnicity, and age (12).

Because VEGFR-TKIs were mainly used for clear cell renal cell cancer (13), its diagnostic codes ("International Classification of Disease for Oncology", 3rd edition, histology coding 8310) were used as inclusion criteria. The presence of histology coding 8310 and AJCC stage M1 (derived AJCC 6th edition) resulted in the identification of 2305 patients with metastatic clear cell renal cell cancer (mCCRCC) from 2006 to 2009. Patients who underwent a radical surgical removal of kidney, were included in the surgery group. Only patients who did not undergo surgery were included in the "no surgery group". The duration of survival after nephrectomy or from the date of mRCC diagnosis was determined according to the SEER survival time definition. We selected 2006 as the initial year because 2005 was the time of initial regulatory approval for VEGFR-TKI's use in renal carcinoma. Follow-up was defined as the time between date of diagnosis and date of death or November 2011 whichever came first.

Statistical analyses

Baseline statistics were analyzed with means for continuous variables (age, tumor size) and proportions for categorical variables (race/ethnicity, stage). The baseline differences of two groups were compared using chi-squared for categorical variables. T-test was used for comparison of age, while Wilcoxon test was used for comparison of tumor size. Cox proportional hazard regression model was used to calculate the survival rate.

As patients were not randomly selected for nephrectomy, a propensity score was calculated reflecting the probability of a person undergoing nephrectomy given a set of known covariates. A multivariable regression model, including these factors univariably associated with nephrectomy, was used to obtain the propensity of nephrectomy for each patient. Then the patients without surgery were matched by the patients with surgery based upon the propensity score. This would adjust the bias due to imbalance of certain prognostic variables associated with nephrectomy to a certain extent. Then a cox survival model for the matched patients, including all variables associated with survival, was made to evaluate the beneficial effect of nephrectomy. Sensitivity analysis for this model on a hazard ratio scale was also performed (14). Analyses were conducted using the R statistical package (the R foundation for Statistical Computing, version 2.15.2).

RESULTS

The radical nephrectomy rate of all 2305 patients was 49.3% (n=1133). 943 patients did not receive any therapy for the local tumor, while 11 patients had no information whether they received the therapy or not. 218 patients receiving other therapy rather than "radical nephrectomy" were excluded, including local tumor destruction, thermal ablation, electrocautery, cryosurgery, "simple nephrectomy" and so on. Additional exclusions consisted of unknown T stage (n=363), unknown N stage (n=170). Only the records of patients with the tumor size available were considered in the present study. This resulted in the exclusion of another 38 patients with an unknown tumor size. So, 1505 patients were included in this study.

Among 1505 assessable patients, 1038 (68.97%) were men, and the average age was 62.1 years. The no-surgery patients (n=460) were significantly older (65.77 vs 60.51 years, P<0.001), had almost the same proportion of women (31.1% vs 31.0%, P>0.5), and had smaller tumors (median size, 7.5 vs 9.0 cm, P<0.001) than the surgery patients (n=1045). Race, T stage and N stage were also associated with nephrectomy (Table-1). At 1, 2 and 3 years of follow-up, the cancer-specific survival rate was 44.9%, 28.3%, and 20.6% for the no-surgery group vs 72.7%, 54.1% and 47.2% for the surgery group, respectively (hazard ratio 0.39, 95%CI: 0.33-0.46, log-rank P<0.001).

Table 1 - Uni- and multivariable regression models to estimate factors associated with nephrectomy.

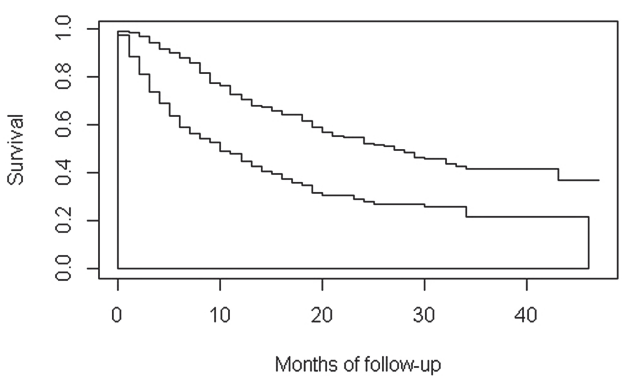
	Nephrectomy *N* (%)	No nephrectomy *N* (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)
N	1045	460		
Gender				
Male[b]	721 (69.5)	317 (30.5)		
Female	324(69.4)	143 (30.6)	1.00 (0.79–1.28)	
Age at diagnosis (per year increase)			0.96 (0.95–0.97)	0.96 (0.95–0.97)
Race				
Black	47(47.0)	53(53.0)		
White	924(70.9)	380(29.1)	2.74 (1.82–4.13)	3.03(1.91–4.80)
Yellow or Unknown	74(73.2)	27(26.7)	3.09 (1.71–5.58)	3.68(1.90–7.10)
Tumor size			1.0055 (1.0025-1.0086)	0.9997(0.997-1.002)
T stage				
T1a	48(48.0)	52(52.0)		
T1b	111(52.1)	102(47.9)	1.18 (0.73-1.9)	1.14(0.69–1.89)
T2	175(62.1)	107(37.9)	1.77 (1.12-2.81)	1.60(0.95–2.70)
T3a	260(86.7)	40(13.3)	7.04 (4.21-11.78)	7.63(4.32–13.47)
T3b	363(83.3)	73(16.7)	5.39 (3.38-8.58)	5.87(3.46–9.98)
T3c	25(73.5)	9(26.5)	3.01 (1.28-7.09)	3.10(1.24–7.75)
T4	63(45.0)	77(55.0)	0.89 (0.53-1.48)	0.92(0.52–1.65)
N stage				
N0	787(71.5)	314(28.5)		
N1	156(63.2)	91(36.8)	0.68 (0.51-0.91)	0.46(0.33–0.64)
N2	102(65.0)	55(35.0)	0.74 (0.52-1.05)	0.51(0.34–0.77)
Median household income (in tens) 2000			1(0.9999-1.0001)	
% Unemployed 2000			0.9998 (0.9993,1.0003)	

OR = odds ratio; **CI =** confidential interval

All factors univariably associated with nephrectomy were included in the multivariable logistic regression model which is presented in Table-1. Race, T stage, N stage and age at diagnosis remained significantly associated with nephrectomy. This multivariable model was also used to estimate the propensity score for each patient (the probability of undergoing a nephrectomy).

After the match process based upon propensity scores, 442 no-surgery patients were matched with 442 surgery patients. In this matched population (n=884), the 1-, 2-, and 3-year estimate was 45.1%, 27.9%, and 21.7% for the no-surgery group vs 70.6%, 52.2%, and 41.7% for the surgery group, respectively (hazard ratio 0.42, 95%CI: 0.35-0.52, log-rank P<0.001, Figure-1).

Figure 1 - Surgery group.



In Table-2 the results of the univariable and multivariable Cox proportional hazard regression analyses are presented. Race, tumor size, T stage, N stage and age at diagnosis were univariablely associated with cancer-specific survival. Less median household income associated with better cancer-specific survival, although this was not statistically significant (P=0.056). In multivariable Cox proportional hazard regression model, race, T stage, N stage, and median household income significantly associated with survival.

Sensitivity analysis on a hazard ratio scale indicated that the hazard ratio might be above 1.00 only when the unknown factor had an opposite effect on survival which was 3-fold than cytoreductive nephrectomy (Table-3).

DISCUSSION

As we know, the use of CN in the cytokine therapy era was supported by two randomized trials conducted by the Southwest Oncology Group and by the European Organization for Research and Treatment of Cancer (4-6). In the era of molecular targeted therapy, there has been some retrospective data about the combined use of CN with systemic targeted therapy (15-17). But their results were controversial and the number of patients was small. The present population-based study may be one of the large sample investigations to explore the prognostic factors associated with CN and evaluate its role in modern molecular targeted therapy era.

Among demographic variables, age and race except gender appeared to be independent factors associated with nephrectomy. Black people appeared less likely to be submitted to CN than White or Asian group, while older people were less likely, either. But these factors may be confounded by performance status, comorbidity, economic conditions and so on. Kader et al. (18) found that the prognosis amongst elderly is comparable to the younger patients if they survive the surgery. So age alone should not be a criterion whether or not to treat patients with cytoreductive surgery (8).

Tumor size and TNM stage were significantly associated with the probability of nephrectomy as well. Local or regional advanced tumors make surgical intervention a high risk and have been shown to be associated with a poor prognosis (19, 20). However, the majority of these patients in the present study were still submitted to CN: more than 70% of patients with T3 disease and more than 60% of patients with positive lymph node. This indicated the importance of surgical removal of primary tumor, tumor thrombus and positive lymph node in the mRCC setting. As T1a were concerned, more than half of these patients included in our study did not receive any therapy for renal carcinoma. However, this did not mean that the local treatment was unimportant. Due to smaller tumors, these patients might choose other local therapy rather than “radical nephrectomy”, including local tumor destruction, thermal ablation, electrocautery,

Table 2 - Cox Proportional Hazards regression analyses including nephrectomy, propensity score and other prognostic variables.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Nephrectomy		
No		
Yes	0.424(0.347–0.519)	0.42(0.34–0.52)
Gender		
Female		
Male[b]	0.86 (0.70–1.06)	
Age at diagnosis (per year increase)	1.009 (1.001–1.018)	1.01 (0.999–1.017)
Race		
Black		
White	0.60 (0.42–0.87)	0.58(0.40–0.85)
Yellow or Unknown	0.57 (0.35–0.93)	0.61(0.37–1.01)
Tumor size	1.002 (1.000–1.003)	1.0013(0.9997–1.0028)
T stage		
T1a		
T1b	1.50 (0.93-2.43)	1.69(1.04–2.75)
T2	2.00 (1.26-3.16)	2.17(1.35–3.53)
T3a	1.37 (0.85-2.21)	1.87(1.13–3.10)
T3b	1.76 (1.11-2.78)	2.11(1.30–3.45)
T3c	2.07 (1.07-4.03)	2.05(1.03–4.08)
T4	2.40 (1.49-3.87)	2.13(1.30–3.51)
N stage		
N0		
N1	2.20 (1.73-2.80)	1.98(1.54–2.55)
N2	3.22 (2.43-4.26)	3.09(2.31–4.12)
Median household income (in tens) 2000	0.9999(0.9998-1.0000)	0.9999(0.9998-1.0000)
% Unemployed 2000	1.0000 (0.9998-1.001)	

HR = hazard ratio; **CI =** confidential interval

cryosurgery and so on. These cases were beyond the scope of the present study and have been excluded, which might result in the low proportion of patients receiving CN.

Our results have demonstrated a survival benefit when CN was performed compared with no surgery. The effect of performing CN was related to 2.5-fold increase in cancer-specific survival rate (P<0.001). The lack of randomization represents a major limitation of the present study, which means differences that could exist between the surgery group and no-surgery groups might not have been optimally adjusted. So propensity scores were used for statistical adjustment of some factors (age, gender, tumor size, race, TNM stage, local economic situation and so on). As

Table 3 - Sensitivity analysis on cytoreductive nephrectomy on a Hazard Ratio scale.

P0	0.2	0.4	0.6	0.8
Gamma=1.5				
P1				
0.1	0.432(0.350–0.533)	0.472(0.382–0.450)	0.511(0.414–0.630)	0.550(0.446–0.679)
0.2	0.413(0.334–0.509)	0.450(0.365–0.555)	0.488(0.395–0.602)	0.525(0.426–0.648)
Gamma=2				
P1				
0.1	0.450(0.365–0.555)	0.525(0.426–0.648)	0.600(0.486–0.740)	0.675(0.547–0.833)
0.2	0.413(0.334–0.509)	0.481(0.390–0.594)	0.550(0.446–0.679)	0.619(0.502–0.764)
Gamma=2.5				
P1				
0.1	0.466(0.378–0.575)	0.574(0.465–0.708)	0.682(0.553–0.841)	0.789(0.640–0.974)
0.2	0.413(0.334–0.509)	0.508(0.412–0.627)	0.603(0.489–0.744)	0.698(0.566–0.861)
Gamma=3				
P1				
0.1	0.481(0.390–0.594)	0.619(0.502–0.764)	0.756(0.613–0.933)	0.894(0.725–1.103)
0.2	0.413(0.334–0.509)	0.530(0.430–0.655)	0.648(0.526–0.800)	0.766(0.621–0.945)

an observational study, other factors unavailable from SEER database may affect the survival rates of the patients with mRCC, including comorbidities, performance status, the number of metastatic sites and laboratory variables (eg, hemoglobin, calcium, lactate dehydrogenase) (21, 22). If these unmeasured variables were included in the analysis it would possibly change the conclusions. Sensitivity analysis is a way to see how much of a relationship needs to exist with the unmeasured variable before the conclusions change. In present study, the sensitivity analysis demonstrated the hazard ratio might be above 1.00 only when the unknown factor had an opposite effect on survival which was 3-fold than cytoreductive nephrectomy. So we could say that the survival benefit related to cytoreductive nephrectomy was not due to an unfavorable performance status or multiple comorbidities in the patients in the no-surgery group, and the lack of performance status and/or baseline comorbidity data did not spuriously inflate the survival benefit of surgery (23).

CONCLUSIONS

Although the data came from the United States and there might be different clinical selection criteria used for cytoreductive nephrectomy candidates in other countries, the results of our study have shown that cytoreductive nephrectomy significantly improves the survival of patients with metastatic clear cell renal cell carcinoma even in the targeted therapy era. According to SEER database, race, T stage, N stage and age at diagnosis were significantly associated with nephrectomy, while race, T stage, N stage and median household income were significantly associated with cancer-specific survival. We hope that our result sheds some light on the ongoing clinical trial of this aspect (24).

ACKNOWLEDGEMENTS

This work was supported by National Natural Science Foundation of China (grant number 81001131).

Wen-Jun Xiao, Yao Zhu contributed equally to this work.

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EDITORIAL COMMENT

In this edition of Int Braz J Urol, Doe et al. describe an interesting retrospective analysis of the role of cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC) from the Surveillance, Epidemiology, and End Results (SEER) database. This is a widely researched and discussed topic in uro-oncology precisely because we have few (possibly none) high quality studies with level of evidence that can guide practice and help clinical management of such patients in the targeted therapy era.

The concept of cytoreduction is one of the pillars of modern surgical oncology and is applied in various types of neoplasms such as ovarian, colonic, bladder and more recently some groups have evaluated its role in prostate cancer (1, 2). In the mRCC scenario, two randomized phase III trials investigated the role of CN in the treatment of patients with mRCC during the immunotherapy era (3, 4). The combined analysis of such trials demonstrated a median survival of 13.6 months in the CN group versus 7.8 months in the systemic therapy-only group. The 31% difference in risk of death was statistically significant (p=0.002) favoring surgery (5). And this was considered the standard approach until the emergence of targeted therapy. Since then, the role of CN has been questioned.

Retrospective studies have confirmed the importance of CN in the targeted therapy era. However, unlike immunotherapy with interferon or IL-2, it is known that TKIs and mTOR inhibitors might present an objective response on the primary tumor too. That said, some key questions must be answered. Who deserves to undergo CN? What are the criteria used to select candidates for CN? When CN must be offered, prior or after systemic therapy? Is there any place for nephron-sparing surgery? Evidence suggests that patients at low or intermediate risk groups, with good performance status, low extrarenal tumor burden and no central nervous system metastasis are the ideal candidates to CN (6). The remaining issues remain unanswered.

The SURTIME trial (EORTC 30073, NCT01099423) and the CARMENA trial (NCT00930033) are currently investigating the utility of CN in the targeted therapy era and its ideal timing. Until preliminary results of such studies are published, the clinical management of mRCC patients will be based on extrapolations from the immunotherapy era; and despite all the limitations, from some interesting retrospective studies such as Doe et al. study.

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ORIGINAL ARTICLE

Vol. 41 (2): 296-303, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.16

Retroperitoneal Laparoscopic Nephroureterectomy for Tuberculous Nonfunctioning Kidneys: a single-center experience

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ABSTRACT

Purpose: To present our surgical techniques and experiences of retroperitoneal laparoscopic nephroureterectomy for the treatment of tuberculous nonfunctioning kidneys.
Materials and Methods: From March 2005 to March 2013, a total of 51 patients with tuberculous nonfunctioning kidney underwent retroperitoneal laparoscopic nephroureterectomy at our medical center. The techniques included early control of renal vessels and dissection of the diseased kidney along the underlying layer outside the Gerato's fascia. The distal ureter was dissected through a Gibson incision and the entire specimen was removed en bloc from the incision. Patient demographics, perioperative characteristics and laboratory parameters as well as postoperative outcome were retrospectively reviewed.
Results: Retroperitoneal laparoscopic nephroureterectomy was successfully performed in 50 patients, whereas one case required conversion to open surgery due to non-progression of dissection. The mean operating time was 123.0 minutes (107-160 minutes) and the mean estimated blood loss was 134 mL (80-650 mL).The mean postoperative hospital stay was 3.6 days (3-5days) and the mean return to normal activity was 11.6 days (10-14days). Most intra-operative and post-operative complications were minor complications and can be managed conservatively. After 68 months (12-96 months) follow-up, the outcome was satisfactory, and ureteral stump syndrome did not occur.
Conclusions: Retroperitoneal laparoscopic nephroureterectomy as a minimally invasive treatment option is feasible for treatment of tuberculous nonfunctioning kidneys.

ARTICLE INFO

Key words:
Tuberculosis; Laparoscopy; Nephroureterectomy; Kidney

Int Braz J Urol. 2015; 41: 296-303

Submitted for publication:
March 09, 2014

Accepted after revision:
June 23, 2014

INTRODUCTION

Since the initial introduction of laparoscopic nephrectomy in 1991 (1), laparoscopic surgery has made tremendous progress in the urological field. Currently, many complex kidney surgeries such as radical nephrectomy, partial nephrectomy and living donor nephrectomy can be successfully completed by laparoscopic approach, and the safety and effectiveness have been confirmed by several studies (2, 3). However, laparoscopic nephroureterectomy for tuberculous nonfunctioning kidney has always been a highly challenging procedure because of significant perinephric and perihilum inflammation and severe adhesion with adjacent structures. To the best of our knowledge, several small case series were reported on the outcomes and feasibility of laparoscopic nephroureterectomy for patients with tuberculous nonfunctioning kidneys (4-8). It is still difficult to

interpret the overall risk of laparoscopic nephroureterectomy for tuberculous nonfunctioning kidney due to the lack of cases in these reports, and large trials are required to draw definitive conclusions. Moreover, few studies dived into whether it is necessary to remove the distal ureter in the laparoscopic nephroureterectomy procedure for the treatment of nonfunctioning tuberculous kidneys.

In the present study, we aim to report our eight years' experience with retroperitoneal laparoscopic nephroureterectomy for the management of tuberculous nonfunctioning kidneys.

MATERIALS AND METHODS

Patients who underwent retroperitoneal laparoscopic nephroureterectomy with unilateral nonfunctioning kidney secondary to tuberculosis were included in the study. Patients with a diseased kidney less than 10 cm in diameter and without surgical history at the same anatomical site were selected for this surgery. Patients were excluded from the study if the final histopathologic examination demonstrated that the diseased kidneys were not associated with tuberculosis. From March 2005 to March 2013, a total of 51 patients were selected for this study. This study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, affiliated with Capital Medical University. The advantages and risks of the laparoscopic surgery and the possibility of conversion to open surgery were fully explained to patients; all patients signed a written consent form before surgery.

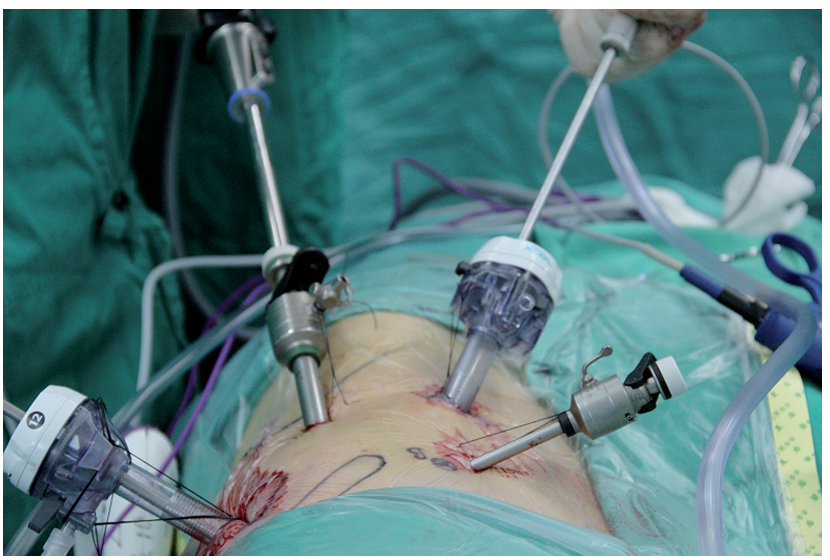
The most common clinical presentation was irritative voiding symptoms (23 cases), followed by recurrent urinary tract infection (18 cases), gross hematuria (6 cases), ipsilateral flank pain (3 cases) and scrotal mass (1 case). Renal tuberculosis was suspected based on symptoms and was confirmed by a positive urine smear, urine polymerase chain reaction for acid-fast bacilli and histopathologic evaluation of bladder biopsy. A computerized tomography was used to demonstrate imaging manifestations of the entire urinary tract. A renal nuclear scan was utilized to evaluate glomerular filtration rates of the diseased kidney and contralateral kidney. Every patient had normal or mild impaired function in the contralateral kidney, and the glomerular filtration rate of the diseased side was less than 10 mL/min/1.73 m^2. All patients initially received an anti-tuberculous remedy for 4 weeks to 3 months before operation. The standard regimen was isoniazid 5 mg/kg orally once daily, rifampicin 10 mg/kg orally once daily and ethambutol 15 mg/kg orally once daily. Symptoms of active tuberculosis, such as fever, night sweats, anemia, anepithymia and a rapid erythrocyte sedimentation rate, were controlled before operations. To avoid data deviations due to surgical learning curve, all surgeries were performed by the same surgeon (Dr. Nianzeng Xing). The intra-operative complications were analyzed using Satava classification (9), and the postoperative complications were graded by modified Clavien classifications (10).

All patients were regularly followed up at the second week, third month and sixth month after discharge and every 6 months thereafter till five years. A physical examination, hematological examination and ultrasonography were done during regular follow-up. An intravenous urography, renal scan and cystography were performed according to above examinations. To ensure maximal chance of bacteriologic cure, all patients received at least 6 months of antituberculous treatment after surgery.

OPERATION TECHNIQUE

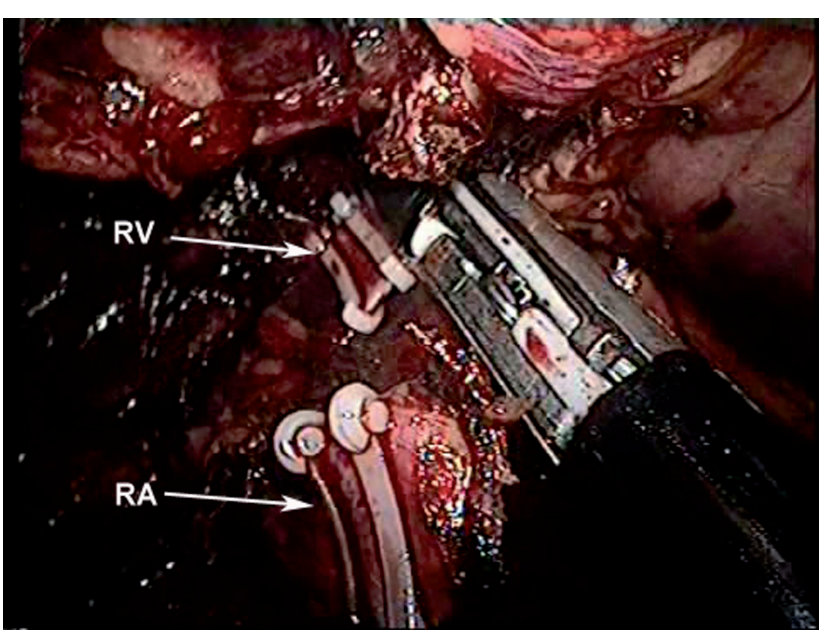
Patients were placed in the lateral flank position with elevation of the diseased kidney bridge after general anesthesia. All surgical procedures were conducted as a retroperitoneoscopic radical nephrectomy, and four trocars were employed (6, 11, 12) (Figure-1). A 2 cm incision was made 2 cm below the costal margin on the posterior axillary line. Using a forceps to bluntly penetrate the muscle layer and lumbodorsal fascia to the retroperitoneal space and an index finger to dilate the space, an enough retroperitoneal space was created to hold an uninflated balloon. Then the balloon was inflated with 1000 mL air and kept for 3 minutes. A 5 mm, 12 mm, and 10 mm trocar were placed respectively at the anterior axillary line around the 11th rib tip, 2 cm inside the anterior superior

Figure 1 - Positions of the four working trocars.



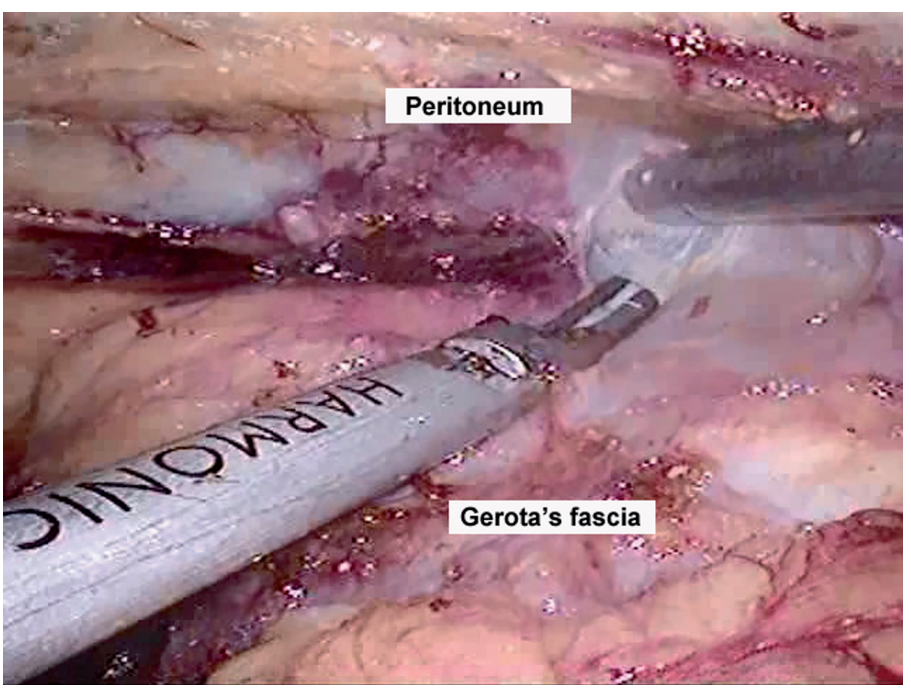
iliac spine, and 2-cm above the iliac crest for the 30º Olympus laparoscope. Finally, a 12 mm trocar was placed in the initial hole. The Gerota's fascia was cut horizontally from the front edge of the psoas muscle up to the diaphragm and down to the lower pole of the kidney, and the renal hilum was accessed by subtle but sharp dissection towards the renal artery pulsation. The renal artery and vein were successively ligated with three Hem-O--Lock clips and dissected (Figure-2). The kidney was subsequently mobilized outside Gerota's fascia as far as possible using sharp dissection and

Figure 2 - The renal artery (RA) and renal vein (RV) were clipped with Hem-o-lok clips and divided by LigaSure.



care was taken to avoid puncturing the kidney sac (Figure-3). The ureter was then identified and dissected as distally as possible at which point it is clipped with a Hem-O-Lock clip and left *in situ.* The retroperitoneal space was inspected with insufflation pressure at 5 mmHg to ensure adequate homeostasis. The trocar incisions were closed and the patient was changed to supine position. An approximately 7-8 cm long Gibson incision was made in the lower abdominal region. The distal ureter was gently dissected until some of the intramural ureter was mobilized, and then the bladder cuff was cut to free the specimen. After the bladder incision was totally sutured, the entire kidney within Gerota's fascia and ureter were removed *en bloc* from the Gibson incision.

Figure 3 - Dissection of the diseased kidney outside the Gerato's fascia.



RESULTS

The demographic profiles and perioperative parameters of patients are shown in Table-1. There were 22 males and 29 females, ranging in age from 23 to 78 years old. Totally, 30 diseased kidneys were at the left side and 21 cases at the right side. The mean disease course was 7.3 months (range: 3-21 mon). Of 51 patients, 6 cases with contracted bladder had mild to moderate renal function impairment (range of serum creatinine level: 189-450 mmol/L) and required sigmoid augmentation cystoplasty.

Retroperitoneal laparoscopic nephroureterectomy was successfully completed in 50 patients. One patient required conversion to open surgery due to lack of progress in dissection, and the open nephroureterectomy was successfully performed. The mean operating time was 123.0 minutes (range: 109-160 min). The mean estimated blood loss was 134 mL (range, 80-650 mL) and two patients required intraoperative transfusion of 2 U packed red blood cells. The mean hospital stay was 3.6 days (range: 3-5 days) and the time of returning to normal activity was 11.6 days varying from 10 to 14 days.

The intra-operative complications analyzed using Satava classification are shown in Table-2.

Table 1 - Preoperative and operative characteristics of patients.

Parameter	Value (range)
Age (years)	39.3 (23-78)
Sex (M/F)	22/29
Side (right/left)	21/30
BMI (kg/m^2)	24.3 (21-27)
Disease course (months)	7.3 (3-21)
Operative time (minutes)	123 (109-160)
Estimated Blood loss (mL)	134 (80-650)
Blood transfusion (n)	2
Hospital stay (days)	3.6 (3-5)
Conversion (n)	1
Return to previous activities(days)	11.6 (10-14)
Follow-up time (months)	68 (12-96)

Table 2 - Peri-operative complication according to Satava classification system.

	No. of cases
Satava grade I (incidents without consequence)	
Sinus arrhythmia	1 (1.96%)
Satava grade II (incidents repaired intraoperatively)	
Renal vein injury	1 (1.96%)
Lumbar vein injury	1 (1.96%)
Peritoneal injury	4 (7.84%)
Spillage of pus	1 (1.96%)
Satava grade III (incidents requiring open conversion)	
Inability to dissect pedicle	1 (1.96%)

The most common complication was peritoneal tear (7.84%), which can be managed laparoscopically with no need to conversion. Renal venous injury (1.96%) occurred in one patient due to severe adhesion. However, the bleeding was successfully controlled and did not hamper the successful completion of the laparoscopic procedure. One diseased kidney was inadvertently punctured (1.96%) during dissection. The working space was thoroughly washed with a copious amount of normal saline plus streptomycin at the end of the procedure, and no disseminated or systemic disease was identified during long-term follow-up. The postoperative complications graded by modified Clavien classifications are shown in Table-3. The grade I and II complications were 19.6% in all. One patient was reoperated for a hematoma in retroperitoneum, which was a grade III complication (1.96%).

The histopathologic examination confirmed the diagnosis of renal tuberculosis in all patients. The common microscopic findings were

Table 3 - Postoperative complications stratified according to the modified Clavien classification.

Clavien Grade	n	Management
Grade I (11.76%)	6	
Fever	1	Antipyretics
Transient elevation in creatinine	2	Observation
Subcutaneous emphysema	3	Observation
Grade II (7.84%)	4	
Blood loss anemia	2	Blood transfusion
Pneumonia	1	antibiotics
Wound infection	1	Wound opening and antibiotics
Grade III (1.96%)	1	
Hematoma in retroperitoneum	1	Re-operation

tuberculous pyelonephritis with caseation, perinephritis and tuberculous pyonephrosis. Similar changes were found in the walls of ureters. The normal tissue was completely or partly replaced by caseous substance or fibrous tissue, and the ureter became thicken and stenotic.

After 68 months (range: 12-96 months) regular follow-up, the outcomes were satisfactory. All patients achieved improvement in symptoms and renal function. No local or disseminated recurrence was identified (evaluated by urine polymerase chain reaction for acid-fast bacilli, hematologic examination and imaging examination). The ureteral stump syndrome did not occur in our patients.

DISCUSSION

Benign kidney diseases are the most common indications for laparoscopic nephroureterectomy (13). However, laparoscopic nephroureterectomy for inflammatory renal conditions such as tuberculous nonfunctioning kidney, long-standing renal stone disease and xanthogranulomatous pyelonephritis has always been considered as a relative contraindication because of higher rate of complications and conversion to open surgery. In this study, we retrospectively reviewed 51 patients with tuberculous nonfunctioning kidneys managed by retroperitoneal laparoscopic nephroureterectomy in respect to surgical techniques, perioperative outcome and follow-up, and the results are encouraging.

In our cases, we performed all surgeries by retroperitoneal laparoscopic approach for we have high volume of experience with this approach (12). Current researches have demonstrated that the laparoscopic operation for inflammatory nonfunctioning kidney can be accomplished through either the transperitoneal or the retroperitoneal approaches (5, 7), and the choice depends mainly on the surgeon's educational background and laparoscopic experiences. Although the retroperitoneal approach has some disadvantages such as the limited working space, difficulty to identify the anatomical structure as well as a longer learning curve compared to the transperitoneal approach, it facilitates to control renal vessels early and avoids contamination with the pus and potential injury to intraperitoneal organs (14).

Only a few small series have been reported addressing laparoscopic nephroureterectomy for tuberculous nonfunctioning kidneys. The reported rates of successive laparoscopic surgery were between 77.8% and 100% (5-8). The largest cohort included only 31 patients (7). In the present study, a total of 51 patients were enrolled and laparoscopic nephroureterectomy was successfully performed in 50 patients (98.0%) with only one conversion due to dense adhesions. The peri-operative data, including mean operative time, estimated blood loss, hospital stay and complications, were consistent with previous reports (4, 15, 16). These data support that retroperitoneal laparoscopic nephroureterectomy is feasible to treat patients with nonfunctioning tuberculous kidneys.

Various technical modifications for laparoscopic nephrectomy in the setting of nonfunctioning tuberculous kidneys and other inflammatory conditions have been proposed to reduce technical difficulties. Early control of renal vessels is an essential step of this procedure which can substantially minimize widespread bleeding and facilitate subsequent dissection (6, 11). Dissection of renal pedicle vessels is extremely challenging because severe inflammatory process makes anatomy layers obliterated and distorted. En bloc ligation of renal hilar has been recommended to simplify the procedure for more difficult cases (17); however, such technique has been reported to be associated with the very rare complication of arteriovenous fistula formation, primarily in inflammatory renal pathologic features (18). Therefore, individual ligation of the renal artery and vein was strongly preferred in our cohort. A careful, slow, patient dissection is utmost important in this procedure. The pulsations of the abdominal aorta and renal artery, and the undulation of inferior vena cava are useful markers. The renal pedicle should be approached as close as possible to the inferior vena cava on the right side and aorta on the left side, and much difficulty was not encountered in the dissection of the fibrous tissue in this region. After ligation of renal vessels, it is crucial to identify an appropriate layer to intactly move the diseased kidney. It has been reported that the

underlying layer outside the Gerota's fascia is less affected by inflammation, and a dissection along this layer offers better progression and far less bleeding (19-21). Subcapsular nephrectomy has also been described for the retroperitoneoscopic approach of LN in inflammatory conditions when dense adhesions were encountered (22, 23). For nonfunctioning tuberculous kidneys, we found that the adhesive bundles and fibrosis were mainly localized inside the Gerota's fasica after a minimum of 4 weeks of anti-tuberculous chemotherapy. Dissection can be performed with minimal difficulty by keeping the plane outside Gerota's fascia. If difficulty with laparoscopic dissection is encountered in one area, the procedure can be carried out in other areas. The surgeon should try to achieve as much dissection as possible. The safe layer is usually visualized in the dense adhesive areas once the diseased kidney has been mostly dissected. Moreover, the introduction of advance equipments, such as the harmonic scalpel, Ligasure and bipolar electric coagulation is an excellent alternative to avoid bothersome bleeding and makes surgeries easier.

Severe ureteral stump syndrome was reported after simple nephrectomy for treatment of nonfunctioning tuberculous kidneys, and powerful anti-tuberculous regimen failed to completely cure the severe irritative symptoms in these cases (24, 25). To ensure optimal effectiveness, it becomes apparent that total ureterectomy should be applied for treatment of nonfunctioning tuberculous kidneys. The final histopathological outcome of all patients in our study demonstrated that ureters were all diffusely invaded by tuberculosis, which supports the essentiality of total ureterectomy for nonfunctioning tuberculous kidneys. Multiple techniques have been used to manage the distal ureter during laparoscopic nephroureterectomy, including open incision and resection via an intravesical or extravesical approach, endoscopic, laparoscopic stapling of the bladder cuff, or combinations of several techniques. Considering the clinical-pathological characteristics of the tuberculosis and our experience, we recommend conventional open surgery to deal with the distal ureter. After completion of the laparoscopic procedure in our series, an approximately 7-8 cm long Gibson incision was made and the distal ureter was dissected till to the bladder wall, and the intact specimen was removed *en bloc* from the incision. This approach facilitates to remove more tuberculous tissue to eliminate the potentiality of ureteral stump syndrome.

There are several limitations in our study. First, our case number is relatively small. Second, this is a retrospective study of a single center. Randomized controlled trials with large sample size are needed to prove the feasibility and superiority of retroperitoneal laparoscopic approach to manage tuberculous nonfunctioning kidneys.

CONCLUSIONS

Our results indicated that retroperitoneal laparoscopic nephroureterectomy is a safe and effective method for the treatment of tuberculous nonfunctioning kidneys with satisfactory long--term follow-up outcomes. However, randomized controlled studies with large sample size and high--quality design are needed to confirm our results.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 304-311, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.17

High-grade Primary Renal Leiomyosarcoma

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ABSTRACT

Objective: To investigate the clinical characteristics, prognosis, survival and diagnosis of high-grade primary renal leiomyosarcoma.
Materials and Methods: From January 2003 to April 2013, 10 cases of high-grade primary renal leiomyosarcoma were retrospectively reviewed. We analyzed clinical manifestations, treatment and prognosis of our group and correlated to the literature.
Results: Ten cases (five male and five female patients; age range 43–77 years, mean=57±std d:12.3) were enrolled. The mean diameter of the tumor masses was 9.35±4.5 cm (range 3-18 cm). 40% of the patients were asymptomatic while the major symptom of 60% patients was lumbar pain. Nephrectomy was performed in 90% of patients. Partial nephrectomy surgery was preferred for only one patient. Pleomorphism and necrosis with high-grade, pink spindle cell cytoplasm were viewed in all patients. All patients were high-grade, pink spindle cell cytoplasm and pleomorfism and necrosis were observed in all. In an immunohistochemical examination, vimentin was seen in 100%, desmin in 90% and smooth muscle actin in 80% of the patients. CD117 was negative in all patients. All of the cases were followed-up, and the time of survival varied from 6 to 68 months (mean 23.9±std d:20.1). No patient received adjuvant CTx and/or RTx.
Conclusion: High-grade primary renal leiomyosarcomas (LMSs) are rare and highly malignant and the prognosis is poor. Early diagnosis and radical nephrectomy can prolong the patient's life. Surgery is the main treatment modality for renal (leiomyosarcoma) LMS.

ARTICLE INFO

Key words:
Sarcoma; Kidney; Leiomyosarcoma; Nephrectomy; Diagnosis; Immunohistochemistry

Int Braz J Urol. 2015; 41: 304-11

Submitted for publication:
March 24, 2014

Accepted after revision:
June 23, 2014

INTRODUCTION

Sarcomas account for 0.8 to 2.7% of malignant kidney tumors. Similar to leiomyomas, leiomyosarcomas (LMSs) originate from the smooth muscles of the renal capsule, pelvis renalis, calyxes, and blood vessels. In general, LMSs are more common in females and occur in the fourth and sixth decades. LMSs are solitary lesions. The major symptoms include pain, palpable mass, and hematuria. The tumor occurs more frequently on the right side (1). LMSs are generally highly aggressive malignant tumors originating from the smooth muscles of the soft tissues, and they exhibit a high potential for metastasis. LMSs of the kidney can originate from the renal pelvis, calyxes, renal capsule, and blood vessels of the kidneys. However, the tumors most commonly arise from the smooth muscles of the kidney veins (1). LMSs account for 50-60% of kidney sarcomas. The differentiation from the other renal masses is extremely challenging before surgery (2). Among the other urogenital sarcomas, LMSs of the kidney are less frequently encountered compared to sarcomas of the prostate and bladder; however, these tumors are associated with poor prognosis

in terms of survival. LMSs of the kidney can reach large sizes, due to the lack of natural barriers for leiomyosarcomas arising from the mesenchymal components. Sarcomas typically possess a pseudocapsule. LMS of the kidney is a rare entity with poor prognosis. LMSs account for only 0.12% of all renal malignancies (3).

MATERIALS AND METHODS

Patients

A total of 10 patients, who underwent surgery due to renal mass between January 2003 and April 2013 and who were diagnosed with high grade primary LMS of the kidney, were included in the present study. During this period, radical nephrectomy was applied to 389 patients. 15(3.8%) of these patients were diagnosed with leimyosarcoma. 10 (2.5%) cases were high-graded. American Joint Committee of Cancer (AJCC) program was used to follow-up the cases. The symptoms at presentation, radiological findings, and immunohistochemical features obtained through pathological examination were evaluated. The therapies (radiotherapy and/or chemotherapy) and survival of the patients were recorded.

Diagnosis and staging of Primary renal leiomyosarcoma

The pathological diagnosis and grade of the tumor were evaluated according to the classification of the National Cancer Institute (NCI) and French Federation of Cancer Centers Sarcoma Group (FNCLCC). The histological grade was scored based in the level of differentiation, presence of mitosis, and necrosis in each high power field (4). All patients were found to a have high grade tumor according to this scoring system (Table-1). The immunohistochemical examination included staining for desmin, smooth muscle actin (SMA), vimentin, Bcl-2, CD-34, Ki-67, S-100, and CD117. Markers, which were used for immunohistochemical analysis, were used to distinguish especially from renal cell carcinoma indicating sarcomatoid differentiation, carcisarcoma and other subtypes of sarcoma. Vimentin is not specific for tumor type. Therefore it is not used in the differential diagnosis. However, it is in favor of tumor cells staining with negative desmin with cytokeratin and positive with smooth muscle actin(SMA). Cytokeratin positivity with absence of myoid markers supports a diagnosis of sarcomatoid renal cell carcinoma. Sarcomatoid carcinomas, however, are not uniformly positive for cytokeratins and may express SMA. Some leiomyosarcomas may also express cytokeratin and or epithelial membrane antigen (EMA). In the latter situation, the presence of desmin is diagnostically helpful since it is positive in leiomyosarcoma and not in sarcomatoid carcinoma (5). The staging of the tumor was based on the system developed by the American Joint Cancer Committee (AJCC-2013) on the staging of soft tissue sarcomas.

Table 1 - The distribution of the patients according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC).

Tumor differentiation		
Score 1	n=1	10%
Score 2	n=6	60%
Score 3	n=3	30%
Mitotic count		
Score 1 (0-9 mitoses per 10 HPF+)	n=0	0%
Score 2 (10-19 mitoses per 10 HPF)	n=4	40%
Score 3 (≥ 20 mitoses per 10 HPF)	n=6	60%
Tumor necrosis		
Score 0 (no necrosis)	n=2	20%
Score 1 (<50% tumor necrosis)	n=6	60%
Score 2 (≥50% tumor necrosis)	n=2	20%
Histologic grade		
Grade 1(total score 2,3)	n=3	30%
Grade 2 (total score 4,5)	n=3	30%
Grade 3 (total score 6,7,8)	n=4	40%

Statistical analysis

SPSS version 16.0 for Windows was used for statistical analysis.

RESULTS

The patients included in the study with the diagnosis of high grade primary LMS of the

kidney were followed for 6-68 months (mean; 23.9±std d:20.1, Median; 19.0).

Clinical features

The mean age was 57 years (range: 43-77 years mean=57±std d:12.3) and the male/female ratio was 1/1. The most common symptom was lumbar pain occurring in 60% (n=6) of patients. Of the patients, 40% (n=4) were asymptomatic, and only 10% (n=1) had hematuria, and 20% (n=2) had systemic and gastrointestinal symptoms (Table-2). According to the staging system of the AJCC-2013, 40% (n=4) of the patients had a stage III tumor, 30% (n=3) had a stage IIb tumor, 10% (n=1) had a stage IIa tumor, 10% (n=1) had a stage Ib tumor, and 10% (n=1) had a stage Ia tumor. The mean diameter of the tumor masses was 9.35±4.5 cm (range 3-18 cm) (Figures 1-3).

Immunohistopathological Findings

The immunohistochemical examination revealed positive staining for desmin (90%, n=9), SMA (80%, n=8), and vimentin (100%, n=10) (Figures 4-6). All patients exhibited negative staining for

Table 2 - Age, gender, clinical appearance, stage, and survival of the cases.

Age	Male / Female	Right / Left	Tumor diameter (cm)	Clinical features	Stage (AJCC-2013)	Treatment	Survival
56	male	L	7 (and 3,3,1)	lumbar pain	T2bN0M0 G2 Stage IIB	Radical nephrectomy	9 months
77	male	R	8	lumbar pain	T2bN0M0 G3 Stage III	Radical nephrectomy	15 months
43	female	L	3.5	asymptomatic	T1bN0M0 G1 Stage IA	Partial nephrectomy	44 months
65	female	L	3	asymptomatic	T1bN0M0 G2 Stage IIA	Radical nephrectomy	68 months
49	male	R	13(and 5)	lumbar pain,hematuria	T2bN1M0 G3 Stage III	Radical nephrectomy	7 months
45	male	R	18	Lumbar pain, nausea, weight loss	T2bN1M0 G3 Stage III	Radical nephrectomy	6 months
46	female	L	10	asymptomatic	T2bN0M0 G2 Stage Iıb	Radical nephrectomy	23 months
66	female	L	13	lumbar pain	T2bN1M0 G2 Stage III	Radical nephrectomy	8 months
73	male	R	6	asymptomatic	T2bN0M0 G1 Stage Ib	Radical nephrectomy	23 mnoths
50	female	L	8	lumabr pain, dyspepsia	T2bN0M0 G2 Stage IIb	Radical nephrectomy	36 months

Figure 1 - Magnetic Ressonance Imaging: Leiomyosarcoma in pelvis renalis of left kidney (arrow).

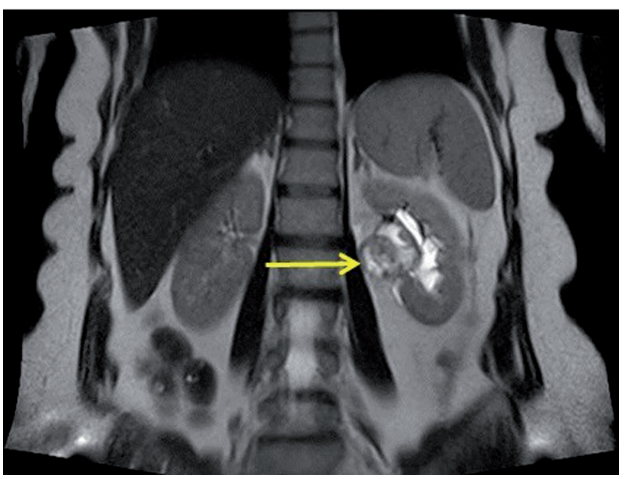


Figure 2 - Magnetic Ressonance Imaging: Leioyosarcoma in pelvis renalis of left kidney (arrow).

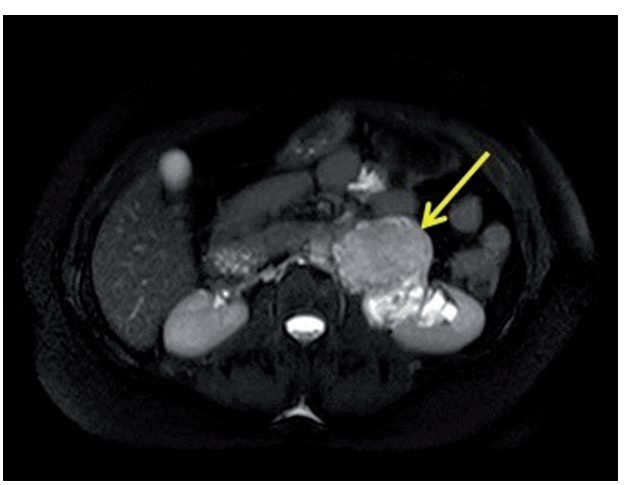


Figure 3 - Surgical specimen; Left renal leiomyosarcoma (arrow).

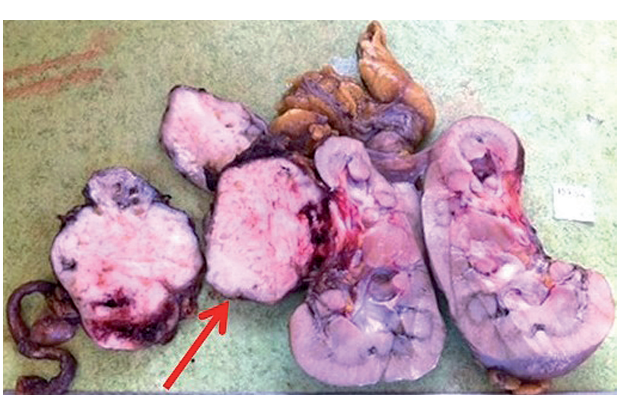


Figure 4 - Hematoxilyn-eosin staining demostrating high-grade sarcomatoid cells. H&E [100, 200x] Pleomorfism(small figure) and necrosis (arrow).

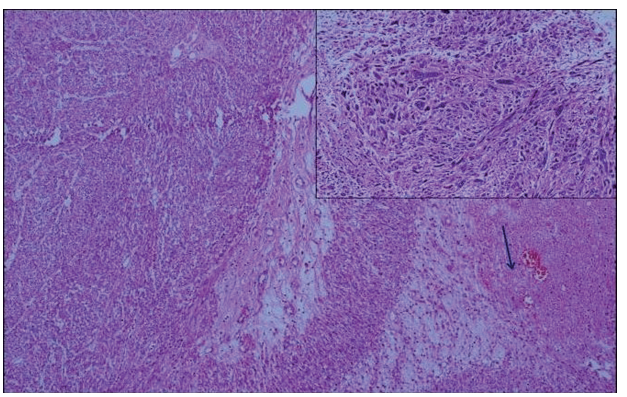


Figure 5 - Immunohistochemistry showing Desmin[200x].

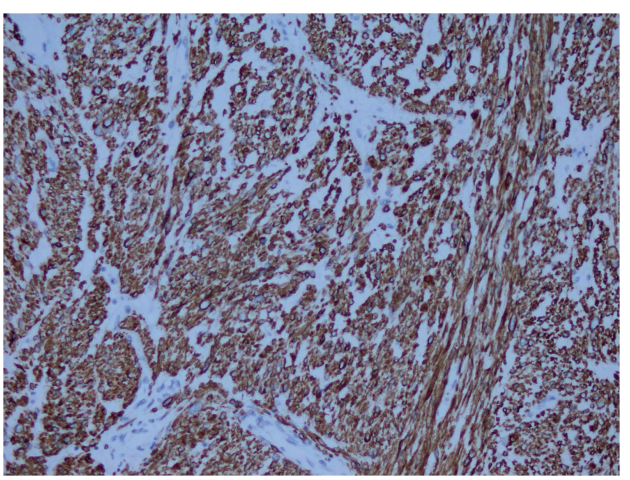
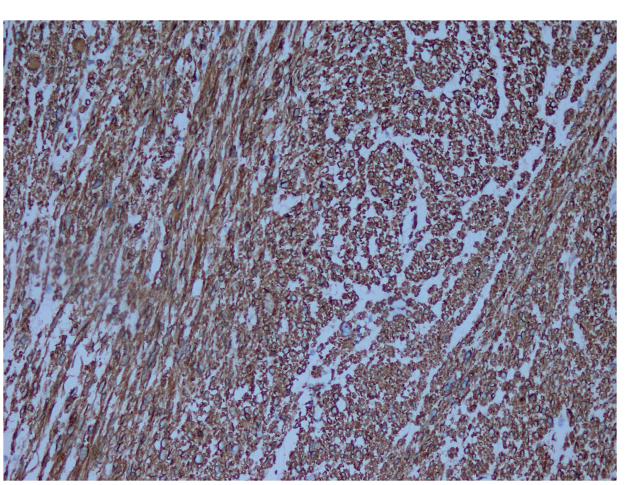


Figure 6 - Immunohistochemistry showing difuse actin expression in smooth muscle fiber cytoplasm. Actin[200x].



Bcl-2. The Ki-67 proliferation index was positive in 60% (n=6) of the patients. All patients showed negative staining for Bcl-2 and CD117 (Table-3).

Treatments and Survival

Ninety percent of the patients (n=9) underwent radical nephrectomy, and 10% (n=1) underwent partial nephrectomy. The mean disease-related survival was 23.9±20.1 months (range: 6-68 months), and none of the patients received adjuvant chemotherapy and/or radiotherapy.

DISCUSSION

The incidence of the primary leiomyosarcoma of the kidney increases with age, and this tumor is more common in females than in males and more common in the right kidney than in the left kidney (6). The tumor becomes symptomatic only with the expansion of the tumor size. The symptoms increase with the advancing disease stage. The compression on the neighboring tissues results in lumbar pain and hematuria and the finding of palpable mass on examination; systemic symptoms can also occur, such as nausea, vomiting, and abdominal pain (6).

It is extremely challenging to differentiate LMS of the kidney from renal cell cancer exhibiting sarcomatoid differentiation. These two tumors exhibit similar clinical, radiological, and pathological features. The most prominent features that differentiate sarcomas from renal cell cancer are that sarcomas originate from the capsule or perisinous region and sarcomas expand to large sizes without lymphadenopathy, and the lesion contains components such as liposarcoma and osteosarcoma. These tumors are avascular lesions, with the exception of hemangiosarcomas. The sarcomas should definitely be considered in the differential diagnosis in the presence of fast-growing renal masses. The sarcomas possess a pseudocapsule; however, these capsules do not represent a reliable barrier from the surgical point perspective. The capsule is often found to be infiltrated by the tumor. In general, high grade LMSs show high metastatic potential. Complete surgical resection is the most effective means of therapy (1). Therefore, early diagnosis and early surgical therapy prolong survival in patients with primary LMS. In the present study, the diagnosis and treatment of high grade LMSs and mean survival were discussed together with the literature data.

Life expectancy is lower with the sarcomas of the kidney compared to the other sarcomas of the urinary tract. The 5-year survival is 82% in patients with retroperitoneal sarcoma, 73% in patients with the sarcomas of the bladder, 44% in patients with prostate sarcoma, and 39% in patients with the sarcomas of the kidney (7). According to Geonseok et al. the 5-year survival was 51.4% in all of the urogenital sarcomas (7). There are two studies in the literature supporting these

Table 3 - The immunohistochemical features of the cases.

Immunohistochemicalantibody	Positive	Negative
Desmin	(n=9), 90%	(n=1), 10%
Smooth muscle actin (SMA)	(n=8), 80%	(n=2), 20%
Vimentin	(n=10), 100%	0%
Bcl-2	0%	(n=10), 100%
CD-34	(n=1), 10%	(n=9), 90%
*Ki-67	(n=6), 60%	(n=4), 40%
S-100	(n=2), 20%	(n=8), 80%
CD117	0%	(n=10), 100%

*Ki-67 proliferation index ranged between 3% and 70% in the positive cases.

findings. These studies reported a mean survival around 50% (8, 9). The surgical resection was the most significant prognostic factor in these patients. Lewis et al. reported that the presence of unresectable disease and incomplete surgical resection were the most significant factors predictive of disease-specific death (10). In a study by van Dalen et al., of 143 patients treated in the Netherlands, complete tumor resection was correlated with better overall survival in the multivariate analysis (11). The common notion in the literature is that surgical excision was nearly the only prognostic factor in LMSs. There was no correlation with the subtypes of the sarcomas and the survival, although statistical evaluation provided limited data due to small number of patients (7). Complete surgical resection with wide margins is the recommended means of therapy in patients with renal LMS. However, the literature also reported cases with renal LMS treated with partial nephrectomy (12). In our series, one patient was treated with partial nephrectomy and this patient survived for 44 months, which is higher than the mean survival time. The tumor size being lower than 5 cm is a good prognostic feature (3). In our series, 20% (n=2) of the patients had a tumor measuring less than 5 cm. These cases achieved the highest survival rate (44 and 68 months). These findings suggest that small tumor diameter was associated with a good prognosis. In LMS, metastasis to the lungs, liver, and colon point to poor prognosis (1). The 5-year survival in patients with sarcoma is around 50% according to the statistical records of the National Cancer Institute (NCI) and AJCC. Vallery et al. reported a survival between 17.9 and 25 months in patients with leiomyosarcoma of the kidney (3). The survival rate of 23.9% in our series was also consistent with the literature data. Although the 5-year mean survival is around 50% in LMS, this rate drops by half in patients with high grade primary LMS of the kidney. This finding suggests that the presence of a high grade tumor decreases life expectancy by half, even if the number of patients was limited in the current cross-sectional study.

In general, it is known that adjuvant/neoadjuvant chemotherapy/radiotherapy in LMS does not provide survival advantage (1). However, Raut et al. reported that adjuvant chemotherapy could be used on partially resected tumors (13). Nagumo et al. administered systemic chemotherapy with gemcitabine and docetaxel in a 64-year-old patient with renal LMS and lung metastasis and obtained an incomplete response in the lung metastasis. The patient developed new metastases in the lungs and pancreas at the end of 29 months. This study is one of the rare reports in the literature the demonstrated the survival benefit of chemotherapy, particularly therapy with gemcitabine and docetaxel (14). There are sporadic reports of cases with primary LMS of the kidney that achieved long-term survival up to 70 months after being submitted to radical nephrectomy and concurrent adjuvant chemotherapy and radiotherapy (15). However, surgery may have provided a complete cure in this patient. It is therefore likely that adjuvant chemotherapy and radiotherapy may have been an unnecessary procedure. There are reports in the literature demonstrating the survival benefits of neoadjuvant chemotherapy in LMSs. Kamba et al. showed that LMS could become resectable with the administration of neoadjuvant chemotherapy with CYVADIC (cyclophosphamide, vincristine, adriamycin, and dacarbazine) (16). There are reports on cases with LMS that achieved an incomplete response with the combination of anti-metabolite gemcitabine and mTOR blocker rapamycin (17). In addition, phase II studies reported the possibility of treating LMS with tyrosine kinase inhibitors such as sunitinib (18).

In their study, Deyrup et al. demonstrated the relationship between increasing histological grade of the renal LMS and survival. The histological grade was defined as a poor prognostic factor (19). Compared to the subtypes of other renal malignancies, primary LMS of the kidney is associated with considerably poor prognosis. The correct diagnosis and proper management of the disease requires detailed morphological analysis and careful interpretation of the immunohistochemical markers (20). In the literature, the Ki-67 proliferation index ranged from 6% to 50% in LMS (21). The Ki-67 proliferation index in our series of patients is parallel to that reported in the literature. The studies in the literature found that p16 and p53 tumor suppressor proteins are over-

-expressed in LMS, and therefore could be used as a prognostic marker (22, 23). Unlike many other soft tissue tumors, the genetic basis of LMSs has been poorly understood. LMSs are known to be genetically complex, often showing 'chaotic' karyotypes including aneuploidy or polyploidy, and no recurrent tumor-specific translocations have been detected (24). Some soft tissue sarcomas are also encountered in patients with EBV, AIDS, and post-transplant patients (24).

CONCLUSIONS

Primary LMS of the kidney is a smooth muscle tumor with complex genetic and molecular basis exhibiting aggressive biological behavior and poor prognosis. The life expectancy in high-grade primary LMS of the kidney is shorter compared to low-grade tumors. It must be kept in mind that mean survival is shorter in patients with high-grade primary LMS, and these patients will die within two years. The elucidation of the biological behavior, molecular and genetic basis of this tumor, and mutagenic factors triggering the disease will increase the understanding of this cancer. Currently, the genetic basis of this tumor is described as "chaotic". However, the primary goal should be the elucidation of the molecular and genetic basis of the cancer. The discovery of new agents other than gemcitabine and docetaxel is required in order to prolong mean survival in metastatic disease. The data presented in this study contribute to the understanding of high-grade primary renal leiomyosarcoma and may help in the development of an optimal therapeutic strategy to treat high-grade primary renal leiomyosarcoma .The only effective means of therapy is the complete resection of the tumor with wide surgical margins. Other than the surgical complete resection, tumor grade and diameter are the important prognostic factors in primary LMS of the kidney.

ABREVATIONS

LMS = Leiomyosarcoma
LMSs = Leiomyosarcomas
CTx = Chemotherapy
RTx = radiotherapy
CK = Cytokeratin
EMA = Epithelial membrane antigen
SMA = smooth muscle actin
Bcl-2 = B-cell lymphoma-2
HMB45 = Mouse anti Human melenoma antibody-45
EBV = Epstein–Barr virüs
FH = fumarate hydratase
RCC = Renal cell carcinoma
NCI = National Cancer Institute
FNCLCC = French Federation of Cancer Centers Sarcoma Group
AJCC = American Journal of Climate Change
CYVADIC = cyclosphosphamide, vincristine, adriamycin and dacarbazine

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 312-318, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.18

Adjustable perineal male sling using tissue expander as an effective treatment of post-prostatectomy urinary incontinence

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ABSTRACT

Purpose: To report our intermediate experience in treating patients with severe incontinence using an adjustable perineal male sling with a tissue expander.

Materials and Methods: An adjustable male sling procedure was performed on 21 patients with severe incontinence. The underlying etiology of urinary incontinence was radical prostatectomy in 13 patients, open prostatectomy in 5 patients and transurethral prostate resection in 3 patients. The difference between the classical and the adjustable sling is that in the latter there is a 25 mL tissue expander between the two layers of polypropylene mesh with an injection port. Adjustment of the sling was performed with saline via an inflation port, in case of recurrence or persistence of incontinence.

Results: The mean age of the patients was 66.2±7.3 (50-79) years and mean pad usage was 6.4±0.6 per day. The mean follow-up time was 40.1±23.2 (6-74) months. The balloon was postoperatively inflated on average with 11.6±5.7 (5-25) mL. After the mean 40.1 months of follow-up, 16 of the 21 patients (76.2%) were dry (11 patients, 0 pads; 5 patients using safety pads), 3 patients (14%) had mild and 2 (9.8%) had moderate degree post-prostatectomy urinary incontinence (PPI). The average maximum urine flow rate of the patients was 15.6±4.7 (10-31) mL/s. No residual urine was found. In 2 patients, all parts of the device were removed due to infection and discomfort, and in 3 patients only the inflation component was removed due to local scrotal infection.

Conclusions: Our results show that using an adjustable perineal male sling with a tissue expander seems to be an efficient, and safe surgical treatment option in patients with PPI.

ARTICLE INFO

Key words:
Suburethral Slings; Urinary Incontinence; Therapeutics

Int Braz J Urol. 2015; 41: 312-8

Submitted for publication:
March 03, 2014

Accepted after revision:
August 10, 2014

INTRODUCTION

Male urinary incontinence is very distressing problem after prostatic surgery. It has a significant impact on the patient's quality of life (1). Post-prostatectomy urinary incontinence (PPI) is a potential complication of prostate surgery and although it is more frequently seen after radical prostatectomy it can also occur after endoscopic or open surgery for benign prostate hyperplasia (BPH) (2). Initial management is usually conservative and includes the use of diapers or pads, penile clamps, or various collecting systems (such as a condom catheter). Mild degrees of PPI in the early postoperative period may be improved by pelvic muscle exercises, physiotherapy, and pharmacotherapy (3). However, for most patients who have moderate to severe PPI, conservative methods are

not sufficient to return to their normal lives. Surgery is usually necessary to treat the more severe cases.

Various male slings and devices are available for the treatment of PPI. Sub-urethral slings can be categorized into adjustable and non-adjustable systems. The present study reports our intermediate experience in men who underwent implantation of adjustable perineal male sling using a tissue expander for PPI.

MATERIALS AND METHODS

This prospective study was approved by the local ethics committee and a comprehensive informed consent was obtained from all the patients before the surgery. Between September 2007 and May 2013, a total of 21 men with PPI underwent implantation of adjustable perineal male sling using a tissue expander. The underlying etiologies of PPI in patients were: radical prostatectomy for prostate cancer in 13 patients (open radical retropubic prostatectomy=12, transperitoneal laparoscopic radical prostatectomy=1), open prostatectomy in 5 patients and transurethral prostate resection for BPH in 3 patients.

Patient evaluation consisted of medical history, physical examination, blood and urine laboratory tests. All the patients underwent a standard urodynamic study including both cystometry and pressure-flow study to evaluate bladder storage and voiding capabilities, and to exclude overactive bladder. Also, an urethrocystoscopy was conducted in all the patients to exclude urethral stricture and/or bladder neck contracture. The patients who had a history of previous surgery for PPI were not included in the study.

Incontinence in the patients was defined according to the use of incontinence pads over a 24 hours period: mild (using 1 to 2 pads), moderate (3 to 5 pads) and severe (more than 5 pads) (4). All the patients reported severe urinary incontinence in the pre-operative period. All operations were performed within 6 to 12 months after the prostatectomy. The post-operative follow-up was carried out in the second week and every 6 months thereafter consisting of daily pad use, physical examination, maximum urine flow rate (Qmax) and post-voiding residual urine volume (PVR) measurement.

SURGICAL PROCEDURE

The surgical procedure was performed using the technique described by Inci et al. (5) in 2008. All patients received prophylactic antibiotics (3rd generation cephalosporin) before the induction of anesthesia. Under general or regional anesthesia, patients were placed in the lithotomy position. After the insertion of a urethral catheter, a midline perineal incision of 40 to 50 mm was made. The critical point is not to remove periurethral fat tissues from urethra. Both sides of urethra were dissected down to the lower border of the pubic bone (Figure-1a). A Eurosilicone™ (Laboratoires Eurosilicone, France) tissue expander device was used with an adjustable male sling in our patients. The device contains a silicone balloon expander, a connecting tube and an inflation component (injection port) that allows the expander to gradually fill up to a volume of 25 mL saline solution (Figure-1b).

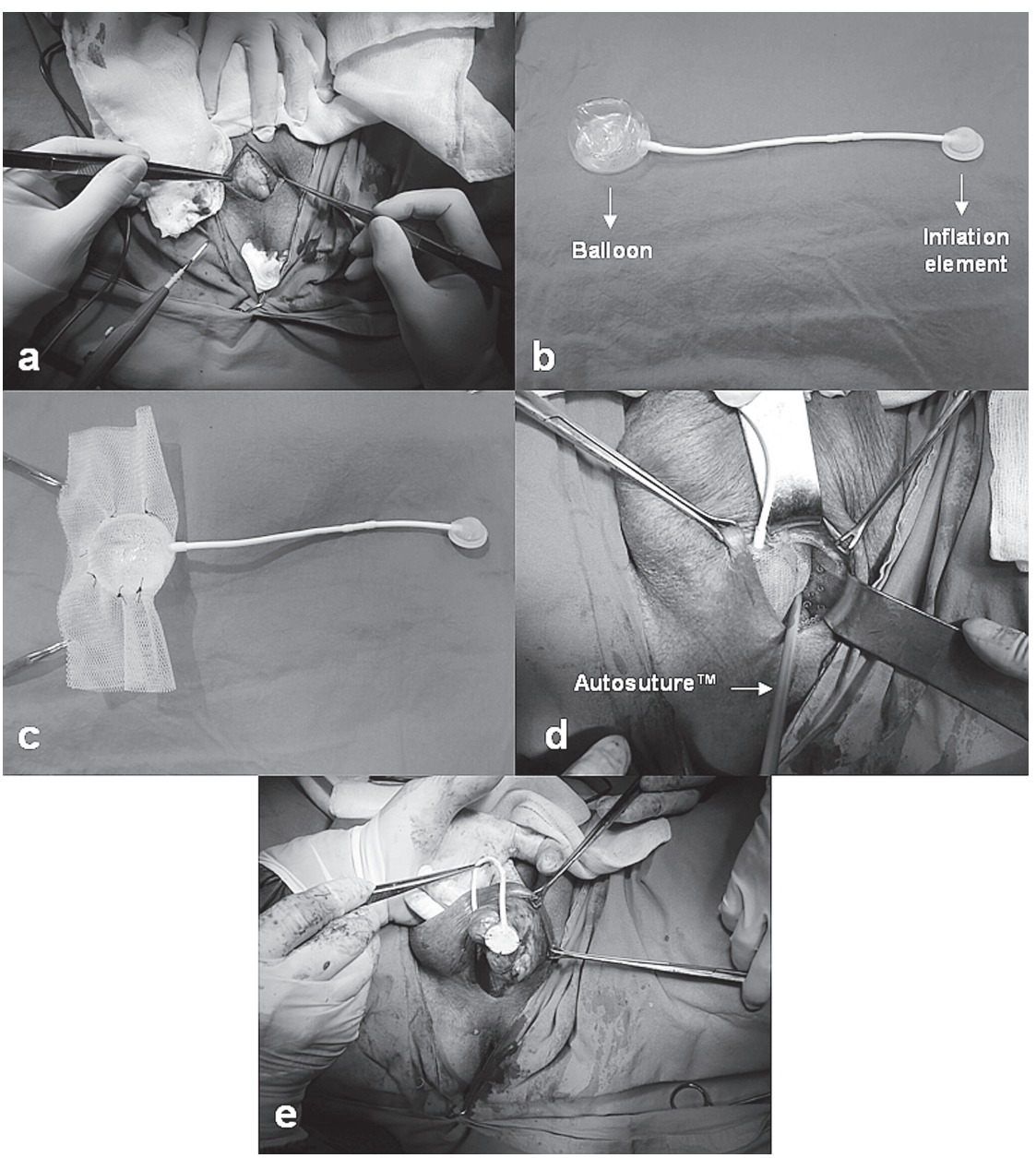
A standard polypropylene mesh of 100 x 100 mm was used as the sling material. First, the mesh was folded and a balloon expander was placed between the two layers of the modification. Secondly, the balloon was completely filled with the saline solution, and the two layers of the mesh were sutured using 2/0 polypropylene suture to create a pocket between the two layers of the mesh (Figure-1c). During this procedure, attention must be paid not to damage the filled balloon. After the pocket was created, the balloon was evacuated. Third, the mesh was stapled on both sides of the lower border of the pubic bone using an Autosuture Stat TackTM (Tyco Healthcare, UK) stapler (Figure-1d). The original surgical method defined by Inci, et al. (5) used a polypropylene mesh that was fixed on the pubic bone with non-absorbable sutures. In our case, this method was modified and staples were used to prevent the sutures and the mesh from loosening and moving.

After the sling tension was properly adjusted, the sling was placed as tightly as possible in all patients since urinary leakage had been observed in our patients postoperatively. Then, the expander was left deflated during surgery. Fourth, a scrotal pouch was created as a sleeve for the inflation component. The inflation component has two

sides (Figure-1e). Finally, the wound was closed with careful hemostasis. In all the procedures, no drain was used. After the surgery, all the patients were asked to take an oral antibiotic (2th generation cephalosporin) for 7 days.

Post-operative success was assessed by the number of pads used per 24 hours as follows; zero to 1 safety pad-dry, 1 to 2 pads-mild, and 3 to 5 pads-moderate. At a minimum of 1 week after surgery, patients were questioned regarding their daily pad use. If incontinence persisted 7 to 10 days after surgery, tension over the urethra was increased by saline injection to expand the tissue expander via the injection port using an insulin

Figure 1 - a) Both sides of urethra are dissected; b) A balloon expander; c) A balloon expander between two layers of the mesh; d) The mesh is stapled to the pubic bone using Autosuture Stat Tack™; e) Prepared scrotal pouch for placing the inflation component.



needle. Injection was started with 3 cc and increased by 2 cc at each injection. In this way the balloon was gradually filled with saline up to 25 mL. The patients were asked to return 2 days after each adjustment to confirm the status of continence. Additional injections were performed in cases of recurrent incontinence.

Statistical analysis

The mean values of the parameters were calculated using the Statistical Package for Social Sciences version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 66.2±7.3 (50-79) years and the mean pad usage was 6.4±0.6 (6-8) per day. Two patients had a history of pelvic radiotherapy. The mean operation time was 56.2±14.7 (45-85) minutes. No blood transfusion was necessary. The mean duration of hospitalization was 2.5 (2-4) days.

The mean follow-up time was 40.1±23.2 (6-74) months. The mean volume of the postoperatively inflated balloon was 11.6±5.7 (5-25) mL. After the follow-up period, 16 of the 21 patients (76.2%) were dry (11 patients, 0 pads; 5 patients using safety pads), 3 patients (14%) had mild degree PPI and 2 patients (9.8%) had moderate degree PPI. In the last assessment of the patients, Qmax and estimated PVR were found to be 15.6±4.7 (10-31) mL/s and 10 mL, respectively.

One patient had scrotal infection and pain, and another patient had perineal discomfort. In these two patients, the polypropylene mesh with balloon, connecting tube and inflation component were removed and they did not undergo any additional intervention. Local scrotal infection developed around the inflation component in three patients. In these patients, only the inflation component was removed, the connecting tube was clipped and the polypropylene mesh with inflated balloon was kept in place. In these patients, polypropylene mesh with inflated balloon provided suitable pressure on the urethra. In the follow-up period, they were completely dry. No complications were encountered in patients with a previous history of pelvic radiotherapy.

No complications occurred in relation to mesh erosion, voiding dysfunction, voiding difficulty or mechanical failure. Six patients reported mild perineal pain in the early postoperative period but this was resolved using non-steroidal anti-inflammatory drugs.

DISCUSSION

PPI represents a significant health problem. The rising elderly population and the increasing number of surgical interventions for prostate cancer mean that the incidence of PPI will rise. Since its introduction in 1973, the artificial urinary sphincter (AUS) has been considered the gold standard treatment for stress urinary incontinence after prostatectomy, offering the patient the greatest chance of a cure (6). The success rates of AUS range from 59 to 90% (7-9). Although, AUS is an effective and durable treatment, many patients are hesitant about implantation or refuse the procedure. Most patients could not manipulate the scrotal pump (10). Furthermore, AUS is expensive and requires a complex surgical procedure that is associated with significant rates of complications. A recent systematic review about AUS reported that infection or erosion occurred in 8.5% of cases (3.3–27.8%), mechanical failure in 6.2% (2–13.8%), and urethral atrophy in 7.9% (1.9–28.6%). Re-operation rate was reported to range from 14.8% to 44.8% (11).

Thus, many minimally invasive alternatives have been investigated as possible alternatives to AUS. The ProACT™ (Uromedica, US) system was first described in 2005 by Hubner et al. (12). In theietlr study, there were 117 patients with PPI followed for a mean period of 13 months, after which 67% of the patients were found to be dry. Lebret et al. (13) reported the results of the ProACT™ intervention in 62 men with PPI and found that 71% of the patients wore no pads or used 1 pad per day after 6 months (following the adjustment). However, in 19 men the device was removed due to infection and erosion (n=5), migration (n=1), and iatrogenic traumatism (n=2). Moreover, 9 patients experienced device failure. In another

prospective study (14), the authors evaluated the results of ProAct™ in 114 men with PPI at a mean follow-up time of 58 months and reported an overall dry rate of 50%. In that study, complications included balloon leakage (11%), migration (5%) and wound erosion (4%). The authors reported that there was a total re-operation rate of 27%, and 12% of the patients underwent AUS or a urethral sling procedures due to ProACT™ not being effective.

The Argus™ (Promedon SA, Argentina) sub-urethral sling with an adjustable system is another treatment option in men with PPI that was first described by Romano et al. (15). The authors reported a cure rate of 73% and the improvement rate was 10% in 48 men with PPI after a mean follow-up of 7.5 months. Dalpiaz et al. (16) reported mid-term complications after the placement of the Argus™ sling in 29 men with PPI at a mean follow-up of 35 months. Overall, 24 patients (83%) experienced complications, consisting of acute urinary retention (35%) and removal of the sling (35%) owing to urethral erosion, infection, system dislocation, urinary retention, and persistent pain. Furthermore, 27% of the patients complained of significant perineal pain. The authors concluded that the ArgusTM sub-urethral sling was associated with serious mechanical and infectious complications, and sparse functional results with negative impact on the patient's quality of life.

Another device used for treating PPI is the bulbo-urethral sling. Several variations of male sling are currently available. A bone anchored sling (BAS) compresses the bulbar urethra with a silicone-coated polypropylene mesh by attaching the sling to the inferior pubic ramus with bone screws. Following initial reports of degradation of organic materials, synthetic mesh (InVance™, American Medical Systems, US) has become the most commonly utilized material with the BAS (17). Rajpurkar et al. (4) reported their results in 46 patients with PPI who undergo BAS implantation. In their study, the total cure rate was 37%. Furthermore, 37% of the patients significantly improved, and the treatment of 26% patients failed after an average of 24 months follow-up. They concluded that the male sling procedure is an effective and safe procedure for the management of stress urinary incontinence. However, it should not be considered as an alternative to AUS. Guimaraes et al. (18) reported their intermediate results of up to 4 years with the InVance™ sling. Their cure rate was 65% and the improvement rate was 23% in 54 men with PPI after a mean follow-up of 28 months. The authors claimed that the InVance™ sling offers a good intermediate cure and improvement rates with acceptably low rate of complications in patients suffering from PPI. Another study investigated the use of the InVance™ sling in 40 patients with PPI (19). The cure rate was 55% at a mean follow-up of 35.2 months. The authors observed perineal pain in 73% of the patients, detrusor overactivity in 5% and sling infection in 15%.

The traditional BAS procedure does not provide for the adjustment of the tension of the sling material in the post-operative period and this can result in progressive failure over time. In a study by Castle et al. (1), 42 patients underwent the BAS procedure. Only 15.8% of the patients were completely dry and 39.5% were socially continent. Social continence was achieved in 67% 50% and 0% of mild, moderate and severe cases, respectively. Comiter (20) speculated that the surgeons left the fatty tissue over the bulbospongious intact, and additionally used a piece of porcine dermis between the urethra and the sling A combination of fat necrosis and absorption of the dermis over time likely contributes to diminution of the compression provided by the sling over the bulbar urethra. Onur et al. (21) reported a median time to recurrent incontinence as 3 months after BAS procedure. Similarly, Cespedes and Jacoby reported an early failure (within 6 months) in 5% of their patients (22). In another study (23), the authors retrospectively reported objective and subjective outcomes in 40 male patients who underwent BAS positioning for stress urinary incontinence due to intrinsic sphincter deficiency. Patients with stress urinary incontinence due to radical retropubic prostatectomy (n=32), robot assisted laparoscopic prostatectomy (n=3) and transurethral prostate resection (n=5) underwent the BAS procedure over a 5 years period. Previous anti-incontinence procedures, radiotherapy and transurethral procedures due to urethral stricture were performed in 5, 11

and 5 patients, respectively. At a mean follow-up of 35.2 months, 22 patients (55%) were cured, the condition of 5 patients (12.5%) improved and the treatment of 13 patients (32.5%) failed. The authors concluded that BAS is a simple and effective procedure that can produce immediate good results with low morbidity, especially when strictly selected patients are treated. Radiotherapy remains a strong predictor of failure.

In the current study, an adjustable perineal male sling technique was used for the treatment of PPI as described previously (5). In that study an adjustable perineal male sling with a 10 mL tissue expander was implanted in 19 consecutive men with severe PPI. According to the results of that study, at a mean follow-up of 17.3 months 15 patients (78.9%) were completely dry and 2 (10.5%) improved significantly using only 1 to 2 pads per day. A total of 11 patients required volume adjustment injections. The average number of adjustments was 2 (range 1 to 3) and the average injected volume was 6.3 cc (range 5 to 10). Regarding the complications, 1 patient had a superficial wound infection, 1 patient required surgical revision due to infection and 8 patients reported mild to moderate perineal pain. The authors concluded that the short term results indicate that this minimally invasive technique seems to be safe and effective, and patient satisfaction appears to be high. The same group presented their long term results in the International Continence Society Annual Meeting 2013. In a study by Ergen and Ozdemir (24), 58 men underwent the same procedure as described above. The mean follow-up time was 52 months. The completely dry rate decreased from 78.9% to 58% in the long term period. The authors concluded that adjustable male sling using a 10 mL tissue expander is an effective method for severe PPI, in the early period, but the effectiveness gradually decreases in the long term.

The review of our intermediate results at 40.1 months showed that 16 of the 21 patients (76.2%) were completely dry, 3 patients (14%) had mild incontinence and 2 patients (9.8%) had moderate incontinence. The success rate of the current study is better than that of the other studies mentioned above (5, 24). A possible explanation for our high success rate may be associated with the high capacity of the silicone balloon. In our patients, we used a larger size of silicone balloon (25 mL) than the other two studies. Additionally, we used a stapler which allows the easier attachment of the polypropylene mesh on the lower border of the pubic bone in both sides. Although previous pelvic radiotherapy history has also been claimed to be a negative predictor of success rate in PPI surgery (19, 23), 2 patients in current study whom had a previous history of pelvic radiotherapy were dry in the intermediate follow-up.

A new device is a perineal sling with a tissue expander, composed of 2 silicone components, a balloon expander and an injection port, connected by a tube. In Turkey, this device is relatively cheap compared with AUS, ProACT™, ArgusTM ($500 vs. $5.000 vs. $2330 vs. $2400) and easy to implant, even in difficult cases.

CONCLUSIONS

Although complications occurred in this study, including the removal of the device and the removal of inflation component due to local scrotal infection, our intermediate follow-up study suggests that an adjustable perineal male sling using a tissue expander appears to be an efficient and safe alternative surgical treatment option for patients suffering from PPI. The major limitations of our study were the small number of patients and the duration of the follow-up period. Additional follow-up and larger series of patients are necessary to confirm our results.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 319-324, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.19

Factors associated with intraoperative conversion during robotic sacrocolpopexy

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ABSTRACT

Objective: To evaluate for potential predictors of intraoperative conversion from robotic sacrocolpopexy (RSC) to open abdominal sacrocolpopexy.
Patients and Methods: We identified 83 consecutive patients from 2002-2012 with symptomatic high-grade post-hysterectomy vaginal vault prolapse that underwent RSC. Multiple clinical variables including patient age, comorbidities (body-mass index [BMI], hypertension, diabetes mellitus, tobacco use), prior intra-abdominal surgery and year of surgery were evaluated for potential association with conversion.
Results: Overall, 14/83 cases (17%) required conversion to an open sacrocolpopexy. Patients requiring conversion were found to have a significantly higher BMI compared to those who did not (median 30.2kg/m^2 versus 25.8kg/m^2; p=0.003). Other medical and surgical factors evaluated were similar between the cohorts. When stratified by increasing BMI, conversion remained associated with an increased BMI. That is, conversion occurred in 3.8% (1/26) of patients with BMI ≤25 kg/m^2, 14.7% (5/34) with BMI 25-29.9 kg/m^2 and 34.7% (8/23) with BMI ≥30 kg/m^2 (p=0.004). When evaluated as a continuous variable, BMI was also associated with a significantly increased risk of conversion to an open procedure (OR 1.18, p=0.004).
Conclusions: Higher BMI was the only clinical factor associated with a significantly increased risk of intra-operative conversion during robotic sacrocolpopexy. Recognition of this may aid in pre-operative counseling and surgical patient selection.

ARTICLE INFO

Key words:
Robotics; Pelvic Organ Prolapse; Obesity

Int Braz J Urol. 2015; 41: 319-24

Submitted for publication:
February 21, 2014

Accepted after revision:
July 28, 2014

INTRODUCTION

Abdominal sacrocolpopexy is considered the "gold standard" in the repair of symptomatic high grade vaginal vault prolapse, secondary to high success rates and durable long-term results (1, 2). Recently, multiple series have shown similar excellent long-term outcomes in patients managed with a robotic approach to sacrocolpopexy (3-5). However, while replicating the anatomic principles of the open sacrocolpopexy and potentially decreasing length of hospitalization and blood loss, one issue unique to a minimally invasive approach (whether laparoscopic or robotic) to sacrocolpopexy is that of the potential for requiring conversion to an abdominal sacrocolpopexy (4, 6).

Prior series on RSC have demonstrated a conversion rate ranging from 0 to 11% (3, 6-8). Furthermore, in other surgeries performed with robotic assistance, multiple potential risk factors for conversion such as surgeon experience (9), technical difficulty/failure to progress/injury to adjacent organs (9, 10), patient risk factors (prior abdominal surgery, obesity, etc.)

(9-11) and equipment malfunction (12) have been proposed. However, there is a paucity of data regarding potential predictors of conversion specifically for RSC. Notably, compared to other robotic pelvic surgeries, RSC presents unique technical challenges such as dissecting in the retroperitoneal fat and potential for hemorrhage from presacral veins. Thus, recognizing specific factors associated with conversion during RSC may aid in patient selection as well as pre-operative patient counseling.

Therefore, in a large cohort of RSC patients we sought to evaluate for clinical predictors of intraoperative conversion from RSC to an open procedure.

PATIENTS AND METHODS

Following Institutional Review Board approval, 83 consecutive patients undergoing RSC at our institution between 2002 and 2012 were identified. RSC was performed for patients with high-grade (Baden Walker-Grade 3 to 4 or Pelvic Organ Prolapse Quantification-Stage 3 to 4) symptomatic post-hysterectomy vaginal vault prolapse.

All patients were treated by a single surgeon via our previously reported technique for RSC (3, 13). Briefly, we utilize the da Vinci-S® system (Intuitive Surgical, Sunnyvale CA, USA) and set up our operative approach with a periumbilical trocar, two standard laparoscopic ports for retraction, and two robotic ports. The sacral promontory is exposed with the use of retraction suture placed through the sigmoid mesentery. The bladder is then dissected from the anterior vaginal wall. The posterior peritoneal reflection is incised and a polypropylene Y-graft is sutured to the sacrum and vagina. Following fixation to the sacral promontory we place the posterior vaginal sutures and then the anterior sutures. The posterior peritoneum is then closed to retroperitonealize the graft.

Clinical variables recorded for evaluation included age, body mass index (BMI), pertinent medical comorbidities (hypertension, diabetes and tobacco use), operative time, estimated blood loss, concurrent procedures performed and post-operative complications.

BMI (weight in kilograms divided by height in meters squared) was examined using the National Institutes of Health definitions of normal weight (BMI <25 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Because of limited patient numbers, patients with mild obesity (BMI ≥30 and <35 kg/m^2, n=15) were combined here for analysis with patients that were moderately (BMI ≥35 and <40 kg/m^2, n=6) and severely (BMI ≥40 kg/m^2, n=2) obese.

The Wilcoxon rank sum test was used to examine the association between BMI, post-operative recovery and conversion to open surgery. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). All statistical tests were two-sided, with a p-value <0.05 considered statistically significant.

RESULTS

We identified 83 females with a median age of 67 years (IQR 59, 74) that were treated by RSC for high grade, symptomatic vaginal vault prolapse from 2002 to 2012. Of these, 14 patients (17%) required conversion to an open sacrocolpopexy. Reasons for conversion included inability to dissect the anterior vaginal wall from bladder secondary to scarring in 5 cases (35.7%), dense abdominal adhesions preventing laparoscopic access in 5 cases (35.7%), and failure to progress during presacral dissection in the remaining 4 cases (28.5%). Overall, the median OR time was 165 minutes, with a median length of hospital stay of 1.6 days (IQR 1,2). Not surprisingly, cases requiring conversion were significantly longer in duration than those that did not convert (median 195 versus 160 minutes; p=0.002) and had a longer post-operative length of hospitalization (median 1 versus 3 days; p<0.0001).

Clinicopathologic demographics for patients undergoing RSC, stratified by whether conversion was required, are shown in Table-1. As can be seen, the cohorts were similar with regard to age at the time of surgery, year of surgery, as well as pertinent medical and surgical comorbidities; aside from BMI. That is, those requiring conversion had a significantly higher BMI compared to those where RSC was completed (median 30.2 kg/m^2 versus 25.8 kg/m^2; p=0.003). Of note, the median BMI for all patients treated was 26.4 kg/m^2

Table 1 - Clinical and demographic information for patient undergoing robotic sacrocolpopexy stratified by requirement for intraoperative conversion.

	No Conversion (N=69)	Conversion (N=14)	p value
Age at surgery, years, median (IQR)	67 (57, 74)	66.5 (63, 72)	0.91
Year of surgery			0.38
2002-2005	31 (44.5%)	1 (3.1%)	
2006-2009	23 (33%)	9 (64.3%)	
2010-2012	15 (21.7%)	4 (28.6%)	
Diabetes mellitus	3 (4.3%)	0 (0.0%)	0.64
Hypertension	29 (42.0%)	6 (42.9%)	0.95
Route of hysterectomy (n=72)			0.38
Vaginal	27 (45.8%)	4 (30.8%)	
Abdominal	32 (54.2%)	9 (69.2%)	
Prior abdominal surgery			0.35
Infraumbilical	31 (75.6%)	9 (75%)	
Supraumbilical	2 (4.9%)	0 (0%)	
Both	8 (19.5%)	3 (25%)	
Prior transvaginal prolapse repair	28 (40.6%)	7 (50%)	0.52
Tobacco use	2 (2.9%)	1 (7.1%)	1.00
Body mass index, kg/m^2, median (IQR)	25.8 (24.1, 29.7)	30.2 (27.9, 35.7)	0.003
Concurrent procedure performed	54 (78.3%)	12 (85.7%)	0.71
Operative time, min, median (IQR)	160 (135, 180)	195 (173, 242)	0.002
Postoperative hospitalization, days, median (IQR)	1 (1, 1)	3 (2, 4)	<0.0001

(IQR 24.3,30.4) and 28% (23/83) had a BMI ≥30 kg/m^2. Notably, in regard to the year of surgery, on further evaluation, there was a linear trend for years of surgery among conversions; however, on univariate logistic model it was not significant (p=0.06). Additionally, patients in the first 3 years of the series (2002-2005) had a significantly lower BMI, compared to the remainder of the patients (25.5 kg/m^2 versus 28.2 kg/m^2, p=0.03).

We next evaluated the impact of BMI on the surgical procedure by stratifying patients by BMI class (≤25 kg/m^2, 25-29.9 kg/m^2, or ≥30 kg/m^2) (Table-2). Here we found that among subcategories, an increasing BMI was associated with a significantly increased risk of conversion. That is, conversion occurred in 3.8% (1/26) of patients with a BMI ≤25 kg/m^2, 14.7% (5/34) with a BMI 25-29.9 kg/m^2 and 34.7% (8/23) with a BMI ≥30 kg/m^2 (p=0.004). Notably, both patients with a BMI >40 kg/m^2 required intraoperative conversion. Furthermore, when evaluated as a continuous variable, BMI remained a significant predictor of conversion to an open procedure (OR 1.18, p=0.004). Interestingly, no significant difference in operative time (p=0.06) or intra-operative blood loss (p=0.52) was identified with increasing BMI.

Table 2 - Outcomes of patients undergoing robotic sacrocolpopexy stratified by body-mass index.

	Normal Weight (BMI<25) (N=26)	Overweight (BMI 25-30) (N=34)	Obese (BMI >30) (N=23)	p value
Age at surgery (years), Median (IQR)	70.5 (59, 74)	69 (58, 73)	65 (59, 74)	0.70
Operative time (min), Median (IQR)	155 (130, 173)	167.5 (150, 195)	180(135, 235)	0.06
Hospital Stay (days), Median (IQR)	1 (1, 1)	1 (1, 2)	1 (1, 2)	0.18
Estimated blood loss (cc), Median (IQR)	50 (25, 100)	50 (25, 100)	50 (25, 100)	0.52
Intraoperative conversion	1 (3.8%)	5 (14.7%)	8 (34.8%)	0.004

DISCUSSION

We found, in a large cohort of patients treated by RSC for symptomatic high-grade vaginal vault prolapse, that only obesity (BMI >25 kg/m^2) was associated with a significantly increased risk of intra-operative conversion from RSC to an abdominal sacrocolpopexy. Furthermore, the risk associated with conversion rose with increasing BMI values. To our knowledge this represents the first report evaluating such risk factors for conversion during RSC.

With regard to conversion from a minimally invasive approach to sacrocolpopexy, previous series on laparoscopic and robotic sacrocolpopexy have demonstrated conversion rates between 0-11% (3, 6-8). Our overall conversion rate (16.9%) is somewhat higher, which may be secondary to early adoption of the technique (3) and broad patient inclusion (median BMI 26.4 kg/m^2, range 18.2-47.3 kg/m^2). This occurred as we have attempted to further application of RSC, while acknowledging that conversion may be necessary when discussing management options with patients pre-operatively.

In other laparoscopic and robotic surgeries, multiple risk factors for conversion have been proposed. For instance, when evaluating patients undergoing laparoscopic colectomy, Chew et al. noted an increased conversion rate with increased patient age at the time of surgery, obesity and more advanced pathologic stage (11). Other potential factors such as surgeon experience (9), technical difficulty/failure to progress (9, 10), injury to adjacent organs (9, 10), prior abdominal surgery (9, 14) and device malfunction (12) have been reported. Our analysis extends these previous series with specific application to RSC. In our series BMI was the only identified predictor of conversion and roughly one-third of the conversions were due to difficulty with the presacral dissection specifically. Notably, this dissection is unique to sacrocolpopexy and can be significantly more technically difficult when a large volume of presacral retroperitoneal adiposity is encountered. This may explain why conversely, some studies on other robotic female pelvic surgeries (for instance, hysterectomy) have reported no association between BMI and conversion (15-17). Furthermore, in our series, year of surgery (a marker for surgeon experience over time), route of hysterectomy, prior prolapse repair and prior abdominal surgery were not associated with conversion. Notably, there was a trend toward increased conversion among patients with prior abdominal versus transvaginal hysterectomy, and the absence of statistical significance may be secondary to the limited number of conversions. Additionally, no device malfunctions requiring conversion were encountered. Recognizing specific challenges of the RSC and identification of potential risk factors for conversion is needed to assist with accurate pre-operative counseling and appropriate patient selection.

One potential area of future study is in pre-operative weight loss and pelvic organ prolapse surgery. It has previously been shown that obesity is associated with an increased risk of pelvic organ prolapse progression over time (18, 19). Interestingly, several reports demonstrate no difference in surgical success rate in obese versus normal weight patients (18, 20). That being said, Bradley et al. reported a higher serious adverse events rate among obese patients (22.4% versus 36.5%; p=0.02) (18). Notably, in the bariatric literature, enhanced post-recovery has been noted in patients with a 5-10% weight reduction preoperatively (21). Thus, in addition to overall health benefits from weigh reduction, highlighting the importance pre-operative weight loss to patients may be beneficial regarding successful completion of RSC and helping to avoid peri-operative complications.

Limitations of our study should be noted including its retrospective, non-randomized design. As such, it is subject to bias from patient selection and alterations in technique over time. Additionally, as expertise with the procedure developed over the timeframe of the study, the complexity of cases including patient BMI increased. This likely contributed to the higher conversion rate reported in the later years of the study. Furthermore, given the retrospective nature of this study, there is potential for additional confounding variables/missing data (such as indication for hysterectomy and in some cases route of hysterectomy) which could not be accounted for. Likewise, many of the conversions were not directly related to issues other than obesity (for instance intra-abdominal adhesions), suggesting that while no other factor was associated with conversion on univariate analysis, the risk of conversion may be multifactorial. However, given the sample size in our series, some differences in the cohorts may not be detected. Additionally, our results represent those of a tertiary care center with a relatively high-volume RSC practice, and thus may not be able to be extrapolated to all surgical practices. Thus, external validation from other centers is needed.

CONCLUSIONS

A higher BMI was the only clinical factor associated with a significantly increased risk for intra-operative conversion during robotic sacrocolpopexy. While external validations of these results are needed, recognition of this may aid in pre-operative counseling and in surgical patient selection.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Rachel Carlson, Mayo Clinic Department of Biostatistics, for her assistance with the statistical analysis.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 325-328, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.20

The value of magnetic resonance imaging in the diagnosis of penile fracture

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ABSTRACT

Purpose: We studied the use of magnetic resonance imaging in the diagnosis of penile fracture.

Materials and Methods: Between 1997 and 2012, fifteen patients (age range 17-48 years, mean age 37 years) with suspected penile fracture underwent MRI examinations. Ten patients were injured during sexual intercourse, whereas four patients were traumatized by non-physiological bending of the penis during self manupilation, one patient was traumatized falling from the bed. Investigations were performed with 1.5T MR unit. With the patient in the supine position, the penis was taped against the abdominal wall and surface coil was placed on the penis. All patients were studied with axial, coronal, sagittal precontrast and postcontrast T1-weighted TSE(TR/TE:538/13 msn) and T2-weighted TSE(5290/110 msn) sequences. All patient underwent surgical exploration. The follow-up ranged from 3 months to 72 months. Clinically all patients showed normal healing process without complications. In 11 patients a shortening and thickening of tunica albuginea was observed. Three patients have post traumatic erectil disfunction.

Results: In all patient corpus cavernosum fractures were clearly depicted on a discontinuity of the low signal intensity of tunica albuginea. These findings were most evident on T1WI and also depicted on T2W sequences. Images obtained shortly after contrast medium administration showed considerable enhancement only in rupture site. Subcutaneous extratunical haematoma in all patients were also recognizable on T2 WI. MRI findings were confirmed at surgery.

Conclusions: Magnetic resonance imaging is of great value for the diagnosis of penile fracture. Furthermore this method is well suited for visualising the post-operative healing process

ARTICLE INFO

Key words:
Penis; diagnosis [Subheading]; Magnetic Resonance Spectroscopy; Penile Induration

Int Braz J Urol. 2015; 41: 325-8

Submitted for publication:
March 28, 2014

Accepted after revision:
July 28, 2014

INTRODUCTION

Penile fracture is a rare urological emergency situation, and is defined as disruption of the tunica albuginea (TA) and corpus cavernosum (CC). It occurs almost exclusively as a result of blunt trauma to the penis in the erect position, usually during coitus. Other mechanisms of injury are direct external blunt trauma, abnormal bending of the penis during manipulation, forceful manipulation and rolling over in bed during erection (1-4). Disruption of the tunica albuginea or associated urethra injury are indications for surgical repair, whereas other cases of blunt penile injury may be treated conservatively. In general, the patient's history and physical examination are su-

fficient to reach a provisional diagnosis of a penile fracture. The role of magnetic resonance imaging (MRI) in imaging penile fractures is to ascertain the integrity of the tunica albuginea. In this study we describe MRI findings at 15 patients with acute penile fracture and its healing process.

MATERIALS AND METHODS

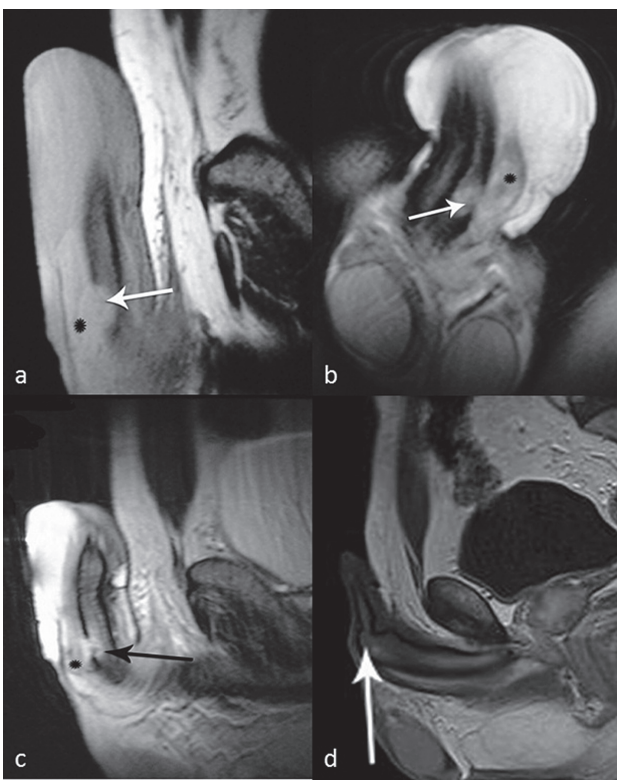
From 1997 to 2012, fifteen patients (age range 17-48 years, mean age 37 years) with suspected penile fracture underwent MRI examinations. Ten patients were injured during sexual intercourse, whereas four patients were traumatized by non-physiological bending of the penis during self manipulation, one patient was traumatized falling from the bed. Investigations were performed with 1.5T MR unit (Magnetom Symphony, Siemens, Erlangen Germany). With the patient in the supine position, the penis was taped against the abdominal wall and surface coil was placed on the penis. All patients were studied with axial, coronal, sagittal T2-weighted TSE (5290/110 msn) and precontrast and postcontrast T1-weighted TSE (TR/TE:538/13msn) sequences.

All patients underwent surgical operation and repair via a longitudinal incision. The follow--up ranged from 3 months to 72 months.

RESULTS

In all patients CC fractures were clearly depicted on a discontinuity of the low signal intensity of TA. These findings were most evident on T1--weighted images (Figures 1a, 2a, 3a and b and 4a) These findings were also depicted on T2-weighted images (Figures 1b and c, 2b, 3c and d and 4b). Images obtained shortly after contrast medium administration showed considerable enhance only in rupture site. Subcutaneous extratunical haematoma in all patients were also recognizable on T2-weighted images. They were much more significant at post--contrast T1-weighted images. On follow-up in 10 patients a shortening and thickening of TA were observed (Figures 1d and 2d). There were erectile difficulties in 2 patients and they did not complain of any voiding difficulties. In all patients MR imaging findings were confirmed at surgery.

Figure 1 - A 37-year-old patient with penile fracture of the left corpus cavernosum. (a) Sagittal T1-weighted image shows a rupture of the tunica albuginea (arrow) and a haematoma extending into the corpus cavernosum (asteriks). Coronal (b) and sagittal (c) T2-weighted images show also disruption of tunica albuginea (arrow) with surrounding haematoma in the distal penile shaft (asteriks). (d) One year later after surgical intervention the tunica albuginea at the rupture site regains its low signal intensity (arrow).

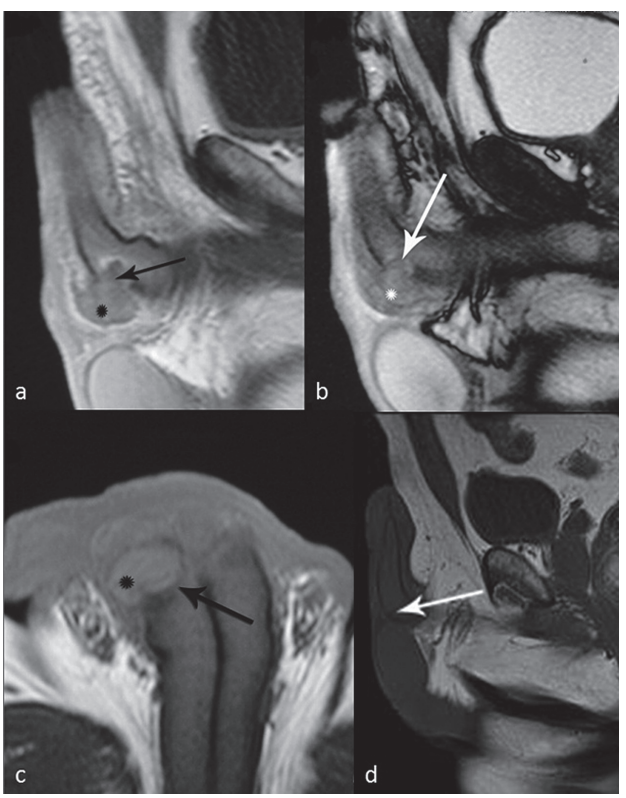


DISCUSSION

Penile fracture has a typical clinical presentation. Patients report hearing a snapping sound during the sexual act, followed by immediate pain and penile detumescence, in addition to the emergence of large edema, hematoma, and penile deformity (5). In general the diagnosis of penile fracture is easily established clinically.

The diagnosis is usually not difficult and often is based on history and physical examination. Patients with atypical clinical findings may require a common diagnostic procedure. Sonography could be also a useful imaging modality for the diagnosis of penile fracture because it is easy to perform, noninvasive, widely available and

Figure 2 - A 30-year-old patient with penile fracture of the right corpus cavernosum. Sagittal T1-weighted (a) sagittal T2-weighted (b) and coronal T1-weighted (c) images show a disruption of the tunica albuginea (arrow) with surrounding haematoma in the penile midshaft (asteriks). (d) Two years later after surgical repair of the the tunica albuginea, T1-weighted image shows a thickening of the rupture site (arrow).



unexpensive (6). However this technique is operator dependent, and the major obstacle is a lack of tissue contrast (7). Other limitations of the sonography are that, edematous swelling of the penis and clots within the tear deteriorate the image contrast and can obscure the defect; furthermore, a rupture in the pendilous area cannot be visualised. Some authors advocate cavernosonography to delinate the corporal rupture, but this invasive and painful procedure may increase heamatoma and involves ionizing radiation with a risk of infection and sometimes a lack image contrast.

Because of MRI multiplanar capabilty and excellent tissue contrast, it can be useful as a diagnostic tool in the evaluation of patients with acute penile fracture (8).

Figure-3 - A 40-year-old patient with penile fracture of the right corpus cavernosum. Unenhanced (a) and enhanced (b) T1-weighted images fail to reveal the tunical tear, whereas axial (c) coronal (d) T2-weighted images identify the tunical tear (arrows) with surrounding haematoma of the right corpus cavernosum in the proximal penile (asteriks).

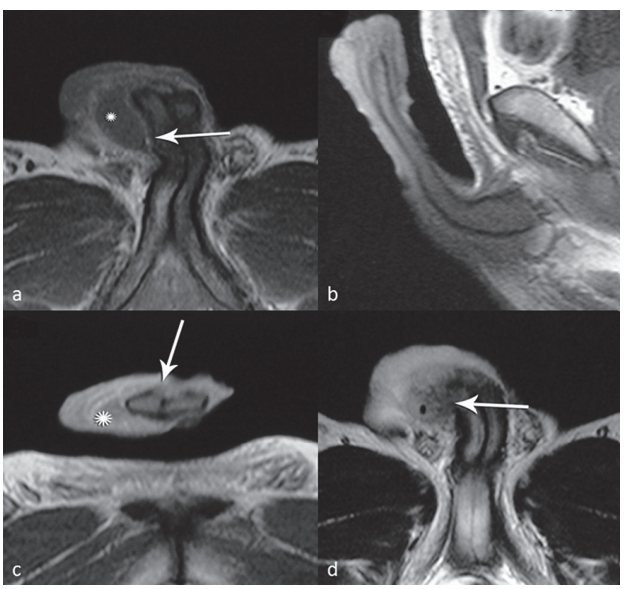
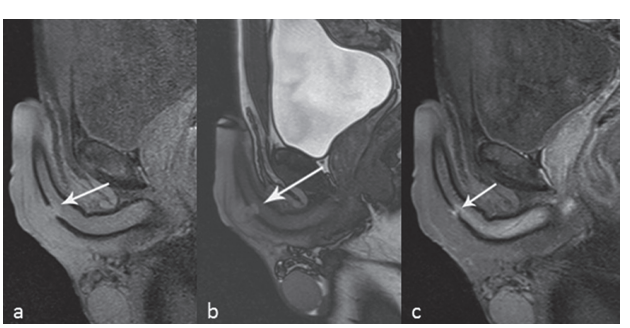


Figure 4 - A 30-year-old patient with penile fracture of the right corpus cavernosum. (a) Sagittal T1-weighted image shows a rupture of the tunica albuginea (arrow). (b) The lesion of the tunica albuginea and soft tissue haematoma surrounding the corpus cevarnosum can be detected on T2-weighted images (arrow). (c) Eight weeks later after surgery, the tunica albuginea in healing process showed heterogeneous signal on unenhanced T1-weighted image (arrow).



But MRI has also some limitations, such as higher cost than ultrasound, and readily not available everywhere. Especially in patients that ultrasound is not conclusive, MR imaging can accurately depict the presence, location and extent of tunical tear which manifest as discontunity of

TA (9). Moreover, because TA is well demonstrated as a low-signal intensity structure on T1 and T2 weighted images, MR imaging is optimal for the evaluation of the integrity of this anatomic structure even in patients with severe pain and swelling of penis as well as hematomas that appear as high signal intensity on both T1 and T2-weighted images (9, 10). Moreover, associated injuries to adjacent structures (eg. corpus spongiosum, urethra) can also be demonstrated (9, 11). MR imaging can demonstrate an intact TA and the presence of intracavernosal and extratunical haematoma. MRI may also detect other pathologies that mimic penile fracture (12).

CONCLUSIONS

MR imaging is an excellent modality for evaluating patients with acute penile trauma. It can accurately demonstrate the integrity of the TA, as well as extent and location of tunical tear and of associated injuries to the CC and urethra.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 329-336, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.21

Does PSA reduction after antibiotic therapy permits postpone prostate biopsy in asymptomatic men with PSA levels between 4 and 10ng/mL?

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ABSTRACT

Purpose: We investigated the effect of antibiotics on PSA in asymptomatic patients with mild PSA elevation.

Materials and Methods: We prospectively evaluated, in a non-randomized design, 106 asymptomatic patients with PSA of 4-10ng/mL, with a negative digital rectal examination and with no urinary tract infection evidence for 2 years. Patients were divided into two groups: those treated with antibiotics for 3 weeks (G1) and those who were not treated (G2). PSA was taken six weeks after and prostate biopsy was performed in all patients.

Results: PCa was diagnosed in 25 of 106 patients (23.6%): 16 (25.0%) in G1 and 9 (21.4%) in G2 ($p>0.05$). PSA normalization was experienced in 24.5%. In G1, PSA returned to <4ng/mL in 15 (23.4%) patients compared to 11 (26%) patients in G2. In the patients with a positive biopsy, no significant variation was noted in PSA, fPSA, %fPSA and DPSA after antibiotic treatment. A significantly lower cancer detection rate was noted with decreased PSA, fPSA, and DPSA after antibiotic use. A PSA reduction rate of ≥10% occurred in 58.5%, and this was similar in both G1 and G2 groups. The sensibility, specificity and accuracy of PSA reduction of ≥10% were 31%, 23% and 25%, respectively.

Conclusion: Empirical antibiotic therapy in asymptomatic male patients is not related to PSA reduction. The greater than 10% PSA reduction after antibiotic in this population cannot postpone prostate biopsy.

ARTICLE INFO

Key words:
prostatic-specific antigen, prostate cancer, antibiotics, screening, biopsy

Int Braz J Urol. 2015; 41: 329-36

Submitted for publication:
September 29, 2013

Accepted after revision:
July 28, 2014

INTRODUCTION

Prostate cancer (PCa) is a frequent cancer that can be cured if early diagnosed (1). However, diagnosis and treatment of localized disease remains a challenge for urologists. Prostate Specific Antigen (PSA) has become an important tool in PCa screening (2, 3) and men with serum PSA greater than 4ng/mL are at higher risk of PCa. These patients are usually referred for a prostate biopsy (BxP). However, increased PSA levels are also associated with conditions other than cancer (3), such as benign prostatic hyperplasia (BPH) and prostatitis (4, 5).

Chronic abacterial prostatitis is a common diagnosis in men of all ages, with widespread demographics, and it is a common reason for yearly visits to the doctor in the United States (3). Only a few studies have linked prostatitis to an increase in serum PSA (6-9). Subclinical inflammation of the

prostate could elevate serum PSA in asymptomatic patients, confounding the use of PSA values to indicate BxP (10). In the majority of cases, prostatitis is an incidental pathological finding that has no clinical relevance. There has been investigation into ways to decrease the misleading diagnosis resulting from inflammation. Repeat PSA measurements after a period of observation in asymptomatic men can help to avoid unnecessary BxP (10-12).

It has been suggested that antibiotic therapy (AT) can also avoid BxP in many patients with prostate inflammation, in the PSA grey zone (4.0 to 10.0ng/mL) (6, 13, 14). Currently, the indications of re-BxP in patients with a negative initial biopsy are few; therefore, the first BxP must be precise. In an effort to improve the reliability of PSA reduction as an indicator, and consequently avoid unnecessary prostate biopsy, we conducted a prospective, controlled, non-randomized study to evaluate the effect of AT on PSA levels in patients who have an initially mild PSA elevation (4.0-10ng/mL).

MATERIAL AND METHODS

A prospective, controlled, non-randomized trial was carried out, with 106 asymptomatic men with total PSA (tPSA) levels between 4.0 and 10.0ng/mL, who underwent routine evaluation from April 2007 to October 2011. The criteria for inclusion in the trial were digital rectal examination (DRE) with no suspicion of malignancy and no history of urologic instrumentation, use of antibiotics, and urinary infection or sexually transmitted disease in the previous 12 months. Patients with diseases like diabetes or alcoholism, those describing the use of illegal drugs, those undergoing treatment for bladder outlet obstruction and patients with previous BxP (positive and negative) were excluded, as were those participants who did not use the AT correctly or who did not carry out the follow-up correctly. After institutional review board (ethical committee) approval, all study participants provided informed written consent before enrolment.

After the initial consultation, the serum levels of total PSA (tPSA) and free PSA (fPSA) were determined. The body mass index (BMI), free PSA fraction (%fPSA), and PSA density (DPSA) were calculated for all patients.

The participants were divided into two groups (Figure-1) according to their decision regarding the use of antibiotics. This decision was made after the authors explained about the lack of evidence for this treatment. Group I patients received antibiotics, while Group II patients chose not to use AT. In Group I, 64 men used ciprofloxacin 500mg twice a day for a period of three weeks. Then, three weeks after the end of AT, the serum PSA, DPSA, and fPSA were again determined (Figure-1). The results of these patients were compared with those of 42 participants with PSA between 4.0 and 10.0ng/mL whose exams were repeated after 6 weeks, without antibiotics, at the participant's discretion. PSA was considered to be normalized after treatment when the values returned to lower than 4ng/dL. All of the participants underwent BxP 2-4 weeks after the second PSA determination. Based on the pre- (PSA_{pre}) and post-treatment (PSA_{post}) PSA values, the variation (PSA_{var}) was calculated: $PSA_{var} = PSA_{post} - PSA_{pre}$. Thus, the variation rate (PSA_{var}) can be calculated with $\Delta PSA = (PSA_{var}/PSA_{pre}).100\%$. The BxP was ultrasound-guided and a minimum of 12 cores were sampled with determination of prostate volume in cubic centimetres (cc). For those participants whose biopsy did not show PCa, PSA was determined after 6 months as in routine practice.

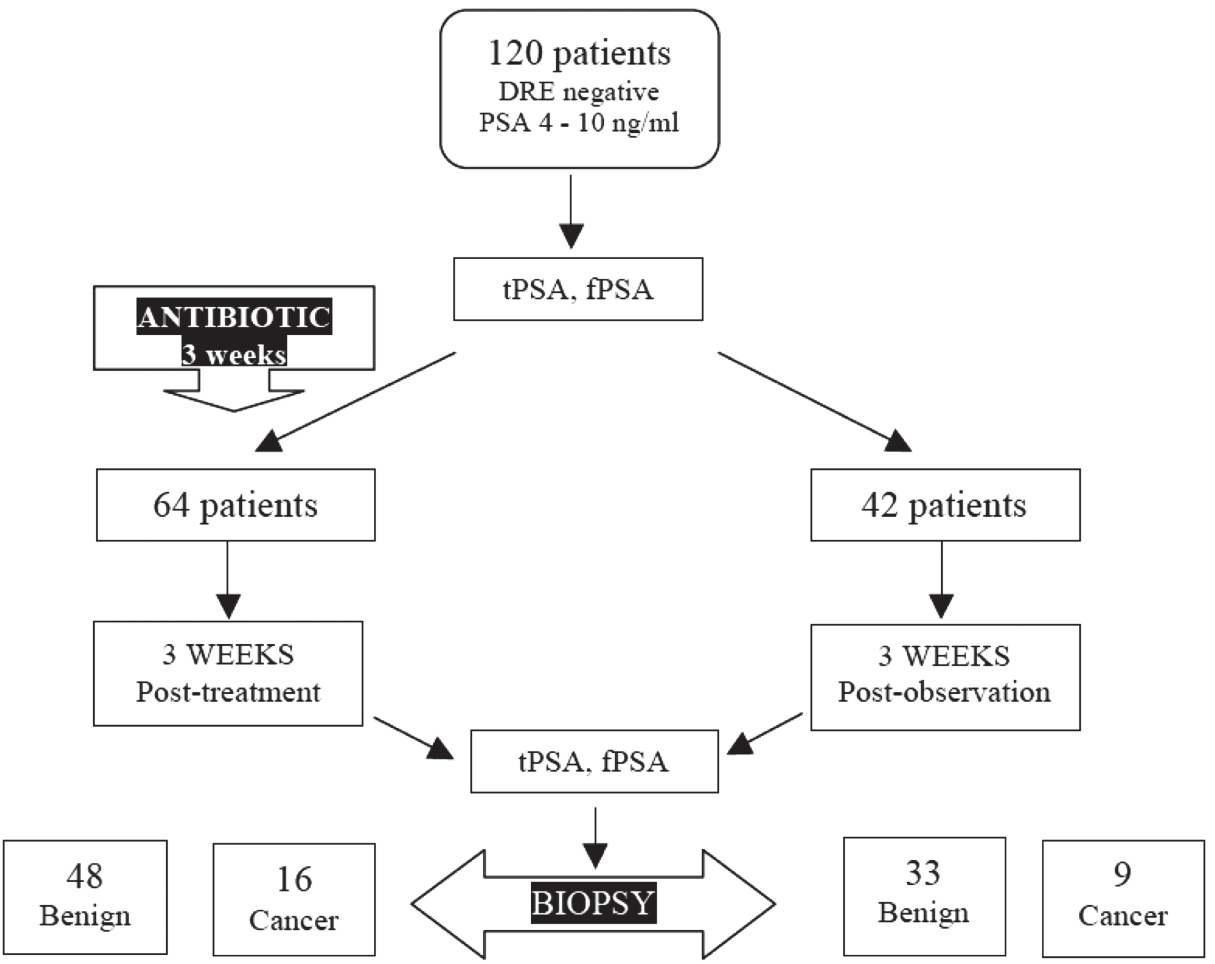
Statistical analysis

The data obtained were analysed by testing the difference between two proportions for incidence of PCa in each group, and evaluation of the decrease in PSA levels. The other data were evaluated using the Student t test, citing the critical t for a significance level of 0.05.

RESULTS

The age of the participants ranged from 47 to 78 years, with a mean age of 66.1 years and median age of 61.8 years. The mean age of G1 was 61.8 years and of G2 was 62.6 years (p=0.60). The prostate volume was 51.1±23.8 gr in G1 and 53.9±19.2 gr in G2 (p=0.52). These values are sho-

Figure 1 - Study design and data organogram. DRE: digital rectal examination; tPSA: PSA total; fPSA: PSA free.



wn in Table-1. The diagnosis of PCa was confirmed in 25 of the 106 participants (23.6%); in 9 out of 42 participants in G2 (21.4%) and in 16 out of 64 in G1 (25%) (z=0.42; p>0.05).

There was a more than 10% PSA decrease in 72 out of 106 patients (67.9%); this rate was 65.6% and 71% in Groups 1 and 2, respectively (z=-0.63; p>0.05). Of the 42 participants from G1 in which the PSA decreased after AT, 6 (14.3%) had a positive and 36 (85.7%) a negative biopsy. In G2, 30 participants had a PSA reduction, with 4 (13.3%) with a positive and 26 (86.7%) a negative biopsy. After the use of AT, the PSA level decreased to <4ng/mL in 26 participants (24.5%); in 15 (23.4%) of those who used AT, and in 11 (26%) from G2 (z=-0.032; p>0.05). The percentage of participants who had a value below 2.5ng/mL in the second PSA was 9.4% for G1, and 7.1% for G2 (z=0.40; p>0.05). The initial and final values for PSA, fPSA, %fPSA and DPSA decreased significantly in both groups (Table-2).

The mean total PSA in G1 was 6.82±1.66 and 5.29±1.8ng/mL before and after treatment, respectively (p<0.001); this represents a PSA_{var} of -1.53±1.93ng/mL. In G2, the mean PSA before and after antibiotics was 6.76±1.68 and 5.38±2.16ng/mL, respectively, with a PSA_{var} of -1.38±1.87 (p<0.001). The ΔPSA in G1 was 25.56, and in G2 was 28.7 (p=0.429). The differences between G1

Table 1 - Comparison of initial values of the variables between groups.

	Group I	Group II	p
	With ATB Mean±SD	Without ATB Mean±SD	
Age (years)	61.81±7.83	62.57±6.37	0.6
BMI (Kg/m^2)	27.86±3.51	29.66±8.09	0.02
Volume (cc)	51.15±23.87	53.97±19.28	0.527
PSA_{pre}	6.82±1.66	6.76±1.68	0.429
PSA_{post}	5.29±1.8	5.38±2.16	0.409
$fPSA_{pre}$	1.25±0.47	1.31±0.40	0.233
$fPSA_{post}$	1.03±0.44	1.06±0.48	0.383
$DPSA_{pre}$	0.15±0.05	0.14±0.06	0.261
$DPSA_{post}$	0.11±0.06	0.11±0.07	0.369

Values expressed in mean ± standard variation. Student t test

Table 2 - Comparison of initial and final PSA values between groups.

Group I				Group II		
	Pre-ATB	Post-ATB	p	PSA initial	PSA final	p
tPSA	6.82±1.66	5.29±1.8	<0.001	6.76±1.68	5.38±2.16	<0.0001
fPSA	1.25±0.47	1.03±0.44	0.0002	1.31±0.4	1.06±0.48	0.0003
%fPSA	18.26±5.08	20.13±6.35	0.0017	19.91±5.56	21.08±6.95	0.072
DPSA	0.15±0.05	0.11±0.06	<0.0001	0.14±0.04	0.11±0.07	0.0003

Values expressed in mean±standard variation. Student t test

and G2 are shown in Table-2, according to the initial and final fPSA and DPSA. There was no statistical difference between these values.

In relation to DPSA, for G1, the initial mean was 0.15±0.05ng/mL/gr of prostate, which decreased to 0.11±0.06ng/mL/gr (p<0.0001). In G2, these figures were 0.14±0.04ng/mL/gr and 0.11±0.07ng/mL/gr, respectively (p=0.0003). Therefore, there was no statistical difference. These same comparisons, analysing the cases with and without PCa, are shown in Table-3. In the participants diagnosed with PCa, there was no statistical difference in relation to variation in PSA, fPSA, %fPSA or DPSA. However, in the participants with negative BxP, there was a significant reduction in PSA, fPSA and DPSA, but not in %fPSA.

The sensitivity to a decrease greater than 10% in PSA after the use of AT to a diagnosis of prostate cancer was 31%, with a specificity of 23%; the positive predictive value (PPV) was 12% and the negative predictive value (NPV) was 23%. The accuracy of the method was 25%. Regarding to the possibility of reducing unnecessary BxP after AT, it should be emphasized that none of the 25 participants with PCa had a final PSA below 4ng/mL.

DISCUSSION

The present study analysed the effect of AT on PSA (tPSA, fPSA, %fPSA and DPSA) and investigated whether a relevant PSA reduction induced

Table 3 - Comparison of PSA values between patients with and without prostate cancer.

Benign				Prostate Cancer		
	PSA initial	PSA final	p	PSA initial	PSA final	p
tPSA	6.85±1.72	4.96±1.98	0.001	6.63±1.49	6.52±1.19	0.2
fPSA	1.35±0.44	1.06±0.47	0.001	1.02±0.37	0.97±0.40	0.077
%fPSA	19.96±5.05	22.20±5.89	0.124	15.52±4.75	15.01±5.69	0.641
PSAD	0.14±0.06	0.10±0.06	<0.00001	0.15±0.02	0.15±0.07	0.61

Values expressed in mean±standard variation. Student t test

by AT could be related to a decreased cancer detection rate at biopsy. PSA is tumour-associated but not tumour-specific. Physiological conditions other than cancer can cause an increase in serum PSA levels that lead to potentially unnecessary biopsy procedures, increasing inconvenience for the patient, and causing over-diagnosis, over-treatment and elevated medical costs (15).

Prostate cancer is determined in only 34% of biopsies performed on the basis of PSA elevation (1), and in 20-30% in patients with normal DRE and PSA values of between 4 and 10ng/mL. Therefore, there is a high level of unnecessary biopsies, particularly in this group (16, 17). The literature demonstrates a relationship between acute and chronic inflammation with elevated PSA, but there have been recent studies that suggest the effects and benefits of chronic prostatitis treatment on PSA (18-21). In our study, PCa was diagnosed more frequently in patients treated with AT (25% versus 21.4%, p>0.05), but without statistical relevance. Antibiotics certainly did not cause changes in PSA in these men with PCa. Scardino (22) suggested that the changes in PSA with AT were similar to the random variations found in healthy men. Also, Potts (23) demonstrated no significant differences in bacterial cultures before or after AT between PSA responders and non-responders.

Okada (24) and Schatteman (25) concluded that subclinical inflammation could cause PSA elevation, and emphasized the fact that nearly half of all clinically asymptomatic men with elevated PSA levels have laboratory signs of prostatitis. They suggest that the use of antibiotics would result in a decrease in PSA levels in almost 50% of patients, thereby avoiding BxP. This approach, however, requires careful follow-up, especially for patients whose PSA levels fail to decrease to within the normal range (26, 27). Kaygisiz (1) and Del Rosso (19) suggested that AT should be administered for 3 weeks, regardless of the presence of inflammation when PSA levels are in the grey zone, before making a decision regarding whether or not to carry out a biopsy.

On the other hand, Serretta et al. (28) found no cancer present if PSA levels decreased to below 4ng/mL, or more than 70%, and postulated that biopsy can be postponed, with only a small risk of failing to detect cancer. In multivariate analysis with other clinical variables, the PSA reduction rate was a significant independent predictor of biopsy results. Although this was not a randomized trial, it was prospective, assessing asymptomatic males without a clinical indication of prostatitis; the study demonstrated that a large reduction in PSA following antibiotics may help to avoid biopsy in selected patients in whom the PSA elevation is probably due to inflammation/infection.

Our data show that those patients who received AT and those who did not had the same rate of normalization of PSA (<4ng/mL). Prostatic Specific Antigen normalization occurred in 24.5% of individuals. In the AT group, PSA returned to normal levels in 23.4% of patients, compared with 26% patients in the non-treatment group. The reason for this is still unclear, although PSA normalization does not rule out PCa diagnosis, and biopsy must still be considered. Magri et al. (29), showed that the presence of BPH may prevent the reduction of PSA induced by combination pharmacological therapy, and suggest that care must be taken in the adoption of PSA as a marker of

therapeutic efficacy in the presence of confounding factors like BPH. According to these authors, PSA should be used as a significant component of a strategy that integrates multiple diagnostic approaches.

Our results are different from those reported by other authors. Hochreiter et al. (11) showed a PSA reduction in 63% of patients following AT, with PSA returning to normal values in 9% of cases, thus avoiding prostate biopsy. After AT, Potts et al. (23) documented PSA normalization in 42% of patients, and Brett et al. (30) found the same in 41% of patients. These studies did not perform BxP in all patients to exclude the diagnosis of PCa after treatment. Our study demonstrated a PSA normalization after antibiotics in only 23.4% of patients. However, our study performed biopsy in all patients (treated and not-treated), comparing the PCa incidence between groups. It is therefore more significant in terms of prostate biopsy decision. However, the entry of participants was not random, but based on the decision made by each participant; this may represent a selection bias. Moreover, the shared decision with the patient is one of the commonalities in international guidelines.

Approximately 10-15% of men will have a PSA level >4ng/mL in any given round of screening. However, the level will return to normal in the subsequent test in 26-37%, and will become normal with the next testing in 40-55%. Heldwein et al. (31) showed that PSA levels tend to fall when repeated after 45 days, regardless of AT. Once normalized, 65-83% of men have normal PSA levels for several years without therapy (32). If PSA levels do not fall, the probability of finding cancer is higher than if levels decrease. This occurs because PCa is more likely to occur in men with sustained PSA elevation than in those with a randomly variable PSA that is temporarily elevated (24).

Our study shows a lower, but not significant, cancer detection rate in patients with decreased PSA, fPSA and DPSA after antibiotic therapy, demonstrating a correlation between PSA normalization and prostatitis or negative biopsy. A PSA reduction rate of 10% occurred in 58.5% of patients; however, it was lower in patients who received antibiotics than in those who received no treatment (65.6% versus 71%), but there was not significant difference ($p>0.05$). The sensitivity, specificity and accuracy of a PSA reduction rate of 10% were 31%, 23% and 25%, respectively. This level is therefore not recommended as a cut-off point for clinical decision-making. Serreta et al. (28) showed a significantly lower cancer detection rate in patients with decreased PSA after antibiotic therapy, demonstrating a correlation between PSA reduction and negative biopsy, with an odds ratio varying from 1.2 to 3.9 for reduction percentages of between 10 and 90%. They suggested that a PSA reduction rate of 50% can be adopted and 11% of biopsies avoided until a further PSA increase occurs. Dirim et al. (33) reported that the f/t PSA ratio appears to be more suggestive of PCa than PSA in these cases. It should be emphasized, however, that a long follow-up time is needed to determine whether any of these men will have prostate cancer in the near future, and wider studies are required to identify the optimal PSA reduction level at which biopsy can be postponed.

The influence of prostatitis on PSA concentrations remains a controversial issue (34). Ozen et al. (35) claimed that BPH and prostatitis appear to be more frequent causes of PSA elevation. Scardino (22) recommended that asymptomatic men presenting with a modestly elevated PSA level (<10ng/mL) and a normal digital rectal examination could be reassured and then the PSA level could be repeated once or twice; if the levels remained elevated, this would be an indication of the need to perform a biopsy. Stopiglia et al. (36), in a prospective randomized and double-blind trial with placebo, demonstrated that PSA reduction occurred after antibiotic and placebo application, and suggested that a decrease in PSA does not indicate the absence of PCa. Recently, Faydaci et al. (37) demonstrated that AT given to patients with PSA levels higher than the threshold value has not led to a significant change in prostate needle biopsy decisions, and suggested that BxP should be considered without the use of AT in patients with high PSA values if a suspicion of prostatitis does not exist. The literature does not support the evidence that antibiotics alter PSA levels except in the presence of bacterial prostatitis, which is an uncommon condition. We should wait for a second PSA assessment before prostate biopsy in asymp-

tomatic male patients once the PSA will spontaneously reduce in a quarter of cases; and that antibiotic use has no role in this clinic scenario (36).

There are several implications in the use of empiric AT for patients with elevated PSA levels. Scardino (22) emphasized some disadvantages of this approach, such as cost, toxicity, and the fact that it can cause complications of infection. Moreover, a decrease in PSA after AT does not absolutely exclude the presence of PCa, even if the PSA decreases to very low levels. In addition, there is concern that the indiscriminate use of empiric antibiotics could lead to the development of resistant bacterial species and thereby expose the patient to more resistant and aggressive sepsis, should a biopsy eventually be performed (38-40).

CONCLUSIONS

Empirical antibiotic therapy in asymptomatic male patients is not related to PSA reduction and that PSA reduction after antibiotic cannot postpone prostate biopsy. Based in our findings, only PSA normalization can postpone prostate biopsy. Additionally, it is not possible to define a safe rate reduction and further studies stratifying the relative values of reduction and cancer risk are needed.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 337-343, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.22

Effect on hemostasis of an absorbable hemostatic gelatin sponge after transrectal prostate needle biopsy

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ABSTRACT

Objectives: To examine the usefulness of an absorbable hemostatic gelatin sponge for hemostasis after transrectal prostate needle biopsy.
Subjects and Methods: The subjects comprised 278 participants who underwent transrectal prostate needle biopsy. They were randomly allocated to the gelatin sponge insertion group (group A: 148 participants) and to the non-insertion group (group B: 130 participants). In group A, the gelatin sponge was inserted into the rectum immediately after biopsy. A biopsy-induced hemorrhage was defined as a case in which a subject complained of bleeding from the rectum, and excretion of blood clots was confirmed. A blood test was performed before and after biopsy, and a questionnaire survey was given after the biopsy.
Results: Significantly fewer participants in group A required hemostasis after biopsy compared to group B (3 (2.0%) vs. 11 (8.5%), P=0.029). The results of the blood tests and the responses from the questionnaire did not differ significantly between the two groups. In multivariate analysis, only "insertion of a gelatin sponge into the rectum" emerged as a significant predictor of hemostasis.
Conclusion: Insertion of a gelatin sponge into the rectum after transrectal prostate needle biopsy significantly increases hemostasis without increasing patient symptoms, such as pain and a sense of discomfort.

ARTICLE INFO

Key words:
prostate, biopsy, hemostasis, gelatin sponge; Gelatin Sponge, Absorbable

Int Braz J Urol. 2015; 41: 337-43

Submitted for publication:
March 22, 2014

Accepted after revision:
July 28, 2014

INTRODUCTION

Transrectal ultrasound (TRUS)-guided prostate biopsy is a standard procedure for the diagnosis of prostate cancer. It is generally a safe procedure with minimal complications including rectal and genitourinary lesions. Rectal bleeding is one of the most common side effects of TRUS-guided prostate biopsy. Although excessive bleeding is rare, it can occur and hemostasis is essential. The utility of the absorbable hemostatic gelatin sponge for hemostasis in anorectal surgery has been reported (1, 2). While the gelatin sponge can be expected to promote hemostasis in rectal bleeding, there are no studies evaluating its efficacy on hemostasis in transrectal ultrasound-guided prostate biopsy.

OBJECTIVE

To clarify the efficacy on hemostasis of the gelatin sponge for rectal bleeding in transrectal ultrasound-guided prostate biopsy in a randomized controlled prospective study.

MATERIALS AND METHODS

This prospective study was approved by the ethical committee at Hiroshima City Asa Hospital. From October 2011 to November 2012, after

informed consent, a total of 278 participants were submitted to a transrectal ultrasound-guided prostate biopsy with an 18G×200mm biopsy needle under local anesthesia (chloride 1% lidocaine in the rectal membrane) by the same surgeon (K.K). For those participants taking antiplatelet agents, the medication was discontinued before the biopsy for an appropriate period until the antiplatelet drug was eliminated from the body, e.g. 14 days for clopidogrel bisulfate and 4 days for warfarin.

Before the biopsy, all the participants were randomly assigned to two groups by the envelope method; gelatin sponge (SPONGOSTAN™ Anal, Ethicon, Inc., Johnson & Johnson, USA, Figure-1) insertion immediately after the biopsy (group A, n=148) and no insertion (group B, n=130). In both groups, no medical procedures, such as a digital rectal examination (DRE), were done. The patients stayed in the hospital at least one day for observation of their postsurgical course by the medical staff, and this 24 hour observation period excluded as much as possible any bias in this study. The hematological value, IPSS (International Prostate Symptom Score), QoL (Quality of Life) score, OABSS (Over Active Bladder Symptom Score), and a questionnaire that was composed of 6 items with 5 levels of response (Appendix) were evaluated in both groups. Figure-2 shows the flowchart of this study.

For both groups, when blood was observed on the underwear or in the bedpan after the biopsy, the DRE was performed to confirm the degree of bleeding. If attached blood on the DRE was marginal and the color was pink or dilute red, we decided that additional measures were unnecessary. If there was considerable attached blood or blood clots, we defined it as significant rectal bleeding. We categorized significant rectal bleeding into two grades for hemostasis management, including mild (slight or moderate bleeding) and severe (profuse bleeding that required endoscopic clipping). When the bleeding was classified as mild, we inserted the gelatin sponge into the participants in either group B or reinserted it into those participants in group A. If the bleeding could not be stopped by this approach, we additionally used index finger pressure for ten minutes or more to promote hemostasis. In the severe cases, an endoscopic clipping was performed to control the bleeding because arterial bleeding was suspected. Those severe cases were given bed rest until the next morning after the prescript hemostatic approach.

The difference in background factors between groups A and B was assessed by the unpaired t-test, Mann-Whitney's U test, and chi-square test. To identify the independent predictive factors for rectal bleeding for all participants, 7 factors,

Figure 1 - The absorbable hemostatic gelatin sponge (SPONGOSTAN™ Anal) made of gelatin is cylindricality-shaped of 3 cm (diameter) X 8 cm. In the center, it has a cylindrical hollow region of 0.8 cm in diameter.

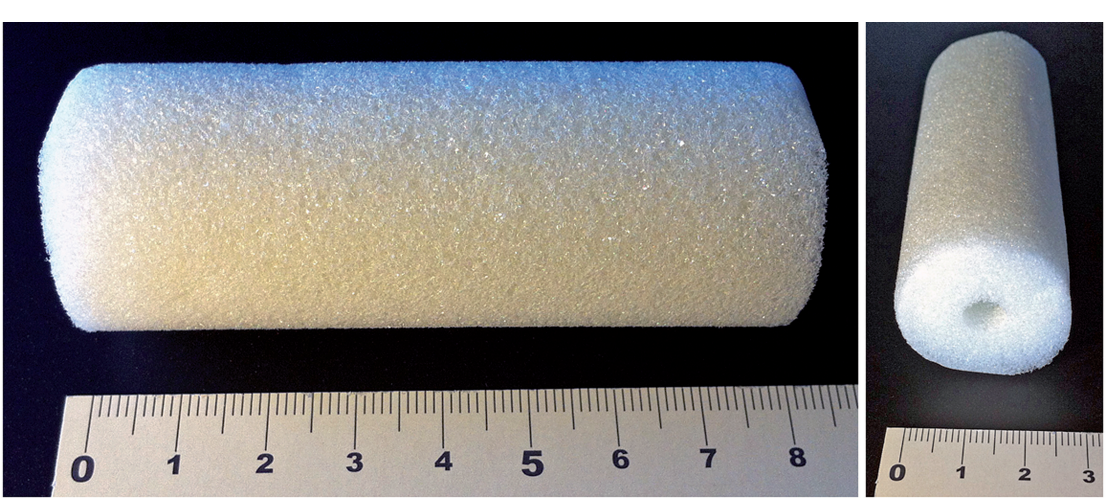
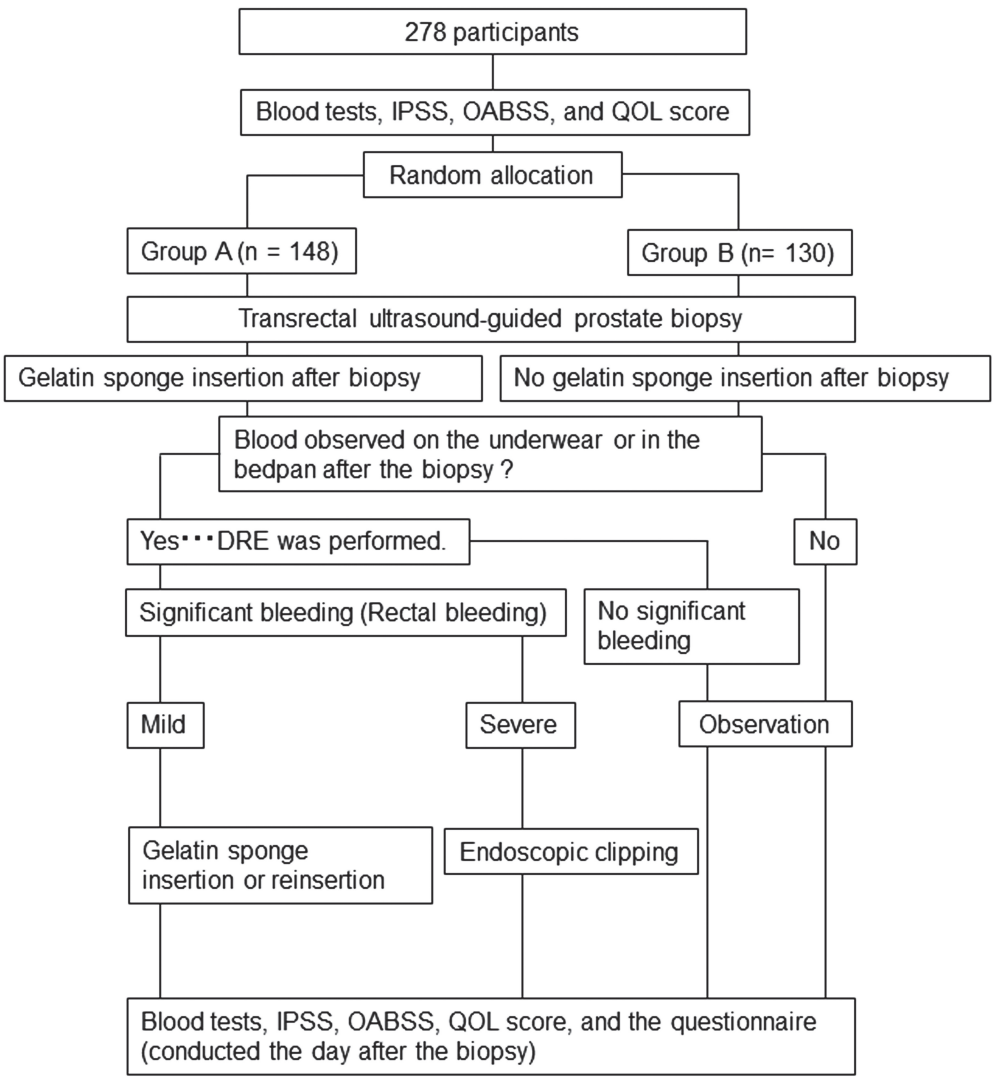


Figure 2 - Flowchart of this study.



including gelatin sponge insertion, age, PSA, prostate volume, antiplatelet drug usage, the number of biopsy samples per procedure, and number of times biopsies were performed, were analyzed by logistic regression analysis. In all analyses, a P value <0.05 was defined as significant.

RESULTS

1) Participants' background

For the 278 participants, the median age, median PSA, and median prostate volume were 71y/o (50-97), 8.4 ng/dL (1.3-4519.7), and 27.4 mL (5.2-129.3), respectively. Two hundred twenty eight of all participants (82.0%) were biopsied for the first time. In our study, 1 participant (0.4%) received 4 core biopsies, 144 participants (51.8%) received 6 core biopsies, 110 participants (39.6%) received 10 core biopsies, and 23 participants (8.3%) received 12 core biopsies. Fifty-five of the participants (19.8%) were taking antiplatelet drugs and were only biopsied after an appropriate washout period. Seven of the participants received heparin before the biopsy. Prostate adenocarcino-

ma was detected in 147 participants (52.9%) and their Gleason scores were 6 (18 patients), 7 (56 patients), and ≥8 (73 patients). The participants' background of groups A and B is shown in Table-1. For each item, there was no significant difference between the two groups.

2) Rectal bleeding

The frequency of major complications after prostate biopsy in all cases was 5.0% (n=14) for rectal bleeding, 33.8% (n=94) for gross hematuria, and 0.7% (n=2) for transitory urinary retention. Though the frequency of rectal bleeding in group A was significantly lower that in group B (P=0.029), there was no significant difference between the frequency of gross hematuria and transitory urinary retention between groups A and B (Table-2). The number of participants experiencing each grade of rectal bleeding was as follows: 3 mild and 0 severe in group A, and 10 mild and 1 severe in group B, respectively. Three cases in group A (100%) and 6 cases in group B (60%) in the mild grade ceased bleeding after reinsertion or insertion of the gelatin sponge. Four cases in the mild grade in group B were submitted to finger pressure for 10 minutes before the insertion of the gelatin sponge. Nevertheless, 2 of those 4 cases in the mild grade in group B had additional finger pressure for ten minutes to completely stop the bleeding. No participant received a blood transfusion.

Table 1 - Participants' background and hematological values in groups A and B.

	Group A	Group B	p-value
Participants	148	130	
Age (year)*	71 (55-97)	71 (50-89)	0.843
PSA (ng/ml)*	8.3 (1.3-1977.3)	8.4 (2.2-4519.7)	0.548
Prostate volume (ml)*	27.4 (5.2-129.3)	27.4 (10.9-105.0)	0.676
Biopsy			
Number of times			
1st	120	108	
2nd	17	14	0.972
3rd	6	4	
4th or more	5	4	
Number of samples			
4	1	0	
6	85	59	0.080
10	50	60	
12	12	11	
Detection of carcinoma	78	67	0.941
Antiplatelet drugs	34	21	0.202
Hematological value*			
Hb (g/dL)	14.2±1.7	15.1±4.4	0.102
Plt (×10⁴/μL)	21.0±5.5	22.8±6.5	0.061

* Median value

The p values were calculated using the t test (age, PSA, prostate volume, hematological value), chi-square test (detection of carcinoma, antiplatelet drugs), and Mann-Whitney's U test (number of times and samples).

Table 2 - Frequency of main complications after the prostate biopsy.

	Total (n=278)	Group A (n=148)	Group B (n=130)	p value
Rectal bleeding	14 (5.0%)	3 (2.0%)	11 (8.5%)	0.029
Mild		3	10	
Severe		0	1	
Gross hematuria	94 (33.8%)	47 (31.8%)	47 (36.2%)	0.439
Urinary retention	2 (0.7 %)	1 (0.7%)	1 (0.8%)	0.926

*Chi-square test

There were no significant differences between the 2 groups for the following six factors: age, PSA value (ng/mL), prostate volume (mL), taking antiplatelet drugs usage (yes), number of biopsy samples per procedure (≥10 places vs.<10 places), and number of times of biopsies (≥2 times vs. first time). The gelatin sponge insertion was the only significantly independent predictive factor that suppressed the rectal bleeding in prostate biopsy as determined by univariable analysis and by multivariate analysis (Table-3).

3) Blood tests and the questionnaires

The findings in the blood tests before and after prostate biopsy were comparable in 149 cases. There were no significant changes found in the blood tests, including hemoglobin and platelet counts between the two groups before the biopsy (table-1). There were no significant differences in the responses to each item in our questionnaire between group A and group B (Q1; Average score 1.7 vs.1.6, p=0.21, Q2; Average score 1.8 vs.1.7, p=0.41, Q3; Average score 1.6 vs.1.5, p=0.58, Q4; Average score 1.5 vs.1.6, p=0.30, Q5; Average score 1.5 vs.1.4, p=0.26, and Q6; Average score 2.2 vs.2.0, p=0.63), respectively. Moreover, there were no significant differences in IPSS, OABSS, and QOL scores before and after biopsy.

DISCUSSION

To our knowledge, this is the first report to show that the absorbable hemostatic gelatin sponge provides significant hemostasis for rectal bleeding in TRUS-guided prostate biopsies. Based on our results, the immediate insertion of an absorbable hemostatic gelatin sponge can reduce the frequency of rectal bleeding without physical bur-

Table 3 - Logistic regression analysis.

	Univariable analysis		Multivariable analysis	
	p value	OR (95%CI)	p value	OR (95%CI)
Gelatin sponge insertion (Yes)	**0.024**	0.223 (0.061-0.821)	**0.016**	0.185 (0.047-0.732)
Age (year old)	0.776	0.989 (0.923-1.061)	0.956	0.998 (0.923-1.078)
Antiplatelet agents (Yes)	0.358	1.755 (0.528-5.820)	0.195	2.416 (0.636-9.183)
PSA (ng/ml)	0.368	0.975 (0.921-1.031)	0.430	0.973 (0.912-1.040)
Prostate volume (ml)	0.303	0.982 (0.948-1.017)	0.257	0.976 (0.935-1.018)
Number of times of biopsies (≥2)	0.947	0.980 (0.538-1.784)	0.791	1.220 (0.278-5.372)
Number of biopsy samples per procedure (≥10)	0.215	2.032 (0.633-6.226)	0.316	1.989 (0.518-7.640)

den for the participants. Furthermore, even when rectal bleeding occurs, it can be stopped in many of the cases by only inserting the gelatin sponge (in mild grade participants: 100% of group A and 60% of group B).

Rectal bleeding in a transrectal prostatic biopsy has an incidence that ranges from 0.9-37% (3-7), because the definition of rectal bleeding is defined differently depending on the institution where it was performed. Based on a large-scale retrospective analysis for 202,065 cases in Japan, the incidence of rectal bleeding in transrectal prostatic biopsy was reported as 5.6% (8). Though clinically serious bleeding is rare, sometimes rectal bleeding requires hemostasis. To date, many methods for hemostasis have been reported, such as pressure by tampon insertion, urethral catheter placement, condom expansion (9-11), and endoscopic clipping at the bleeding points (12), and endoscopic injection of epinephrine and polidocanol in cases of severe bleeding (6).

SPONGOSTAN™ Anal is an absorbable hemostatic gelatin sponge made of neutral purified gelatin (pig origin) with uniform porosity, a cylindrical shape 3 cm (diameter) X 8 cm, and a central hollow region of 0.8 cm in diameter. It has a non-water-soluble property, attaches to the bleeding tissue, and absorbs considerable amounts of blood equal to approximately 35 times the product weight. Furthermore, it provides pressure to the bleeding site while conforming to the shape of the anal canal, and platelets are trapped within the pores and form an insoluble fibrin clot that controls bleeding. In addition, after insertion in the anus, the sponge is absorbed and excreted with the stool within 1-2 days (13).

In the rectal region, there are three veins, including superior, middle, and inferior rectal veins that comprise a dense anastomosis and form the rectal venous plexus. Most rectal bleeding in transrectal prostate biopsy is thought to originate in the rectal venous plexus and can be controlled with comparative ease (9).

In this study, the gelatin sponge was placed on the needle puncture site located at approximately 3-5 cm from the anus. Unlike conventional usage, this site was located near the rectal ampulla rather than at the anal canal. The effect of the gelatin sponge on inducing hemostasis in part by pressure is not expected in the rectal ampulla because this site has considerable elasticity though there are individual patient differences. Our study suggested that the gelatin sponge when applied to the bleeding site absorbed blood and might provide a hemostatic effect. However, in severe cases and in a few mild cases, the gelatin sponge apparently could not be applied to the bleeding site directly and did not establish hemostasis because the rectal ampulla expanded due to blood retention. The branch of the inferior rectal artery forms a vascular bed among inferior vesical arteries. Severe bleeding cases requiring endoscopy may be due to arterial bleeding. In such cases, the gelatin sponge may not work, and thus, endoscopic clipping is necessary as soon as severe bleeding is observed. Evaluation of the severity of bleeding was essential for selecting the hemostatic approach, such as whether to use an endoscopic approach, to apply pressure to the site, to insert the gelatin sponge, or to only monitor the bleeding.

For those taking antiplatelet drugs, though the bleeding risk was considered low (15, 16), we discontinued the use of these drugs prior to the biopsy in order to exclude that variable. As for other factors, several reports showed that the incidence of complications did not correlate in prostate biopsy when considering the size of the biopsy needle or the number of biopsies (17, 18). In cases of patients with hemorrhoids, they did have a bleeding risk because the rectal venous plexus was enlarged (12). In this study, none of the participants had hemorrhoids in the 14 rectal bleeding cases.

This study has some limitations, such as the data being based on a relatively small number of participants and the lack of selection for the best candidates. Based on our results, although we demonstrated that the immediate insertion of a gelatin sponge into the rectum after transrectal prostate needle biopsy was probably useful, simple, effective, and safe, it was difficult to prove the 'true' benefit of the gelatin sponge in comparison with other hemostatic procedures. We demonstrate that use of the gelatin sponge for those who have bleeding after a biopsy can be an option. Further study is required to clarify these issues.

CONCLUSIONS

Immediate insertion of the absorbable hemostatic gelatin sponge into the rectum after transrectal ultrasound-guided prostate needle biopsy significantly decreases rectal bleeding without increasing patient symptoms, such as pain and a sense of discomfort.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 344-352, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.23

Unraveling Brazilian Indian population prostate good health: clinical, anthropometric and genetic features

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ABSTRACT

Purpose: To compare dietary, lifestyle, clinical, anthropometric, genetic and prostatic features of Brazilian Indians and non-Indians (Amazon).

Methods: 315 men, 228 Indians and 89 non-Indians, ≥40 years old were submitted to digital rectal examination, serum prostate specific antigen (PSA), testosterone, TP53 and GSTP1 genotyping, anthropometric, lifestyle, dietary, personal and familial medical history. Prostatic symptoms were evaluated with the International Prostate Symptom Score (IPSS).

Results: Macuxis and Yanomamis represented 43.6% and 14.5% of Indians respectively who spontaneously referred no prostate symptoms. Mean IPSS was 7, range 3-19, with only 15% of moderate symptoms (score 8-19); Mean age was 54.7 years, waist circumference 86.6 cm, BMI 23.9 kg/m^2. Yanomamis presented both lower BMI (21.4 *versus* 24.8 and 23.3, p=0,001) and prostate volume than Macuxis and "other ethnic groups" (15 *versus* 20, p=0.001). Testosterone (414 *versus* 502 and 512, p=0.207) and PSA (0.48 *versus* 0.6 and 0.41, p=0.349) were similar with progressive PSA increase with aging. Val/Val correlated with lower PSA (p=0.0361).

Indians compared to control population presented: - TP53 super representation of Arg/Arg haplotype, 74.5% *versus* 42.5%, p<0.0001. -GSTP1 Ile/Ile 35.3% *versus* 60.9%; Ile/Val 45.9% *versus* 28.7%; Val/Val 18.8% *versus* 10.3%; p=0.0003.

Conclusions: Observed specific dietary, lifestyle, anthropometric and genetic profile for *TP53* and *GSTP1* may contribute to Brazilian Indian population prostate good health.

ARTICLE INFO

Key words:
Prostatic Diseases; Neoplasms; Tumor Suppressor Protein p53; GSTP1 protein, human [Supplementary Concept]; Testosterone; Genetic Therapy; Polymorphism, Genetic

Int Braz J Urol. 2015; 41: 344-52

Submitted for publication:
April 22, 2014

Accepted after revision:
September 05, 2014

INTRODUCTION

The Indian populations in Brazil and in other countries worldwide are not well studied, with rare published reports. The study of culturally distinct indigenous populations, as well as their contact with and influence of non-indigenous groups in relation to their behavior and merging of new habits as risk factors for prostate diseases is intriguing.

Many studies have been reporting for many years the huge ethnical difference of the incidence of prostate diseases, including prostate cancer (PCa) as well as the concentration of prostatic specific antigen (PSA) in different populations around the World (1). It is discussed if these differences are derived from biological diversity of populations or from environmental factors that would modify their hereditary traits, mainly dietary habits and lifestyle (2).

Age, black race and familial history of cancer are well stablished factors for high risk of prostate cancer (1). Most studies suggest that the ingestion of fatty food, cooked food, selenium, exposure to pesticides and fertilizers, physical activity and socio-economic status are factors that can contribute to observed differences in many countries, regions or eventually races (3).

Variations of frequency of PCa among Caucasians, native Alaskans and Indians are well documented in the USA (4, 5). However, in the indigenous population of Brazil, data regarding incidence, prevalence and risk factors for prostate disease are rare and only a few studies addressed clinical and anthropometric data in that population (6-8).

In view of scarce information about the profile of male health of indigenous populations of extreme North of Brazil, we decided to analyze *GSTP1* and *TP53* polymorphisms, PSA and testosterone serum values and digital rectal exam, correlating the results with anthropometric characteristics, lifestyle, and especially dietary habits in order to elucidate the interaction of genetic background and environmental exposure in relation to prostatic diseases.

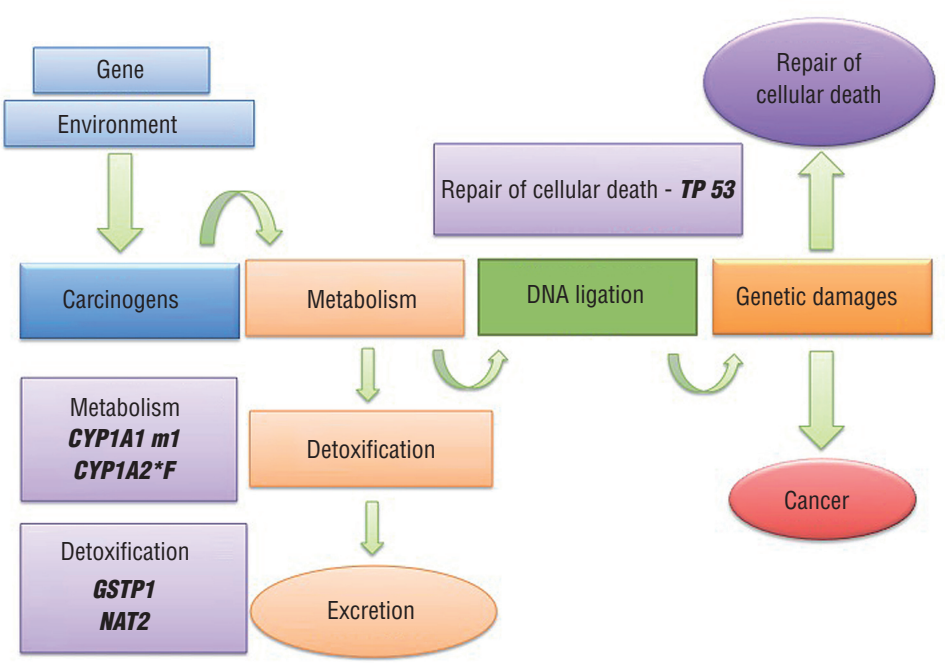
MATERIALS AND METHODS

From March, 2010, to March, 2011, a total of 315 healthy men with 40 or more years old were prospectively evaluated by the same examiner, after signing a written consent form. 228 Indians were admitted to Indian House of Health in Boa Vista, Roraima, Brazil (CASAI/RR), through a campaign, and 87 non-indigenous healthy men that donated blood were included in the control group. They resided in the Boa Vista Region, Brazil. Those who presented a personal or family history of prostate cancer were excluded.

Polymorphisms of codon 72 of *TP53* and *GSTP1* were analyzed; they are involved in the detoxification and repair of DNA (9) (Figure-1). The data were correlated to anthropometric values, lifestyle habits, serum PSA and testosterone and digital rectal exam (DR) of the indigenous populations of northern Brazil. Prostatic symptoms were evaluated with the IPSS (*International Prostate Symptom Score*) questionnaire validated to Portuguese (10).

Genomic DNA was extracted using the standard protocol of phenol-chlorophorm, adap-

Figure 1 - Mechanism of detoxification and repair of DNA related to TP53 and GSTP1.



ted from the Cancer Genetic Molecular Laboratory of the University of Campinas-Unicamp, Brazil. In order to verity the DNA purity and quality of the extract, the samples were quantified using the UV--spectrophotometer *Picodrop Limited* (Cambridgeshire, UK).

Genotyping of the two proposed polymorphisms *GSTP1* codon 105 (rs1695) and *TP53 codon 72 (rs1042522)* was conducted using TaqMan® SNP Genotyping (7500 Real Time PCR Systems) essay.

In order to understand the impact of the introduction of new dietary habits, lifestyle and behaviors from the non-indigenous population, we identified and compared two different ethnic groups, with bigger and smaller distance from the urban centers, with consequent greater of smaller contact and merging of habits of non-indigenous people: respectively, *Macuxis* and *Yanomamis*.

All local authorities were officially notified (FUNASA and CASAI), and agreed with this research.

Statistical analysis

Categorical variables were compared using the exact Fisher test of Chi-square test, as appropriated. Non-normally distributed numerical variables were compared using the Mann-Whitney test (two groups) or Kruskal-Wallis (three of more groups).

The analysis of allelic and genotypic frequencies was made using the laws of equilibrium of Hardy-Weinberb. Values with $P<0.05$ were considered statistically significant.

RESULTS

No Indian reported prostatic symptoms; median age was 54.7 years, abdominal circumference was 86.6 cm and BMI was 23.9 kg/m2; 64.8% had normal BMI (18.5 to 25,0 kg/m^2), 29.5% overweight (25,0 to 30 kg/m^2), 3.5% obesity (≥30.0 kg/m^2) and 2.2% low weight (<18.5 kg/m^2). Median PSA was 0.52 with values ≤2.5 ng/mL in 91.3%, >2.5 ng/mL in 9 cases (8.7%), and 5.8% with PSA ≥4 ng/mL (Table-1). Control group is described at Table-2.

83 Indians completed the question form; mean age was 53 years. Most informed absence of symptoms or light symptoms (score ≤7) and only 15% moderate symptoms (score 8-19); IPSS varied from 3 to 19, median 7.

Cassava (manioc) (98.7%), fish (25.2%) and animal hunt meat (86.4%) were the most frequent food ingested during basic Indian meals, followed by flour (41.7%), fruits (28.9%) and vegetables (27.2%). Meat, chicken and pork were referred only by 17.1%, 16.7% and 5.7% respectively.

Table 1 - Clinical and laboratory characteristics of Indians (n=228).

Characteristic	Value or n
Age, years	
Interval	40 to 91
Mean±SD	54.69±12.06
Median	52.5
BMI, Kg/m^2	
Interval	17.3 to 33.8
Mean±SD	23.94±3.11
Meann	23.9
Abdominal circumference, cm	
Interval	62 to 110
Mean±SD	86.64±8.25
Median	86
Smoking	
Yes	78 (34.2)
No	150 (65.8)
Alcohol abuse	
Yes	95 (41.7)
No	133 (58.3)
Testosterone, ng/dL (n=65)	
Interval	14 to 889
Mean±SD	495±1.78
Median	472
Digital rectal exam, grams (n=224)	
Interval	10 to 80
Mean±SD	21.56±8.74
Median	20
PSA, ng/mL (n=103)	
Interval	0.02 to 13.95
Mean±SD	1.10±1.89
Median	0.52

Table 2 - Demographic characteristic of non-Indians (controls).

Characteristic	n (%)
Age, years (n=87)	
Interval	18 to 86
Mean±SD	41.1±15.3
Median (IQR)	39 (30-51)
Ethnical group (n=87)	
White	66 (75.9%)
Non-white	21 (24.1%)
Smoking (n=45)	
Yes	9 (20.0%)
No	36 (80.0%)

IQR= interval interquartis; **SD=** standard deviation

When the ethnic groups were compared, the Yanomamis were younger with lower values of BMI and lower prostate volume at DR. There were no differences between testosterone and PSA levels, and PSA increased with age (Table-3).

Indian and non-indigenous showed super--representation of haplotype Arg/Arg, 74.5% versus 42.5%, p<0.0001, polymorphism TP53 and Ile/Ile 35.3% versus 60.9%; Ile/Val 45.9% versus 28.7% and Val/Val 18.8% versus 10.3%, for GSTP1, p=0.0003, respectively (Table-4).

We observed an association of GSTP1 genotype and serum PSA, with predominance of polymorphic homozygous genotype Val/Val in individuals with lower PSA levels (p=0.0361).

Tables 5 and 6 show demographic and clinical characteristics, according to variants of TP53 and GSTP1, respectively.

DISCUSSION

Our data show that the indigenous population presents low prostate volume, BMI close to normality and healthy dietary habits, different from the Brazilian population. Also, Indians present lower incidence of prostatic symptoms (according to IPSS, only 15% moderate) in relation to non-indigenous Brazilians with same age evaluated in a screening program of prostate cancer (29%, with 24% of moderate symptoms and 5% with severe symptoms (11).

Among the ethnic groups, the Yanomamis were younger, with lower values of BMI and prostatic volume, although with similar serum values of PSA and testosterone.

The analysis of polymorphism of TP53 codon 72 and GSTP1 demonstrated significant differences between Indians and non-indigenous and the homozigous polymorphic genotype Val/Val was related to significant lowers levels of serum PSA.

These differences may be related to age differences, but also due to behavior and dietary habits between the ethnic groups, although without clinical significant difference of age in regard to prostatic evaluation. The greater contact of the Macuxi population with non-indigenous populations may have merged new behavior and dietary habits similar to non-Indians.

In contrast, the greater geographic distance from urban centers may have contributed to preservation of dietary habits and lifestyle of the Yanomamis. In this group, all participants ate animal hunt meat and fish, none reported ingestion of bovine meat and only two reported chicken ingestion.

Also, genetic differences associated to racial and ethnical factors have influence on the predisposition to prostatic diseases. Recently our group identified genetic polymorphisms related to the metabolism of carcinogens that can distinguish patients with high or low risk of PCa or benign prostatic hyperplasia (12).

The incidence of prostate cancer in the Brazilian Indian population is unknown. At "Hospital Geral de Roraima (Saúde Indígena Hospitalar)", reference to this ethnical group, there were 10 cases per year (median) in the last 5 years.

Several studies have demonstrated that American Indians present low risk for PCa (13-15). In one of the first studies that described the epidemiological profile of Indians compared to white Americans, Dunham et al. (1973) identified similar prevalence of PCa among groups (5). On the contrary, Gilland et al. (1998) found different patterns of incidence and mortality of PCa among American Indians, blacks, Hispanics from New

Table 3 - Demographic and clinical characteristic of Macuxis, Yanomamis and "others ethnical groups".

Characteristic	Macuxi n (%)	Yanomami n (%)	Other ethnical groups	P (Macuxi x Yanomami)	P (Macuxi x Yanomami x Other ethnical groups)
Age, years	n=99	n=33	n=95		
Interval	40 to 91	40 to 73	40 to 81		
Mean±SD	57.7±13.1	50.0±9.7	53.3±11.0	0.002	0.0034
Median (IQR)	56 47-65	48 42.5-55.7	52 44-60		
BMI, kg/m^2	n=99	n=33	n=95		
Interval	17.4 to 33.8	17.3 to 26.9	18.3 to 31.0		
Mean±SD	24.8±3.2	21.4±2.3	23.3±2.9	<0.001	<0.001
Prostatic volume (DR) (g)	n=99	n=32	n=93		
Interval	10 to 45	10 to 30	10 to 80		
Median (IQR)	20 15-30	15 15-20	20 15-25	<0.001	0.0014
Prostatic volume (DR) (g)	n=99	n=32	n=93		
≤20	52 (52.5)	27 (84.4)	57 (61.3)		0.0058
>20	47 (47.5)	5 (15.6)	36 (38.7)		
Total Testosterone (ng/dL)	n=34	n=8	n=23		
Interval	99-826	66-550	14-889		
Mean±DP	502.2±177.7	414.4±155.6	512.2±185.0	0.207	0.390
PSA (ng/mL)	n=54	n=11	n=38		
Interval	0.1-13.9	0.03 and 6.2	0.02-5.1		
Median (IQR)	0.6 0.4-1.0	0.48 0.11-1.02	0.41 0.23-0.96	0.349	0.3573
PSA (ng/mL)	n=54	n=11	n=38		
≤2.5	49 (90.7)	10 (90.9)	35 (92.1)		0.9734
>2.5	5 (9.3)	1 (9.1)	3 (7.9)		
Free PSA (ng/mL)	n=54	n=11	n=38		
<0.52	23 (42.6)	6 (54.5)	22 (57.9)		0.3306
≥0.52	31 (57.4)	5 (45.4)	16 (42.1)		

n=number of individuals with available data; **DR=**digital rectal exam; **IQR**=interval interquartis; **PSA=**prostatic specific antigen; **SD**=standard deviation

Table 4 - Frequency of variants TP53 and GSTP1 in non-Indians and Indias.

Characteristic	Non-Indians	Indians	P*
TP53			
Arg/Arg (GG)	37 (42.5%)	152 (74.5%)	
Arg/Pro (GC)	39 (44.8%)	42 (20.6%)	<0.0001
Pro/Pro (CC)	11 (12.6%)	10 (4.9%)	
GSTP1			
Ile/Ile (A/A)	53 (60.9%)	73 (35.3%)	
Ile/Val (A/G)	25 (28.7%)	95 (45.9%)	0.0003
Val/Val (G/G)	9 (10.3%)	39 (18.8%)	

A=Adenin; **Arg=**Arginin; **C=**Citosine; **G=**Guanine; **Ile=**Isoleucin; **Pro=**Proline; **Val=**Valin.

*Chi-square

Table 5 - Demographic and clinical characteristics according to P53 variant.

Factors	Arg/Arg n (%)	Arg/Pro n (%)	Pro/Pro n (%)	P
Ethnical group	n=151	n=42	n=10	
Macuxi	70 (46.4)	13 (30.9)	2 (20)	
Yanomami	21 (13.9)	7 (16.7)	0	0.0637*
Other ethnical groups	60 (39.7)	22 (52.4)	8 (80)	
Smoking	n=152	n=42	n=10	
No	55 (38.7)	15 (35.7)	4 (40.0)	0.9674*
Yes	97 (63.8)	27 (64.3)	6 (60.0)	
Alcohol abuse	n=152	n=42	n=10	
No	65 (42.8)	16 (38.1)	7 (70)	0.1840*
Yes	87 (57.2)	26 (61.9)	3 (30)	
Age, years	n=152	n=42	n=10	
Interval	40.0 a 91.0	40.0 a 81.0	40.0 a 78.0	
Median (IIQ)	52.0 (44.0-63.0)	54.5 (45.0-61.0)	56.0 (47.0-68.0)	0.7303**

IIQ=interval interquartil; **Arg=**Arginin; **Pro=**Prolin.

*Chi-square; **Kruskal-Wallis.

Mexico and non-hispanic whites, with the lower incidence among Indians (1).

Although different incidences of PCa among ethnic groups exist due to different screening methods and access to health care (13), several exogenous risk factors may contribute to the disparity of risks, including dietary habits, lifestyle and genetic predisposition (16).

The association of prostate cancer, ingestion of saturated fat, BMI and physical activity was observed in many ethnic groups (14), along with the association of the size of body, in particular waist-hip, with PCa in Chinese men (17).

Several studies suggest that PCa incidence is related to the visited country. Changes in lifestyle and dietary habits have great impact, increa-

Table 6 - Demographic and clinical characteristic, according to GSTP1 variant.

Fatores	Ile/Ile n (%)	Ile/Val n (%)	Val/Val n (%)	P
Ethnical group	n=73	n=94	n=39	
Macuxi	29 (39.7)	42 (44.7)	16 (41.0)	0.6513*
Yanomami	12 (16.4)	14 (14.9)	3 (7.7)	
Other ethnical groups	32 (43.8)	38 (40.4)	20 (51.3)	
Smoking	n=73	n=95	n=39	
No	27 (37.0)	33 (34.7)	14 (35.9)	0.9553*
Yes	46 (63.0)	62 (65.3)	25 (64.1)	
Alcohol abuse	n=73	n=95	n=39	
No	37 (50.7)	38 (40.0)	15 (38.5)	0.2997*
Yes	36 (49.3)	57 (60.0)	24 (61.5)	
Age, years				
Interval	40.0 a 88.0	40.0 a 91.0	40.0-84.0	0.3975**
Median (IIQ)	50.0 (44.0-63.0)	53.0 (45.0-62.0)	55.0 (45.2-64.7)	

IIQ=interval interquartil; **Ile=**Isoleucin; **Val=**Valin.

*Chi-square: **Kruskal-Wallis

sing three to seven times the incidence of PCa in first generation of American Japanese and Chinese, whose fathers migrated to USA (18, 19). However, the impact of diet is still controversial and data related to Indian nutritional status are rare.

In men, testosterone is the main circulating androgen, with major role in male physiology, in particular prostate. We observed that Yanomamis present lower levels of testosterone (414 ng/dL) in relation to other ethnic groups (502/512 ng/dL), but still within normal limits (350-1000 ng/dL).

We have also observed a particular difference of size and consistency of prostate during DR in Indians in relation to non-indigenous patients. It was observed a "minimum" gland with a more fibroelastic consistency, sometimes not detectable during digital rectal exam in the Indian population. We think that, more than isolated hormonal factors, the ingestion of several plants and the genetic background are the principal causes of this characteristic of physical exam of Indians.

The analysis of serum PSA using different thresholds revealed that 5.8% of participants had total PSA≥4.0 ng/mL and 8.7% >2.5 ng/mL. In accordance to other studies (20-23), we have observed a rise of PSA levels with age in our population, indicating that the rise of PSA with age of Brazilian Indians is in accordance to general population.

In our casuistic abdominal circumference (90 cm is the threshold value) did not correlated to lower urinary tract symptoms (obstructive and/or irritative), as well as to prostatic cancer, in accordance do European results (24, 25).

Genetically, our data show that none patients of Yanomami group presented the genotype Pro/Pro of p53, compared to 2.02% of Macuxi, 8.3% in other ethnic groups and 12.6% in the control group, highlighting the miscegenation of the genotype Pro/Pro of p53.

Wu et al. demonstrated that genotypes Arg/Pro and Pro/Pro related to the susceptibility to Pca in Chinese men (26), in accordance to Quiñones et al. in Chilean patients (27). However, Henner et al. reported that the genotype Pro/Pro could be related to protection against PCa in Caucasian men (28).

Genotypic divergence of Yanomami population may be explained by intercrossing of consanguineous marriages, and the genes being transmitted from only one ancestral. Another aspect is the subdivision of population in isolated groups, separated by geographic, political, socioeconomic, religious and cultural barriers, preventing the exchange of genes by interethnic marriages (29).

When we evaluated the genotypic profile results of GSTP1, again we observed difference between Indians and non-Indians. The frequency of variant genotypes Ile/Val and Val/Val is lower among Indians, raising again the hypothesis of the above factors for p53 being related to such genotypic profile. Among the Yanomami studied, the homozygous genotype Val/Val was observed in only three cases (7.7%).

A meta-analysis study of genotypes GSTM1, GSTT and GSTP1 including 11 studies (2.528 patients and 3.076 controls) concluded that these three polymorphisms are not important factors for the susceptibility to PCa (30) but Indian populations were not represented.

In our sample, the number of participants per ethnic group is relatively small and the estimates of race, ethnic group and comparison among groups were restricted to Macuxis, Yanomamis and "other ethnic groups" as a third group.

On the other hand, this study so far is one with the biggest casuistic of Amazon Indians evaluated urologically, anthropometrically and genetically (P53 codon 72 and GSTP1). Although with a restrict number of controls (n=87), the results suggest differences of the genetic profile of Indians, maybe related to risk-protection patterns that explain the low prostate volume and the relatively low incidence of prostatic diseases in these populations.

Limits of the study: although we had not compared dietary details with the ingestion of satured fat or industrial products among ethnical groups, it is evident that hunt meat is the basis of Indian diet; although the detailed comparison between ethnical groups more or less culturalized was obtained, the comparison with the control group of non-indigenous individuals was limited to genetic, age and tobacco use.

New Indian population studies are necessary to measure and follow the epidemiological modifications due to contact among Indians and non-Indians, in order to stablish health care guidelines, in particular preventive ones, directed to the new reality of the studied population. These new studies may reveal the impact of inheritance of detoxification genes as polymorphisms of GSTP1 and TP53, along with the recognition and elimination of toxic dietary products related to prostatic diseases.

CONCLUSIONS

Indians, in particular Yanomamis, present low prostatic volume, lower BMI and different genotypic profile of GSTP1 and TP53 codon 72, although with similar PSA and testosterone levels to other ethnic groups. These aspects may be related to good prostatic health of the studied indigenous population.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 353-359, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.24

Analysis of monotherapy prostate brachytherapy in patients with prostate cancer. Initial PSA and Gleason are important for recurrence?

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ABSTRACT

Purpose: To evaluate the clinical outcome of a cohort of localized prostate cancer patients treated with 125-I permanent brachytherapy at the São José Hospital – CHLC, Lisbon.

Materials and Methods: A retrospective analysis was carried out on 429 patients with low and intermediate-risk of prostate adenocarcinoma, according to the recommendations of the EORTC, who underwent 125I brachytherapies in intraoperative dosimetry "real-time" system between September 2003 and September 2013.

Results: The mean follow-up was 71.98 months. Biochemical relapse of disease by rising PSA (Phoenix criterion) was observed in 18 patients (4.2%). Through the application of Kaplan-Meier survival curves in this sample, the rate of survival at 6 years without biochemical relapse was higher than 95%. By Iog rank test comparing biochemical relapse with initial PSA (15-10 and <10) and Gleason values (7 and <7), there was no statistical difference (P=0.830) of the initial PSA in the probability of developing biochemical relapse. In relation to Gleason score, it was noted a statistical difference (P<0.05), demonstrating that patients with Gleason 7 are more likely to develop biochemical relapse.

Conclusions: Brachytherapy as monotherapy is at present an effective choice in the treatment of localized prostate adenocarcinoma. Biochemical relapses are minimal. The initial PSA showed no statistically difference in the rate of relapses, unlike the value Gleason, where it was demonstrated that patients with Gleason 7 have a higher probability of biochemical relapse. Cases with PSA bounce should be controlled before starting a salvage treatment.

ARTICLE INFO

Key words:
Brachytherapy; Prostate; Patient Outcome Assessment; Disease Management

Int Braz J Urol. 2015; 41: 353-9

Submitted for publication:
December 15, 2013

Accepted after revision:
July 27, 2014

INTRODUCTION

Currently, active treatment of prostate carcinoma in patients with localized disease and long life expectancy is recommended (1). Clinically localized prostate cancer is typically managed by well established therapies like radical prostatectomy, brachytherapy, and external beam radiation therapy. Permanent brachytherapy (BT) with 125-I seed implant gets PSA control 10 years higher than that reported with external radiotherapy (ERT), and comparable to radical prostatectomy (RPT) (2-7). Brachytherapy was developed to treat prostate cancer 50 years ago and already have a lot of publication in the entire world and there are already publications with 15 years

of monitoring (8). There is a perception that only large centers obtain satisfactory long-term results. Therefore, we decided to review our experience in 429 patients treated according to the American (9) and European (10) recommendations, with braided seeds according to a transperineal ultrasound-guided radioactive seed implantation, in a "real-time" system; if we had adequate results, the technique could be improved or the indications of the BT should be adjusted further. In Portugal, about 8 centers have implemented this technique, but there aren't published results. So, it was time to start our evaluation in Portugal.

MATERIALS AND METHODS

In September 2003, we started the treatment of prostate carcinoma with radioactive I-125 seeds. Until September 2013, we performed 429 implants with intraoperative dosimetry "real-time" system by transperineal ultrasound-guided - Mount Sinai School of Medicine (11). This review included consecutive low and intermediate-risk patients, according to the classification of D'Amico (12) modified according to the recommendations of the EORTC (10): low risk with PSA<10, Gleason 2-6, stageT1-T2a; intermediate risk with PSA 10-20, Gleason score 7, stage T2b-c (T2c was included as intermediate risk according to the EORTC criteria). No high-risk cases (PSA>20, Gleason 8-10, T3) or with three intermediate-risk factors were included. Other exclusion criteria were: life expectancy <5 years, compromised urinary function (International Prostate Symptoms Score: IPSS>20), and transurethral resection (TUR) in the last 6 months. All patients signed a specific informed consent.

The mean age was 67.4 years (46-75 years). The median PSA level before BT (Initial PSA) was 6.8ng/mL (2, 10-15), 86% <10 and 14% 10-15. Clinical stage was T1-T2a in 98.1% and T2b-c in 1.9%. All patients were diagnosed with adenocarcinoma through ultrasound-guided biopsy. The Gleason score was 6 in 90% and 7 in 10%. Low-risk cases were 74% and intermediate-risk 26% (Table-1). In all patients with intermediate-risk was required a negative biopsy of seminal vesicles. Only two patients presented two intermediate-risk factors. Hormonal therapy (HT) was used in 105 patients (24.5%), to reduce prostate volume > 60 cc (LH-RH analogue for three months).

Table 1 - Characteristics of the 429 patients.

	Patients	Percentage
Age < 55	11	2.6%
Age 55–59	51	11.9%
Age 60–64	91	21.3%
Age 65–69	147	34.2%
Age 70–75	129	30%
Clinical stage		
T1a-b	9	2.1%
T1c	263	61.3%
T2a	149	34.7%
T2b	5	1.2%
T2c	3	0.7%
Gleason		
G6	386	90%
G7	43	10%
PSA		
PSA < 10	369	86%
PSA 10-15	60	14%

The volumetry was calculated three and four weeks before the implant using transrectal ultrasound. If the volume was greater than 60 cc, hormonal treatment was offered and repeated at three months.

All patients (low and intermediate-risk) underwent a brachytherapy as monotherapy by transperineal ultrasound-guided "real-time" system, and the prescribed minimum peripheral dose for prostate was 140 Gy. The main objective was to achieve the following constraints: V100>98% (prostate volume receiving 100% dose); D90>140 Gy (dose that 90% of the prostate receives); V150 urethra <1% (volume of the urethra receiving 150% dose), and rectal V100<5% (volume of the

rectum that receives 100% dose). The number of seeds and the implant location were prepared in the operating room. The median seed activity was 0.508 mCi (0.399-0.603 mCi). The patients were discharged the following day. They were given an appointment a month after the implant for CT definitive dosimetry.

The PSA control was performed every three months the first year, every four the second, every 6 months up to 5 years and annually thereafter. Biochemical relapse (BR) was considered according to the Phoenix criterion: PSA nadir+2ng/mL (13). Toxicity was measured with the RTOP/EORTC scale and urinary function also with IPSS. Sexual function was measured by the scale of the National Cancer Institute. For biochemical control statistical analysis, the Kaplan-Meier test was performed. We applied the Iog rank test by crossing the biochemical relapses with initial PSA values (Group 1) and the values of Gleason (Group 2) to evaluate its statistical significance.

RESULTS

The mean follow-up was 71.98 months (6 years), maximum 119.73 months and at least 3 months. Eleven patients died of concurrent disease not associated with prostate cancer. Twenty-five patients had PSA elevations with risk of biochemical relapse. Seven patients (1.6%) with theoretical BR remained untreated because the PSA remained at levels below the diagnostic ones and below 10, with negative extension studies and/or negative biopsy, and in them PSA declined spontaneously. Therefore, only 18 patients actually had BR (4.2%). Sixteen of them had a positive prostate biopsy and were treated with HT (two with cryotherapy). Two cases were not biopsied due to advanced age and starting HT because PSA was >10ng/mL. The mean age of the 18 patients with BR was 67.8 years (56-75). All the 18 patients had local recurrences and did not undergo HT previously to BT for prostate downsizing.

The actuarial survival free of BR at 6 years was 95.8% (Figure-1). In cases of low and intermediate risk it was 95.5% and 89.2%, respectively. There were no statistical differences according to Initial PSA on the BR - Group 1. Patients with PSA <10 had a BR-free survival of 96.2%, compared to 95.7% with PSA 10-15 (p=0.830) (Figure-2). However, when we compared the Gleason score on the BR – Group 2, the patients with Gleason 6 had a BR-free survival of 95.6% compared to 87.5% with Gleason 7 (p<0.05) (Figure-3). Time until BR was between 14 and 104 months (mean 46.8 months). Transient PSA elevation was studied in a subgroup of 120

Figure 1 - Results of the total actuarial biochemical control by Kaplan-Meier test.

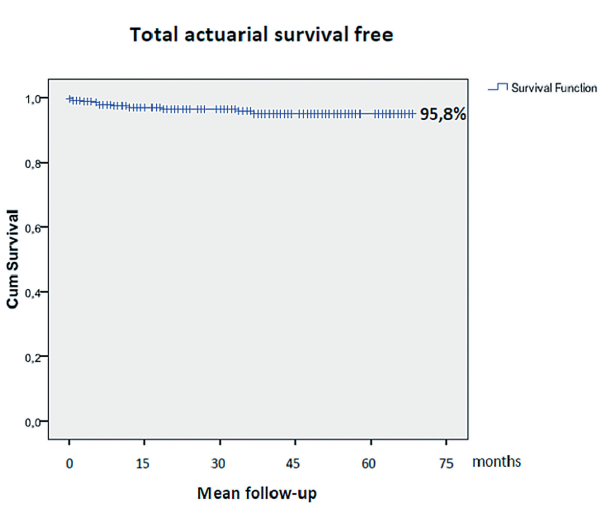


Figure 2 - Results of crossing the biochemical relapses with Initial PSA values (Group 1) by log rank test.

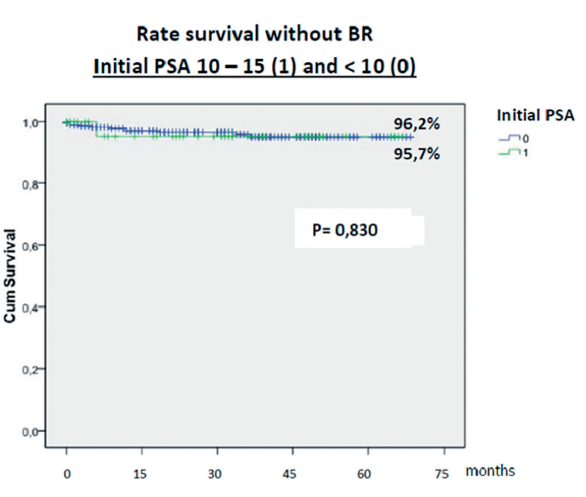
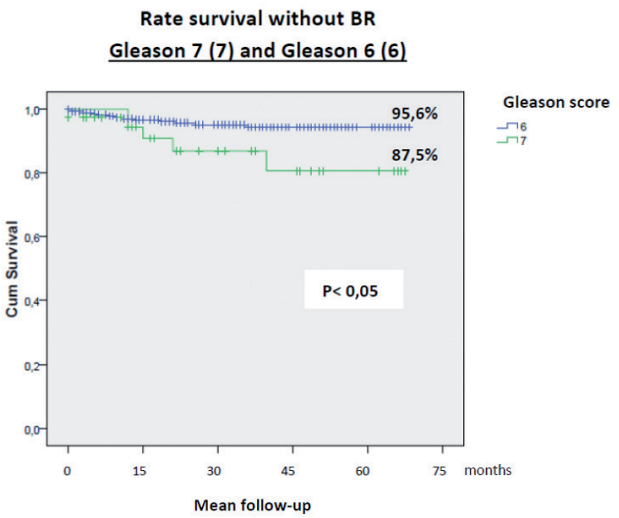


Figure 3 - Results of crossing the biochemical relapses with Gleason score (Group 2) by log rank test.



patients in a 6 months follow-up. An increase of >0.1ng/mL was detected in 49% (28% without HT, 79% with HT). When an increase of >0.4ng/mL was considered, the transient elevations was 14% (8.5% without HT, 21% with HT). The median PSA nadir in the group PSA<10 was 1.08ng/mL and in the group PSA 10-15 was 1.56ng/mL. The median PSA nadir in the group Gleason 6 was 1.46ng/mL and in the group Gleason 7 was 1.63ng/mL.

Rectal acute complications are related to the endorectal probe, G2: 0.6%, G1: 17%. Rectal late toxicity was minimal with only five cases of rectal bleeding (1.2%) (G2: 2, G1: 3). Post-treatment rectal fistulas were not found. Hematuria occurred in some cases during the first and second day. No case of long-term incontinence or hematuria has been detected (G0). Mean IPSS before the implant was 8 (0-18) and mean time for full recovery was 5.5 months (range 0-16 months). We had to probe 6.5% patients due to acute urinary retention, which resolved within two months. The side effects were of low intensity in 58% of the patients. Desobstructive TUR-P was necessary in 10 patients, average of 27 months (16-39 months) after treatment. 141 patients (33%) have only mild to moderate urinary complaints (dysuria, urinary frequency) controlled with oral therapy (α-blockers).

Sexual function was determined in the first 260 patients (using International Index of Erectile Function - IIEF) and discarding previous cases of impotence, it was preserved in 60% of the patients. Analyzing only the cases that did not receive HT, 12% had prior impotence, and those with some degree of erection, one year after implantation, 76% of patients had regained the same level of prior sexual activity.

Regarding the CT dosimetric data at one month of the implant, a mean V100 of 93.7% (81.08-98.98%) and D90 of 177.68 Gy (140-225 Gy) was obtained. Mean prostate size was 43.9 cc (14-65 cc).

DISCUSSION

All the patients, of low and intermediate risk, received prostate brachytherapy as monotherapy. Permanent TB in low-risk cases gets biochemical control at 10 years between 87% and 96%, and in intermediate-risk ones between 63% and 86% (14). Our study at 6 years (95.5% low risk, 89.2% intermediate) confirms the same results, however, most of the cancers treated in this cohort were probably clinically insignificant cancers.

Many clinical factors have been described that influence the result, PSA level, Gleason, T stage, percentage of positive biopsy cylinders, (10, 14) but in our study only the Gleason score was significant.

A quarter of cases in our study received HT (24.5%), but it did not improve the results. In the series of Mount Sinai School of Medicine (11) and Leeds (15), the HT did not influence the BR significantly. It is queried whether permanent implants are suitable for young men. In our study, of 62 patients <60 years, only one suffered a relapse, and all preserved sexual potency. A study by the Mount Sinai School of Medicine confirms that men up to 60 years old achieve an excellent biochemical control at 8 years, comparable to older ones (16).

Transient PSA elevations are another datum to be studied. They are defined as an elevation of the PSA above the initial nadir, which later declines without any treatment. However, different

definitions of the BR lead to false positives while transient elevations last (17). In our work, 7 of 25 cases with theoretical BR were monitored without treatment and the PSA declined. Mean time to the onset of the PSA elevation is a useful indicator. In our series, the real BR occurred at an average of 46.8 months and the false ones at 24 months. A study in Toronto with 292 patients showed that the median time to the PSA elevation indicative of the BR was 30 months, and concluded that caution is advised in interpreting an early increase in the PSA level in the first 30 months (18). The time to the first PSA elevation is the most valuable factor to distinguish between a transient increase and a BR, considering that transient elevations are more common in young men and that these cases have a better prognosis, as demonstrated in a study of 820 patients: control rate at 5 years in patients with elevation ≥0.2 was 97.7% vs. 91% in those who did not have transient PSA elevation (19).

Performing a post-implant dosimetry in patients undergoing permanent prostate BT is essential (20) to know the D90 and V100, which correlate with the result (21). Doses higher or lower than 150 Gy were the only prognostic factor in 558 patients at intermediate risk at Memorial Sloan Kettering Cancer Center (22). With D90 >140 Gy control reached 93% at 10 years. At the Mount Sinai School of Medicine, in 243 patients on monotherapy, a group of optimal dose (≥140 Gy D90) was distinguished with control at 8 years of 82% and suboptimal (D90 <140 Gy) of 68%. In low-risk cases, this difference was 94% vs. 75% (11). The Leeds experience was similar (23), significant only in low-risk cases (24).

We used the intraoperative dosimetry system that allows the immediate calculation of each seed when inserted into the prostate gland. The dose distribution for the implant is calculated in ''real time'' in the operating room, and new seeds can be inserted if cold areas are detected. When the implant is finished, the dosimetry reflects the dose distribution in agreement with the position in which the seeds have remained, properly identified with ultrasound images, which makes possible to get a better D90 and V100. Although there are slight differences between the results of intraoperative dosimetry and that performed monthly by CT, the intraoperative implant dosimetric system allows for a good approximation to the real administered dose (25). When it was performed right at the end of the implant, in the operating room and under ultrasound control, the V100 reached 97% and the D90 177 Gy. Planning based on real-time ultrasound does not accurately reflect dosimetry based on postoperative CT (26), although the prostate edges are better defined by ultrasound than by CT.

In a study of 2,693 patients from 11 institutions treated with permanent BT monotherapy, the only controllable factor with long-term impact was the D90, which reflects the quality of the implant (27). The impact of these changes will lead to better results, obtained through a closer integration of planning processes with the actual implant and the way to place the seeds (28).

In conclusion, the result of the monotherapy treatment with 125-I seeds in patients with low and intermediate-risk carcinoma is very good and with few complications. The hormone treatment did not affect the results. The PSA elevations must be controlled and, thus, a premature salvage therapy avoided. Biochemical relapses are minimal. In our sample, the initial PSA showed no statistically differences in the rate of relapses, unlike the value Gleason, where it was demonstrated that patients with Gleason 7 have a higher probability of biochemical relapse.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 360-366, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.25

Heterogeneous methodology of racial/ethnic classification may be responsible for the different risk assessments for prostate cancer between Black and White men in Brazil

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ABSTRACT

Objectives: To evaluate if the different results of prostate cancer risk between black and white Brazilian men may be associated with the varying methodology used to define participants as either Blacks or Whites.

Patients and Methods: We evaluated median PSA values, rate of PSA level ≥4.0 ng/mL, indications for prostate biopsy, prostate cancer detection rate, biopsy/cancer rate, cancer/biopsy rate, and the relative risk of cancer between blacks versus whites, blacks versus non-blacks (browns and whites), non-whites (browns and blacks) versus whites, African versus non-African descendants, and African descendants or blacks versus non-African descendants and non-blacks.

Results: From 1544 participants, there were 51.4% whites, 37.2% browns, 11.4% blacks, and 5.4% African descendants. Median PSA level was 0.9 ng/mL in whites, browns, and non-African descendants, compared to 1.2 ng/mL in blacks, and African descendants or blacks, and 1.3 ng/mL in African descendants. Indications for prostate biopsy were present in 16.9% for African descendants, 15.9% of black, 12.3% of white, 11.4% for non-African descendants, and 9.9% of brown participants. Prostate cancer was diagnosed in 30.3% of performed biopsies: 6.2% of African descendants, 5.1% of blacks, 3.3% of whites, 3.0% of non-African descendants, and 2.6% of browns.

Conclusions: Median PSA values were higher for Blacks versus Whites in all classification systems, except for non-white versus white men. The rate of prostate biopsy, prostate cancer detection rate, and relative risk for cancer was increased in African descendants, and African descendants or blacks, compared to non-African descendants, and non-African descendants and non-blacks, respectively.

ARTICLE INFO

Key words:
Epidemiology; Prevalence; Prostatic Neoplasms; Race Relations

Int Braz J Urol. 2015; 41: 360-6

Submitted for publication:
December 27, 2013

Accepted after revision:
October 19, 2014

INTRODUCTION

Prostate cancer is the most common visceral malignant neoplasm in men. The incidence of prostate cancer varies according to racial differences in several countries, as well as the estimated lifetime risk of disease and the mortality rate for cancer (1-3).

Black men have the highest reported incidence of prostate cancer in the World, with a relative risk of 1.6 compared with white men in the United States (US) (1, 2). Furthermore, age-adjusted

prostate cancer mortality is 2.4 times higher for Black patients than for Whites (2, 3).

In Brazil, most studies demonstrated a similar risk of prostate cancer between Black and White men (4-11), while only some verified an increased prevalence of prostate cancer in Black participants, compared to White ones (12-14). These results have been frequently attributed to the high race mixture index in the Brazilian population as a consequence of centuries of interethnic crosses between Europeans, Africans, and Amerindians, but they may as well be the result of the different methodology used to define participants as either Blacks or Whites in each study, because there is still no consensus in the Brazilian society (15, 16).

In Brazil, unlike US and Europe, race is frequently associated to the skin color and physical appearance of the individual, rather than ethnic origin or ancestry, with a number of classification systems available to characterize the vast majority of Brazilians along a white-to-black color continuum, each with a set of categories that vary in number and degree of complexity (15).

To evaluate if the heterogeneous methodology of racial/ethnic classification may be responsible for the different risk assessments for prostate cancer in Black and White Brazilian men, we stratified a single cohort of men undergoing prostate cancer screening within five working systems of classification, and compared the median PSA values, rate of PSA level ≥4.0 ng/mL, indications for prostate biopsy, prostate cancer detection rate, biopsy/cancer rate, cancer/biopsy rate, and the relative risk of cancer between Black and White groups within each racial/ethnic classification system.

PATIENTS AND METHODS

All men attending a prostate cancer education program in our Institution that accepted to be tested for prostate cancer underwent a free prostate cancer screening that included medical history, digital rectal examination (DRE), and serum PSA determination. The program was conducted in the city of Curitiba, PR, located in the south region of Brazil, as part of the city employees' health care system. The study protocol was reviewed and approved by the Institutional Ethics Committee on Human Research (registry number 2253.147/2010-06).

At evaluation, all participants were categorized by a single examiner as white, brown (pardo) or black (hetero-identification), and responded an open-ended question regarding their origin or ancestry (self-identification).

Individuals were classified as blacks when they presented typical physical features of the black race, including dark skin on clothing-covered areas, and characteristic hair texture and shape of the lips and nose; whites when they had white to pale pink skin color on covered areas; and browns when they did not fit the black or white variables. Participants were also included in two groups: African descendants, when they reported any African origin or ancestry in the family, regardless of their skin color; or non-African descendants.

A Microsoft® Excel® database was specifically design for the study purposes. Outcomes of interest included the number of participants, proportion of black, brown, and white men, percentage of African descendants, and non-African descendants, median (range, mean±SD) PSA value, rate of participants with a PSA level ≥4.0 ng/mL, indications for prostate biopsy, prostate cancer detection rate, biopsy/cancer rate, cancer/biopsy rate, and the relative risk of cancer between Blacks and Whites in the different racial/ethnic classification systems. For comparison means, participants were grouped as blacks versus whites, blacks versus non-blacks (browns and whites), non-whites (browns and blacks) versus whites, African versus non-African descendants, and African descendants or blacks versus non-African descendants and non-blacks.

Statistical analyses were performed using univariate (non-adjusted), and multivariate (adjusted) analysis. In the first, Pearson's chi-square test or Fisher exact test were used for categorical variables and student's t-test for continuous variables. In the latter, linear or logistic regression were performed, whichever appropriate, adjusted for age (≥60 years versus <60 years), education (incomplete elementary school level or lower versus complete elementary school level or higher), family history of prostate cancer, and personal history of increased blood pressure, diabetes melli-

tus, vasectomy, and sexually transmitted urethritis (yes versus no, to all). Computations were performed using IBM® SPSS Statistics®, version 20.0.0. Statistical significance was considered for $p<0.05$.

RESULTS

Among 1544 participants included in the study, 794 (51.4%) men were identified as whites, 574 (37.2%) as browns, and 176 (11.4%) as blacks. African ancestry was reported by 5.4% of participants: 23.3% of blacks, 4.6% of browns, and 1.9% of whites. Demographics of the racial groups are summarized in Table-1.

The PSA level was ≥4 ng/mL in 12.0% of African descendants, 11.4% of blacks, 8.6% of whites, 8.0% of non-African descendants, and 7.0% of browns. The median PSA level was 0.9 ng/mL in white men, brown individuals, and non-African descendants, compared to 1.2 ng/mL in blacks, and African descendants or blacks, and 1.3 ng/mL in African descendants. Median PSA level was higher for Blacks versus Whites in all classification systems, except for non-white versus white individuals (Table-2).

Indications for prostate biopsy were present in 183 (11.9%) participants, including a PSA level at or above 4.0 ng/mL in 59.6%, a suspicious

Table 1 - Demographics.

Racial Classification System	Black[1] versus White[2]	Black versus non-black[3]	Non-white[4] versus white	African descendant[5] versus non-African descendant[6]	African descendant or black versus non-African descendant and non-black
Black group – No. (%)	176 (18.1)	176 (11.4)	750 (48.6)	83 (5.4)	218 (14.1)
White group – No. (%)	794 (81.9)	1368 (88.6)	794 (51.4)	1443 (94.6)	1326 (85.9)

[1] Participants with typical physical features of the black race, including dark skin on clothing-covered areas, and characteristic hair texture and shape of the lips and nose; [2] Participants with white to pale pink skin color on covered areas; [3] White and brown participants together; [4] Brown and black participants together; [5] Participants with any African origin or ancestry in the family, regardless of their skin color; [6] Participants with no African origin or ancestry in the family

Table 2 - Median PSA values between different racial classification systems.

Racial Classification System	Median PSA value (range, mean±SD)	Univariate analysis(*)	Multivariate analysis(**)
Black	1.2 (0.0-134.5, 2.8±10.7)	0.007	0.004
White	0.9 (0.0-28.3, 1.6±2.2)	0.001	0.003
Black	1.2 (0.0-134.5, 2.8±10.7)		
Non-black[1]	0.9 (0.0-61.0, 1.6±2.7)	0.339	0.062
Non-white[2]	0.9 (0.0-134.5, 1.9±6.0)		
White	0.9 (0.0-28.3, 1.6±2.2)	<0.001	<0.001
African descendant	1.3 (0.2-134.5, 3.4±15.3)		
Non-African descendant	0.9 (0.0-61.0, 1.6±2.8)		
African descendant or black	1.2 (0.0-134.5, 2.6±9.6)	0.006	0.015
Non-African descendant and non-black	0.9 (0.0-61.0, 1.6±2.7)		

SD = Standard deviation; **[1]** White and brown participants together; **[2]** Brown and black participants together; * T-Student test; ** Linear regression, including race/ethnicity, age, education, family history of prostate cancer, and personal history of increased blood pressure, diabetes mellitus, vasectomy, and sexually transmitted urethritis.

DRE in 30.0%, or both in 10.4%. The indication rate for prostate biopsy was 16.9% for African descendants, 15.9% for blacks, 12.3% for whites, 11.4% for non-African descendants, and 9.9% for browns, being higher for African descendants versus non-African descendants (16.9% versus 11.4%, $p<0.05$ in multivariate analysis), and for African descendants or blacks versus non-African descendants and non-blacks (16.5% versus 11.1%, $p<0.05$ in univariate and multivariate analyses).

Among 165 performed biopsies, prostate cancer was detected in 50 (30.3%) subjects. Cancer rate was 6.2% in African descendants, 5.1% in black men, 3.3% in white men, 3.0% in non-African descendants, and 2.6% in brown men. The detection rate of prostate cancer was increased in African descendants versus non-African descendants (6.2% versus 3.0%, $p<0.05$ in multivariate analyses), and in African descendants or blacks versus non-African descendants and non-blacks (5.2% versus 3.0%, $p<0.05$ in univariate and multivariate analyses).

The number of biopsies required for the diagnosis of each prostate cancer increased from 2.8 in African descendants and 3.1 in blacks, to 3.8 in browns, and 3.9 in whites and non-African descendants, resulting in a prostate cancer/biopsy rate of 41.7% in African descendants, 36.0% in black, 30.0% in brown, 28.2% in non-African descendants, and 27.8% for white participants.

The relative risk of prostate cancer between black and white groups in each racial/ethnic classification system is summarized in Table-3.

DISCUSSION

PSA levels and the risk of prostate cancer are increased in Black men compared to White men in several regions around the world, including the US, Canada, Caribbean, and England (12, 17-20). In Brazil, most studies evaluating the correlation between prostate cancer and different racial/ethnic groups did not demonstrate a significant difference in the prevalence of prostate cancer between Black and White individuals (4-11). These results have been frequently attributed to the high race mixture index in the Brazilian population, but other potential source of bias may include the use of different methodology to classify individuals into racial groups.

The racial/ethnic classification model in Brazil is more complex than the bifurcated US and European model. Brazilian classification is usually based on skin color and other physical characteristics such as facial features, hair texture, and the shape of lips and nose, with a diversity of systems currently in use (15, 16).

Within the several systems of racial/ethnic classification evaluated in this study, we observed that the proportion on men grouped as Blacks varied from 5.4% to 48.6%, suggesting that the methodology of racial classification substantially modifies the racial/ethnic pattern of the population in study, with potential implications on the results.

Median PSA levels were higher in all definitions of Black group, similarly to other studies (19, 20), except for non-white versus white men.

Evaluating prostate cancer detection rates, although the relative risk of cancer was increased by 56% to 2-fold in all Black versus White groups, excluding the non-white versus white classification system, the results were statistically significant only in multivariate analysis for the groups defined as African versus non-African descendants, and African descendants or blacks versus non-African descendants and non-blacks. The groups of blacks versus whites, blacks versus non-blacks, and non-whites versus whites did not reach statistically significant difference.

The relatively wide range in the risk of prostate cancer among the different racial/ethnic classification systems reported in the present study, as well as the non significant results reported in other Brazilian studies (4-11), may reflect the relatively poor accuracy in the assignment of race/ethnicity based exclusively on anthropometric features, since these traits are believed to be a combination of genetic inheritance and adaptations to geographical factors such as solar radiation and heat (20).

Another difficulty includes the uncertainty about assigning individuals from the brown category into a separate classification group, within the White group, or within the Black group. While whites and blacks refer to the ends of the spec-

Table 3 - 95% CI relative risk between different ethnic/race/color classification groups.

Univariate analysis (*)		
Racial Classification System	RR (95% CI)	p value
Black versus white	1.56 (0.74-3.27)	0.082
Black versus non-black[1]	1.71 (0.84-3.45)	0.056
Non-white[2] versus white	0.98 (0.57-1.69)	0.934
African versus non-African descendant	2.06 (0.84-5.08)	0.070
African descendant or black versus non-African descendant and non-black	1.60 (0.94-2.75)	0.096
Multivariate analysis (**)		
Racial Classification System	RR (95% CI)	p value
Black versus white	1.90 (0.83-4.33)	0.129
Black versus non-black[1]	2.08 (0.96-4.50)	0.064
Non-white[2] versus white	0.81 (0.43-1.53)	0.520
African versus non-African descendant	3.11 (1.13-8.55)	0.027
African descendant or black versus non-African descendant and non-black	2.23 (1.09-4.59)	0.029

[1] White and brown participants together; [2] Brown and black participants together; * Fisher exact test or Pearson's Chi-square; ** Logistic regression, including race/ethnicity, age, education, family history of prostate cancer, and personal history of increased blood pressure, diabetes mellitus, vasectomy, and sexually transmitted urethritis.

trum, the Brown group serves as an umbrella category for various mixed-race terms such as mulattos (descendants of Blacks and Whites), caboclos (Amerindians and Whites), and cafuzos (Amerindians and Blacks) (15). Paschoalin et al. (13) demonstrated by genetic studies that, in Brazil, a higher proportion of Amerindian alleles may be associated with a lower prevalence of prostate cancer, while a higher proportion of African alleles is significantly related to a higher predisposition for cancer. Therefore, studies that group together brown men either with blacks as non-whites, or with whites as non-blacks, may join distinct groups of race admixture that counterbalance each other in their susceptibility to prostate cancer.

There is also disagreement about the ideal methodology of data collection for racial/ethnic classification in Brazil. Self-identification refers to a race/ethnic choice made by the respondent, and hetero-identification to a race/ethnic attribution assigned by the interviewer to the respondent (15, 16). In the present study, we used hetero-identification to classify individuals in different color groups (black, brown, or white), and self-identification to stratify participants by their origin/ancestry (African, or non-African descendants).

It is interesting to note that, although it is known there are a large number of people with at least partial African origin in Brazil, 76.7% of black participants self-reported to be non-African descendants. A large previous study showed similar results, with only about 10% of blacks considering themselves as African descendants (17). The apparent low identity of Brazilians with African ancestry may be explained because mixing usually occurred during the slavery period or in a state of degradation of the mother, resulting in a widespread social prejudice that can be observed even in present-day. This may explain why people with a darker complexion associated their skin color preferably with Amerindian (or Brazilian) ancestry, rather than African origin (16).

Some limitations of our study should be noted. Even though we adjusted PSA levels to age and other confounding variables, we did not include prostate volume and prostate symptoms

score in the multivariate analysis. Furthermore, our sample included a relatively small proportion of blacks and African descendants, and a small number of prostate cancers in each subgroup, which can result in relatively wide confidence intervals and limit the statistical power of the study.

In summary, the racial/ethnic classification system most accepted recently by government, Black movement, and media, which uses only two terms (non-white or *negro*, and white), is apparently the least adequate model for prostate cancer risk stratification. The assignment of race/ethnicity based either on anthropometric features (black, brown, and white), or on ethnic origin/ancestry (African descendant, and non-African descendant) are practical, although they are less accurate when used separately. Therefore, anthropometric features should be preferably used in combination with origin/ancestry to increase the accurateness of racial/ethnic classification in the risk assessment of prostate cancer, especially in populations with a high miscegenation index like the Brazilian people.

CONCLUSIONS

Based on several classifications systems used to stratify a single cohort of Brazilian men in different groups of Blacks and Whites, median PSA values were higher in Black versus White groups classified as blacks versus whites, blacks versus non-blacks, African descendants versus non-African descendants, and African descendants or blacks versus non-African descendants and non-blacks. Median PSA values were similar between the groups categorized as non-whites versus whites.

Black groups defined as African descendants, and as African descendants or blacks, had an increased rate of prostate biopsy, prostate cancer detection rate, and relative risk for cancer, compared to the white groups categorized as non-African descendants, and non-African descendants and non-blacks, respectively. The indication rate for prostate biopsy, prostate cancer detection rate, and relative risk for cancer were comparable between blacks versus whites, blacks versus non-blacks, and non-whites versus whites.

ACKNOLEDGEMENTS

This article is part of a post-doctoral dissertation developed by the main author at the Federal University of Paraná, Brazil.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 41 (2): 367-372, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.26

Predictive criteria of insignificant prostate cancer: what is the correspondence of linear extent to percentage of cancer in a single core?

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ABSTRACT

Objective: The aim of active surveillance of early prostate cancer is to individualize therapy by selecting for curative treatment only patients with significant cancer.
Epstein's criteria for prediction of clinically insignificant cancer in surgical specimens are widely used. Epstein's criterion "no single core with >50% cancer" has no correspondence in linear extent. The aim of this study is to find a possible correspondence.
Materials and Methods: From a total of 401 consecutive patients submitted to radical prostatectomy, 17 (4.2%) met criteria for insignificant cancer in the surgical specimen. The clinicopathologic findings in the correspondent biopsies were compared with Epstein's criteria for insignificant cancer. Cancer in a single core was evaluated in percentage as well as linear extent in mm.
Results: Comparing the clinicopathologic findings with Epstein's criteria predictive of insignificant cancer, there was 100% concordance for clinical stage T1c, no Gleason pattern 4 or 5, ≤2 cores with cancer, and no single core with >50% cancer. However, only 25% had density ≤0.15. The mean, median and range of the maximum length of cancer in a single core in mm were 1.19, 1, and 0.5-2.5, respectively. Additionally, the mean, median, and range of length of cancer in all cores in mm were 1.47, 1.5, and 0.5-3, respectively.
Conclusion: To pathologists that use Epstein's criteria predictive of insignificant cancer and measure linear extent in mm, our study favors that "no single core with >50% cancer" may correspond to >2.5 mm in linear extent.

ARTICLE INFO

Key words:
Prostate; Biopsy, Needle
Adenocarcinoma; Prostatectomy;
Prostatic Neoplasms; Risk

Int Braz J Urol. 2015; 41: 367-72

Submitted for publication:
July 01, 2014

Accepted after revision:
September 28 , 2014

INTRODUCTION

Due to widespread of PSA screening, an increasing number of T1c prostate carcinomas are diagnosed as well as the so-called clinically insignificant tumors. Many of these malignancies would most probably not have caused any symptoms during a man's lifetime if they had remained undiagnosed. This so-called overdiagnosis due to screening often results in overtreatment, subjecting men to unnecessary costly and invasive treatment with risk of important side effects (1). The aim of active surveillance of early prostate cancer is to individualize therapy by selecting for curative therapy only patients with significant cancer (2). The best possible selection of patients with prostate cancer with low risk progression is the main factor for a successful active surveillance.

Epstein's criteria on biopsies for prediction of clinically insignificant cancer in the radical prostatectomy specimens are widely used (3, 4). The criteria include: clinical stage T1c, PSA density ≤0.15, no Gleason score 4 or 5, ≤2 biopsy cores with cancer, and ≤50% cancer per core. An alternative measure to the latter criterion is to evaluate the maximum length in mm of cancer per core. A survey among pathologists showed that an estimate of the linear extent of cancer in a core was made by 81% (5). This assessment was most often given in millimeters for each core by 53% followed by estimation of percentage of cancer in each core by 39%.

Considering that a high number of pathologists evaluate tumor extent on biopsies in millimeters, which length in mm corresponds to ≤50% cancer per core when using Epstein's criteria? The aim of this study is to find this possible correspondence.

MATERIALS AND METHODS

This retrospective study was based on prostate specimens from 401 patients submitted to radical retropubic prostatectomy by one surgeon (UF). All biopsies and surgical specimens were reviewed by a senior uropathologist (AB). The tumors were graded according to the 2005 International Society of Urological Pathology (ISUP) modified Gleason score values (6). After radical prostatectomy, serum PSA was drawn every 3 months during the first year, every 6 months during the second year, and annually thereafter. No patient of this series had radiotherapy or androgen manipulation before or after surgery. Total serum PSA was measured utilizing previous validated Immulite® PSA kit. Biochemical recurrence following surgery was considered as PSA ≥0.2 ng/mL with a second confirmatory level of PSA >0.2 ng/mL according to recommendation of the American Urological Association (7). Patients without evidence of biochemical recurrence were censored at last follow-up. The present study was approved by the Institutional Committee of Ethics of our Institution.

The surgical specimens were step-sectioned at 3 to 5 mm intervals and totally embedded in paraffin. A mean of 32 paraffin blocks were processed and 6 µm sections from each block were stained with hematoxylin and eosin. Each transverse section of the prostate was subdivided into 2 anterolateral and 2 posterolateral quadrants. Using the cone method, 8 sections from the bladder neck and 8 sections from the apex were obtained.

Positive surgical margin was defined as cancer cells in contact with the inked specimen surface. Extraprostatic extension was diagnosed whenever cancer was seen in adipose tissue and, in case of desmoplastic response, whenever a protuberance corresponding to extension of tumor into periprostatic tissue was seen. Seminal vesicle invasion occurred whenever there was involvement of the muscular coat. Tumor extent at radical prostatectomy was evaluated by a semiquantitative point-count method previously described (8). Briefly, drawn on a sheet of paper, each quadrant of the transverse sections contained 8 equidistant points. During the microscopic examination of the slides, the tumor area was drawn on the correspondent quadrant seen on the paper. At the end of the examination the amount of positive points represented an estimate of the tumor extent. A total of ≤10 positive points (minimal tumor extent) correspond to ≤0.5 cm^3 tumor.

We defined insignificant cancer in radical prostatectomy, patients with organ-confined tumor (p T2), ≤0.5 cm^3 tumor (minimal tumor extent), negative surgical margins, and Gleason score ≤6. Several clinicopathologic findings of the patients were studied: age, race, clinical stage, preoperative serum PSA, weight of the prostate in surgical specimen, pathologic PSA density (serum PSA/weight of the prostate in surgical specimen); and, on the correspondent needle biopsies number of cores with cancer, maximum percentage of cancer in a single core, maximum length of cancer in a single core in mm, length of cancer in all cores in mm, and number of cores. Linear extent of carcinoma in mm was measured using a single Olympus (Olympus Optica Co., Ltd., Tokyo, Japan) micrometer eyepiece with a linear array. In cases of discontinuous foci 1 mm apart, the tumor was considered as continuous and the measure included 1 mm. In discontinuous foci more than 1 mm apart, the final extent was the sum of the measures.

RESULTS

From 401 consecutive patients submitted to radical prostatectomy over a period of 13.8 years, 17 (4.2%) patients met criteria for insignificant cancer in the surgical specimens. The mean follow-up after surgery of these 17 patients was 81 months (median 79, range 32-148). All patients were clinical stage T1c and no patient during this period had biochemical recurrence. The mean and median age (range) was 61 and 64 (46-70) years. From the total of 17 patients, 12 (70.6%) were Whites and 5 (29.4%) were African-Brazilians. From the total of 17 needle biopsies, 12 were extended. The mean and median number of cores was 10 and 9, respectively.

The clinicopathologic findings in these 17 patients are shown in Table-1. The mean, median and range of the maximum length of cancer in a single core in mm were 1.19, 1, and 0.5-2.5, respectively. No core showed length of cancer >2.5 mm.

Additionally, the mean, median, and range of length of cancer in all cores in mm was 1.47, 1.5, and 0.5-3, respectively. In no biopsy the length of cancer in all cores was >3 mm. Figure-1 illustrates a focus of adenocarcinoma in a biopsy core; it measures 0.5 mm corresponding to 4.5% of the total linear extent of the fragment which measured 11 mm.

In Table-2 we compare the clinicopathologic findings with Epstein's criteria on needle biopsy predictive of insignificant cancer in surgical specimens. The findings were concordant in 100%, 100%, 100%, 100%, and 24% patients for stage T1c, no Gleason pattern 4 or 5, ≤2 cores with cancer, no core with >50% cancer, and PSA density ≤0.15, respectively.

Table 1 - Clinicopathologic findings on the correspondent needle biopsies of 17 patients submitted to radical prostatectomy with insignificant cancer in the surgical specimen.

Preoperative PSA (ng/mL)	
Mean±SD	7.76±2.26
Median	7.3
Range	4.4-12.30
Pathologic PSA density	
Mean±SD	0.19±0.06
Median	0.17
Range	0.11-0.27
Weight of the prostate (g)	
Mean±SD	43.53±10.03
Median	45
Range	26-60
Number of cores with cancer	
Mean±SD	1.41±0.51
Median	1
Range	1-2
Maximum length of cancer in a single core (mm)	
Mean±SD	1.19±0.63
Median	1
Range	0.5-2.50
Maximum length of cancer in a single core (%)	
Mean±SD	13.69±6.63
Median	12
Range	4.5-25
Length of cancer in all cores (mm)	
Mean±SD	1.47±0.67
Median	1.5
Range	0.5-3

DISCUSSION

In this novel approach we found that comparing the findings of 17 prostatectomy specimens with insignificant cancer, there was 100% concordance with Epstein's predictive criteria on biopsies for clinical stage T1c, no Gleason pattern 4 or 5, ≤2 cores with cancer, and no core with >50% cancer per core. The mean and median (range) maximum length in a single core in mm was 1.2 and 1 (0.5-2.5). No single core in the biopsy showed cancer length >2.5 mm. An additional finding was a maximum length not more than 3 mm considering the 2 cores.

A review article has stated that no optimal method is available but advises measurements of tumor burden being in millimeters as well as percentage terms (9). We consider that the correspon-

Table 2 - Clinicopathologic findings on needle biopsy of 17 patients with insignificant cancer in comparison with Epstein's criteria predictive of insignificant cancer in surgical specimens.

Clinical stage T1c	17/17 (100%)
No Gleason pattern 4 or 5	17/17 (100%)
≤2 cores with cancer	17/17 (100%)
No core with >50% cancer	17/17 (100%)
PSA density ≤0.15	4/17 (23.53%)

dence we found in our study is important for pathologists who do not use percentage for evaluation of cancer extent. Using Epstein's criteria on biopsies to predict insignificant prostate cancer in the radical prostatectomy specimens, an alternative to the criterion "no core with >50% cancer" is "no core with >50% cancer and >2.5 mm in linear extent".

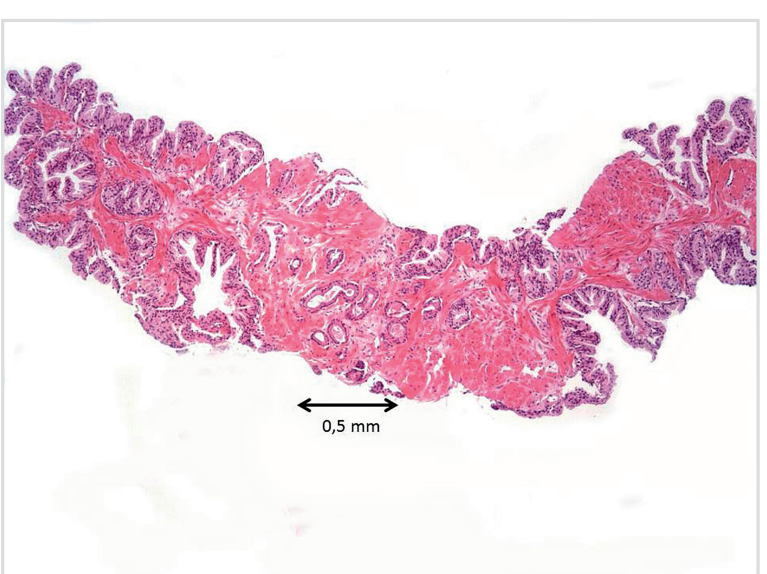
Cancer length can be measured and reported in many ways but no optimum method exists for assessing tumor burden in prostate cores (10). The amount of cancer reported may affect eligibility for active surveillance programs. A survey among pathologists showed that most pathologists estimate cancer on biopsies as linear extent in mm and not in percentage (5). Among the arguments in favor of linear extent in mm, is that percentage of core involvement is dependent on the length of the cores (11).

Millimetric measurements are preferable to percentages (e.g., 100% of a 4 mm core is very different from a 100% of a 15 mm core) (5). Other advantage of using millimetric measurements is in fragmented specimens due to the fact that percent core involvement may vary with different core lengths.

A concern exists when there are two or more foci of cancer in a single core separated by benign intervening stroma. Currently, there is no consensus as to the optimal method for measuring discontinuous cancer on biopsy from one end to the other as opposed to "collapsing" the cancer by subtracting out the intervening benign prostate tissue (11-13). In this study only one core showed two foci <1 mm apart. This case was considered as a single focus and the total linear extent of the tumor was 1.5 mm.

The frequency of insignificant cancer in radical prostatectomy surgical specimens in our study was 4.2%. Sengupta S et al. found a frequency of

Figure 1 - Illustration of a focus of adenocarcinoma in a biopsy core measuring 0.5 mm and corresponding 4.5% of the total linear extent of the fragment which measured 11 mm (hematoxylin-eosin, 100x).



5.5% (14), Augustin H et al. 5.8% (15), and Loeb S et al. 2.6% (16). No patient had biochemical recurrence in a mean follow-up period after surgery of 81 months (median 79, range 32-148). The clinicopathologic findings of these patients favor a very low risk cancer and could have been candidates for active surveillance.

The only discrepancy with Epstein's criteria in our findings was related to PSA density. The mean and median (range) was 0.19, 0.17 (0.11-0.27). According to our result, a cutoff for PSA density ≤0.15 seems to be very restrictive. Most entry criteria for active surveillance consider PSA density <15 ng/mL but others, however, consider higher cutoffs (1, 15-22). The entry criteria for active surveillance in the PRIAS study include: clinical stage T1c-T2b, no Gleason pattern 4 or 5, fewer than 3 positive cores, serum PSA <10 ng/mL, and PSA density <0.20 ng/mL/cm^3 (1). We must consider, however, that in our study PSA density was calculated by dividing preoperative PSA level by prostate weight in surgical specimen and in most studies the weight (volume) of the prostate is calculated by ultrasound. In spite of studies showing that the correlation between pathologic PSA density and actual PSA density using transrectal ultrasound is almost perfect (3, 23), these different measures may influence the results.

The serum PSA level is also variably considered in entry criteria for active surveillance.

It may be considered <10 ng/mL, <15 ng/mL, and even not considered as an entry criterion (1, 3, 17, 18, 20, 21). In our study the mean, and median (range) preoperative serum PSA value was 7.8, and 7.3 (4.5-12.30) ng/mL.

Some study limitations warrant discussion. The follow-up could be longer, however considering the favorable clinicopathologic findings (clinical stage T1c, organ-confined tumor, no Gleason 4 or 5, no positive surgical margins, and the minimal tumor extent, the probability of biochemical recurrence can be considered highly improbable.

These patients belong to the very low risk group for biochemical recurrence and could have been candidates for active surveillance. The study was based on a small number of patients. The low frequency of 4.2% for this group of patients submitted to radical prostatectomy was between 2.6% and 5.8% of other studies (14-16) and in our study reflects the involvement of our Institution in proposing to patients with criteria for insignificant cancer, active surveillance instead of definitive treatment. Not all needle biopsies were extended 12-core. From the total of 17 needle biopsies, 12 were extended; the mean and median number of cores was 10 and 9. In case all needle biopsies were extended, results could have been different. Therefore, other studies with only extended biopsies and higher number of patients are needed to support our study. We must consider, however, that in Epstein's original 1994 study the median number of cores sampled was 5 and the results were valid in the contemporary analysis of 2011 with extended biopsies (3, 4).

CONCLUSIONS

From a total of 401 patients submitted to radical prostatectomy, 17 harbored insignificant cancer in the surgical specimen. Comparing the clinicopathologic findings with Epstein's criteria on needle biopsies predictive of insignificant cancer, there was 100% concordance for clinical stage T1c, no Gleason pattern 4 or 5, ≤2 cores with cancer, and no single core with >50% cancer. However, only 24% had density ≤0.15.

We found that Epstein's criterion of "no single core with >50% cancer" corresponded to >2.5 mm in linear extent. An additional finding was a maximum length not more than 3 mm considering all cores. This correspondence is important because many pathologists estimate linear extent in mm of cancer instead of percentage. To pathologists that use Epstein's criteria predictive of insignificant cancer and measure linear extent in mm, our study favors that "no single core with >50% cancer" may correspond to >2.5 mm in linear extent.

CONFLICT OF INTEREST

None declared.

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SURGICAL TECHNIQUE

Vol. 41 (2): 373-378, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.27

An inexpensive yet realistic model for teaching vasectomy

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ABSTRACT

Purpose: Teaching the no-scalpel vasectomy is important, since vasectomy is a safe, simple, and cost-effective method of contraception. This minimally invasive vasectomy technique involves delivering the vas through the skin with specialized tools. This technique is associated with fewer complications than the traditional incisional vasectomy (1). One of the most challenging steps is the delivery of the vas through a small puncture in the scrotal skin, and there is a need for a realistic and inexpensive scrotal model for beginning learners to practice this step.
Materials and Methods: After careful observation using several scrotal models while teaching residents and senior trainees, we developed a simplified scrotal model that uses only three components–bicycle inner tube, latex tubing, and a Penrose drain.
Results: This model is remarkably realistic and allows learners to practice a challenging step in the no-scalpel vasectomy. The low cost and simple construction of the model allows wide dissemination of training in this important technique.
Conclusions: We propose a simple, inexpensive model that will enable learners to master the hand movements involved in delivering the vas through the skin while mitigating the risks of learning on patients.

ARTICLE INFO

Key words:
Vasectomy; Models, Biological; Surgical Procedures, Operative; Teaching

Int Braz J Urol. 2015; 41: 373-8

Submitted for publication:
May 16, 2014

Accepted after revision:
July 28, 2014

INTRODUCTION

The modern no-scalpel vasectomy has distinct advantages over the traditional incisional technique. Complication rates are lower (1), with lower rates of hematoma, infection, and pain than the incisional technique (2). The no-scalpel technique is recommended in the most recent American Urologic Association vasectomy guidelines as one of the preferred methods of isolating the vasa (3). A disadvantage of the no-scalpel technique is that the delivery of the vasa through the scrotal skin is challenging initially and can be difficult to learn. Using a model can help learners master this step. Several studies have demonstrated the positive effects of using surgical simulation models for the acquisition of surgical skills and improvement in performance. (4) Furthermore, the use of a model allows learners to practice the tricky delivery without risk of harming a patient.

TRAINING TECHNIQUE

Purchasing anatomic models can be expensive. For example, a visually realistic scrotal model sold in the US costs around $220 US from a medical supply house (http://www.ameditech.com/vasectomy/ved9.php). A simpler model, developed by Dr. John Pfenninger in 1995 (5), provides the most tactile realism we have encountered. The Pfenninger model is available by mail order from the National Procedures Institute for around $ 35 US, plus shipping. We have further simplified this model to develop a low-cost vasectomy training

tool that has a realistic feel and allows learners to gain confidence in delivering the vasa.

The major difference between our model and the Pfenninger model is the simplification of the model to the most basic components. We also concentrated on using readily available, inexpensive items as the basis for each part. This very simple scrotal model can be made using three components–a length of bicycle inner tube, a piece of latex tubing, and a Penrose drain.

After carefully analyzing other more expensive scrotal models, and after much trial and error, we have developed the optimal sizes for each part.

Inner tube from a bicycle tire. The "mountain bike" or 26x2.125 inch tubes are wider than "road" tubes, and thus better simulate the average scrotum.

Latex tubing. Latex tubing, also called "amber surgical tubing," is available in many different sizes. The size that best replicates the feel of vasa is 1/8 inch outer diameter, 1/16 inch inner diameter, 1/32 inch wall. The tubing can be purchased from many sources, including scuba supply stores. A very similar tubing made from silicone can also be found. This silicone tubing is more brittle than the latex and does not have the same realistic feel. The silicone tubing should be avoided for vasectomy training.

Penrose drain. ¼ inch penrose drains fit nicely over the latex tubing and provide a realistic simulation for delivering the vas through fascia. A widely available size is 18 inch x ¼ inch, and this size works well in our scrotal model.

To construct the scrotal model, the latex tubing is placed inside the Penrose drain. This simulates the vas inside the fascia. This combination is placed inside the bicycle tube. This simulates the vasa inside the scrotum (Figure-1).

For practicing the delivery of the vasa using the no-scalpel technique, the two key instruments are the vas ring clamp and the pointed vas dissector. These tools, specifically developed for the no-scalpel procedure, allow the vasa to be delivered from the scrotum through a tiny puncture (Figure-2).

Figure 1 - The "vasa and fascia" inside the "scrotum".

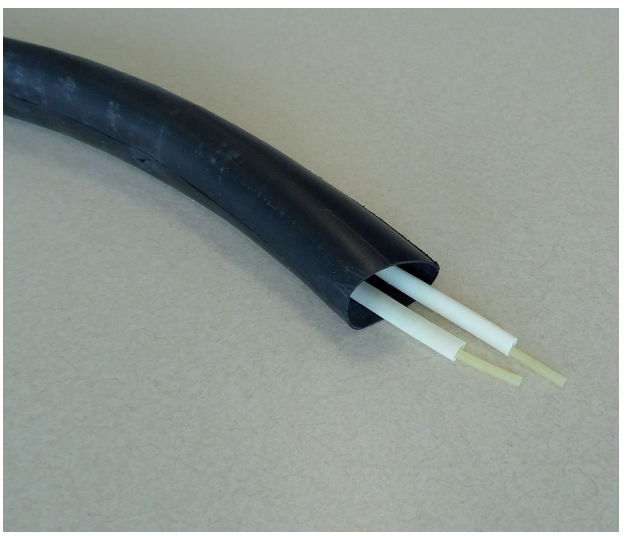
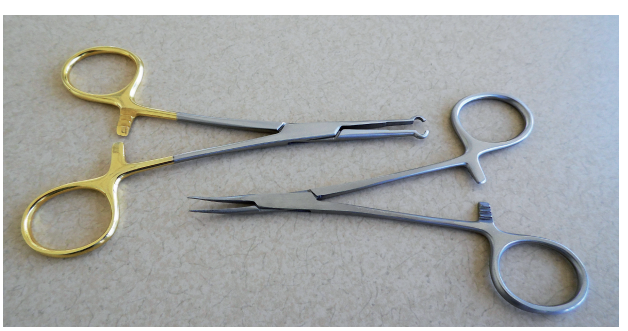


Figure 2 - Vas ring clamp and pointed vas dissector.



Steps of the procedure

When performing the no-scalpel vasectomy, the key components to the delivery of the vas are:

1. The "three finger grasp"
2. Grasping the vas with the vas ring clamp
3. Piercing the skin with the vas dissector
4. Spreading the skin and fascia
5. Hooking the vas
6. Pulling the vas through the skin
7. Grasping the vas with the vas ring clamp
8. Cleaning the fascia from the vas with the vas dissector

Each of these steps can be practiced with the simple scrotal model, and we will review them below.

For the sake of simplicity, we will refer to spatial directions as "upwards", "up," and "above", and "downwards," "down", and "below." Of course

during a vasectomy, a patient would be lying supine, so the anatomically correct directions would be "patient anterior" and "patient inferior." This can be confusing while training on a model, so the more simple concepts "up" and "down" are used during initial training and in this article.

Step 1 - The three-finger grasp

Using the non-dominant hand, place the middle finger below the scrotum and the index finger and thumb above the scrotum. Using the thumb and middle finger, palpate the vas within the scrotum. Using rolling and squeezing movements with the fingers, move the vas into the midline of the scrotum. The goal is to immobilize the vas, while simultaneously stretching taut the overlying skin. Push upward with the middle finger, and push downward with the index finger and thumb. The vas should be stretched taut between these fingers, thus tenting up the anterior skin (Figure-3).

Figure 3 - The three-finger grasp.

Step 2 - Grasping the vas with the vas ring clamp

Hold the vas ring clamp with the dominant hand. Hold the palm of that hand facing away from your body, and open the tines of the ring forceps. With one tine on each side of the vas, push the ring clamp down into the skin. Simultaneously, use the middle finger of the non-dominant hand to push the vas into the ring clamp by applying pressure from below the scrotum.

As the middle finger of the non-dominant hand pushes up, close the vas ring clamp, thus trapping the vas within the ring (Figure-4).

Figure 4 - The vas ring clamp around the skin, fascia, and vas.

Step 3 - Piercing the skin with the vas dissector

After the vas is trapped within the vas ring clamp, lift the distal tip of the forceps to create a knuckle of skin (with the vas within that knuckle). Using the index finger of the non-dominant hand, gently stretch the skin of the knuckle away from you, thus making the skin taut at the top of the knuckle. Using the dominant hand, open the vas dissector and pierce the top of the knuckle with a single tine, i.e. with a single pointed tip of the vas dissector. It is important to pierce through the skin, through the fascia, and into the lumen of the vas in one smooth motion.

A slight "pop" is felt as the tine of the vas dissector enters the lumen of the vas (Figure-5).

Step 4 - Spreading the skin and fascia

Once the single tine has pierced through the skin, fascia, and vas, withdraw the single tine and close the vas dissector. Using the same opening you created with the single tine, insert the closed tip of the vas dissector to pierce the skin,

Figure 5 - Piercing the skin, fascia and vas with a single tine.

fascia and vas with both tines. Open the tines widely to make a small tear in the upper aspect of the vas and to spread open the skin and fascia.

While opening the fascia and skin, it is very important to open the vas dissector widely in order to facilitate the subsequent delivery of the vas (Figure-6).

Figure 6 - Spreading the skin and fascia with the vas dissector.

Step 5-Hooking the vas

Once an opening is made in the skin and fascia, withdraw the vas dissector from the skin.

Then, with the point of the vas dissector facing downward, insert the right tine of the forceps into the lumen of the vas. While slightly dropping the right elbow, rotate the right wrist such that the tips of the vas dissector point up. This lifts the vas (Figure-7).

Figure 7 - Hooking the vas.

Step 6 - Pulling the vas through the skin

As the dominant hand is hooking the vas with the vas dissector, open the vas ring clamp with the non-dominant hand. This frees the vas from the skin and allows the vas to be pulled upwards by the vas dissector as you rotate the wrist of your dominant hand. With the tip of the tine still pointing upwards, gentle traction is applied and the vas is lifted out of the skin. The open vas ring clamp can be used to gently push the skin downwards to further free the vas (Figure-8).

Step 7 - Grasping the vas with the vas ring clamp

After lifting the vas as far as comfortably possible out of the skin, grasp the top of the loop of vas with the vas ring clamp. This is easier if a small opening has been made in the vas when the vas was initially punctured during step 4. It is important to try to not encircle the vas with the vas ring clamp, but instead to grasp the vas firmly with the tips of the vas ring clamp (Figure-9).

Figure 8 - Pulling the vas through the skin.

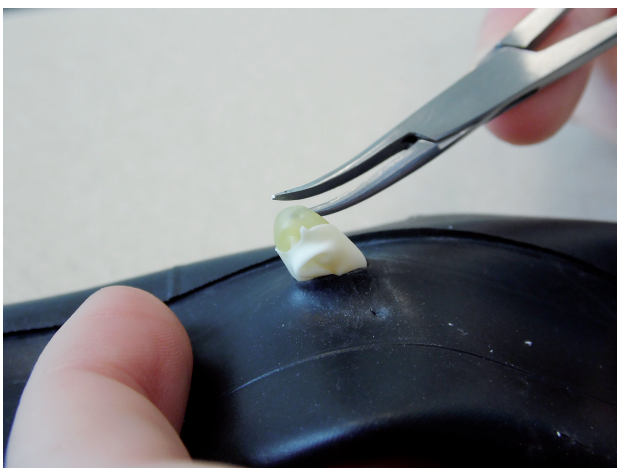
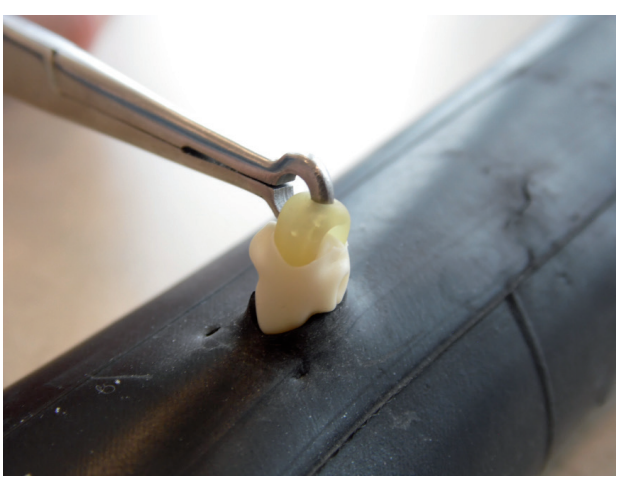


Figure 9 - Grasping the vas with the vas ring clamp.



Step 8 – Cleaning the fascia from the vas with the vas dissector

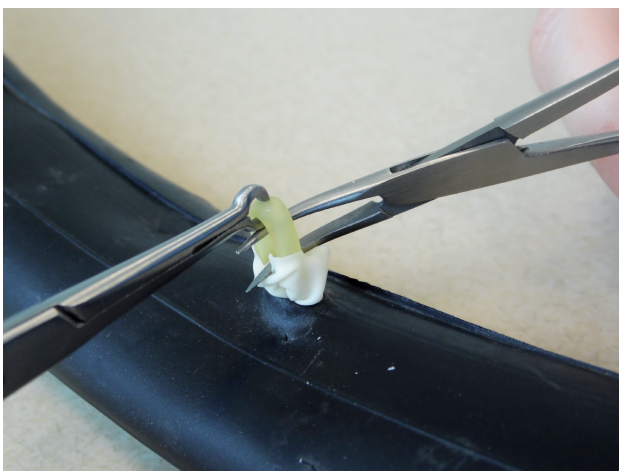
Once the vas is grasped firmly by the vas ring clamp, use one tine of the vas dissector to pierce the fascia just underneath the vas ring clamp. This opening should be within the loop of vas. Once a small opening is made with a single tine, withdraw the vas dissector. Close the vas dissector and reinsert the closed tip into the small opening in the fascia. Then open the vas dissector gently to enlarge to opening in the fascia. (Figure-10).

Once the vas is delivered and cleaned of fascia, the learners can repeat these steps until they feel comfortable with the procedure. Of course, during a vasectomy on a patient, the next steps are to occlude the vas in some manner (6). A method of vas occlusion with much evidence to support its efficacy is thermal cautery of the vas lumen combined with fascial interposition (7).

This can be covered in a different workshop.

This model can be reused many times. After the learner has delivered the vas, the vas can be returned back into the scrotum by removing the tools and applying traction to the ends of the vas as they protrude from the open end of the model. Each component is easily replaceable and components can be changed individually as they wear out.

Figure 10 - Cleaning the fascia off the vas.



CONCLUSIONS

We have developed a realistic scrotal model that enables learners to practice a challenging step in the no-scalpel vasectomy. This model is composed of inexpensive and easily obtained materials and is straightforward to construct. We expect that this model will facilitate dissemination of the no-scalpel vasectomy, which is a safe and effective method of contraception with minimal complications.

ACKNOWLEDGEMENTS

The scrotal model developed by Dr. John Pfenninger has provided inspiration for the simplified model presented in this article.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

Vol. 41 (2): 379-381, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.28

Bilateral isolated Epididymal Agenesis in a 32 year old man

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ABSTRACT

Epididymal agenesis is defined as the absence of the epididymis totally or segmentally, unilateral or bilateral, which is secondary to the Wolffian duct malformation (1). Rete testis, epididymis, vas deferens and seminal vesicle are believed to develop from Wolffian ducts.

ARTICLE INFO

Key words:
Epididymis; Leydig Cells; Testosterone; congenital [Subheading]

Int Braz J Urol. 2015; 41: 379-81

Submitted for publication:
June 08, 2014

Accepted after revision:
June 25, 2014

INTRODUCTION

Testosterone secretion produced by Leydig cells leads to vas deferens development arising from nephric duct (Wolffian duct) between eighth and twelfth gestational week.

The appendix epididymis is the remnant of cranial nephric duct and a portion of nephric duct that is contiguous with the testis develops to epididymis .

Congenital anomalies of accessory structures of testis are commonly combined with anomalies of testicular descent into the inguinal canal or sexual maldevelopment, albeit, some cases of isolated anomalies or as a part of some syndromes have been reported (1). Epididymal anomalies (i.e., fused caput medusa, epididymal tail, elongated epididymis, and epididymal atresia) are seen in 35%-75% of patients with cryptorchidism.

Congenital absence of the vas deferens (CAVD) commonly is secondary to cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation. Two types of CAVDs are: congenital bilateral absence of the vas deferens (CBAVD), usually because of CFTR gene mutation; and congenital unilateral absence of the vas deferens (CUAVD) that is commonly concomitant with ipsilateral anomalies of kidney and seminal vesicle. CUAVD is commonly secondary to different disorders of mesonephric duct morphogenesis before

the 7th gestational week (1). Epididymal agenesis may be partial or complete in these conditions.

Isolated epididymal agenesis have been reported only in animals, rams and bulls, and there is not any report of this condition in human, yet.

CASE REPORT

A 32 year-old patient without any history of previous surgery or drug use with 3 years of infertility got surveyed. At physical examination, secondary sex characteristics were completely developed and external genitalia (i.e., penis, meatus, and scrotum) were normal. Both testes were located in the scrotum with normal size and shape and related vasa deferentia were normal.

Prostatic volume was about 20cc, symmetric, and soft at digital rectal examination (DRE).

Semen analysis revealed normal semen volume and normal range of semen fructose, but azoospermia. Seminal vesicles and ejaculatory ducts were normal at transrectal ultrasonography (TRUS). Hormones (i.e., FSH, Testosterone) were in normal range. Based on clinical examinations, imaging and laboratory studies, we decided to operate the patient and vasoepididymostomy was our selected surgery. A longitudinal incision in scrotal midline raphe made a good exposure of both testes and tissues inside both hemiscrotum. Vasa deferentia were dissected toward the attachment sites to testes. There was no evidence of epididymis in any hemiscrotum and vas deferens was directly attached to the testis (Figures 1 and 2). The vasoepididymostomy was not possible, thus, biopsy of both testes was performed for pathological assessments and freezing for future artificial reproductive surgeries.

DISCUSSION AND FUTURE PERSPECTIVES

Because the epididymis, vas deferens, rete testis and seminal vesicle, altogether are developed from Wolffian ducts (1), therefore, epididymal anomalies are typically seen concomitant with other anomalies in organs that are developed from Wolffian ducts. Any epididymal agenesis in animals in previous case reports was unilateral (2, 3), but our patient had bilateral epididymal agenesis. Along with fetal development, the effect of testosterone on Wolffian duct leads to development of epididymis, vas deferens, and other organs that are related to Wolffian duct. Sometimes in disorders of sex development, evidences of incorrect or imperfect effect of testosterone on sex organs are seen, but isolated lack of epididymis has not been reported yet.

Figure 1 - Vas deference inserted to testis directly.

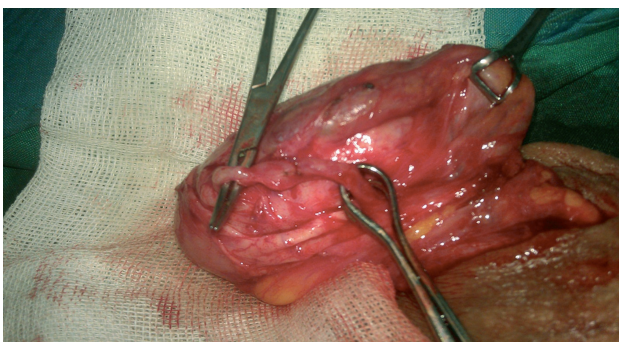
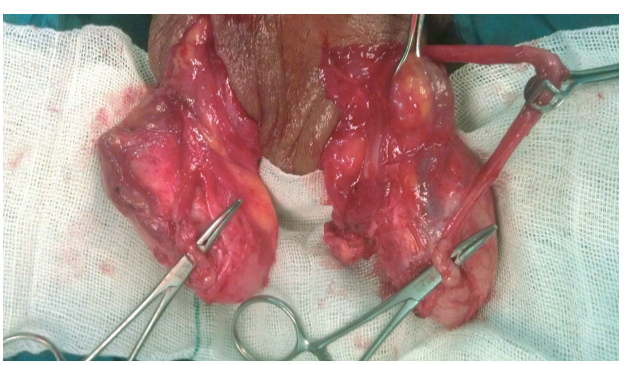


Figure 2 - Bilateral epididmal agenesis.



Because of isolated epididymal agenesis with normal development of testes and vasa deferentia in our patient, this anomaly is probably due to unknown fetal mutation after vasal development. Because of normal range of testosterone and normal development of other testosterone dependent organs, it is not reasonable that hormones interfere with this anomaly.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

Vol. 41 (2): 382-387, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.29

Migration of endotacker into the bladder 7 years after laparoscopic retroperitoneal burch application

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ABSTRACT

Laparoscopy began to be used widely since the second half of 1990s as an alternative to laparotomy or vaginal approaches in incontinence and pelvic diseases in women, based on its claimed better success rates. Injuries were reported in the bladder, gastrointestinal system and the entry of the Verress cannula in early and late laparoscopic applications. *De-novo* urging, voiding dysfunctions, marked recurrences and surgical inefficiencies were observed in 5-year follow-ups after laparoscopic incontinence surgery. Although tension-free midurethral sling operations replaced open laparoscopic colposuspensions nowadays, laparoscopic colposuspension is still preferred in cases where simultaneous laparoscopic paravaginal repair or sacrocolpopexy is considered or where synthetic graft implantation is contraindicated.

Moreover, meshes and endotackers are still frequently used in many laparoscopic applications in various clinics. The migration of the tacker used in mesh fixation in a patient where retroperitoneal laparoscopic Burch was performed 7 years ago due to stress urinary incontinence and the extraction of the ossified tacker from the bladder will be presented.

ARTICLE INFO

Key words:
laparoscopy, Burch, tacker, bladder, migration

Int Braz J Urol. 2015; 41: 382-7

Submitted for publication:
June 06, 2014

Accepted after revision:
July 17, 2014

INTRODUCTION

Although more than 100 operations have been defined as success for preventing incontinence in women, laparoscopic Burch operation was launched as the first-line option due to its high success rate and low complication rate (1). At first, it was defined as the laparoscopic Burch colposuspension procedure in 1991 (2). The fact that cystocele could also be corrected in the laparoscopic Burch operation was described as an advantage. The extraperitoneal approach was recommended more especially for patients who underwent abdominal and retro-pubic surgery and for whom a simultaneous pelvic surgery was not planned (3). It was presented as an advantageous approach due to easy entry into the Retzius space, minimum blood loss, minimum post-operative pain, shorter period of hospitalization and more rapid return to daily activities (2, 4, 5). The method of fixing the mesh with a tacker was also defined in addition to the standard laparoscopic method and it was indicated that the success rates were lower compared to the conventional sutured method (6). Complications such as the long duration of the operation, bladder injuries, *de novo* urgency, voiding dysfunctions, intestine and large vessel injuries and venous thromboembolism were previously reported in groups where the laparoscopic method was applied (7). The migration of the endotacker used for fixing the mesh into the bladder in a patient in whom retroperitoneal Burch was applied 7 years ago will be presented as a different late complication.

CASE

A 48-year old female patient with complaints of blood clots in the urine, burning during urination, frequent urination and incontinence was examined in the out-patient department. It was learned that retroperitoneal laparoscopic Burch was performed on the patient by obstetricians 7 years ago due to incontinence and bladder prolapse. The patient reported that she constantly felt urgency after the surgery. She also indicated that she had urgency type incontinence after the surgery. The patient reported that in addition to the use of gentamicin, ciprofloxacin for recurring urinary tract infections after the laparoscopic Burch procedure, and even ceftriaxone due to pyelonephritis, she received continuous anticholinergic therapy for irritative urinary complaints and ongoing incontinence. Grade II cystocele was observed at physical examination. Marshall-Marchetti-Krantz and Bonney test resulted (+). Urethral hypermobility was observed at the Q type test. The blood urea was 18 mg/dl, creatinine was 1.1 mg/dl and the leucocyte level was 3200/µL. A high level of leucocytes, erythrocytes and oxalate crystals were detected in the urinalysis. *E. coli* 100.000 cfu/ml proliferation was observed in the urine culture. No pathology was observed in the upper urinary system at ultrasonography, while it was reported that there was a stone in the bladder (Figure-1a). Prior to the assessment of the pelvic tomography, the radiologist recorded that tackers were observed around the bladder and urethra upon being informed about laparoscopic Burch and endotackers and indicated that probably one of these was inside the bladder while another one was behind the bladder (Figures 1b, c and d). A stone adhered on the right lateral wall of the bladder was observed during cystoscopy performed on the patient with spinal anesthesia (Figure-2). When the stone was removed from the bladder wall with forceps, the metallic helical structure of its adhered part was revealed and it was understood that this was an ossified tacker utilized in laparoscopy which had migrated in the bladder (Figure-2). The tacker was extracted via forceps accompanied by cystoscopy. The integrity of the bladder wall was monitored in the control cystoscopy conducted 45 days after the cystoscopic removal of the ossified endotacker which had migrated into the bladder. Grade III cystocele was detected in the vaginal examination of the patient. The patient's mixed incontinence was verified urodynamically and vaginal anterior colpography as well as transobturator tape were performed on the patient in the same session. In the physical examination of the patient, who had no incontinence complaints after surgery, it was observed that the Marshall-Marchetti-Krantz and Bonney tests were normal and that her urethral hypermobility to the Q type test recovered. No proliferation was observed in the urine culture in the post-surgical follow-ups.

A consent was received from the patient, indicating that her data would be archived and that her post-surgery data would be used for a scientific presentation.

DISCUSSION

Laparoscopic retroperitoneal Burch colposuspension has entered into our practice for the purpose of achieving urinary continence, simultaneous repair of the cystocele and lowering morbidity. The duration of the operation which was longer in the initial cases, shortened with technical support and with experience. Bladder perforation, hypotension, pneumomediastinum and pneumothorax were reported during the procedure in the initial cases (7-9). Urgent laparotomy was per-

Figure 1a - Ultrasonography image of bladder stone.

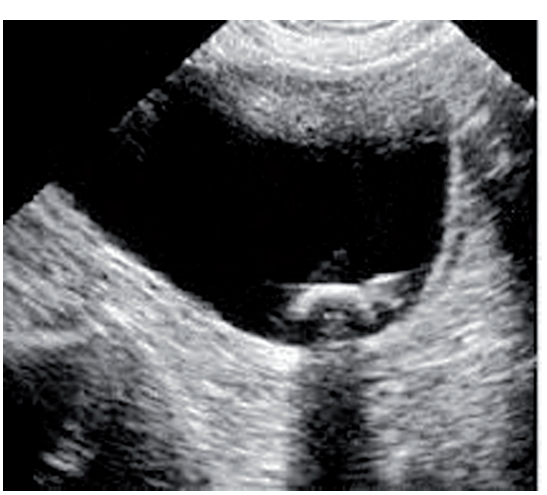


Figure 1b - Tomography (CT) image of endotacker inside the bladder.

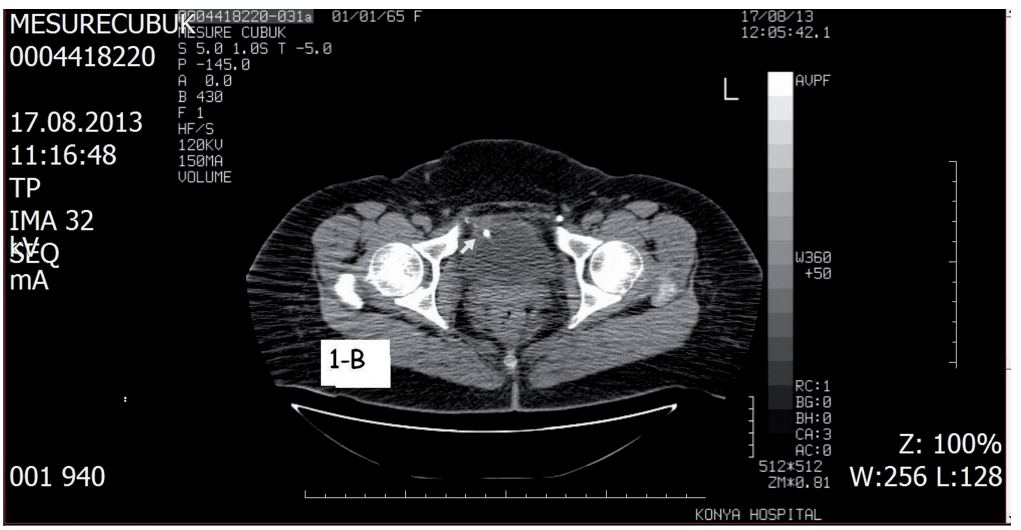
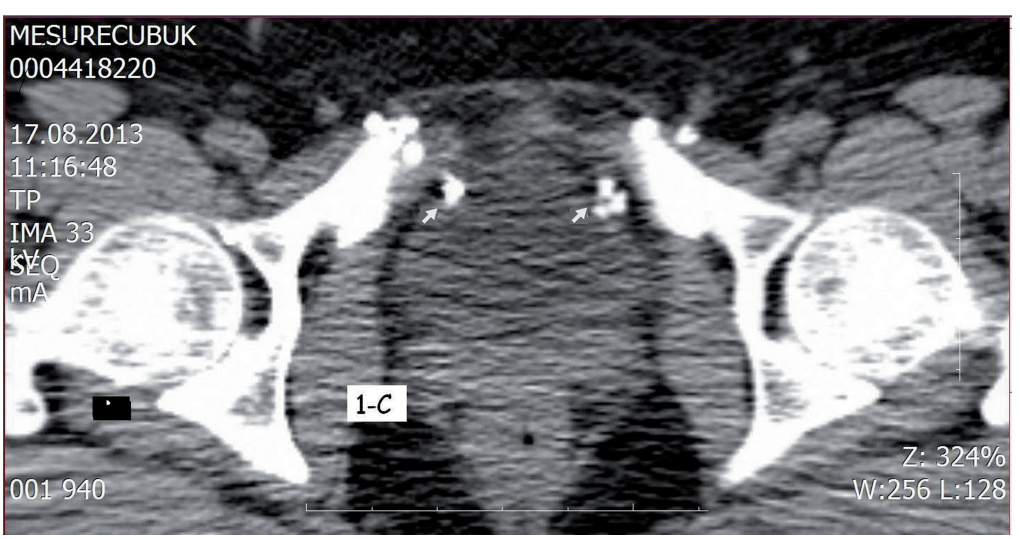


Figure 1c - CT image of normally localized endotackers.



formed in complications such as bowel damage, large vessel injury and venous thromboembolism on 280 patients who underwent laparoscopic Burch (22.2%) within the group of 1.265 patients on whom laparoscopy was performed in the multi-centric prospective case loading analysis (10). In the comparison of sutures and tackers in colposuspensions comprising 254 women, it was also claimed that tacker was more risky and that the recurrence of incontinence was higher after tacker (11). Retroperitoneal hematoma as well as bladder injury were observed in the same patient after laparoscopic Burch performed with tacker (12). Bladder damage, hemorrhage, urinary infection, fever, sepsis, *de novo* urgency, subcutaneous emphysema were reported in a 800-case series where laparoscopic Burch procedure was performed (13). Tackers are used widely used in general surgery for mesh fixation at laparoscopic inguinal hernia repairs and single-incision laparoscopic surgeries are performed with the assistance of an arthroscopic cannula and tacker (14, 15). Iatrogenic bladder

Figure 1d - CT image of endotacker migrated behind the bladder.

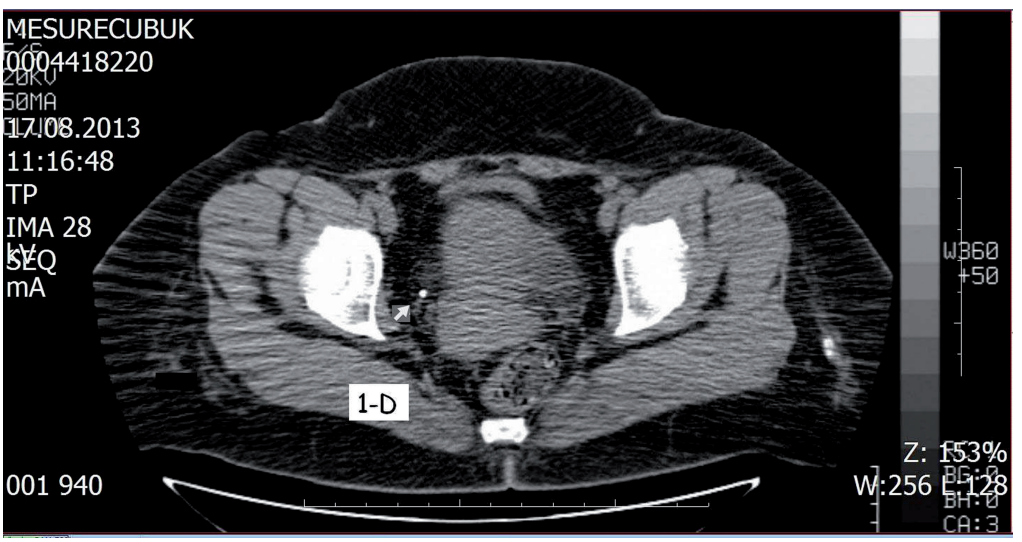
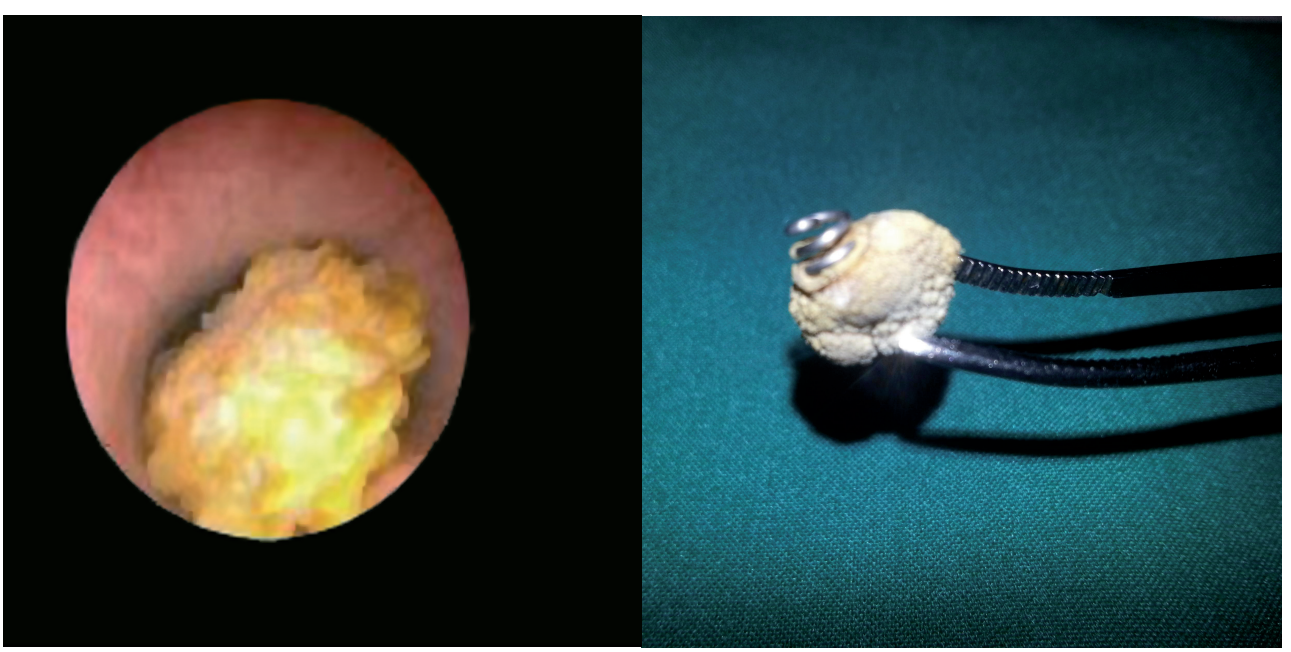


Figure 2 - Migrated tacker adhered on the bladder wall at cystoscopy and post-surgery images.



stone formation associated with non-absorbable sutures passing through the bladder after the Burch colposuspension applied again in the treatment of urinary incontinence was reported previously and dispareunia lasting 2 years as well as irritative symptoms were observed in these patients (16). It was proposed to perform cystoscopy post-surgically in these patients, where necessary, and to apply the sutures more laterally from the bladder.

Although the complication rates vary within the past 20 years, they were always similar in nature. The investigation of retrospective laparoscopic Burch complications did not reveal any endotacker migration into the bladder similar to

our case. It was indicated only in one report that bladder stones on the surgical tape were removed via cystoscopy 6 years after laparoscopic colposuspension for stress incontinence occurring as a long term complication and this was stated to be the first such case (17). Although we initially thought that the tacker was placed upon directly perforating the bladder in our patient, the fact that no pathology was detected in the bladder in numerous ultrasonographies and cystoscopies performed in different centers throughout 7 years made us shy away from this thought. We were more convinced that the tacker partially perforated the bladder during the surgical procedure and entered into the bladder upon eroding with time. We believe that our thought is more substantiated with the ossified suspended tacker image on the right lateral wall of the bladder (Figure-2). Although this is a tacker whose tip is in partial contact with the bladder, the fact that it is inside the bladder supports our claim of migration. Furthermore, the fact that one of the tackers placed on the right side was outside its normal position towards the back of the bladder, gave the impression of a tacker which was either not suitably positioned or missed or again of a perivesically migrated tacker (Figure-1d). It was observed in this case that the endotacker may have migrated inside the bladder after years and it was considered that it could have been one of the late complications of laparoscopic Burch procedure.

Nowadays, tension-free midurethral slings (such as transobturator tapes) have replaced laparoscopic and open colposuspensions. Due to their easy application, minimum invasiveness, low recurrence rate in 10-year follow-ups and contribution to the correction of sphincter impairment unlike other operations, tension-free midurethral slings have become the first-line choice. It was also recorded that tension-free mid sling may be applied in the same session with anterior colporaphy in the presence of cystocele and that the success rate was further increased. However, in the consideration of laparoscopic vaginal repair or laparoscopic sacrocolpopexy or in vaginal applications where synthetic graft implantation is contraindicated in obstetrics and urology in the laparoscopic applications of various clinics, laparoscopic colposuspension Burch procedures and endotacker comprising kits are still used simultaneously nowadays. In the light of our clinical experience, we prefer mostly transobturator tape (TOT) and transvaginal tape (TVT) procedures in urinary incontinence surgery especially for supporting external urinary sphincter, ensuring urethral hypermobility stabilization and repairing in the same session the cystocele which determines success in such surgical procedures. It was observed in the patient that the endotacker migrated behind and inside the bladder similarly to the migration of teflon which is a synthetic material used in the treatment of vesicoureteral reflux in the past. We recommend TOT and TVT even in laparoscopic gynecological approaches if urinary incontinence is to be treated in the same session.

In conclusion, we believe that it should not be forgotten that endotackers may migrate as a late complication in radiological images at different anatomic sites including stones in the bladder of patients with a history of laparoscopic incontinence where endotackers are used.

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

Vol. 41 (2): 388-392, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.30

A comparative study of ascending urethrogram and sono-urethrogram in the evaluation of stricture urethra

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ABSTRACT

To compare the efficacy of sono-urethrogram and ascending urethrogram in the evaluation of stricture urethra.

Materials and Methods: In this prospective study 40 patients with obstructive lower urinary tract symptoms and suspected to be having stricture urethra were subjected to ascending urethrogram and sonourethrogram. The radiologist was blinded to the findings of ascending urethrogram. All the sonourethrograms were done by the same radiologist. The findings of sonourethrogram & ascending urethrogram were compared with the findings of cystoscopy and intra-operative findings. The specificity, sensitivity,positive predictive value and negative predictive value of each modality in the diagnosis of various urethral anomalies were estimated.

Results: The sonourethrogram identified stricture disease in all the patients who had abnormal ascending urethrogram. In addition, other abnormalities like spongiofibrosis, diverticula and stones which were not picked up in ascending urethrogram were diagnosed by sonourethrogram. The cystoscopic and intra-operative findings with respect to stricture length, diameter and spongiofibrosis correlated well with sono-urethrogram findings. 5 patients who had stricture in the ascending urethrogram were found to be having the normal urethra in sonourethrogram and confirmed by cystoscopy.

Conclusion: sonourethrogram is an effective alternative to ascending urethrogram in the evaluation of stricture urethra. It is more sensitive in the diagnosis of anterior urethral strictures than posterior urethral strictures. It is superior to ascending urethrogram in the identification of spongiofibrosis, diameter and length of the stricture. The complications were lower in sonourethrogram group compared to ascending urethrogram.

INTRODUCTION

Stricture urethra in Males is a common problem encountered by the urologists.

Besides history and physical examination, ascending urethrogram remained the Gold Standard for evaluating Male Urethral Stricture (Cunningham et al. 1910) (1-3). It has a Sensitivity of 91% and specificity of 72% for diagnosing anterior urethral strictures (4).

However some authors have reported that this imaging study is not ideal for posterior urethral strictures. For posterior urethra, combining ascending urethrogram with MCUG is more rewarding (2). Moreover it under estimates the length of proximal Bulbar urethral stricture and has the disadvantage of underestimating peri-urethral fibrosis. This has been elaborated as this segment of urethra is fixed in the same axis as pelvis. This leads to an 'End-on View' of bulbar strictures radiographically, which reduces their apparent length.

Ascending urethrogram leads to radiation exposure of 1-2 msv, equivalent to 6 months of background radiation and 20 chest X-rays (5, 6). Procedure related infection- Contributes to 0.6% to 1.6% of all hospital acquired infections (7, 8).

The initial experiences with ultrasound evaluation of the urethra were described separately in the late 1980s by McAninch et al. (2) and Merkle and Wagner (5). Early studies identified not only the ability of ultrasound to demonstrate the exact length of strictures but also the added ability to define the periurethral tissues, as opposed to contrast urethrography, which only demonstrates the lumen. In particular, the presence and degree of periurethral fibrosis can be shown with a view to guiding surgery (9, 10).

The aim of the study was to compare the efficacy of Sono-urethrogram with Ascending urethrogram in the evaluation of Male urethral strictures.

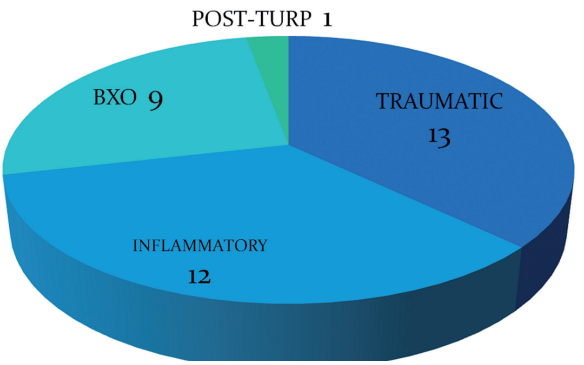
MATERIALS AND METHODS

This study was conducted in the department of urology, JSS hospital, Mysore, done between march 2011 to March 2012. Male Patients with age group between 25-75 years (mean 43 years) presenting with obstructing voiding symptoms suggestive of stricture urethra were subjected to ascending urethrogram (AUG) under aseptic precautions and antibiotic coverage. A written consent was taken from all the patients before subjecting to the study.

40 patients with evidence of stricture in AUG further underwent sono-urethrogram. Among 40 patients with evidence of stricture in AUG; 13 were secondary to traumatic, 12 inflammatory, 9 BXO and 1 post TURP respectively (Figure-1). Patients with recurrent stricture were excluded from the study.

The Radiologist was blinded to the findings of ascending urethrogram. All the sono--urethrograms were done by the same Radiologist. The findings of sono urethrogram & ascending urethrogram were compared with the findings of cystoscopy and intra-operative findings.

Figure 1 - Etiology of stricture.



TECHNIQUE

AUG: 20 mL of contrast medium (urografin 76%) was injected into the urethra using 20 ml syringe and spot films were taken. The procedure time was 15-20 min.

The following data were recorded

- Stricture location, length and diameter were measured using a scale. 20% deduction was made to correct for magnification.
- Complications.

Sono-Urethrogram: Was done using 10 MHz frequency linear array transducer. Xylocaine jelly or sterile water (20-30 ml) injected using 20 ml syringe taking care not to inject air bubble. The urethra was screened up to BMJ-using trans-scrotal and trans-perineal approach. Longitudinal and transverse images were obtained. Procedure time was 10 to 15 min.

The following data were recorded

- The stricture location, diameter, length, spongiofibrosis.
- Other peri-urethral pathology and Complications.

The specificity, sensitivity, positive predictive value and negative predictive value in the diagnosis of urethral strictures and associated abnormalities were estimated.

All the statistical calculations were done through SPSS 16.0 (2007) for windows.

RESULTS

Among 40 patients who were diagnosed as having stricture urethra by Ascending urethrogram, 5 were found to be normal in Sono--urethrogram. The findings were confirmed later by cystoscopy. One patient who had evidence of posterior urethral stricture in SUG had normal urethra in cystoscopy. The assessment of stricture was incomplete in 2 patients due to posterior location. These pts subsequently required MCUG for complete stricture evaluation (Table-1).

Table 1 – Results of Sono-urethrogram.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Anterior	100%	100%	100%	100%
Posterior	75%	50%	75%	50%

Average stricture length in AUG group was 9.3 mm (Figure-2). Stricture length could not be assessed correctly in 5 patients in AUG group due to complete cut- off. Average stricture length in SUG group was 14.1 mm (Figure-3). Mean difference between 2 groups was 4.8 mm (P value- <0.01). The cystoscopic and intra-operative findings correlated well with the findings of SUG.

Average diameter of stricture in AUG group was 0.9 mm. Average diameter of stricture in SUG group was 1.1 mm. Mean difference between 2 modalities was 0.2 mm (P-value- <0.01).

Figure 2 - Stricture as seen in Ascending urethrogram.

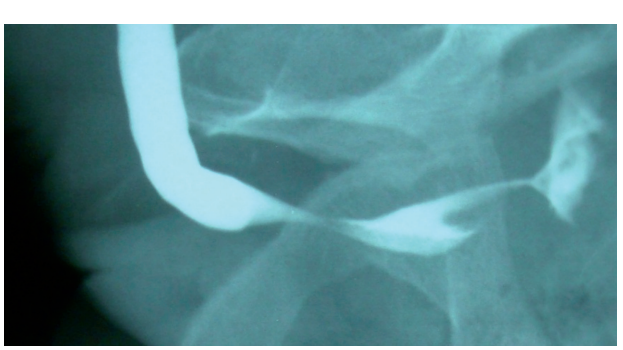
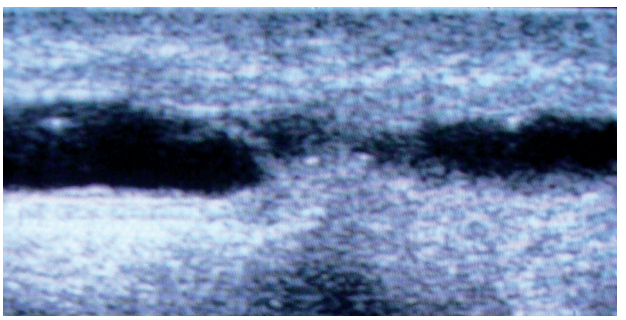


Figure 3 - Same stricture as seen in sono-urethrogram.



Spongiofibrosis was demonstrated in 12 patients with traumatic strictures, 4 patients with inflammatory strictures, 7 patients with BXO and in 1 patient with Post- operative (TURP) stricture. The findings of SUG correlated well with intra-op findings who underwent open surgery. Ascending urethrogram did not identify spongiofibrosis in any patient.

In Ascending urethrogram group, 3 patients had False tracts, 2 patients had urethral calculi and 4 patients had urethral diverticulum. In Sono-urethrogram group, 3 patients had False tracts, 3 patients had urethral calculi, 5 patients had urethral diverticulum and 2 patients had Periurethral abscess (Figures 4 and 5).

Minor bleeding was seen in 5 patients, Intravasation of contrast in 6 patients and Dysuria in 6 patients in ascending urethrogram group. In SUG group, Minor bleeding was seen in 2 patients and Dysuria in 4 patients. None of the patients developed procedure related infection.

Figure 4 - Diverticulum as seen in Sono-urethrogram.

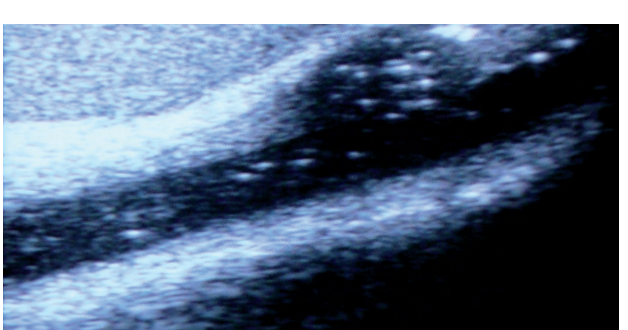
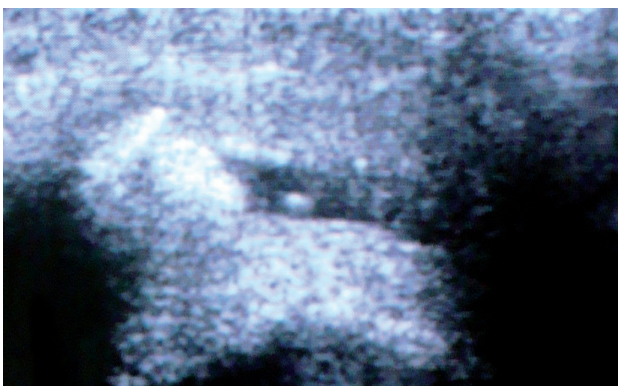


Figure 5 - Urethral calculus in sono-urethrogram.



DISCUSSION

Ascending urethrogram has been the gold standard investigation in the evaluation of stricture urethra. But it is associated with radiation exposure and underestimates the length of the stricture. Hence to overcome these shortcomings of ascending urethrogram, ultrasound evaluation of stricture urethra called sono-urethrogram has been tried.

Sono-urethrogram was more sensitive and specific in diagnosing urethral stricture disease in our study as compared to Ascending urethrogram. The false positive rate was less with sono--urethrogram as compared to ascending urethrogram. Sono-urethrogram was 100% specific, 100% sensitive in identifying anterior urethral strictures, with positive and negative predictive values being 100% (Table-1). But the accuracy of sono--urethrogram decreased dramatically in evaluating posterior urethral strictures. It was only 75% sensitive and 50% specific in diagnosing posterior urethral strictures. Voiding cysto-urethrogram is the gold standard investigation in the evaluation of posterior urethral strictures, such as PFUDD. It gives adequate information regarding the location and length of the stricture in most of the cases. AUG alone cannot give adequate information in these cases. But in some cases with inadequate opening of the bladder neck during VCUG, it needs to be complimented by either pre-operative or intra-operative antegrade cystoscopy. Hence it is not 100% sensitive in identifying all the details of posterior urethra. Sono-urethrogram is also limited in its ability to define the posterior urethral strictures at present. The accuracy of sono--urethrogram may be improved by the addition of antegrade dynamic study using perineal USG or TRUS. In our study we have not directly compared VCUG and sono-urethrogram in the evaluation of posterior urethral strictures. Till the time advances in sono-urethrogram happens, VCUG along with antegrade cystoscopy is considered as standard for the evaluation of posterior urethral strictures.

Ascending urethrogram underestimates the length of anterior urethral stricture due to end on view. It results in wrong decision making regarding the type of intervention. This is may be overcome by the addition of sono-urethrogram which accurately estimates the length of the urethral stricture in real time. In our study the average length of the stricture in Ascending urethrogram group was 9.3 mm, whereas the length in sono-urthrogram group was 14.1 mm. the difference between 2 groups was 4.8 mm, which was statistically significant (P value-0.01). The findings of sono-urethrogram correlated well with the cystoscopic and intra-operative findings. But the sono-urethrogram is not the ideal study for estimating the length of posterior urethral strictures. Combining voiding cysto-urethrogram with the retrograde study still remains the gold standard in evaluating posterior urethral stricture. Sono-urethrogram is better than Ascending urethrogram in estimating the length of anterior urethral stricture.

Sono-urethrogram is also better in assessing the diameter of the stricture. The average diameter of the stricture in ascending urethrogram group was 0.9 mm, whereas in sono-urethrogram group it was 1.1mm with the difference being statistically significant (P value- 0.01). Cystoscopic and intra-operative findings correlated well with sono-urethrogram. Hence sono-urethrogram is more accurate in assessing the diameter of the stricture as compared to sono-urethrogram.

Spongiofibrosis is the important determinant of outcome of surgical procedure. It is a poor prognostic factor, which results in recurrence of stricture if not excised completely during surgery. Hence presence of dense spongiofibrosis predicts failure of endoscopic procedures. Spongiofibrosis cannot be identified with ascending urethrogram.

Sono-urethrogram accurately estimates the thickness and length of spongiofibrosis in all the patients which helps in better planning of surgery. Hence sono-urethrogram scores over Ascending urethrogram in estimating the spongiofibrosis.

Stricture urethra is complicated in some cases. It may be associated with diverticulum, stones, false tracts and abscesses which may complicate the surgery (False tracts in our study are because of attempted catheterization or urethral dilatation before AUG or Sono-urethrogram). Hence identifying these complicating factors before surgery is very important.

Sono-urethrogram identifies all these factors more accurately than Ascending urethrogram. Periurethral abscess cannot be identified by Ascending uretrhrogram, whereas sono-urethrogram identifies the abscess more precisely. Hence sono--urethrogram helps in identifying the complicating factors and better planning of surgery.

Ascending urethrogram is associated with complications like urinary tract infection, Bleeding and intravasation. Eventhough sono-urethrogram is also associated with similar complications, the incidence is less compared to Ascending urethrogram. Hence sono-urethrogram is more accurate in assessing the diameter of the stricture as compared to sono-urethrogram.

CONCLUSIONS

Sono-urethrogram is a highly sensitive and specific investigation in the diagnosis of anterior urethral strictures.

Sono-urethrogram is not ideal for the evaluation of posterior strictures.

Stricture length can be estimated more precisely with Sono-urethrogram compared to Ascending urethrogram.

Spongiofibrosis-The thickness and length can be appreciated by Sono-urethrogram, which is not possible with Ascending urethrogram.

Associated findings such as diverticulum and peri-urethral abscess can be detected with higher sensitivity by Sono-urethrogram.

In future Sono-urethrogram might replace Ascending urethrogram as the investigation of choice in the diagnosis of stricture urethra.

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ARTICLE INFO

Int Braz J Urol. 2015; 41: 388-92

Submitted for publication:
June 16, 2014

Accepted after revision:
September 18, 2014

RADIOLOGY PAGE

Vol. 41 (2): 393-394, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.31

18F-FDG PET/CT with unusual bone and CNS metastases from testicular seminoma

Francisco Javier García Gómez [1], Irene Acevedo Báñez [1], Roberto Lasso Vega González [2], Pedro Jiménez-Granero [1], Isabel Borrego Dorado [1]

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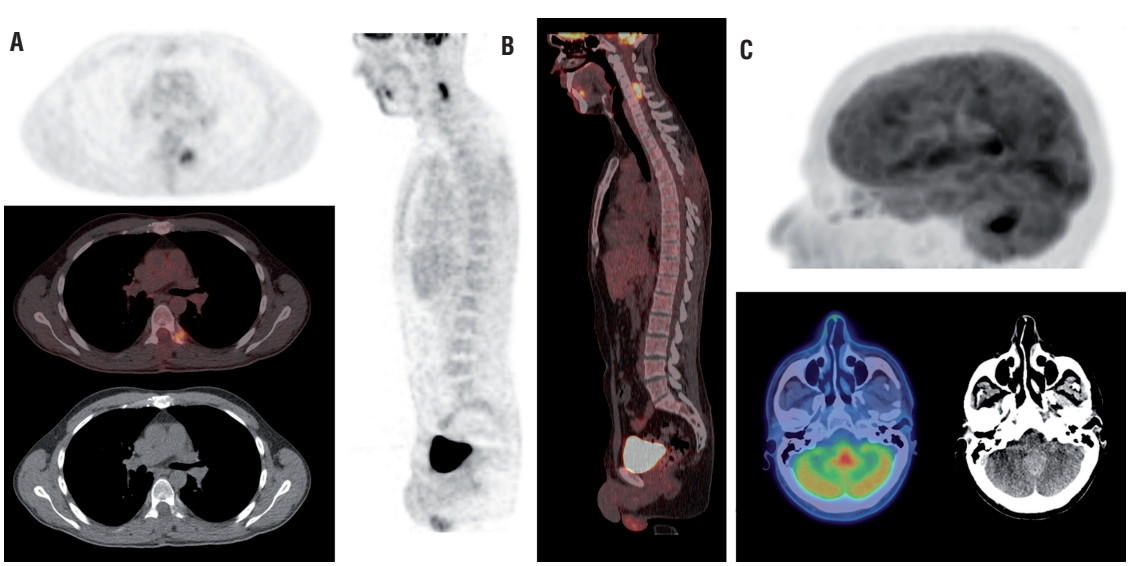
A 31 year old male with a previous history of testicular seminoma with complete reponse after orchiectomy and three cycles of BEP scheme, was referred for 18F-FDG PET/CT with a standard procedure for progressive decline consistent in spinal pain, gait difficulty and Charcot's neurologic triad (scanning speech, intention tremor and nystagmus) initiated eight month after third course of chemotherapy. Dorsal spine MRI revealed a space-occupying lesion at left T6 lamina. Histology examination confirmed a seminoma metastatic to spine.

A wholebody and cerebral 18F-FDG PET/CT scan was performed 60 minutes after intravenous injection of 370 MBq of 18F-FDG. PET/CT scan demonstrated an augmentation of soft tissue due laminectomy with increased uptake of radiotracer and a Standardized Uptake Value (SUV) maximum of 4.84 (Figure-1, Panel a), so persistence of tumour tissue cannot be excluded. Furthermore, two focal hypermetabolic areas in CNS were revealed. First, located in the spinal cord at C4-C5 vertebral levels

Figure 1 - Wholebody and cerebral 18F-FDG PET/CT scan after i.v. administration of 370 MBq of 18F-FDG. Panel a) Axial images that revealed an augmentation of soft tissue due left T6 laminectomy with increased uptake of radiotracer and SUV maximum of 4.84 that cannot allow to excluded the persistence of tumour tissue. Panel b) Sagital images showed a spinal cord metastasis with increased uptake of radiotracer at C4-C5 vertebral levels with a SUV maximum of 7.49. Panel c) Cerebral scan revealed a hypermetabolic mass in cerebellum, with high uptake of 18F-FDG (SUV maximum of 11), corresponding with 3.9 cm mass in vermix observed at post-hoc MRI scan.



with a SUV maximum of 7.49 (Figure-1, Panel b) and second, in the cerebellum with a SUV maximum of 11 (Figure-1, Panel c), corresponding with 3.9 cm mass in vermix observed at post-hoc MRI scan.

This is an unusual intra-extracranial metastatic tumor merits active treatment.

Most relapses of seminoma occur within the first 3 years after orchiectomy. Bone and CNS metastases involvement are an extremely rare event. A report of 2,550 patients revealed bone metastases only in 3 patients with seminoma (0.12%) (1). Moreover, CNS occurred only once in a series of 142 patients (0.7%) (2). Higher uptake in seminomas than in nonseminomas testicular carcinomas (3) makes 18F-FDG PET/CT a powerful tool in evaluating postchemotherapy seminoma relapses.

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ARTICLE INFO

Int Braz J Urol. 2015; 41: 393-4

Submitted for publication:
July 27, 2014

Accepted after revision:
December 10, 2014

VIDEO SECTION

Vol. 41 (2): 395-396, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.32

Single port varicocelectomy using SILS™ multiple access port

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ABSTRACT

Purpose: Several surgical approaches have been used for varicocelectomy. We report single port varicocelectomy using SILS™ (Covidien, Norwalk, CT) multiple access port.
Case : The greade III varicocele patient was 23 years old and placed in supine position. About 2 cm vertical skin incision was made in a crease just lateral to the umbilicus and SILS™ port was placed with three 5-mm trocars. Incision to posterior peritoneum from the point 3 cm superior to the internal inguinal was made by needle holder with a broken 15th blade tip. The testicular vessels were exposed. The lymphatic vessels and testicular artery were identified and separated from the testicular vein with flexible laparoscopic instruments and conventional rigid instruments. Three testicular veins were clipped with hemoclips (EndoClip , Autosuture, Norwalk, CT). Posterior peritoneum was repaired with 4-0 vicryl with one side of 5 mm Hem-o-lok clip (Weck Research,Triangle Park, NC). Than the distal end of suture site was also closed with Hem-o-lok.
Results : The whole procedure was completed with no complication. The operative time was 85 minutes, and blood loss was minimal. The patient was discharged 2 days after the operation. Left scrotal pain and vein engorgement was disappeared.
Conclusions: Our single port varicocelectomy method is a safe and effective alternative to conventional method. This will provide minimally invasive surgical option for varicocele and we can expect more potential cosmetic benefit and less morbid.

ARTICLE INFO

ARTICLE INFO Available at: www.brazjurol.com.br/videos/march_april_2015/ Bae _395_396video.htm

Int Braz J Urol. 2015; 41 (Video #2): 395-6

Submitted for publication:
January 10, 2015

Accepted after revision:
February 20, 2015

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EDITORIAL COMMENT

This video demonstrates the incredible versatility of single port laparascopy, and its implementation in the management in varicoceles. It allows the patient a quicker recovery, while still providing resolution of the pathology. We applaud the authors for their novel and innovative way of managing a very common urologic problem seen by most Urologists. With further improvement in the technology of minimally invasive therapies, the management of many more urologic diseases will become easier and hopefully more efficient and precise.

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VIDEO SECTION

Vol. 41 (2): 397-398, March - April, 2015
doi: 10.1590/S1677-5538.IBJU.2015.02.33

Reduction Corporoplasty

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ABSTRACT

Objective: Here we present the first video demonstration of reduction corporoplasty in the management of phallic disfigurement in a 17 year old man with a history sickle cell disease and priapism.
Introduction: Surgical management of aneurysmal dilation of the corpora has yet to be defined in the literature.
Materials and Methods: We preformed bilateral elliptical incisions over the lateral corpora as management of aneurysmal dilation of the corpora to correct phallic disfigurement.
Results: The patient tolerated the procedure well and has resolution of his corporal disfigurement.
Conclusions: Reduction corporoplasty using bilateral lateral elliptical incisions in the management of aneurysmal dilation of the corpora is a safe an feasible operation in the management of phallic disfigurement.

ARTICLE INFO

ARTICLE INFO Available at: www.brazjurol.com.br/videos/march_april_2015/Hakky_397_398video.htm

Int Braz J Urol. 2015; 41 (Video #3): 397-8

Submitted for publication:
November 01, 2014

Accepted after revision:
December 09, 2014

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EDITORIAL COMMENT

In this video by Hakky et al., the authors nicely depict a surgical technique of reduction corporoplasty using bilateral lateral elliptical incisions in the management of aneurysmal dilation of the corpora cavernosa. This surgical approach is both novel and nicely depicted by the authors. In the continual goal of penile reconstructive surgery to preserve/optimize penile length and functionality, the present surgical approach adds to our present surgical. The merits of this versus other techniques are ultimately at the discretion of the surgeon appreciating his personal surgical outcomes with a given technique weighed along with the expectations and treatment goals of the individual patient.

Philippe E. Spiess, MD
Video Section Editor,
International Brazilian Journal of Urology
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Books:
▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

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