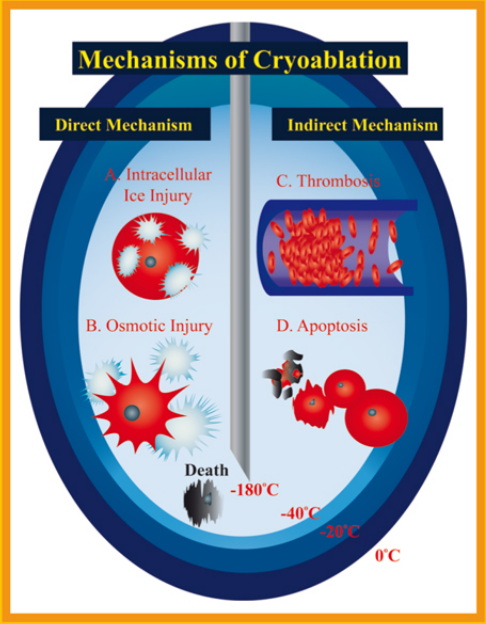
ISSN 1677-5538

IBJU

INTERNATIONAL BRAZ J UROL

Official Journal of the Brazilian Society of Urology
Volume 37, Number 6, November - December, 2011



Mechanisms of Cryoablation. (Page 694)

International Braz J Urol

EDITOR'S COMMENT

The November - December 2011 issue of the International Braz J Urol presents interesting contributions.

The editor's comment highlights some of those papers.

Dr. Valentini et al, from France, determined the relationships between phasic (P) and terminal (T) detrusor overactivity (DO) with age, urodynamic findings and sphincter behavior during involuntary detrusor contraction in woman. Steady sphincter during both P and T detrusor overactivity, and occurrence of TDO appear as specific of aging. The last result could be related to structural changes in the detrusor muscle with aging.

Dr. Fontenete et al, from Portugal, evaluated the efficacy of the urinary detection of PCA3 mRNA and PSA mRNA without performing the somewhat embarrassing prostate massage. They also intended to optimize and implement a methodological protocol for this kind of sampling. The urine samples from 57 patients with suspected prostate disease were collected, without undergoing prostate massage. RNA was extracted by different methods and a preamplification step was included in order to improve gene detection by Real-Time PCR. It was observed an increase in RNA concentration with the use of TriPure Isolation Reagent. Despite this optimization, only 15.8% of the cases showed expression of PSA mRNA and only 3.8% of prostate cancer patients presented detectable levels of PCA3 mRNA. The use of a preamplification step revealed no improvement in the results obtained. This work confirms that prostate massage is important before urine collection for gene expression analysis. Since PSA and PCA3 are prostate specific, it is necessary to promote the passage of cells from prostate to urinary tract, in order to detect these genetic markers in urine samples.

Dr. Glina et al, from Brazil, compared the efficacy and safety of parecoxib versus an nsNSAID in subjects with acute renal colic. A Phase i.v., multicenter, double-blind, noninferiority, active-controlled study was performed. 338 subjects with acute renal colic were randomized to parecoxib 40 mg i.v. plus placebo (n = 174) or ketoprofen 100 mg i.v. plus placebo (n = 164). The authors demonstrated that Parecoxib was as effective as ketoprofen in the treatment of pain due to acute renal colic, was well tolerated and had a comparable safety profile.

Dr. Terrell et al, from USA, evaluated whether cytology provides additional diagnostic information in patients with a negative NMP22® BladderChek® test (BladderChek) and negative cystoscopy. They performed subset analyses of 2 large prospective multi-center databases evaluating BladderChek for UCB detection and surveillance. These cohorts were analyzed for presence of cancer and result of urine cytology in setting of a negative cystoscopy and negative BladderChek. Based on their results the authors concluded the in patients with negative cystoscopy and BladderChek, very few cancers are missed and cytology was not effective in detection. Use of a point-of-care test in conjunction with cystoscopy in lieu of cytology could decrease cost, provide immediate results, improve negative predictive value and reduce the uncertainty that results from inconclusive cytologic results.

Dr. Miriam Dambros
Editor in Chief
International Braz J Urol

Review Article
International Braz J Urol
Vol. 37 (6): 693-696, November - December, 2011

Biophysiologic Considerations in Cryoablation: A Practical Mechanistic Molecular Review

Michael Maccini, David Sehrt, Alexandre Pompeo, Felipe A. Chicoli, Wilson R. Molina, Fernando J. Kim

Denver Health Medical Center, Division of Urology, Tony Grampsas Cancer Center, University of Colorado Health Science Center

BRIEF HISTORY OF CRYOTHERAPY

Cryotherapy techniques date back as far as the mid-1800s, when James Arnott demonstrated the effectiveness of salt/ice mixtures in palliation of breast, uterine, and skin cancers. Subsequent advances saw the use of liquid air and solid carbon dioxide in the treatment of various conditions, particularly benign dermatologic lesions (1). Cooper and Lee introduced the first automated cryosurgical apparatus cooled by circulating liquid nitrogen in 1961 and initially used it for treating neuromuscular disorders (2). Liquid nitrogen probes were soon being used in the treatment of benign prostatic hypertrophy and prostate cancer, though complications were quite common, resulting in the procedures falling out of favor until the 1990s, when intraoperative ultrasound techniques were developed, allowing more accurate monitoring of the freezing process (1). The advent of "third-generation" argon and helium gas probes in 2000 and preoperative computer thermal mapping techniques have allowed even more precise placement, temperature control, and further reduction in post-procedural morbidity (3). Cryosurgical techniques are currently used to treat a wide variety of conditions, but significant urologic indications include treatment of low and intermediate risk prostate cancer and renal cell carcinoma < 4 cm in diameter.

Key words: *cryosurgery; prostatic neoplasms; kidney neoplasms*
Int Braz J Urol. 2011; 37: 693-696

MECHANISMS OF CELLULAR DESTRUCTION

The cryosurgical site is characterized by two zones a central zone of total coagulative necrosis, and a peripheral zone characterized by varying degrees of cellular death and injury. The mechanisms by which acute, direct cellular death occurs in the central zone are quite well-established. The two mechanisms involved include intracellular ice crystal formation resulting in mechanical trauma, and cellular dehydration with associated osmotic damage. Subsequent cell death is mediated by ischemia and apoptosis. These mechanisms of cell death are summarized in Figure-1.

Because water diffusion through the cellular membrane is rate-dependent, rapid cooling of tissue (near the cryoablation probe) results in intracellular ice crystal formation, as water cannot leave the cell fast enough to equilibrate the intracellular and extracellular compartments (4). Intracellular ice crystal formation results in direct mechanical trauma to the plasma membrane and organelles and is lethal (4-7). Rubinsky demonstrated dramatically increased rates of cell death at lower temperatures in ND-1 prostate cancer cells at a cooling rate of 25 degrees Celsius/min versus both 1 degree/min and 5 degrees/min (4).

Extracellular ice crystal formation occurs below -15 degrees Celsius during slow freezing (regions farther from the probe) and effectively removes water from the space surrounding cells. This creates an osmotic gradient which draws water out of the cells, stressing cell membranes and organelles and increasing intracellular electrolyte concentra-

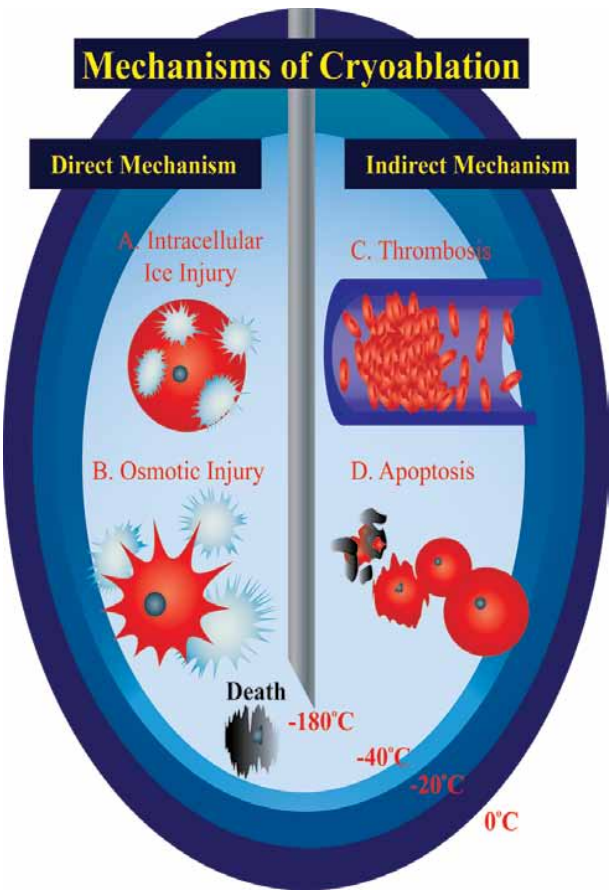


Figure 1 - A) *Closest to the cryoablation probe, rapid cooling results in intracellular ice formation, directly damaging cells and resulting in immediate cell death.* ***B)*** *In regions farther from the probe, cooling is slower, resulting in extracellular ice formation, which creates an osmotic gradient resulting in dehydration and subsequent osmotic damage to cells, in addition to mechanical injury to membranes caused by ice crystals.* ***C)*** *Cryoablation also damages blood vessels, resulting in platelet activation, thrombosis, and ultimately ischemia after reperfusion.* ***D)*** *Lastly, cells which sustain damage – particularly damage to mitochondria (M) – not severe enough to kill them during the freezing process may undergo delayed programmed cell death (apoptosis). This may be a target for adjuvant therapies but may also be a potential mechanism for tumor resistance to cryoablation.*

tions. Ice crystals outside the cell continue to grow and can cause mechanical trauma to cell membranes as well. The longer this process continues, the more likely cell death is to occur (4-7).

Slow thawing between freezing cycles results in recrystallization and further propagation of extracellular ice crystals, disrupting tissue structure (4). Thawing eventually results in a decrease in extracellular osmolarity as ice melts, which can result in an influx of water into cells, resulting in cellular swelling and bursting (5). Repeating the freeze-thaw cycle results in markedly increased cell death rates (4). This is especially important in the treatment of tumors, as there is evidence in animal models that some tumors are more resistant to damage in single freeze-thaw cycles than normal tissue, likely due to increased fibrotic tissue. Repeated freeze-thaw cycles improved local tumor control in these studies (8).

In the post-thaw period, ischemia induces further cell death in the central and peripheral zones. Endothelial damage to blood vessels results in platelet activation and thrombus formation as demonstrated in Rupp et al. histologic examination of changes in porcine post-cryoablation kidney tissue (9) leading to decreased perfusion. Additionally, Kimura et al. demonstrated decreased microvessel density and a positive correlation between hypoxia and necrosis in a mouse model of prostate cancer treated with cryosurgery (10). Ischemia induces regional hyperemia by the release of vasoactive mediators, resulting in an influx of inflammatory cells (neutrophils and macrophages). The ensuing "cleanup" process continues for weeks to months, with coagulation necrosis in the center of the surgery site and a band of neutrophils around the periphery (5).

Recent investigations have established the role of apoptosis in peripheral zone cell death. These mechanisms are not as well understood as the immediate direct injury caused by the procedure. One hypothesis is that mitochondrial damage may activate caspase cascades, resulting in programmed cell death (5,11). Recognition of the role of the apoptotic pathway of cell death in cryosurgery raises questions regarding the potential for resistance to cryotherapy, particularly in the treatment of prostate cancer, as it is not possible to include the entire prostate in the central necrotic zone to ensure negative margins due to the proximity of neurovascular bundles and the rectum. This means that the peripheral portions of the prostate will be in the peripheral "injury zone" of the cryosurgical lesion, where cellular death is at

least partially dependent on apoptosis. Given that many cancers have mutations resulting in derangements of gene-regulated cell death pathways, this could be a potential risk for recurrent disease. Baust et al. examined survival rates of in vitro prostate and colorectal cancer cell lines after a single cycle of cryoablation and found an increased cell survival rate when the cells were exposed to caspase inhibitors (12). Another study by Klossner et al. demonstrated that androgen insensitive prostate cancer cell lines showed significantly increased survival rates versus androgen sensitive cell lines after treatment (13). There are, however, also encouraging indications that adjuvant therapies may increase tumor sensitivity to cryotherapy. For example, Clarke et al. demonstrated that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and cryoablation have a synergistic effect on a PC-3 cell line (14). This suggests that there may be cancers which are more amenable to cryosurgical treatment and cancers which are more likely to be resistant, and that there may be a role for adjuvant therapies. It should be noted, however, that these studies examined the effects of a single freeze-thaw cycle on the target cell populations, rather than multiple freeze-thaw cycles.

DISCUSSION/CONCLUSIONS

Cryosurgery has seen a resurgence in use in the past two decades, with the development of more advanced and precise equipment dramatically improving procedure safety. The mechanisms of cellular destruction and damage include both direct, immediate physical damage to cells and more delayed cell death due to local hypoxia and apoptosis. The role of apoptosis in the peripheral zone is a promising target for combination therapy, but also raises concerns due to the derangement of apoptotic pathways in many tumor cell populations, as evidenced by at least one study showing increased tumor survival after cryoablation in the presence of caspase inhibitors. If these pathways are not intact, cryoablation-mediated apoptosis may be impaired, rendering some tumors relatively resistant to cryosurgery. Further studies are needed to examine the effects of abnormal apoptotic pathways to identify potential adjuvant therapies and tumor characteristics which suggest the effective road to cryotherapy. In addition, using two freeze-thaw cycles in subsequent studies would more accurately simulate clinical situations.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Gage AA: History of cryosurgery. Semin Surg. Oncol. 1998; 14: 99-109.
2. Cooper IS, Lee AS: Cryostatic congelation: a system for producing a limited, controlled region of cooling or freezing of biologic tissues. J Nerv Ment Dis. 1961; 133: 259-63.
3. Babaian RJ, Donnelly B, Bahn D, Baust JG, Dineen M, Ellis D, et al.: Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol. 2008; 180: 1993-2004.
4. Rubinsky B: Cryosurgery. Annu Rev Biomed Eng. 2000; 2: 157-87.
5. Erinjeri JP, Clark TW: Cryoablation: mechanism of action and devices. J Vasc Interv Radiol. 2010; 21(8 Suppl): S187-91.
6. Baust JG, Gage AA: The molecular basis of cryosurgery. BJU Int. 2005; 95: 1187-91.
7. Gage AA, Baust J: Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998; 37: 171-86.
8. Weber S, Lee F: Cryoablation: History, Mechanism of Action, and Guidance Modalities. Tumor Ablation. Springer, New York, 2005; pp. 250-65.
9. Rupp CC, Hoffmann NE, Schmidlin FR, Swanlund DJ, Bischof JC, Coad JE: Cryosurgical changes in the porcine kidney: histologic analysis with thermal history correlation. Cryobiology. 2002; 45: 167-82.
10. Kimura M, Rabbani Z, Mouraviev V, Tsivian M, Vujaskovic Z, Satoh T, et al.: Morphology of hypoxia following cryoablation in a prostate cancer murine model: its relationship to necrosis, apoptosis and, microvessel density. Cryobiology. 2010; 61: 148-54.
11. Yang WL, Addona T, Nair DG, Qi L, Ravikumar TS: Apoptosis induced by cryo-injury in human colorectal cancer cells is associated with mitochondrial dysfunction. Int J Cancer. 2003; 103: 360-9.
12. Baust JG, Gage AA, Clarke D, Baust JM, Van Buskirk R: Cryosurgery--a putative approach to molecular-based optimization. Cryobiology. 2004; 48: 190-204.

13. Klossner DP, Baust JM, VanBuskirk RG, Gage AA, Baust JG: Cryoablative response of prostate cancer cells is influenced by androgen receptor expression. BJU Int. 2008; 101: 1310-6.

14. Clarke DM, Robilotto AT, VanBuskirk RG, Baust JG, Gage AA, Baust JM: Targeted induction of apoptosis via TRAIL and cryoablation: a novel strategy for the treatment of prostate cancer. Prostate Cancer Prostatic Dis. 2007; 10: 175-84.

Submitted for publication:
July 25, 2011

Accepted after revision:
August 23, 2011

Correspondence address:
Dr. Fernando J. Kim
Chief of Urology, DHMC
Associate Professor of Surgery/Urology, UCHSC
Director of Minimally Invasive Urological Oncology
Tony Grampsas Cancer Center, UCHSC
FAX: + 1 303 436-6572
E-mail: fernando.kim@dhha.org

Clinical Urology
International Braz J Urol
Vol. 37 (6): 697-705, November - December, 2011

Efficacy and Safety of Parecoxib in the Treatment of Acute Renal Colic: A Randomized Clinical Trial

Sidney Glina, Ronaldo Damiao, Joao Afif-Abdo, Carlos Francisco Santa Maria, Raúl Novoa, Carlos Eurico Dornelles Cairoli, Dalia Wajsbrot, Gaston Araya

Hospital Ipiranga (SG), Sao Paulo; Hospital Universitario Pedro Ernesto (RD), Rio de Janeiro, Hospital Santa Cruz (JAA), Sao Paulo, Brazil; Clinica Anglo Americana (CFSM), Lima, Peru; Hospital del Salvador (RN), Santiago, Chile; Hospital Sao Lucas (CEDC), Porto Alegre, Brazil; Pfizer Inc. (DW), New York, NY, USA; Pfizer Central America & Caribbean (GA), Heredia, Costa Rica

ABSTRACT

Purpose: Although nonselective nonsteroidal anti-inflammatory drugs (nsNSAIDs) and opioids are effective treatments for acute renal colic, they are associated with adverse events (AEs). As cyclooxygenase-2 selective NSAIDs may provide a safer alternative, we compared the efficacy and safety of parecoxib versus an nsNSAID in subjects with acute renal colic.

Materials and Methods: Phase i.v., multicenter, double-blind, noninferiority, active-controlled study: 338 subjects with acute renal colic were randomized to parecoxib 40 mg i.v. plus placebo (n = 174) or ketoprofen 100 mg i.v. plus placebo (n = 164). 338 subjects with acute renal colic were randomized to parecoxib 40 mg i.v. (n = 174) or ketoprofen 100 mg i.v. (n = 164) plus placebo. Subjects were evaluated 15, 30, 45, 60, 90 and 120 minutes after treatment start and 24 hours after discharge. Primary endpoint was the mean pain intensity difference (PID) at 30 minutes by visual analog scale (VAS) (per-protocol population). An ANCOVA model was used with treatment group, country, and baseline score as covariates. Noninferiority of parecoxib to ketoprofen was declared if the lower bound of the 95% confidence interval (CI) for the difference between the two groups excluded the pre-established margin of 10 mm for the primary endpoint.

Results: Baseline demographics were similar. The mean (SD) mPID30 min was 33.84 (24.61) and 35.16 (26.01) for parecoxib and ketoprofen, respectively. For treatment difference (parecoxib-ketoprofen) the lower bound of the 95% CI was 6.53. The mean change from baseline in VAS 30 minutes after study medication was ~43 mm; AEs were comparable between treatments.

Conclusions: Parecoxib is as effective as ketoprofen in the treatment of pain due to acute renal colic, is well tolerated and has a comparable safety profile.

Key words: *parecoxib; ketoprofen; renal colic; lithiasis; pain; analgesia; COX-2 selective*
Int Braz J Urol. 2011; 37: 697-705

INTRODUCTION

Acute renal colic or nephrolithiasis occurs when mineral or organic solids pass though the upper urinary tract and obstruct the urinary flow (1). It is a common, often recurrent condition with an annual incidence of 1-2 cases per 1000 and a lifetime risk that is greater in men than women (between 10-20% and 3-5%, respectively) (2). Patients usually present with a sudden onset of severe urinary pain that radiates from the flank to the groin and requires immediate treatment (within 30 minutes of the onset of symptoms) (1). In addition to severe pain, the main signs and symptoms of renal colic include nausea,

vomiting, hypertension, swollen abdomen, fever and chills and hematuria.

Pain relief often takes the form of a nonselective, nonsteroidal anti-inflammatory drug (nsNSAID) or an opioid (1). Nonselective NSAIDs such as ketoprofen reduce pain and inflammation by inhibiting the cyclooxygenase (COX) enzyme (3). The COX enzyme exists in two distinct isoforms: COX-1, the primary site of action for nsNSAIDs, is present in many tissues and is necessary for physiological (homeostatic) functions such as gastric mucosal protection and normal platelet aggregation (4,5); COX-2 is an inducible form of the COX enzyme and is expressed locally in inflamed tissues (6,7). Although nsNSAIDs have been shown to be effective for acute and chronic pain relief, a number of adverse events (AEs) have been associated with their use. Common side effects from their use include rash, headaches, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation and the retention of fluid.

Parecoxib, an injectable COX-2 selective NSAID, is currently the only available nonopioid analgesic and anti-inflammatory agent indicated for parenteral use that does not interfere with platelet aggregation (8,9). As parecoxib is intended for the short-term treatment of acute pain it may, therefore, offer advantages versus nsNSAIDs in the treatment of acute renal colic; however, to date, no clinical studies have evaluated the use of parecoxib in acute pain due to renal colic.

The objective of this study was to compare the analgesic efficacy and safety of parecoxib 40 mg intravenous (i.v.) administration versus ketoprofen 100 mg i.v. to demonstrate noninferiority of parecoxib related to ketoprofen for reducing pain during an acute renal colic attack.

MATERIALS AND METHODS

Study Population

Subjects aged 18-65 years, with a confirmed diagnosis of renal colic either prior to or after randomization (as confirmed by radiography, i.v. pyelogram, helical computed tomography, magnetic resonance imaging, ultrasonography, or who had a diagnosis of renal colic confirmed by the subject's self-reported spontaneous elimination of the kidney stone at any time during the study) who presented with moderate to severe pain (baseline pain intensity [PI] score on a 100-mm visual analog scale [VAS] of > 50 mm and "moderate to severe" on a PI categorical scale) were eligible for inclusion in this study. All subjects provided written informed consent before entering the trial.

Subjects were excluded if they had significant renal or hepatic conditions (other than uncomplicated kidney stones), acute pain (other than renal colic), had been a recipient of a renal allograft, or were being treated for a urinary tract infection, pyelonephritis or clinical suspicion of such infection. In addition subjects were excluded if they had: a history of active peptic ulceration, active dyspepsia, gastrointestinal bleeding (i.e. Crohn's disease or ulcerative colitis), and an esophageal, gastric or duodenal ulcer within 1 month prior to the screening evaluation.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines and local regulatory requirements. The protocol was approved by the local institutional review boards and independent ethics committees and all subjects provided written informed consent. The ClinicalTrials.gov identifier is NCT00553605.

Study Design

This study was a phase i.v., multicenter, randomized, double-blind, double-dummy, comparative, active-controlled study to assess the analgesic activity and safety of i.v. doses of parecoxib 40 mg relative to i.v. doses of ketoprofen 100 mg for the treatment of renal colic in outpatients presenting at emergency room settings and was designed to show noninferiority of parecoxib related to ketoprofen.

Subjects were stratified by baseline PI into those with moderate or severe pain, according to the categorical PI scale. Using a computer-generated, block randomization schedule (block size 4), subjects were randomized 1:1 within each stratum and each study site to receive parecoxib 40 mg i.v. (n = 174) plus placebo or ketoprofen 100 mg i.v. (n = 164) plus placebo. To ensure both physicians and nurses were blinded to treatment, the randomiza-

tion schedule was distributed in a sealed envelope to the pharmacist in charge of preparation and dispensing of the study drug. Subjects were evaluated at screening, initiation of drug infusion (time 0), and at 15, 30, 45, 60, 90 and 120 minutes after study drug administration; follow-up was conducted 24 hours after discharge. If required, rescue medication (i.v. morphine) was allowed.

Efficacy Assessments

The primary efficacy variable was the mean pain intensity difference (PID) at 30 minutes after administration of study medication ($mPID_{30min}$) assessed by VAS for the per-protocol (PP) population. The $mPID_{30min}$ for each subject is the sum of the PID at 15 minutes (VAS at baseline - VAS at 15 minutes) and at 30 minutes (VAS at baseline - VAS at 30 minutes), divided by two. This represents the mean reduction in PI across 30 minutes.

Secondary endpoints included: 1) PI assessed through VAS scores at all time points; 2) PID - change from baseline in VAS scores - at all time points; 3) mean PID at 120 minutes after the administration of study medication ($mPID_{120min}$);

$$mPID_{120min} = \frac{15(PID_{15}+PID_{30}+PID_{45}+PID_{60})+30(PID_{90}+PID_{120})}{120}$$

4) response in PI (decrease of > 20 mm on the pain VAS score) at 30 minutes; 5) pain relief (PR) at 30 and 120 minutes; 6) sum of time interval weighted PR scores through 120 minutes ($TOTPAR_{120min}$) - $TOTPAR_{120min} = 30\,PR_{30min}+90PR_{120min}$; 7) subjects' global evaluation of study medication at 30 and 120 minutes, and at day 2; 8) physician's global evaluation of study medication at 30 and 120 minutes, and at day 2; and 9) time to rescue medication up to 120 minutes.

The PP population was used for the analysis of the primary efficacy variable and included all subjects from the modified intent-to-treat (mITT) population who also satisfied the following criteria: 1) had no major pre-existing protocol violations; 2) received the appropriate dose of study medication; 3) had valid baseline (time 0), 15- and 30-minute VAS pain assessments according to the protocol; 4) did not take rescue medication during the first 30 minutes; and 5) had a confirmed diagnosis of nephrolithiasis or ureterolithiasis. The mITT population included all randomized subjects who took at least one dose of study drug and provided at least one postbaseline pain assessment. The mITT population was used for the analysis of all secondary efficacy endpoints.

Safety Assessments

The safety population included all subjects who were randomized and received at least one dose of study medication.

Statistical Analysis

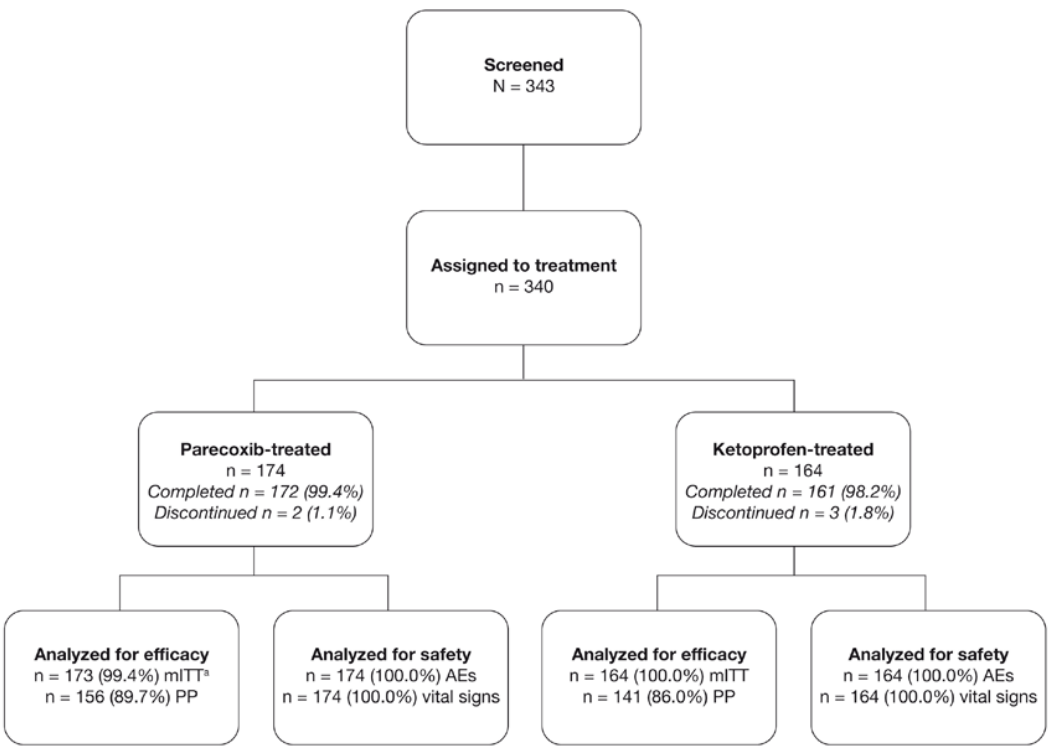
The trial was intended to show noninferiority of parecoxib versus ketoprofen. Using a sample size of 168 subjects per group and assuming a standard deviation of 25 mm and a Type I error rate of 0.050, the trial had 80% power to reject the null hypothesis (that parecoxib and ketoprofen were not equivalent) in favor of the alternative hypothesis of noninferiority. Noninferiority would have been declared for parecoxib if the lower bound of the two-sided 95% confidence interval (CI) of the treatment difference (parecoxib - ketoprofen) was greater than - 10 mm. The CI of the treatment difference was generated from the least squares means of an analysis of covariance (ANCOVA) model with terms for treatment, baseline VAS scores and country. All continuous variables were analyzed using this type of ANCOVA model. The Cochran-Mantel-Haenszel method with Ridits score (controlling for country) was used for the analysis of categorical variables; Kaplan-Meier techniques and log-rank tests were used for the analysis of the time to rescue medication.

RESULTS

Subjects

The study was conducted at 16 centers (emergency departments at orthopedic hospitals and general hospitals, and general practices) in Latin America (Brazil, Chile, Costa Rica, Ecuador, Honduras and Peru) between June 2007 and June 2009. Three hundred forty subjects were randomized to treatment, of which 338 received study medication and 333 (98.5%) completed the study (Figure-1). A

Figure 1 *– Subject disposition.*



[a]*One subject was excluded from the efficacy analysis (mITT) for the parecoxib group due to absence of any postbaseline assessment.*

total of 10 (5.7%) subjects from the parecoxib group and 14 (8.5%) subjects from the ketoprofen group were excluded from the primary analysis because they did not have a confirmed diagnosis of renal colic. One subject in the parecoxib group and three subjects in the ketoprofen group discontinued the study because they did not meet the entrance criteria and one subject in the parecoxib group discontinued due to infusion problems (Figure-1). Demographics and clinical characteristics of subjects at randomization were similar in both treatment groups (Table-1). The majority of subjects were aged 18-64 years (99.1%), 63.0% of subjects were male and 58.9% were white (Table-1). In addition, 60.3% and 57.3% of subjects in the parecoxib and ketoprofen groups, respectively, had severe pain at screening.

Efficacy Results

The noninferiority criterion was met for the primary efficacy endpoint, the $mPID_{30min}$. The 95% CI of the treatment difference (parecoxib - ketoprofen) was -6.53; 4.30 and it excluded the noninferiority margin of -10 mm (Table-2). There were no significant differences observed between the treatment groups with regard to the secondary efficacy endpoints.

There were no significant differences observed between the two treatment groups with regard to pain VAS scores at any time (Figure-2).

The average $mPID_{120min}$ of both treatment groups was approximately 52 mm (SD of ~26) and ~77% of subjects had a decrease of at least 20 mm on the pain VAS score at 30 minutes.

Although differences between treatment groups were not statistically significant, more subjects in the parecoxib group reported “a lot” or “complete” pain relief at minute 30: 61% of subjects in the parecoxib group and 55% of subjects in the ketoprofen group. The percentage of subjects who reported “a lot” or “complete” pain relief by minute

Table 1 – *Summary of baseline demographic characteristics.*

	Parecoxib (n = 174)	**Ketoprofen (n = 164)**
Gender, number (%) of subjects		
Male	110 (63.2)	103 (62.8)
Female	64 (36.8)	61 (37.2)
Age, years		
Mean (SD)	38.6 (10.3)	40.1 (12.1)
Range (minimum-maximum)	16-69	19-71
Ethnicity, number (%) of subjects		
White	99 (56.9)	100 (61.0)
Black	2 (1.1)	3 (1.8)
Asian	2 (1.1)	3 (1.8)
Other	71 (40.8)	58 (35.4)
Weight, kg		
Mean (SD)	75.4 (15.1)[a]	74.4 (15.3)
Range (minimum-maximum)	46-130[a]	50-125
Categorical Pain Scale, number (%) of subjects		
Moderate Pain	69 (39.7)	70 (42.7)
Severe Pain	105 (60.3)	94 (57.3)

n = number of subjects; SD = standard deviation
[a] n = 172

Table 2 - *Mean pain intensity difference at minute 30 by VAS (mm) for the PP population.*

	Parecoxib (n = 156)	**Ketoprofen (n = 141)**
Mean (SD)	33.84 (24.61)	35.16 (26.01)
Median (minimum, maximum)	35 (-32, 92)	31 (-43, 98)
LS Mean (SE)	34.147 (3.35)	35.266 (3.46)
Parecoxib-ketoprofen		
LS Mean (SE)[a]	-1.12 (2.75)	
95% CI[a]	-6.53, 4.30	

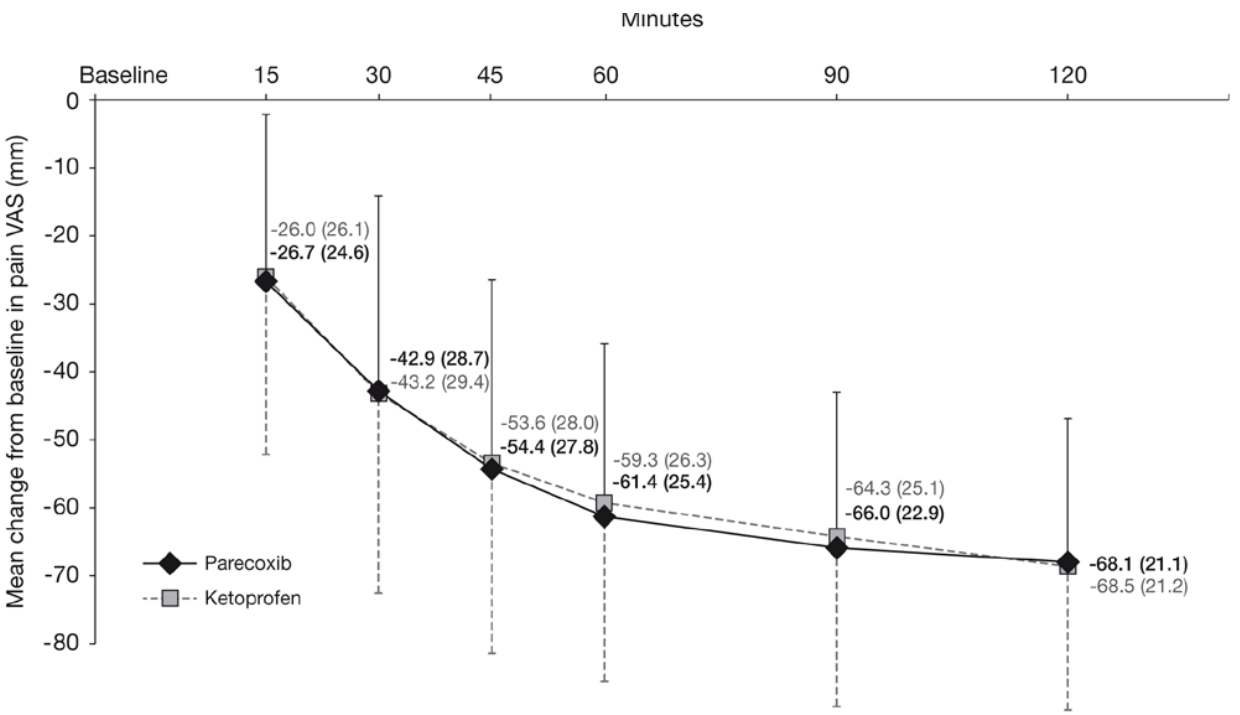
n = number of subjects; SD = standard deviation; LS = least squares; SE = standard error; CI = confidence interval; VAS = visual analog scale; PP = per-protocol
[a] Based on ANCOVA model with terms for treatment group, country and baseline as covariates.

120 in the parecoxib and ketoprofen groups was 88% and 91% respectively.

Subjects treated with parecoxib reported a slightly higher mean (± SD) score for $TOTPAR_{120min}$ than subjects in the ketoprofen group (365.6 ± 122.8 vs. 355.0 ± 126.1, respectively); however, this difference was not statistically significant.

The percentage of subjects that assessed the medication as "good" or "excellent" at minute 30, minute 120 and day 2 time points, was 81%, 86%

Figure 2 *– Mean (SD) of the change from baseline in pain VAS (mm) scores at all time points for the mITT population.*



and 90% for the parecoxib group and 83%, 87% and 86% for the ketoprofen group, respectively. Again, no significant treatment differences were observed.

Similarly the physician's assessment of the medication was "good" or "excellent" at minute 30, minute 120 and day 2 time points for 81%, 87% and 89% for the parecoxib group and 79%, 86% and 86% for the ketoprofen group, respectively.

The time to rescue medication was similar for both treatment groups. Twenty-six subjects took rescue medication up to 120 minutes after the administration of study medication in the parecoxib group compared with 25 subjects in the ketoprofen group. For both treatments, more than one-half of these subjects took the rescue medication within 60 minutes of dosing.

Safety

The incidence of AEs was similar for the two treatment groups. In the parecoxib group 25.9% of subjects experienced a total of 56 AEs; for the ketoprofen group 28.0% of subjects experienced a total of 63 AEs. Overall, AEs were mainly mild or moderate in severity. A total of 16 subjects reported serious AEs; eight in each group (4.6% in the parecoxib group and 4.9% in the ketoprofen group); none were considered by the investigator to be related to study drug and all resolved. No deaths were reported in either treatment group.

Pain (preferred terms pain, abdominal pain, renal colic and renal pain) was the most frequently reported AE, experienced by 8% of subjects in the parecoxib group and 12.8% of subjects in the ketoprofen group (Table-3); again, none of these pain episodes was considered to be treatment-related. Although nausea was the second most frequently reported AE only two subjects in the parecoxib group and three subjects in the ketoprofen group experienced nausea that was considered to be treatment-related.

In terms of treatment-related AEs, dizziness was the most frequently reported. Furthermore, dizziness was more frequently reported for sub-

Table 3 - *Most frequently reported adverse events by preferred term.*

Number (%) of Subjects With Preferred Term AE	Parecoxib (n = 174)		Ketoprofen (n = 164)	
	All Causality	**Treatment-related**	**All Causality**	**Treatment-related**
Pain, abdominal pain, renal colic, or renal pain	14 (8.0)	0	21 (12.8)	0
Nausea	7 (4.0)	2 (1.1)	5 (3.0)	3 (1.8)
Dizziness	7 (4.0)	5 (2.9)	2 (1.2)	1 (0.6)
Vomiting	4 (2.3)	1 (0.6)	5 (3.0)	2 (1.2)
Headache	3 (1.7)	2 (1.1)	4 (2.4)	3 (1.8)
Flatulence	0	0	4 (2.4)	3 (1.8)

AE = adverse event; n = number of subjects
Table shows adverse events reported for more than 2% of subjects (all causality) in at least one treatment group.

jects treated with parecoxib (2.9%) than ketoprofen (0.6%). Worsening of renal colic was reported by 2.9% of subjects in the parecoxib group and by 4.3% of subjects in the ketoprofen group.

DISCUSSION

A common cause of acute severe pain, renal colic requires rapid medical attention, often prior to a diagnosis being made. Strong opioids such as morphine are commonly used in the treatment of pain associated with renal colic; however, although highly effective, opioids can cause a number of serious side effects in the central nervous system (i.e. dizziness, somnolence, respiratory depression, confusion and addiction), which may limit their use in the long-term.

Current evidence suggests that, like opioids, nsNSAIDs are efficacious in controlling the signs and symptoms of renal colic (1); those drugs reduce urinary system distension and the associated pain through the inhibition of prostaglandins (10). As nsNSAIDs lack the addiction risk and known side effects of opioids, they may be the preferred treatment choice for the majority of patients with acute pain due to renal colic.

The COX-2 selective NSAID parecoxib has also been used in the treatment of acute pain; however, unlike ketoprofen, parecoxib -another largely used drug to treat pain associated with renal colic- does not cause inhibition of platelet function (11,12) and, thus, avoids the risk of bleeding. In contrast to certain parenteral NSAID formulations that require setting up a slow i.v. infusion, parecoxib can be injected rapidly and directly into a vein; a useful property in the busy emergency room setting.

Phillips and colleagues have previously evaluated the use of celecoxib, the only other currently approved COX-2 selective NSAID available for the management of acute renal colic (13). In this prospective, randomized, controlled clinical trial of 53 patients they found that there were no significant differences between celecoxib and placebo for either pain scores or narcotic requirements (13). However in our study, reporting here for the first time the use of parecoxib in this study population, and based on the findings of the primary analysis, parecoxib was shown to be noninferior to ketoprofen in the treatment of acute pain due to renal colic. In addition, there were no significant treatment differences between parecoxib and ketoprofen for any of the secondary efficacy endpoints.

Parecoxib was well-tolerated in this study and demonstrated a comparable safety profile to ketoprofen. Although there were no obvious safety concerns relating to the administration of either parecoxib or ketoprofen in this study, previous reports suggest that parecoxib is associated with fewer side effects than ketoprofen (8,9).

One of our main study limitations was that many patients with severe pain were unable to tolerate their pain for long enough to be able to read and sign the informed consent form prior to receiving pain-relief medication. As a result, many of these patients took additional medications and were, therefore, ineligible for enrollment in the study, which could have potentially created a selection bias.

CONCLUSIONS

Parecoxib is as effective as ketoprofen in the treatment of pain due to acute renal colic, is well tolerated and has a comparable safety profile.

ACKNOWLEDGMENTS

As the corresponding author, I can confirm that all authors had access to all the study data, took responsibility for the accuracy of the analysis, and had full authority concerning preparation of the manuscript and the decision to submit the manuscript for publication. This study was sponsored by Pfizer Inc. Editorial support was provided by L. Prevost, BSc, of PAREXEL, and was funded by Pfizer Inc.

We would also like to thank Dr Raymond Cheung for his invaluable input and support at the study design phase. In addition, we would also like to thank all the principal investigators who participated in this study (please see Appendix 1) and who have provided support and technical assistance during the development of this manuscript.

We can also confirm that results from this trial were presented in poster form at the Confederation of American Urology (CAU) meeting in Chile (September 8-11, 2010).

DISCLOSURES

Drs. Sidney Glina, Ronaldo Damiao, Joao Afif-Abdo, Carlos Francisco Santa Maria, Raul Novoa, Carlos Eurico Dornelles Cairoli do not have any conflicts of interest to disclose.

ABBREVIATIONS:

AE = adverse event
ANCOVA = analysis of covariance
CI = confidence interval
COX = cyclooxygenase
i.v. = intravenous
mITT = modified intent-to-treat
ns = nonselective
NSAID = nonsteroidal anti-inflammatory drug
PI = pain intensity
PID = pain intensity difference
PP = per protocol
PR = pain relief
SD = standard deviation
VAS = visual analog scale

Appendix 1: Investigators

Dr. Eduardo Berna Bertero, Brazil
Dr. Ronaldo Damiao, Brazil
Dr. Sidney Glina, Brazil
Dr. Carlos Eurico Dornelles Cairoli, Brazil
Dr. Eric Roger Wroclawski, Brazil
Dr. Walter J. Koff, Brazil
Dr. João Afif-Abdo, Brazil
Dr. Antonio Martins BRAZIL

CONFLICT OF INTEREST

Drs Dalia Wajsbrot and Gaston Araya are both currently full-time employees of Pfizer Inc.

REFERENCES

1. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. Cochrane Database Syst Rev [Internet]. 2005 Apr 18 [Accessed 2011 May 25]; (2). Available at: http://www2.cochrane.org/reviews/en/ab004137.html
2. Clinical Knowledge Summaries. Renal colic - acute [Internet]. [s.l.]: National Institute for Health and Clinical Excellence; c2011. [Accessed 2010 November 1]. Available at: http://www.cks.nhs.uk/renal_colic_acute/view_whole_topic

3. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971; 231: 232-5.
4. Gudis K, Sakamoto C: The role of cyclooxygenase in gastric mucosal protection. Dig Dis Sci. 2005; 50(Suppl 1): S16-23.
5. Brzozowski T, Konturek PC, Konturek SJ, Brzozowska I, Pawlik T: Role of prostaglandins in gastroprotection and gastric adaptation. J Physiol Pharmacol. 2005; 56(Suppl 5): 33-55.
6. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, et al.: Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A. 1994; 91: 12013-7.
7. Otto JC, Smith WL: Prostaglandin endoperoxide synthases-1 and -2. J Lipid Mediat Cell Signal. 1995; 12: 139-56.
8. Emery P: Clinical implications of selective cyclooxygenase-2 inhibition. Scand J Rheumatol Suppl. 1996; 102: 23-8.
9. Simon LS: Nonsteroidal antiinflammatory drugs and their effects. J Clin Rheumatol. 1996; 2: 135-40.
10. Tiselius HG, Ackermann D, Alken P, Buck C, Conort P, Gallucci M, et al.: Guidelines on urolithiasis. Eur Urol. 2001; 40: 362-71.
11. Noveck R, Laurent A, Kuss M, Talwalker S, Hubbard RC: Parecoxib sodium does not impair platelet function in healthy elderly and non-elderly individuals: Two randomized, controlled trials. Clin Drug Invest. 2001; 21: 465-76.
12. Munsterhjelm E, Niemi TT, Ylikorkala O, Neuvonen PJ, Rosenberg PH: Influence on platelet aggregation of i.v. parecoxib and acetaminophen in healthy volunteers. Br J Anaesth. 2006; 97: 226-31.
13. Phillips E, Hinck B, Pedro R, Makhlouf A, Kriedberg C, Hendlin K, et al.: Celecoxib in the management of acute renal colic: a randomized controlled clinical trial. Urology. 2009; 74: 994-9.

Submitted for publication:
December 20, 2010

Accepted after revision:
June 24, 2011

Correspondence address:
Dr. Sidney Glina
Rua Cincinato Braga 37 / 102
São Paulo, SP, 01333-011, Brazil
Fax: +55 11 3515-7900
E-mail: glinas@terra.com.br

Clinical Urology
International Braz J Urol
Vol. 37 (6): 706-711, November - December, 2011

Patients with a negative cystoscopy and negative Nmp22® Bladderchek® test are at low risk of missed transitional cell carcinoma of the bladder: a prospective evaluation

John D. Terrell, Keren J. Elias, Arthur I. Sagalowsky, Yair Lotan

Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

ABSTRACT

Objectives: Urine based tumor markers have uncertain utility in diagnosis or surveillance of patients with bladder cancer while cytology is commonly used. We evaluated whether cytology provides additional diagnostic information in patients with a negative NMP22® BladderChek® test (BladderChek) and negative cystoscopy.
Materials and Methods: We performed subset analyses of 2 large prospective multi-center databases evaluating BladderChek for UCB detection and surveillance. These cohorts were analyzed for presence of cancer and result of urine cytology in setting of a negative cystoscopy and negative BladderChek. Subsequently, we prospectively performed cystoscopy, cytology and BladderChek on 434 patients at our institution being evaluated for UCB.
Results: In the detection database (n = 1331), 1065 patients had a negative cystoscopy and BladderChek. There were 3 cancers (stages Ta, Tis and T1) and cytology was atypical in one and reactive in two. In the surveillance cohort (n = 668) patients, 437 patients had negative cystoscopy and BladderChek. Cancer was found in 2 patients (stages Tis and Ta). The patient with Tis has dysplastic cytology and Ta tumor had reactive cytology. In our cohort of 434 patients, 288 pts had negative cystoscopy and BladderChek. One cancer was missed, a Ta ureteral urothelial carcinoma with a reactive cytology.
Conclusions: In patients with negative cystoscopy and BladderChek, very few cancers are missed and cytology was not effective in detection. Use of a point-of-care test in conjunction with cystoscopy in lieu of cytology could decrease cost, provide immediate results, improve negative predictive value and reduce the uncertainty that results from inconclusive cytologic results.

Key words: *Kidney Neoplasms; Population Surveillance; Diagnosis; Nuclear Matrix Protein 22; Cytology*
Int Braz J Urol. 2011; 37: 706-711

INTRODUCTION

Urothelial carcinoma of the bladder (UCB) is the 4th most common cancer in men and the 5th most common cancer overall (1). Up to 70% to 80% of patients diagnosed with UCB present with either gross or microscopic hematuria, and muscle invasion is present in 25% of patients at diagnosis (2). Overall UCB survival rates are stage dependent and 5-year survival for tumors confined to the mucosa are significantly higher than for cancers that are muscle invasive or metastatic (3).

Unfortunately, despite successful treatment, 50%-70% of non-muscle invasive tumors will recur within 5 years and 10%-30% will progress to invasive cancer (4). Due to the aggressive and recurrent nature of UCB, diligent hematuria evaluation and surveillance is required. Currently, cystoscopy along with urine cytology (UC), are the most commonly utilized tests for both UCB detection and surveillance. However, these tests are not perfect. Cystoscopy has been reported to have up to a 30% false negative rate (5,6). Likewise, cytology suffers frequently from inconclusive findings, a low sensitivity

(especially for low grade tumors), an increased expense and a delay in result availability (7,8). These shortfalls can create a clinical conundrum for the physician and increased anxiety for the patient especially when the cytology is inconclusive or atypical. An increased understanding of the biology of urothelial carcinoma has lead to the development and evaluation of multiple urinary markers to help aid in both cancer detection and surveillance (9). One such marker is NMP22 (Nuclear Matrix Protein 22). The NMP22 BladderChek Test (Matritech Inc, Newton, Mass) is Food and Drug Administration approved for the diagnosis of UCB in high risk patients (include patients with hematuria and patients undergoing UCB surveillance). The BladderChek Test is a point-of-care test that provides immediate results without the need for a clinical laboratory for evaluation (9). It detects elevated amounts of nuclear mitotic apparatus protein, a component of the nuclear matrix essential for cell division that is released into the urine during cell death. Previous reports have noted a very high negative predictive value for the BladderChek test and we hypothesized that patients with a negative BladderChek test and negative cystoscopy would have a very low risk of missed malignancy (10,11). In this prospective analysis we examined the databases of 2 published multi-institutional studies with a cohort of over 2000 patients who had cystoscopy, cytology and BladderChek either in the setting of detection or surveillance of bladder cancer. The goal was to evaluate how often patients with both a negative NMP22 BladderChek test and a negative cystoscopy have missed cancer and whether urine cytology provides any additional diagnostic role in these patients. We then prospectively evaluated 434 consecutive patients who presented to our clinic for evaluation for hematuria or surveillance for bladder cancer to determine the value of cytology in the setting of a negative cystoscopy and negative BladderChek test.

MATERIALS AND METHODS

All studies were performed with the approval and oversight of the Institutional Review Board for the Protection of Human Subjects. Initially we performed subset analyses of 2 large prospective multi-center databases evaluating the BladderChek test. Subsequently, the results were validated in a prospective cohort of subjects at our institution who had a BladderChek test prior to evaluation for bladder cancer with cystoscopy and barbotage cytology.

Database analyses and the prospective evaluation at our institution were to establish if urine cytology would have provided any addition diagnostic role in the setting of both a negative BladderChek test and cystoscopy.

The first prospective multi-center database evaluated the role of the BladderChek test for bladder cancer detection (10). This study involved 23 geographically dispersed clinical sites, including academic, Veteran's Affairs Hospitals, and private practice facilities that prospectively recruited 1331 consecutive patients with bladder cancer risk factors or symptoms, such as hematuria, dysuria, or smoking from September 2001 to May 2002. None of these subjects had a prior history of bladder malignancy. This cohort of subjects provided a voided urine sample for BladderChek test prior to cystoscopy as well as cytology specimens.

The second prospective multi-center database evaluated BladderChek test utility in bladder cancer surveillance (11). This study also involved 23 clinical facilities in 9 US, states, including academic, Veteran's Affairs Hospitals, and private practice facilities. From September 2001 to February 2002, 668 consecutive subjects with a history of bladder cancer were enrolled. In this cross-sectional study, each participant provided a voided urine sample for cytology and BladderChek prior to cystoscopy.

Lastly, a total of 434 consecutive subjects were solicited from urology clinics from the University of Texas Southwestern Medical Center at Dallas and Parkland Health and Hospital Systems (Dallas, TX) from January of 2008 to September of 2009. Subjects recruited were presenting for initial hematuria workup (gross and microscopic), dysuria, other suspicious symptoms, and for routine BC surveillance. Only participants with known, active bladder cancer at the time of evaluation were excluded. Each subject provided a voided urine sample in order to perform the BladderChek test. The test was performed by adding 4 drops of voided urine to the sample well of the point-of-care device. Posi-

tive or negative results were read 30 to 50 minutes later in the test window. A built in control indicated that the assay was complete. Four patients were omitted from the study because of 2 consecutive inconclusive findings on BladderChek test. Subjects undergoing the BladderChek test subsequently had a cystoscopy and a barbotage urine cytology. The cytology sample was sent and examined according to institutional protocols by staff pathologists with expertise in genitourinary cytopathology.

RESULTS

In the first multi-center database of 1331 subjects examining NMP22 BladderChek test's ability to detect bladder cancer in high risk individuals, 1065 subjects had both a negative cystoscopy and BladderChek test. There were only 3 cancers (stages Ta grade 2, Tis and T1 grade 1) diagnosed in this group. In these patients, cytology was atypical in one and reactive in 2 of the subjects.

With respect to the second multi-center database that examined the BladderChek test's ability to detect bladder cancer during surveillance for recurrent bladder cancer, 437 of 668 subjects met inclusion criteria with a negative cystoscopy and BladderChek test. Cancer was diagnosed in 2 patients (stages Tis and Ta grade 2). The patient with Tis had a history of BCG and cytology showed dysplasia. The patient with the Ta tumor had a reactive cytology.

Validation was then performed in our institution's cohort of 434 subjects. Of the original cohort, 288 patients met the study inclusion criteria of having both a negative cystoscopy and BladderChek test. There were 83 patients undergoing evaluation for hematuria (gross (n = 43) and microscopic (n = 40)). There were 203 patients undergoing cystoscopy for bladder cancer surveillance. One patient had evaluation for suspicious imaging and one for unclear reasons. There were 176 and 112 men and women, respectively. The mean age was 64 (range 20-92). Further evaluation showed the presence of only one diagnosed cancer. The tumor was a Ta ureteral urothelial carcinoma with a reactive cytology.

Cumulative analysis of the data for these 3 prospective studies revealed only 6 subjects with cancer from a cohort of 1790 subjects having both a negative cystoscopy and a negative BladderChek test (Table-1). Of these 6 subjects diagnosed with cancer, only 1 patient with a history of BCG and Tis had dysplasia on cytology. In the remainder of these patients, cytology was either atypical or reactive.

DISCUSSION

This study evaluated a large cohort of patients with a negative cystoscopy and negative BladderChek test and found that these patients are at an exceedingly low risk for missed malignancy (n = 6, 0.3%). The addition of cytology in these patients did not detect any of these missed malignancies except for finding dysplasia in one patient with Tis. The strength of this study is the fact that all the patients were prospectively evaluated both in the setting of detection and surveillance using cystoscopy, cytology and the BladderChek test. This type of design reduces the risk of selection bias in the cohort. The data from the 2 large multicenter studies was performed in 23 centers and their results were confirmed at our institution in a prospective fashion.

Even though cystoscopy has a very high sensitivity and specificity, most urologists use adjunct testing such as cytology to assure that no tumors were missed. NMP22 BladderChek test has a very high negative predictive value (96.8% in setting of detection and 90.5% in setting surveillance) (10,11). Our hypothesis was that combining the 2 tests would miss very few cancers and in fact this was the case. While cytology is usually used as an adjunct to cystoscopy, it provided little benefit in patients with negative cystoscopy and negative BladderChek with the exception of the patient with history of CIS who had dysplastic cells in his urine. The combination of cystoscopy and BladderChek had a higher sensitivity and negative predictive value than cystoscopy and cytology in both prospective multicenter studies (10,11). There is also evidence that the sensitivity of cytology has decreased over time (12).

Several other studies have evaluated the utility of cytology. Falebita et al. retrospectively evaluated urine cytology over a 6 year period at their institution (13). They found that out of 2,568 urine cytological examinations, only 25 were positive for

Table 1 *- Study Cohorts.*

Study	Total Number of Patients	Number of patients with Negative Cytology and Negative BladderChek	Missed Cancers (n)	Missing Tumor Pathology	Cytology
Detection (16)	1331	1065	3	Ta, Tis, and T1	1 atypical 2 reactive
Surveillance (17)	668	437	2	Ta, Tis	1 reactive 1 dysplastic
UTSW Validation Cohort	434	288	1	Ta Ureteral	1 Reactive

malignant cells with a cost of 210,000 euros. They concluded that routine urine cytology was not cost effective and did not add to the diagnostic yield beyond cystoscopy and diagnostic imaging. Feifer et al. evaluated 200 consecutive low-risk patients with microscopic hematuria and found that none had a positive cytology, 23 (11.5%) had atypical cytology, and 177 (88.5%) had negative urinary cytology (14). Cytology missed 8 bladder cancers and the cost of performing urinary cytology was estimated at $262 per patient.

There are additional disadvantages to cytology including atypical findings which raise concern for malignancy especially in patients with a history of bladder cancer (15). Furthermore, cytology is not a point of care test such that urologists must contact patients with results and possibly schedule additional visits to discuss outcomes. Patients also have the added anxiety of waiting for the result. In addition, cytology is more costly than a BladderChek test. Cytology can cost from $50-100 while the BladderChek test costs $20-$24 (16). While these differences in cost are not very large, they can add up considering the frequency of cystoscopy and the high prevalence of patients who are evaluated for bladder cancer based on hematuria or undergoing routine surveillance. Adjunct tests contribute to bladder cancer being the most expensive cancer from diagnosis to death (17).

One potential unanswered question in our study is what to do with a positive BladderChek test and a negative cystoscopy. The specificity of urine-based tumor markers is inferior to cytology and false positive results can raise a concern of missed malignancy. In the absence of imaging to evaluate the upper tract, one should consider whether the abnormal marker is detecting a malignancy in the kidney or ureter. Imaging of the upper tracts may be helpful in this setting. The use of a secondary marker such as the Urovysion FISH assay or cytology may be of value and is something that we are currently evaluating.

Close surveillance of these patients is probably advisable as some studies suggest the possibility of a higher risk of cancer recurrence in patients with positive urine markers even if a tumor is not identifiable (18,19).

In patients with low grade disease, we are planning to initiate a study comparing use of cystoscopy with BladderChek compared to cystoscopy and cytology. At this time, it is unclear whether cytology should not remain standard in patients with high grade disease or CIS. There was one patient with a history of CIS whose recurrence was identified based on a dysplastic urine cytology despite a negative cystoscopy and negative BladderChek. At the same time, a meta-analysis of the literature found a similar sensitivity for detecting high grade bladder cancer for cytology and most urine-markers (including NMP22) (9).

CONCLUSIONS

In patients with a negative cystoscopy and BladderChek, there are very few missed cancers. Cytology also missed of these tumors except one

patient with a history of CIS. Use of a point of care test in conjunction with cystoscopy in lieu of cytology could decrease cost, provide immediate results, improve negative predictive value and reduce the uncertainty that results from inconclusive cytologic results. This may be particularly valuable in patients with history of low grade cancers.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

BladderChek: NMP22® BladderChek®
UCB: Urothelial carcinoma of the bladder
CIS: Carcinoma in situ

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E: Cancer statistics, 2010. CA Cancer J Clin. 2010; 60: 277-300. Erratum in: CA Cancer J Clin. 2011; 61: 133-4.
2. National Cancer Institute. Surveillance Edpidemiology and End Results: providing information on cancer statistics to help reduce the burden of this disease on the U.S. population [Internet]. Bethesda, MD: National Cancer Institute; [Last Updated: 20 Jun 2011]. Available at: http://seer.cancer.gov/data
3. American College of Surgeons. National Cancer Data Base [Internet]. Chicago, IL: American College of Surgeons; c2007-2011 [Accessed 2005 Sept 7]. Available at: http://www.facs.org/cancer/ncdb/index.html
4. Lotan Y, Svatek RS, Sagalowsky AI: Should we screen for bladder cancer in a high-risk population: A cost per life-year saved analysis. Cancer. 2006; 107: 982-90.
5. Daniltchenko DI, Riedl CR, Sachs MD, Koenig F, Daha KL, Pflueger H et al.: Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. J Urol. 2005; 174: 2129-33, discussion 2133.
6. Denzinger S, Burger M, Walter B, Knuechel R, Roessler W, Wieland WF, Filbeck T: Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-year results of prospective randomized study. Urology. 2007; 69: 675-9.
7. Nabi G, Greene DR, O'Donnell M: How important is urinary cytology in the diagnosis of urological malignancies? Eur Urol. 2003; 43: 632-6.
8. Páez A, Coba JM, Murillo N, Fernández P, de la Cal MA, Luján M, et al.: Reliability of the routine cytological diagnosis in bladder cancer. Eur Urol. 1999; 35: 228-32.
9. Lotan Y, Roehrborn CG: Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology. 2003; 61: 109-18; discussion 118.
10. Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, et al.: Detection of bladder cancer using a point-of-care proteomic assay. JAMA. 2005; 293: 810-6.
11. Grossman HB, Soloway M, Messing E, Katz G, Stein B, Kassabian V, et al.: Surveillance for recurrent bladder cancer using a point-of-care proteomic assay. JAMA. 2006; 295: 299-305.
12. Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, et al.: A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. J Urol. 2000; 164: 1768-75.
13. Falebita OA, Lee G, Sweeney P: Urine cytology in the evaluation of urological malignancy revisited: is it still necessary? Urol Int. 2010; 84: 45-9.
14. Feifer AH, Steinberg J, Tanguay S, Aprikian AG, Brimo F, Kassouf W: Utility of urine cytology in the workup of asymptomatic microscopic hematuria in low-risk patients. Urology. 2010; 75: 1278-82.
15. Schlomer BJ, Ho R, Sagalowsky A, Ashfaq R, Lotan Y: Prospective validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. J Urol. 2010; 183: 62-7.
16. Lotan Y, Roehrborn CG: Cost-effectiveness of a modified care protocol substituting bladder tumor markers for cystoscopy for the followup of patients with transitional cell carcinoma of the bladder: a decision analytical approach. J Urol. 2002; 167: 75-9.
17. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R: The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics. 2003; 21: 1315-30.

18. Giannopoulos A, Manousakas T, Mitropoulos D, Botsoli-Stergiou E, Constantinides C, Giannopoulou M, et al.: Comparative evaluation of the BTAstat test, NMP22, and voided urine cytology in the detection of primary and recurrent bladder tumors. Urology. 2000; 55: 871-5.

19. Yoder BJ, Skacel M, Hedgepeth R, Babineau D, Ulchaker JC, Liou LS, et al.: Reflex UroVysion testing of bladder cancer surveillance patients with equivocal or negative urine cytology: a prospective study with focus on the natural history of anticipatory positive findings. Am J Clin Pathol. 2007; 127: 295-301.

Submitted for publication:
March 24, 2011

Accepted after revision:
June 22, 2011

Correspondence address:
Dr. Yair Lotan
The University of Texas Southwestern Medical Center
Department of Urology, J8.112
5323 Harry Hines Blvd.
Dallas, TX, 75390, USA
Fax: + 1 214 648-8786
E-mail: yair.lotan@utsouthwestern.edu

Clinical Urology
International Braz J Urol
Vol. 37 (6): 712-718, November - December, 2011

Assessment of the short-term functional outcome after urethroplasty: a prospective analysis

Lumen N, Spiers S, De Backer S, Pieters R, Oosterlinck W

Dept. of Urology (NL, PR, WO), Ghent University Hospital, Ghent and University of Ghent (SS, SDB), Faculty of Medicine and Health Sciences, Ghent, Belgium

ABSTRACT

Objectives: To assess the short-term functional outcomes on urinary symptoms, erectile function, urinary continence and patient's satisfaction after urethroplasty.
Materials and Methods: A prospective analysis was done in 21 patients who underwent urethroplasty. An assessment of the urinary flow, urinary symptoms (International Prostate Symptome Score <IPSS>), erectile function (International Index of Erectile Function-5 <IIEF-5>) and urinary continence (International Consultation Committee on Incontinence Questionaire male Short Form <ICI-Q-SF>) was done before urethroplasty and 6 weeks and 6 months after urethroplasty. Patients were also asked to score their satisfaction with the urethroplasty after 6 weeks and 6 months.
Results: Mean patient's age was 48 years (range: 26-80 years). Mean stricture length was 4.2 cm (range: 1-12 cm). Three patients suffered a stricture recurrence. Mean maximum urinary flow increased from 5.83 mL/s to 24.92 mL/s ($p < 0.001$). Mean IPSS preoperative, 6 weeks and 6 months postoperative was respectively 15.86, 4.60 and 6.41($p < 0.001$). The mean IIEF-5 score preoperative, 6 weeks and 6 months postoperative was respectively 15, 12.13 and 11.62 (not significant). The mean ICI-Q-SF score preoperative, 6 weeks and 6 months postoperative was respectively 10.47, 8.33 ($p = 0.04$) and 9.47 ($p = 0.31$). Patient's satisfaction 6 weeks and 6 months postoperative was respectively 17.14/20 and 17.12/20.
Conclusions: Urethroplasty leads to a significant improvement in urinary flow and IPSS and urinary continence is tending to improve. Although not significant, erectile function was slightly diminished after urethroplasty. Functional outcome should be assessed when urethroplasty is performed.

Key words: *urethral stricture; erectile dysfunction; urinary incontinence; urethra; treatment outcome*
Int Braz J Urol. 2011; 37: 712-718

INTRODUCTION

Urethral stricture disease causes obstructive and irritative voiding symptoms that might have an impact on the patient's quality of life. The different techniques of urethroplasty in the treatment of urethral stricture disease are well described (1-3). Although international accepted guidelines about the treatment are lacking, some recommendations have been made (4-6). The primary outcome parameter of papers assessing the different techniques of urethroplasty has been stricture recurrence. The need for further instrumentation or reoperation is considered a stricture recurrence by the majority of urologists (7). Since urethroplasty is performed on the penis and/or in the perineum, it might have an impact on the patient's erectile function (8). Postoperative sequestration of urine in the urethra and diminished tone of the perineal muscles can lead to (an increase of) postvoid dribbling (8). Posterior urethroplasty is considered to jeopardize the function of the external urethral sphincter and might lead to urinary incontinence. All these possible alterations in urinary and sexual function might have an impact on the patient's satisfaction with the procedure. It has previously been reported that patient's satisfaction is not

always the same as what the surgeon defines as success (9). This study mainly focusses on the impact of urethroplasty on the patient's short-term functional outcome and the satisfaction with the procedure.

MATERIAL AND METHODS

A prospective analysis on the functional outcome of urethroplasty was started in June 2008 and patient recruitment was stopped in December 2008. Only Dutch-speaking patients with a urethral stricture treated with urethroplasty and who approved the informed consent document were included. Non-Dutch speaking patients, transsexual patients, patients not giving their consent to the study and patients who were lost to follow-up were excluded.

Preoperative evaluation included history taking, physical examination, uroflowmetry, echographic residual urine measurement and urethrography. Our in-home treatment algorithm of urethroplasty has been recently described (10) and the operations were done by the same surgical team (W.O. and N.L.). The urinary catheter was removed after 2 weeks when a voiding cysto-urethrography showed absence of urinary extravasation. Follow-up in this study was done after 6 weeks and 6 months with history taking, physical examination and uroflowmetry. In case of clinical symptoms and/or a maximum urinary flow (Q_{max}) < 15 mL/s a urethrography was performed. After closure of the study, the patients were further followed on a regular base. Stricture recurrence was defined as the need for any further instrumentation or reoperation. The functional outcome on urinary and sexual function was assessed using validated questionnaires that were offered to the patient before operation and at the 6 weeks and 6 months follow-up visits. These questionnaires are:

-The International Prostate Symptom Score (IPSS) assessing the patient's voiding symptoms. This score is mainly used for the evaluation of symptoms in patients with benign prostatic hyperplasia (BPH). Seven questions are asked with 6 possible answers leading to a score from 0 (no symptoms) to 35 (very severe symptoms).

-The International Index of Erectile Function-5 (IIEF-5) assessing the patient's erectile function. Five questions are asked with 5 possible answers leading to a score from 5 (severe erectile dysfunction) to 25 (normal erectile function). Only patients that were sexually active were asked to complete this questionnaire.

-The International Consultation Committee on Incontinence Questionnaire male Short Form (ICI-Q-SF) assessing the patient's urinary continence. Six questions are asked about urgency, urge incontinence, stress incontinence, no awareness of urine loss, nocturnal incontinence and post-void dribbling with 5 possible answers leading to a score from 5 (no symptoms) to 30 (severe urinary incontinence).

During the 6 week and 6 month follow-up visit the patients were also asked to score their satisfaction with the urethroplasty from 0 (very dissatisfied) to 20 (very satisfatied).

Twenty-one patients were recruited for the study. Mean patient's age was 48 years (range: 26-80 years). Mean stricture length was 4.2 cm (range: 1-12 cm). Stricture etiology was idiopathic, iatrogenic, post-infectious and lichen sclerosus in respectively 9, 7, 1 and 1 patient. Three patients underwent urethroplasty for a pelvic fracture related posterior urethral distraction defect. Previous interventions were intermittent dilations, one or more internal urethrotomies, urethroplasty, a combination of internal urethrotomy with urethroplasty and none in respectively 1, 5, 1, 4 and 10 patients. The technique used for urethral reconstruction was anastomotic repair, free-graft urethroplasty, combined urethroplasty and perineostomy in respectively 8, 10, 2 and 1 patient.

The preoperative scores of uroflowmetry, IPSS, IIEF-5 and ICI-Q-SF were compared with the scores after 6 weeks and 6 months. Statistical analysis was done using the Student t-test with PASW Statistics™. A p-value < 0.05 was considered statistically significant.

The study was approved by the local ethics committee (EC/UZG/2008/234).

RESULTS

Three patients suffered a recurrence: one patient during the study at 4 months and two patients at 11 and 13 months, thus after closure of study recruitement.

The preoperative mean Q_{max} was 5.83 mL/s (range: 0-13 mL/s) and raised to 24.92 mL/s (range: 7-61.9 mL/s) 6 months postoperative. This amelioration was statistically significant ($p < 0.001$). In the successful cases, the mean 6 months postoperative Q_{max} was 26.9 mL/s vs 10.9 mL/s in failures ($p = 0.03$).

The mean IPSS preoperative, 6 weeks and 6 months postoperative were respectively 15.96, 4.60 and 6.41. The scores after 6 weeks and 6 months were significantly better compared to the preoperative score. The raise in IPSS (thus a worsening) 6 weeks versus 6 months postoperative was not significant (Table-1). Comparing the 3 patients with a recurrence versus the other patients, there was a higher 6 weeks (10.3 vs 4.07) and 6 months (13 vs 6.41) IPSS in the patients with a recurrence.

Table 1 *- Results IPSS.*

IPSS	**Mean (95% Confidential Interval)**	
Preoperative	15.86 (11.86 - 19.85)	
6 weeks postoperative	4.60 (2.00 - 7.20)	
6 months postoperative	6.41 (3.29 - 9.53)	
IPSS	**Mean Difference (95% Confidential Interval)**	**P-value**
Preoperative versus 6 weeks postoperative	10.40 (6.13 - 14.67)	< 0.001
Preoperative versus 6 months postoperative	9.00 (5.17 - 12.84)	< 0.001
6 weeks versus 6 months postoperative	-1.00 (-2.53 - 0.53)	0.179

Twenty patients were sexually active and filled in the IIEF-5scores. The mean IIEF-5 scores preoperative, 6 weeks and 6 months postoperative were respectively 15, 12.13 and 11.62. There was a mean decline (thus worsening) in IIEF-5 scores preoperative versus 6 weeks and 6 months postoperative. Comparing the scores 6 weeks versus 6 months postoperative there was a mean raise (thus amelioration) in IIEF-5 scores of 0.75. The mean differences in IIEF-5 scores preoperative and 6 weeks and 6 months postoperative didn't reach statistical significance (Table-2). Erectile function was the worst in the 3 patients with pelvic fracture related urethral distraction defect with a preoperative, 6 weeks and 6 months postoperative IIEF-5 score of respectively 6, 5 and 7. In 50% of patients undergoing anastomotic repair and 40% of patients undergoing free graft urethroplasty the IIEF-5 scores were worse 6 weeks and 6 months postoperative compared to the preoperative scores.

The most frequent reported preoperative complaint was urgency. Eighteen (86%) patients reported urgency: 11 occasional, 4 regular, 2 most of the time and 1 always. Another important preoperative complaint was postvoid dribbling which was present in 17 (81%) patients: 10 (48%), 5 (24%) and 2 (9%) patients reported respectively occasional, frequent and always postvoid dribbling.

The mean ICI-Q-SF score preoperative was 10.48. This score declined (thus an amelioration) to 8.33 and 9.47 respectively 6 weeks and 6 months postoperative. The mean difference in ICI-Q-SF score preoperative and 6 weeks postoperative even reached statistical significance (Table-3). The postoperative decline in ICI-Q-SF score was mainly due to an amelioration in urgency, urge incontinence and postvoid dribbling. Urgency dropped to 47% and 53% respectively 6 weeks and 6 months postoperative. Urge-incontinence was reported preoperatively by 43% of the patients and this also dropped to 27% and 29% 6 weeks and 6 months postoperative. Postvoid dribbling diminished to 27% and 29% 6 weeks and 6 months postoperative.

The mean scores of satisfaction with the operation were 17, 14 and 17, 12/20. After 6 weeks no one was dissatisfied (score ≤ 10) but after 6 months, one patient was dissatisfied with the operation because of a post-operative fistula.

Table 2 *- Results IIEF-5 scores.*

IIEF-5 score	**Mean (95% Confidential Interval)**	
Preoperative	15 (11.55-18.45)	
6 weeks postoperative	12.13 (7.38-16.88)	
6 months postoperative	11.62 (7.62-15.63)	
IIEF-5 score	**Mean difference (95% Confidential Interval)**	**P-value**
Preoperative versus 6 weeks postoperative	-1.50 (-4.51-1.51)	0.30
Preoperative versus 6 months postoperative	-2.31 (-5.18 - 0.56)	0.11
6 weeks versus 6 months postoperative	0.75 (-1.84 - 3.34)	0.54

Table 3 *- Results ICI-Q-SF score.*

ICI-Q-SF score	**Mean (95% Confidential Interval)**	
Preoperative	10.47 (8.65 - 12.30)	
6 weeks postoperative	8.33 (6.90 - 9.76)	
6 months postoperative	9.47 (7.18 - 11.76)	
ICI-Q-SF score	**Mean difference (95% Confidential Interval)**	**P-value**
Preoperative versus 6 weeks postoperative	2.27 (0.10 - 4.44)	0.042
Preoperative versus 6 months postoperative	1.24 (-1.28 - 3.75)	0.313
6 weeks versus 6 months postoperative	-0.08 (- 1.53 - 1.36)	0.901

DISCUSSION

Q_{max} and IPSS

Reconstruction of a normal urethral diameter should lead to a normalisation of the urinary flow and a reduction of lower urinary tract symptoms. In this study, a significant amelioration of Q_{max} was observed 6 months after urethroplasty. Moreover, successful cases had a significant better Q_{max} compared to the failures. These findings suggest that uroflowmetry is a useful examination in the follow-up of patients after urethroplasty. A significant positive correlation between Q_{max} and urethral diameter has been reported by Heyns and Marais (11). In Europe, the most frequently used questionnaire about urinary symptoms is the IPSS. The American equivalent (identical 7 questions) is the American Urological Association Symptom Score (AUA-SS). Although IPSS/AUA-SS were initially designed and validated to assess treatment for BPH, it can be used to evaluate other causes of lower urinary tract obstruction. A significant inverse correlation between the urethral diameter and the AUA-SS has been reported (11,12). Our study shows a significant amelioration of the postoperative IPSS score suggesting that the reconstruction of a normal urethral diameter is responsible for this. Comparing the patients with a recurrence versus the other patients, there was a higher 6 weeks and 6 months IPSS in the patients with a recurrence. This suggests that a high IPSS might be a predictor of stricture recurrence. This was also observed in other studies using the AUA-SS (11,12): a persistent high symptom score correlated well with a recurrent stricture. The drawback of the use of both maximum urinary flow and IPSS is the lack of specificity for recurrence of urethral stricture disease (13). Other factors affecting the lower urinary tract such as BPH, dysfunctional voiding and neurogenic bladder can also explain a persistent low Q_{max} and high IPSS. Nevertheless, rapid deterioration of Q_{max} and IPSS,

especially in young and otherwise healthy patients should be considered as a sign of stricture recurrence and justifies further and more invasive examinations such as urethroscopy and urethrography. It was recently reported that to detect stricture recurrence, a 2-tier approach seems to be the most frequently used (7). This strategy consists of a non-invasive screening method in the first tier, followed by more invasive tests (e.g. urethrography or urethroscopy) if the first tier is suspicious for stricture recurrence. In the first tier, questionnaires about urinary symptoms (IPSS or AUA-SS) and uroflowmetry were often used.

IIEF-5

For decades, urethral surgeons haven't paid much attention to erectile function after urethroplasty except in case of pelvic fracture related urethral injuries (14,15). A possible explanation for this is that in urethroplasty the urethra and corpus spongiosum are manipulated and not the corpora cavernosa which are responsible for the erectile rigidity. During the last years, there is emerging interest about the erectile function after anterior urethroplasty. Coursey et al. were the first to ascertain the effect of anterior urethroplasty on erectile function (16): they were able to detect a significant transient decline in erectile function, but only for long urethral strictures. No validated questionnaires were used in this retrospective study. Recently, 2 prospective studies have been published using the IIEF to assess erectile function after urethroplasty. These studies of Erickson (17) (52 patients) and Xie (18) (125 patients) came to similar conclusions: about 40% reported diminished erectile function post-operatively with recovery in most patients after 6 months. These studies also showed that bulbar and especially anastomotic repair appears to have a greater effect on erectile function. Although our study was not able to show any statistical differences (probably due the limited number of patients), our findings are consistent with the 2 latter studies: a decline in erectile function after urethroplasty which was more prevalent in the group of anastomotic repair compared to free-graft urethroplasty. These alterations in sexual function may have several explanations: in deep bulbar urethroplasty, dissection in the space between the cavernosal bodies just under the pubic arch can damage the cavernosal nerves at the site where they perforate the urogenital diaphragm (19). Especially in anastomotic repair this dissection is done more extensively to gain urethral length in order to be able to perform a tension free anastomosis. Moreover, extensive dissection of the corpus spongiosum can lead to penile shortening and chordee certainly if done beyond the level of the penoscrotal angle. Another explanation is the disruption of the perineal nerves when splitting the bulbospongious muscle. Extensions of the perineal nerves to the frenular area are described and damage can lead to an altered sensation of this normally higly sensitive frenular area. Furthermore, intimate connections are described between the cavernosal nerves and the perineal nerves suggesting that the perineal nerves might also aid in obtaining erectile rigidity (19).

Erectile function after urethroplasty for pelvic fracture related urethral injuries was the worst, but the erectile function was already bad before operation. The pelvic trauma itself can damage the cavernosal nerves and/or to the blood supply of the corpora cavernosa (branches of the A.pudenda interna) (20). The difficult dissection at the membranous urethra during posterior urethroplasty can further damage the neurovascular structures related to the corpora cavernosa (18), although others have observed spontaneous recovery of erectile function after posterior urethroplasty (21,22).

ICI-Q-SF

Urge and urge-incontinence were very frequent preoperative complaints, explained by secondary detrusor hypertrophy and instability as a consequence of chronic obstruction. These complaints were less frequent, but not absent after urethroplasty. The reason for this is that detrusor hypertrophy and instability will not directly vanish after relieve of the obstruction but will need some time to recover. Postvoid dribbling was another frequent preoperative complaint. This might be explained by difficulties of expulsing the last drops of urine because of the narrowed urethral lumen. This also strongly diminished after operation, but remained in about one fourth of the patients. Possible explanations for postoperative

postvoid dribbling are stricture recurrence, damage to the M.bulbospongiosum and/or sacculation of the graft. In the study of Kessler et al., postoperative postvoid dribbling was even present in 58.9% of the patients (9).

Patient satisfaction

Mean patient satisfaction after urethroplasty in this series was high. The only dissatisfied patient in this series was because of a postoperative fistula. It has been reported that postoperative complications might have an influence on the patient satisfaction (9). The other 20 patients were satisfied by the operation despite some functional disturbances (erectile dysfunction, urge-incontinence, post-void dribbling). Even the patients with a recurrence were still satisfied with the operation. This again shows that patient satisfaction is not the same as what the surgeon defines as success (9).

CONCLUSIONS

Urethroplasty leads to a significant improvement in urinary flow and IPSS. Urinary continence is tending to improve, mainly due to postoperative amelioration of urge, urge-incontinence and postvoid dribbling. Although not significant, erectile function was slightly diminished after urethroplasty. Patient satisfaction after urethroplasty was high and not related to absence of recurrence. Functional outcome should be assessed after urethroplasty. Studies with more patients and a longer follow-up are needed to assess the long-term functional outcome.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Barbagli G, Lazzeri M: Surgical treatment of anterior urethral stricture diseases: brief overview. Int Braz J Urol. 2007; 33: 461-9.
2. Barbagli G, Palminteri E, Lazzeri M, Guazzoni G: Anterior urethral strictures. BJU Int. 2003; 92: 497-505.
3. Oosterlinck W, Lumen N, Van Cauwenberghe G: Surgical treatment of urethral stenoses: technical aspects. Ann Urol (Paris). 2007; 41: 173-207.
4. Andrich DE, Mundy AR: What is the best technique for urethroplasty? Eur Urol. 2008; 54: 1031-41.
5. Lumen N, Hoebeke P, Oosterlinck W: Urethroplasty for urethral strictures: quality assessment of an in-home algorithm. Int J Urol. 2010; 17: 167-74.
6. MacDonald MF, Santucci RA: Review and treatment algorithm of open surgical techniques for management of urethral strictures. Urology. 2005; 65: 9-15.
7. Meeks JJ, Erickson BA, Granieri MA, Gonzalez CM: Stricture recurrence after urethroplasty: a systematic review. J Urol. 2009; 182: 1266-70.
8. Barbagli G, De Stefani S, Annino F, De Carne C, Bianchi G: Muscle- and nerve-sparing bulbar urethroplasty: a new technique. Eur Urol. 2008; 54: 335-43.
9. Kessler TM, Fisch M, Heitz M, Olianas R, Schreiter F: Patient satisfaction with the outcome of surgery for urethral stricture. J Urol. 2002; 167: 2507-11.
10. Lumen N, Hoebeke P, Oosterlinck W: Ventral longitudinal stricturotomy and transversal closure: the Heineke-Mikulicz principle in urethroplasty. Urology. 2010; 7: 1478-82.
11. Heyns CF, Marais DC: Prospective evaluation of the American Urological Association symptom index and peak urinary flow rate for the followup of men with known urethral stricture disease. J Urol. 2002; 168: 2051-4.
12. Aydos MM, Memis A, Yakupoglu YK, Ozdal OL, Oztekin V: The use and efficacy of the American Urological Association Symptom Index in assessing the outcome of urethroplasty for post-traumatic complete posterior urethral strictures. BJU Int. 2001; 88: 382-4.
13. Stoevelaar HJ, van de Beek C, Nijs HG, Casparie AF, McDonnell J, Janknegt RA: The symptom questionnaire for benign prostatic hyperplasia: an ambiguous indicator for an ambiguous disease. Br J Urol. 1996; 77: 181-5.
14. Corriere JN Jr, Rudy DC, Benson GS: Voiding and erectile function after delayed one-stage repair of posterior urethral disruptions in 50 men with a fractured pelvis. J Trauma. 1994; 37: 587-9; discussion 589-90.
15. Pierce JM Jr: Sexual function after a urethroplasty for membranous-prostatic urethral stricture. Trans Am Assoc Genitourin Surg. 1975; 67: 77-80.
16. Coursey JW, Morey AF, McAninch JW, Summerton DJ, Secrest C, White P, et al.: Erectile function after anterior urethroplasty. J Urol. 2001; 166: 2273-6.

17. Erickson BA, Granieri MA, Meeks JJ, Cashy JP, Gonzalez CM: Prospective analysis of erectile dysfunction after anterior urethroplasty: incidence and recovery of function. J Urol. 2010; 183: 657-61.
18. Xie H, Xu YM, Xu XL, Sa YL, Wu DL, Zhang XC: Evaluation of erectile function after urethral reconstruction: a prospective study. Asian J Androl. 2009; 11: 209-14.
19. Yucel S, Baskin LS: Identification of communicating branches among the dorsal, perineal and cavernous nerves of the penis. J Urol. 2003; 170: 153-8.
20. Shenfeld OZ, Kiselgorf D, Gofrit ON, Verstandig AG, Landau EH, Pode D, et al.: The incidence and causes of erectile dysfunction after pelvic fractures associated with posterior urethral disruption. J Urol. 2003; 169: 2173-6.
21. Lumen N, Hoebeke P, Troyer BD, Ysebaert B, Oosterlinck W: Perineal anastomotic urethroplasty for posttraumatic urethral stricture with or without previous urethral manipulations: a review of 61 cases with long-term followup. J Urol. 2009; 181: 1196-200.
22. Koraitim MM: The lessons of 145 posttraumatic posterior urethral strictures treated in 17 years. J Urol. 1995; 153: 63-6.

Submitted for publication:
January 14, 2011

Accepted after revision:
April 26, 2011

Correspondence address:
Dr. N. Lumen
Dept. of Urology,
Ghent University Hospital,
De Pintelaan 185, 9000 Ghent, Belgium
E-mail: nicolaas.lumen@uzgent.be

Clinical Urology
International Braz J Urol
Vol. 37 (6): 719-726, November - December, 2011

Controversies in using urine samples for Prostate Cancer detection: PSA and PCA3 expression analysis

S. Fontenete, J. Silva, A.L. Teixeira, R. Ribeiro, E. Bastos, F. Pina, R. Medeiros

Molecular Oncology Group and Virology LB (SF, JS, ALT, RR, RM), Portuguese Institute of Oncology of Porto; ICBAS, Abel Salazar Institute for the Biomedical Sciences (SF, JS, ALT, RR, RM), University of Porto; Research Department - Portuguese League Against Cancer (NRN) (JS, ALT, RR, RM), Porto; Centre of Genetics and Biotechnology (EB), University of Trás-os-Montes and Alto Douro; Department of Urology (FP), S. João Hospital, University of Porto Medical School; CEBIMED, Faculty of Health Sciences of Fernando Pessoa University (RM), Porto, Portugal

ABSTRACT

Purpose: Prostate cancer (PCa) is one of the most commonly diagnosed malignancies in the world. Although PSA utilization as a serum marker has improved prostate cancer detection it still presents some limitations, mainly regarding its specificity. The expression of this marker, along with the detection of PCA3 mRNA in urine samples, has been suggested as a new approach for PCa detection. The goal of this work was to evaluate the efficacy of the urinary detection of PCA3 mRNA and PSA mRNA without performing the somewhat embarrassing prostate massage. It was also intended to optimize and implement a methodological protocol for this kind of sampling.
Materials and Methods: Urine samples from 57 patients with suspected prostate disease were collected, without undergoing prostate massage. Increased serum PSA levels were confirmed by medical records review. RNA was extracted by different methods and a preamplification step was included in order to improve gene detection by Real-Time PCR.
Results: An increase in RNA concentration with the use of TriPure Isolation Reagent. Despite this optimization, only 15.8% of the cases showed expression of PSA mRNA and only 3.8% of prostate cancer patients presented detectable levels of PCA3 mRNA. The use of a preamplification step revealed no improvement in the results obtained.
Conclusion: This work confirms that prostate massage is important before urine collection for gene expression analysis. Since PSA and PCA3 are prostate specific, it is necessary to promote the passage of cells from prostate to urinary tract, in order to detect these genetic markers in urine samples.

Key words: *Prostatic Neoplasms; Biomarkers; Urine; prostate-specific antigen*
Int Braz J Urol. 2011; 37: 719-726

INTRODUCTION

Prostate cancer (PCa) is one of the most commonly diagnosed malignancies in the developed world (1). Since this disease is more common among older men, its incidence is expected to increase as the population ages. Application of emerging genomic technologies to high-quality PCa models and patient samples, in multiple contexts, has made significant contributions to our molecular understanding of the development and progression of this disease (2).

An ideal marker for the early detection of PCa should also be able to differentiate between men with isolated high grade prostatic intraepithelial neoplasia (HGPIN) and those with associated PCa (2). Prostate-specific antigen (PSA) measurement, obtained from a simple blood sample, has been widely proposed as a screening tool for PCa, being currently the leading cancer diagnosis in men in several developing countries (2). PSA is prostate-specific but not cancer-specific, since other benign prostate diseases often cause its increase in serum. On the other

hand, most men with high levels of PSA do not have PCa (3). Due to this lack of specificity, many studies have proposed modifications of PSA measurement in an attempt to improve the performance of this analysis. These modifications include PSA density, age-specific PSA ranges, free to total PSA ratios, complexed PSA, transition zone PSA density, PSA velocity and other PSA isoforms such as proPSA (4). Despite these changes, there are still inherent limitations to PSA use as a screening tool for PCa. This highlights the need to complement this test, by using for example high performance biomarkers capable of distinguish, with greater specificity, cancer from non-cancer patients. At the same time, this approach will identify men with aggressive cancer with highly precision, thereby reducing unnecessary biopsies.

The development of biomarkers for PCa screening, detection and prognostication has revolutionized the management of this disease (5). Nowadays, there are many clinical studies which evaluate biomarkers in urine (1). This type of sample represents a good fluid to seek biomarkers, mainly because it is readily available and obtained noninvasively. On the other hand, it can be used to detect either exfoliated cancer cells or secreted prostatic products that could indicate the presence of PCa (1). Prostate cells are believed to be present in urine, especially in the first voided sample after prostate massage.

The prostate cancer antigen 3 (PCA3) gene was identified because of its differential expression between prostate cancer and noncancerous prostate tissue (normal gland or benign hypertrophy) (6). Its RNA is regarded as a member of the non-coding RNA family and is thought to participate in the regulation of gene expression at various levels (7). Reverse transcriptase (RT)-PCR on urine sediments obtained after prostatic massage showed a sensitivity and specificity of PCA3 detection of 66% and 89%, respectively (8). Analysis of changes in the expression levels of large numbers of genes during PCa progression have provided a better understanding of the basis of the disease, yielding new molecular markers with potential use in diagnosis and prognosis of this disease, when combined with PSA and PCA3 (9).

This work represents a pilot study, with the intention to evaluate the efficacy of PCA3 mRNA and PSA mRNA detection in urine samples without performing the somewhat embarrassing prostate massage, as well as to optimize and implement a methodological protocol for this kind of sample.

MATERIALS AND METHODS

From February 2009 to January 2010, whole urine specimens were collected from 57 men before ultrasound-guided prostate biopsy according to a protocol approved by the Hospital of São João, Porto. Patient characteristics and diagnostic information are listed in Table-1. All men who presented for prostate biopsy were approached about participating in this study. Inclusion criteria included adult men who were undergoing prostate biopsy for suspicion of prostatic disease. Before prostate biopsy and without performing a prostatic massage, patients collected their initial void of 20 mL to 30 mL of urine, and the sample was then processed at the Portuguese Institute of Oncology, Porto. The samples were subsequently stabilized a TriPure® Isolation Reagent (Roche Applied Science, Cat Nº 11 667 165 001) and kept at -80º C. There were added 2µL of glycogen to the urinary sediment, as a carrier (Roche Applied Science, Cat Nº 10 901 393 001). Total RNA was extracted from these urinary sediments, using TriPure® protocol adapted from Keck Foundation Biotechnology Resource Laboratory at Yale Microarray University. RNA (100µg/µL) was used as a template for cDNA synthesis, using cDNA synthesis kit *ThermoScript*™ RT-PCR System (Invitrogen, Cat nº 11146-016), and stored at -40ºC until quantitative PCR analysis. To develop a qPCR-based test for PCa, we assessed two putative biomarkers in 57 patients. The genes under analysis and the endogenous control *GAPDH*, all from TaqMan® Gene Expression Assay (Applied Biossystems), had to be analyzed by quantitative real time PCR (qPCR) (Table-2). We also applied two preamplification techniques, using the commercial kit TaqMan® PreAmp Master Mix Kit (Applied Biosystems, PN 4384267), in order to verify if this would affect the detection of RNA transcripts. This step was performed according to the manufacturer's instructions. Reactions were then carried out on a StepOne™One qPCR machine and the threshold levels were set into the exponen-

Table 1 *- Patient characteristics.*

	Prostate Ca	Nonprostate Ca	p value
No. pts	25	32	
Mean ± SD age	69.16 ± 7.40	65.19 ± 7.38	0.051
Mean ± SD PSA level, ng/mL	24.95 ± 56.78	7.92 ± 6.13	0.097
No. Gleason score (%)			
5-6	5(20)	-	
7-8	18(72)	-	

Table 2 *- Gene characteristic and TaqMan®GeneExpression Assay (Applied Biossystems).*

Gene	Official Full Name	Chromosome location	Assay ID
PCA3	Prostate cancer antigen 3 (non-protein coding)	9q21-q22	Hs01371938_m1
PSA	Prostate specific antigen	19q13.41	Hs02576345_m1
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	12p13	Hs99999905_m1

tial phase of the qPCR. Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) was used to normalize the results, since it presents a constant expression level, regardless of the variables in study. The data analysis was carried out using the *StepOne Software v2.1* (Applied Biossystems) with the same baseline and threshold set for each plate, in order to generate threshold cycle (C_t) values for all the genes in each sample.

RESULTS

qPCR was performance on cDNA from urine collected from 32 biopsy-negative patients and 25 patient with prostate cancer (biopsy-positive). All the samples had gene C_t values of > 30. It was observed an increase in RNA concentration with the use of TriPure Isolation Reagent. Despite this optimization, only 15.8% of the cases showed expression of PSA mRNA (16% within PCa cases and 15.6% in benign cases) and only 3.8% of prostate cancer patients presented detectable levels of PCA3 mRNA.

Our results demonstrated that TaqMan® PreAmp doesn't overcome the difficulties usually caused by low yields of RNA extraction.

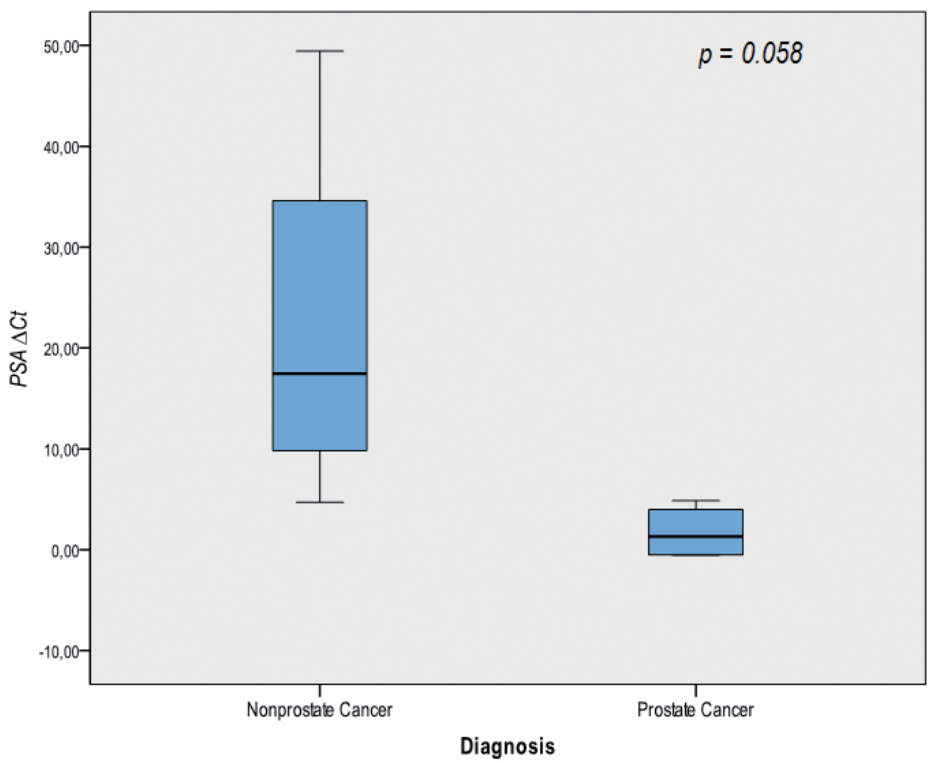
PSA serum levels and PSA mRNA were first tested by univariate analysis, showing no significant association for discrimination patients with prostate cancer from patients with non-oncological disease (p = 0.097 and 0.058 (Figure-1), respectively).

DISCUSSION

PSA is currently the gold standard for PCa screening (3). However, there have been a few drawbacks in its use, mainly regarding sensitivity and specificity values, leading to an overdiagnosis. It is therefore fundamental to diminish the number of unnecessary biopsies in men without cancer. Furthermore, it is crucial to improve tumor detection in men who presents normal values of PSA. This could be achieved by discovering other biomarkers that can be useful in the diagnosis of PCa, avoiding its progression to metastatic disease (5).

Molecular biomarkers are capable of detecting tumors in early phases before these could be identified by other approaches. The use of such markers can also help us understand the causes and mechanisms involved in tumor development (10). All of this highlights the importance of biomarker

Figure 1- *Box plot of prostate-specific antigen (PSA) normalized expression.*



studies, in order to discover new screening techniques for PCa. However, the establishment of these biomarkers represents a challenge, mainly on methodological and analytic levels. It is therefore necessary to optimize its use, so that the results obtained are valid.

We employed a novel TaqMan® PreAmp technique which we found to be a practical solution to decrease Ct values, and in particular suitable in our hands to generate real time PCR results from limited amounts of input RNA (11). The results obtained using TaqMan® real time PCR, with or without PreAmp procedure were not enough to be analyzed, since there where only a few cases where the detection was possible (only 15.8% of the cases showed expression of PSA mRNA and only 3.8% of prostate cancer patients presented detectable levels of PCA3 mRNA). Previous studies have also revealed some difficulties in urinary mRNA detection (12,13). This may be caused by various factors, being one of the most emerging the type of sample used. In the case of urine samples, they require tumor cells exfoliation, which can be obtained by application of prostate massage before sample collection (9). However, this is an invasive approach that goes against some of the advantages of urinary samples, as its easy collection.

When we analyze the results for PSA mRNA detection, we verified only a few positive cases. Since this gene is prostate specific, it would be expected that all samples showed some level of expression. These results may be due to the lack of prostate massage before urine collection (14). The biomarkers concentration in the samples might therefore be low, not allowing its detection. Despite the invasiveness associated with prostate massage, it is important to evaluate whether this procedure presents more advantages to the patient when compared, for instance, with biopsy.

Interestingly, it was found some differences in PSA mRNA expression levels between the two groups analyzed (p = 0.058). Men diagnosed with PCa appear to express higher levels of PSA mRNA,

when compared to men without oncologic disease. However, when we accessed PSA serum levels by medical records review, we found no statistical differences between the two groups (p = 0.097). Previous studies have proposed the existence of some factors which may affect PSA serum levels such as the initiation of stating treatment and NSAID consumption (15,16). On the other hand, it was also suggested that some prostate manipulation, namely DRE and prostate biopsy, may also affect serum PSA levels (17,18). Nonetheless, a previous study led by Croccito et al. revealed low values of sensitivity and specificity for biomarker detection, regardless of prostate massage application (19). This highlights the existence of other variables that should be optimized, in order to create a universal protocol capable of providing feasible results.

The company Gen-Probe Inc. has developed a technology based on transcription-mediated amplification (TMA) (20) for mRNA detection in urine samples. However, it presents some disadvantages, including the cost per sample and the need for repetition and forprostate massage. Comparative analysis of the results obtained in several studies using RT-PCR or TMA show that the levels of detection in terms of sensibility and specificity are similar (Table-3) (20-25).

Another issue to be concerned regards the variability showed by urinary samples, namely its volume, protein concentration and pH value. An additional problem that has to be considered is related to the use of first morning urine. Despite its advantage in leading to a greater likelihood of prostate cells detection, this kind of sample may also incite to further degradation of RNA, since it contains a higher concentration of proteins. Thus, the use of urine samples analyzed on the "spot of collection" prevents this increase in RNA degradation. However, on the other hand, this kind of sample makes it difficult to detect specific cells of the prostate.

It is also necessary to be aware of the variability that exists in urine samples not only among cases but also in the same individual. In addition, it is crucial to provide good storage for the samples so their degradation can be prevented (26). Previous studies on PSA mRNA detection in blood revealed conflicting results, which suggests the existence of others variables that should be controlled, like the kind of biomarker in study. The use of RNA presents a few drawbacks, mainly regarding degradation and isolation. Studies using this molecule become therefore more difficult when it is not possible to process the samples right after its collection (27).

The cDNA synthesis is another step that should also be optimized, since it could affect the reaction efficiency by making it more difficult to detect RNA transcripts. Many reagents such as guanidine, reverse transcriptase, and dithiothreitol have a deleterious effect on downstream enzymatic reactions (28). The secondary structures and the complexity of proteins present in samples of RNA can interfere with the enzymatic reaction, leading to the arrest of the enzyme or its dissociation from the chains of cDNA or heel regions (29).

Table 3 *- Several studies in urine based PCA3.*

Study	Methodology	Patients number	Sensitivity (%)	Specificity (%)
Hessels et al., 2003 (21)	RT-PCR fluorescent based	108	67	83
van Gils et al., 2007 (20)	RT-PCR fluorescent based	534	65	66
Groskopf et al., 2006 (22)	TMA	70	69	79
Marks et al., 2007 (23)	TMA	233	58	72
Deras et al., 2008 (24)	TMA	570	54	74
Hessels et al., 2009 (25)	TMA	470	47	72

The population chosen for the study could also affect the results, so its selection is extremely important. Attending the slow progression of PCa, it is expected that some genes and pathways may involved only in some stages of the disease. Therefore, the inclusion of men with only localized disease, for example, may influence any results regarding the expression of selected genes. This is due to the fact that highly differentiated tumors tend to present less cell exfoliation in urine, when compared with more advanced tumors. This results in a more difficult detection of biomarkers in patients who present more initial stages of the disease, which does not necessarily mean that the genes in study do not have a role in tumor development. The results can therefore be deceiving, since these genes can be involved in later stages of the disease. Nevertheless, they can be very useful in prognosis.

CONCLUSIONS

According to the results obtained in the present study we may hypothesised that PSA mRNA is not affected by the same factors which influence PSA serum concentration, making the first a better option for PCa diagnosis, since it presents a higher efficacy.

One approach that should be explored is the use of positive markers along with negative markers, i.e. markers which expression increases and diminishes, respectively, in tumor tissues. This is expected to improve tumor detection specificity, thereby improving PCa screening. However, the use of several markers can also adversely affect the test's sensitivity and specificity for cancer detection, so test selection is crucial. The use of multiple biomarkers with high sensitivity, high specificity, and that are complementary may approach the optimal detection model.

The use of urinary biomarkers is still in an early stage, so more studies are necessary. The results of this work highlight the importance of a universal protocol for sample collection and process. This will decrease the variability of the results obtained, making the approach clinically valid. It is also important that such protocol can be applied to screening tests, which implies the selection of stable and resistant biomarkers, so that may be possible to send the urine samples from population to adequate labs, without its degradation.

This study reinforces the need to perform prostate massage before urine collection, as suggested before. However, there are other variables that should be taken into account, namely the challenging manipulation of RNA and the importance of implementing a universal protocol. Despite all limitations, the use of urinary biomarkers represents a major change in oncologic investigation, providing new insights to tumor developing.

ACKNOWLEDGMENTS:

This work was realized with the support from Calouste Gulbenkian Foundation (Oncology/2008/ Project nº 96736). We also acknowledge the support from FCT- Science and Technology Foundation (FCT/PTDC/SAU-FCF/71552/2006) ALT and RR are recipients of a Doctoral degree grant from FCT (SFRH/BD/47381/2008, SFRH/BD/30021/2006, respectively).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Downes MR, Byrne JC, Pennington SR, Dunn MJ, Fitzpatrick JM, Watson RW: Urinary markers for prostate cancer. BJU Int. 2007; 99: 263-8.
2. Morote J, Fernández S, Alaña L, Iglesias C, Planas J, Reventós J, et al.: PTOV1 expression predicts prostate cancer in men with isolated high-grade prostatic intraepithelial neoplasia in needle biopsy. Clin Cancer Res. 2008; 14: 2617-22.
3. Loeb S, Catalona WJ: What to do with an abnormal PSA test. Oncologist. 2008; 13: 299-305.
4. Lin DW: Beyond PSA: utility of novel tumor markers in the setting of elevated PSA. Urol Oncol. 2009; 27: 315-21.
5. Schiffer E: Biomarkers for prostate cancer. World J Urol. 2007; 25: 557-62.

6. Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, Schalken JA, et al.: DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Res. 1999; 59: 5975-9.
7. Mattick JS, Makunin IV: Non-coding RNA. Hum Mol Genet. 2006; 15(Spec No 1): R17-29.
8. Fradet Y, Saad F, Aprikian A, Dessureault J, Elhilali M, Trudel C, et al.: uPM3, a new molecular urine test for the detection of prostate cancer. Urology. 2004; 64: 311-5; discussion 315-6.
9. Laxman B, Morris DS, Yu J, Siddiqui J, Cao J, Mehra R, et al.: A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. Cancer Res. 2008; 68: 645-9.
10. Steuber T, Helo P, Lilja H: Circulating biomarkers for prostate cancer. World J Urol. 2007; 25: 111-9.
11. Gibson UE, Heid CA, Williams PM: A novel method for real time quantitative RT-PCR. Genome Res. 1996; 6: 995-1001.
12. Jerónimo C, Usadel H, Henrique R, Silva C, Oliveira J, Lopes C, et al.: Quantitative GSTP1 hypermethylation in bodily fluids of patients with prostate cancer. Urology. 2002; 60: 1131-5.
13. Gonzalgo ML, Isaacs WB: Molecular pathways to prostate cancer. J Urol. 2003; 170: 2444-52.
14. Papatsoris A, Bourdoumis A, Chrisofos MÇ Re: Accuracy of PCA3 Measurement in Predicting Short-Term Biopsy Progression in an Active Surveillance Program J. J. Tosoian, S. Loeb, A. Kettermann, P. Landis, D. J. Elliot, J. I. Epstein, A. W. Partin, H. B. Carter and L. J. Sokoll J Urol 2010; 183: 534-538. J Urol. 2010; 184: 396-7.
15. Hamilton RJ, Goldberg KC, Platz EA, Freedland SJ: The influence of statin medications on prostate-specific antigen levels. J Natl Cancer Inst. 2008; 100: 1511-8.
16. Singer EA, Palapattu GS, van Wijngaarden E: Prostate-specific antigen levels in relation to consumption of nonsteroidal anti-inflammatory drugs and acetaminophen: results from the 2001-2002 National Health and Nutrition Examination Survey. Cancer. 2008; 113: 2053-7.
17. Collins GN, Martin PJ, Wynn-Davies A, Brooman PJ, O'Reilly PH: The effect of digital rectal examination, flexible cystoscopy and prostatic biopsy on free and total prostate specific antigen, and the free-to-total prostate specific antigen ratio in clinical practice. J Urol. 1997; 157: 1744-7.
18. Lin YH, Jiang YG, Li MC, Luo Y, Wang JS: Effects of prostate manipulation on serum total and free prostate specific antigen, and free-to-total prostate specific antigen ratio. Saudi Med J. 2010; 31: 999-1004.
19. Crocitto LE, Korns D, Kretzner L, Shevchuk T, Blair SL, Wilson TG, et al.: Prostate cancer molecular markers GSTP1 and hTERT in expressed prostatic secretions as predictors of biopsy results. Urology. 2004; 64: 821-5.
20. van Gils MP, Hessels D, van Hooij O, Jannink SA, Peelen WP, Hanssen SL, et al.: The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. Clin Cancer Res. 2007; 13: 939-43.
21. Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, et al.: DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol. 2003; 44: 8-15; discussion 15-6.
22. Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, et al.: APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem. 2006; 52: 1089-95.
23. Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SM, et al.: PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. Urology. 2007; 69: 532-5.
24. Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, et al.: PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol. 2008; 179: 1587-92.
25. Hessels D, Schalken JA: The use of PCA3 in the diagnosis of prostate cancer. Nat Rev Urol. 2009; 6: 255-61.
26. Thomas CE, Sexton W, Benson K, Sutphen R, Koomen J: Urine collection and processing for protein biomarker discovery and quantification. Cancer Epidemiol Biomarkers Prev. 2010; 19: 953-9.
27. Medeiros M, Sharma VK, Ding R, Yamaji K, Li B, Muthukumar T, et al.: Optimization of RNA yield, purity and mRNA copy number by treatment of urine cell pellets with RNAlater. J Immunol Methods. 2003; 279: 135-42.

28. Tichopad A, Didier A, Pfaffl MW: Inhibition of real-time RT-PCR quantification due to tissue-specific contaminants. Mol Cell Probes. 2004; 18: 45-50.
29. Liss B: Improved quantitative real-time RT-PCR for expression profiling of individual cells. Nucleic Acids Res. 2002; 30: e89.

Submitted for publication:
November 24, 2010

Accepted after revision:
June 01, 2011

Correspondence address:
Dr. Rui Medeiros
Molecular Oncology Group Coordinator
Portuguese Institute Of Oncology
Associate Professor, Icbas
Instituto Ciências Biomédicas
Abel Salazar (University Of Porto)
Largo Prof. Abel Salazar, 2
Porto, 4099-003, Portugal
Telephone: + 3 51 22 2062-200
E-mail: ruimedei@ipoporto.min-saude.pt

Clinical Urology
International Braz J Urol
Vol. 37 (6): 727-732, November - December, 2011

Findings concerning testis, vas deference, and epididymis in adult cases with nonpalpable testes

Coskun Sahin, Mehmet Kalkan, Soner Yalcinkaya

Department of Urology (CS, MK), Sema Hospital, Istanbul and Department of Urology (SY), Antalya Education and Research Hospital, Antalya - Turkey

ABSTRACT

In this study, we aimed to state the relationship between testis, epididymis and vas deference, in adult cases with nonpalpable testis.

Between January 1996 and December 2009, we evaluated 154 adult cases with nonpalpable testes. Mean age was 23 years (20-27 years). Explorations were performed by open inguinal incision, laparoscopy, and by inguinal incision and laparoscopy together on 22, 131 and 1 patient, respectively.

Of all the unilateral cases, 32 were accepted as vanishing testis. In five of these cases, vas deference was ending inside the abdomen, and in the others, it was ending inside the scrotum. In the remaining 99 unilateral and 22 bilateral cases, 143 testes were found in total.

Testes were found in the inguinal canal as atrophic in one case, at the right renal pedicle level with dysmorphic testis in one case, and anterior to the internal ring between the bladder and the common iliac vessels at a smaller than normal size in 119 cases. One (0.69%) case did not have epididymis. While epididymis was attached to the testis only at the head and tail locations in 88 (61.53%) cases, it was totally attached to the testis in 54 (37.76%) cases.

There is an obviously high incidence rate of testis and vas deference anomalies, where epididymis is the most frequent one. In cases with abdominal testes, this rate is highest for high localised abdominal testes.

Key words: *testis; surgery; abnormalities; Vas Deferens*
Int Braz J Urol. 2011; 37: 727-732

INTRODUCTION

Testes are the predominant endocrine organs, which have been localised posterior to the abdominal cavity in the early fetal period. Although they are in the abdomen in most (90.54%) of the cases until the 23rd week, they begin to migrate down to the scrotum around 28th week (1). During this migration, testes can occasionally be localised at the higher or lower abdomen, inner opening of the inguinal canal and between the opening of the external inguinal canal and the scrotum (2). It is hypothesized that the epididymis has a major role in the localisation of the testis in the scrotum. In fact, the situation which states that, epididymal anomalies are present in more than 50% of the higher abdominal testes, supports this theory (3,4).

In this study, we report our results of testis, epididymis and vas deference abnormalities in patients with nonpalpable testes by open surgical exploration and laparoscopic interventions.

MATERIALS AND METHODS

Explorations were performed by open inguinal and laparoscopic intervention.

During laparoscopic interventions, 3 port accesses (sub-umbilical 1 port, and pararectal 2 ports) were used. In 9 of bilateral nonpalpable testis cases, for who single session laparoscopic orchiopexy

was performed; a 4th port was placed trans-scrotally, whereas in 13 of these cases, double session orchiopexy was performed. Of the 32 cases with vanishing testis, vas deference excision was performed by inguinal exploration in 5 cases, and by laparoscopic intervention in the remaining 27 cases. Testis dimensions were calculated according to the graphical method. This method includes graphics of testis figures and predefined testicular volumes on paper (Figure-1). Abdominal testicular dimensions were compared with normal scrotal testicular values.

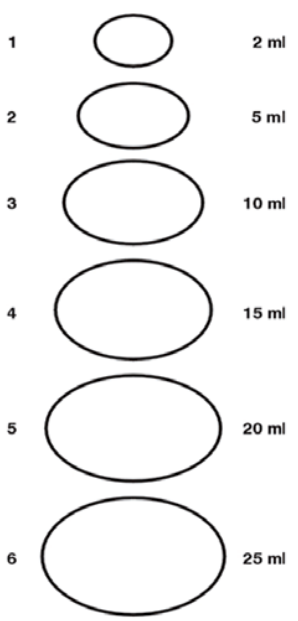


Figure 1 - *Scheme for graphic measurement of testicular volume.*

Epididymal configurations were evaluated with a 1 to 5 classification system which defines the relation between epididymis and testis. Normal epididymis is completely attached to the testis at the upper pole of it. However, it is attached to the testis by a fibrous film at the lower pole. Such a configuration is known as type I, and the configuration where the epididymis is completely attached to the testis is known as type II. In type III and IV, head and tail portions are attached respectively to the testis and in type V the epididymis is completely unattached to the testis.

Laparoscopic orchiectomy was performed on unilateral nonpalpable testis cases. Excised testicular tissues and nubbins were evaluated pathologically.

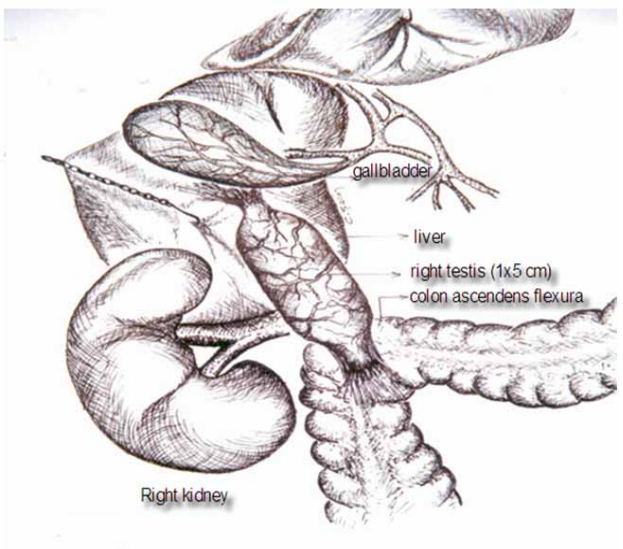
RESULTS

No testis could be found in 32 patients during explorations or laparoscopy, and these patients were accepted as having vanishing testes. Vas deference was ending inside the abdomen in 5 cases and in the scrotum in 27 cases (Table-1). In one patient however, while the testis was located inside the abdomen, vas deference on the same side, was ending at the scrotum independent of the testis. Viable testis tissue was diagnosed pathologically, in only 4 (12.5%) of the 32 patients, who had vas deference excision. In one patient, right testis was found at the renal pedicle level with an dimorphic structure (Figure-2). In another patient however, during inguinal exploration, the testis was found as atrophic in size (1 cm). Both testes were at lower intra-abdominal re-

Table 1 *- Findings concerning the vas deference.*

Finding	**no**
Absence of vas deference	1
Independent of the testis	1
Blunt ending at the abdomen	2
Blunt ending at the scrotum	20
Together with the testis	113
Total	**137**

Figure 2 - *Right testes is localised in the right renal pedicle and no epididymis (type V epididymal configuration).*



gion in 22 patients with bilateral nonpalpable testes. In 99 of the 131 cases with unilateral nonpalpable testis, testes were found at either anterior to the internal ring, or over the common iliac vessels, or between the bladder and the common iliac vessels.

In all of the cases with intra-abdominal testis, testis volumes were determined as 12.5-22.5 cm^3 (average 17.5 cm^3). Mean testicular volume was 22.5 cm^3 in the control group. While the testes were tense (Tight) in 3 cases, they were less dense than the normal density value in the remaining cases (Table-2). One case did not have epididymis (Type V epididymal configuration, Figure-2). While the epididymis was attached to the testis only at the head and tail locations (Type I epididymal configuration, Figure-3) in 88 of the remaining 143 testes, it was totally attached to the testis (Type II epididymal configuration, Figure-4) in the other 54 testes (Table-3).

Carcinoma in-situ was not determined in any of the orchiectomy applied cases. No spermatogenetic activity was detected in testis specimens. Sertoli cells were present in only 4 testicular tissues (Sertoli cell only syndrome). All other testicles had leydig cells.

DISCUSSION

Cryptorchidism is a congenital anomaly seen in 3 % of term born children. Cases with nonpalpable testes comprise 20-34% of such anomalies (5,6). It is known that, the frequency of testis-epididymis anomalies is higher in high localised testes (7). In the literature, the frequency of epididymal anomalies is reported to be between 36% and 75% and such anomalies are divided into 5 groups (8). However, some investigators claim that there is not a correlation between the testis localisation, and epididymal anomaly (3). It had also been reported that, the frequency of epididymal anomalies among healthy children with undescended testis was 40% (8). Normal epididymis is completely attached to the testis at the upper pole. However, it is attached to the testis by a fibrous film at the lower pole. In this study of fetal testes, Favorito had determined that as high as 89 % of the cases were in type I, 7.53 % were in type II, 2.05 % were in type III, and 0.68 % were in type IV configuration. He did not detect any type V configuration (3). In their studies about chil-

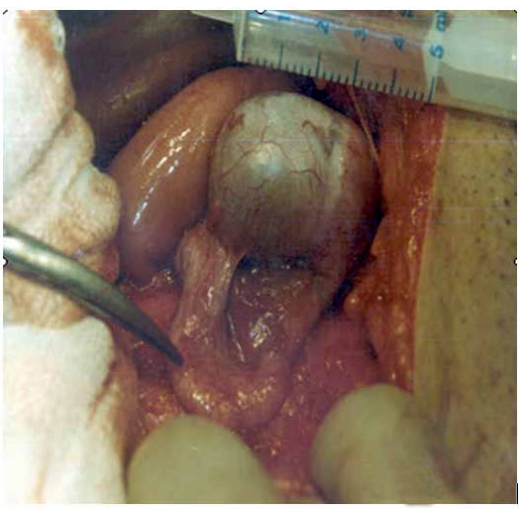
Table 2 - *Testis anomalies.*

	Normal size (n)	**Small size*** **(n)**	**Dysmorphic testis (n)**	**Atrophic size**** **(n)**	**Total (n)**
High abdominal testis	-	-	1	-	1
Low abdominal testis	17	94	-	-	111
Inguinal testis	-	-	-	1	1
Total (n)	**17**	**94**	**1**	**1**	**113**

**: Testicular Volume = 12.5 - 22.5 mL (17.5 mL)*

***: Testicular Volume = 1 mL*

Figure 3 - *Head and tail portions of epididymis attached to the testis (type I configuration).*



dren aged between 1 month and 18 years, Turek et al. reported that the frequency of type II cases, where the epididymis was completely attached to the testis, was 12% (9). In our study we determined that 88 (61.53 %) cases were type I and 54 (37.76 %) cases were type II configuration. While type V configuration was determined in only 1 (0.69 %) case, we did not coincide with type III and IV configurations. The case with type V epididymal anomaly had also testicular anomaly located at the higher abdomen. The testis in this case was at the renal pedicle level with the dimensions of 1x1.5x5 cm. When hold by a grasper, it appeared as a tubular organ, and it did not look like a testis. In fact, decisive diagnosis was performed pathologically on this case. It is obvious that, in patients with nonpalpable testes, such high abdominal testes will not be found during inguinal exploration, and will be evaluated as agenetic.

Figure 4 - *Epididymis is completely attached to the testis (type II configuration).*

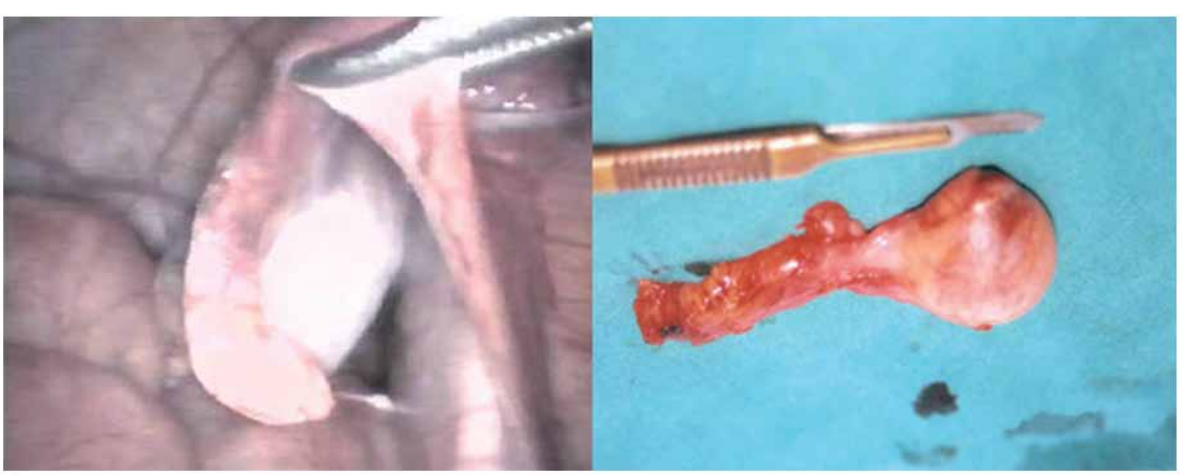


Table 3 - *Epididymal configurations.*

	Type I	Type II	Type III	Type IV	Type V
High abdominal testis	-	-	-	-	1 (0.9%)
Low abdominal testis	72 (64%)	39 (34.2%)	-	-	-
Inguinal testis	-	1 (0.9%)	-	-	-
Total n (%)	**72 (64%)**	**40 (35.1%)**	**-**	**-**	**1 (0.9%)**

There are different theories about testicular descent in embryogenic life. Epididymal factor is one of them (8). In our Type V epididymal configuration subject who didn't contain an epididymis, testis remained in its embryogenic location.

Adult testis dimensions are usually 4x3x2.5 cm. Testis volume is usually measured by Prader orchidometer or the graphic method (10-12). We used the graphical method to measure the testis volumes (Figure-1). Except the higher abdominal located testis, all testes were in ellipsoidal structure. In one patient, the testis was inside the inguinal canal at an atrophic size (1x1 cm). Lower abdominal testes are usually located either just proximal to the internal ring, over the common iliac vessels, or between the bladder and the common iliac vessels. In these patients, the testis volumes were measured between 12.5 and 22.5 cm^3 (average 17.5 cm^3). Average testis volume in the control group of 20 adults who did not have any scrotal pathology was measured as 22.5 cm^3. While normal testes were tense and tight when they were palpated, abdominal testes were softer. Higher abdominal testes however, were even softer than the abdominal testes, and the testicular walls were so elastic that they could contact each other upon squeezing. Although the testicular volume of the abdominal testes in our cases seemed to be high at first glance, this situation can be explained by the age group of our cases, which is between 20 and 27 years.

Testes that are not detected by laparoscopy and inguinal exploration are known as vanishing testes. The etiological reason underlying this phenomenon on is thought to be intrauterine testes torsions (10). We did not detect any testes in 32 of our patients. In 8 cases, which had open exploration, vas deference was observed to be blunted at the scrotum. In one of these patients, testis was found inside the abdomen, and vas deference was ending at the scrotum independent of the testis. As seen in this case, observing blunt ended vas deference during exploration does not mean that testis is absent. Testicular vessels should definitely be seen. In 2 patients however, vas deference was observed to extend higher from the small pelvis and end over the common iliac vessels with the testicular vessels. In patients with vanishing testes, viable testicular tissue ratio was reported to be 0% to 16% (13). Some authors are recommending inguinal exploration for laparoscopically undetected testes in cases with nonpalpable testes (14). Only 4 testicular nubbin were contained viable testicular tissues. It is reported that laparoscopic intervention is unnecessary in palpable scrotal testicular nubbins as there was no testis in the abdomen (15).

Inguinal exploration was performed on the first 4 of the vanishing testis cases, whose vas deference and testicular vessels were observed to enter the internal inguinal ring during laparoscopy. While atrophic testis was detected in 1 of these 4 patients, vas deference was ending blunted in the remaining three. After we gained more experience on laparoscopy, vas deference was laparoscopically excised instead of applying inguinal exploration, in these cases. Technically, following the circular incision of peritoneum at the level of internal inguinal ring, testicular vessels and vas deference were excised as being tied with end clip, after they were taken inside the abdomen. In 28 of the 32 patients, who were evaluated as having vanishing testes, no testicular tissue was detected pathologically, whereas in 4 cases viable testicular tissue was found. Viable testicular tissue detection rate is low as seen in these cases. Nearly all of these testicles are located in the scrotal cavity as these testicular nubbins are palpable position in the event of cancer, we don't recommend prophylactic excision.

Abdominal testes were found to be smaller and softer in comparison with the normal ones. We determined that, the incidence of higher abdominal testes was extremely low, but the testis-epididymis anomaly was obvious in such testes. If laparoscopic exploration is not performed in higher abdominal testicles, it may not be always possible to find them during open abdominal surgery. However we think that laparoscopy is not necessary in every nonpalpable case; also it is not needed to perform any intervention including laparoscopy in palpable scrotal nubbin cases.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Moore KL, Persaud TVN: The Developing Human (Clinically Oriented Embryology). 5th ed. Philadelphia. WB Saunders Company; 1993. pp. 265-301.
2. Sampaio FJ, Favorito LA: Analysis of testicular migration during the fetal period in humans. J Urol. 1998; 159: 540-2.
3. Favorito LA, Sampaio FJ: Anatomical relationships between testis and epididymis during the fetal period in humans (10-36 weeks postconception). Eur Urol. 1998; 33: 121-3.
4. Kirsch AJ, Escala J, Duckett JW, Smith GH, Zderic SA, Canning DA, et al.: Surgical management of the nonpalpable testis: the Children's Hospital of Philadelphia experience. J Urol. 1998; 159: 1340-3.
5. Husmann DA, Levy JB: Current concepts in the pathophysiology of testicular undescent. Urology. 1995; 46: 267-76.
6. Sampaio FJ, Favorito LA, Freitas MA, Damião R, Gouveia E: Arterial supply of the human fetal testis during its migration. J Urol. 1999; 161: 1603-5.
7. Kiely EA: Scientific basis of testicular descent and management implications for cryptorchidism. Br J Clin Pract. 1994; 48: 37-41.
8. Marshall FF, Shermeta DW: Epididymal abnormalities associated with undescended testis. J Urol. 1979; 121: 341-3.
9. Turek PJ, Ewalt DH, Snyder HM 3rd, Duckett JW: Normal epididymal anatomy in boys. J Urol. 1994; 151: 726-7.
10. Tanagho EA, McAninch JW: Smith's General Urology. 15th (ed.), New York. McGraw-Hill Company. 2000.
11. Takihara H, Sakatoku J, Fujii M, Nasu T, Cosentino MJ, Cockett AT: Significance of testicular size measurement in andrology. I. A new orchiometer and its clinical application. Fertil Steril. 1983; 39: 836-40.
12. Chipkevitch E, Nishimura RT, Tu DG, Galea-Rojas M: Clinical measurement of testicular volume in adolescents: comparison of the reliability of 5 methods. J Urol. 1996; 156: 2050-3.
13. Nishizawa S, Suzuki K, Tachikawa N, Nukui A, Kumamaru T, Shioji Y, et al.: The vanishing testis: diagnosis and histological findings. Nihon Hinyokika Gakkai Zasshi. 2000; 91: 537-41.
14. Merry C, Sweeney B, Puri P: The vanishing testis: anatomical and histological findings. Eur Urol. 1997; 31: 65-7.
15. Sahin C, Yigit T, Ozbey I: Adult nonpalpable testis: is laparoscopy always required? J Laparoendosc Adv Surg Tech A. 2002; 12: 431-4.

Submitted for publication:
January 24, 2011

Accepted after revision:
May 05, 2011

Correspondence address:
Dr. Soner Yalcinkaya
Antalya Education and Research Hospital
Varlık Mah. Kazım Karabekir Cad.
Soğuksu, 07070, Antalya, Turkey
Fax: + 90 242 249 4462
E-mail: drs1092@gmail.com

Clinical Urology
International Braz J Urol
Vol. 37 (6): 733-738, November - December, 2011

The Effect of Cardiopulmonary Bypass in Coronary Artery Bypass Surgeries (On-Pump versus Off-Pump) on Erectile Function and Endothelium-Derived Nitric Oxide Levels

Onder Canguven, Selami Albayrak, Ahmet Selimoglu, Muhsin Balaban, Ahmet Sasmazel, Ayse Baysal

Clinic of Urology II (OC, SA, AS, MB), Kartal Teaching and Research Hospital; Department of Cardiac Surgery (AS) and Anesthesiology (AB), Kartal Kosuyolu Heart and Research Center, Istanbul, Turkey

ABSTRACT

Purpose: To investigate the effects of on-pump and off-pump coronary artery bypass grafting (CABG) on the erectile function and endothelium-derived nitric oxide (eNO) levels.
Materials and Methods: Twenty-eight consecutive patients were randomized into two groups depending on use of cardiopulmonary bypass in CABG surgery. The erectile function was evaluated by using the IIEF-5 questionnaire. The plasma eNO levels were determined at baseline and after reactive hyperemia before and after surgery. Blood was collected in one minute after cuff deflation from the radial artery on the same side.
Results: After CABG surgery the mean IIEF-5 score increased insignificantly over baseline from 14.8 to 15.8 ($p = 0.29$) and 12.4 to 14.3 ($p = 0.11$) after on-pump and off-pump CABG surgeries, respectively. The baseline plasma NO levels before surgery were 18.16 ± 7.63 nmol/L in on-pump and 21.76 ± 11.08 nmol/L in off-pump CABG. After reactive hyperemia the plasma NO levels were 22.14 ± 10.52 nmol/L in on-pump and 21.49 ± 9.13 nmol/L in off-pump CABG before the surgery. The difference in the plasma NO levels before surgery was not significant ($p = 0.51$). Two hours after surgery, the difference of the plasma NO levels at baseline (24.44 ± 12.31on-pump and 20.58 ± 6.74 nmol/L off-pump CABG) and after reactive hyperemia (35.55 ± 23.54 nmol/L on-pump and 23.00 ± 15.40 nmol/L off-pump CABG) were not significantly different from each other ($p = 0.11$).
Conclusions: Patients who had on-pump or off-pump CABG surgeries had higher IIEF-5 scores. Nevertheless, the improvement was insignificant in both groups. Meanwhile, on-pump or off-pump CABG surgeries did not have significant effect on plasma eNO levels.

Key words: *coronary artery bypass; Blood Vessel Prosthesis; Erectile Dysfunction*
Int Braz J Urol. 2011; 37: 733-738

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED is a vascular disorder and all men with ED should be considered at risk of cardiovascular disease until proven otherwise (1). Endothelial dysfunction is a key variable in the pathogenesis of atherosclerosis and its complications, including ED. Coronary artery bypass grafting (CABG) is mainly performed for patients who cannot be treated medically or by stent placement. In the last decade, off-pump choice is successfully performed by cardiac surgeons. CABG surgery with cardiopulmonary bypass (CPB) may have adverse effects on endothelial functions. CPB reduces the ability of endothelium to synthesize and release of plasma nitric oxide (NO) and this leads to increased

risk of the postoperative complications (2). Quality of life and clinical morbidity after off-pump versus on-pump CABG were investigated in assorted articles (3-5). However, there are limited number of studies published the effect of different CABG types on erectile function.

Aims

The aim of this study is to compare the effects of CPB on erectile function and the endothelium-derived NO (eNO) levels in on-pump and off-pump CABG surgeries.

Methods

Study Protocol

Twenty-eight male patients with coronary artery disease (CAD) from September 2008 to October 2009 were prospectively enrolled in the study depending on the use of CPB in CABG or not. The inclusion criteria included all patients between 45 to 75 years of age, NYHA Class I-II, and CAD confirmed by angiographic study. The exclusion criteria included diabetes mellitus, renal or hepatic impairment (blood creatinine > 1.5 mg/dL, blood aspartate aminotransferase (AST), blood alanine aminotransferase (ALT) levels higher than two fold of normal values) congestive heart failure, active inflammatory diseases, or a history of myocardial infarction in the past 6 months. The reasons for exclusion criteria are mainly related to the other comorbiditiesthat are associated with endothelial dysfunctions. The comorbidities have been documented to be associated with impaired response to flow mediated dilatation (FMD). These include elevated sympathetic activation (congestive heart failure), diabetes mellitus, and patients with renal or hepatic dysfunctions (6). Pre- and post-operative uses of all medications were recorded.

Evaluation of Erectile Function

The erectile function was evaluated using the IIEF-5 questionnaire (7) by one examiner who was blinded to treatment groups. Patients were stratified by baseline (preoperative) and six months after surgery, the erectile function was revaluated according to the same preoperative measures. IIEF-5 scores were measured ED severity using IIEF-5 scores of 22-25 (no ED) and ≤ 21 (mild to severe ED) (7).

Evaluation of plasma NO

Blood samples for plasma NO were drawn a total of four times and in the following sequence: in the surgical room before start of the surgery prior to the reactive hyperemia procedure (basal level), after the reactive hyperemia procedure two hours after operation, and before and after reactive hyperemia procedures. The measurement of plasma NO level was based on the method introduced for reactive hyperemia (8,9). A pressure cuff was placed at the brachial artery and inflated up to 250 mmHg for 5 minutes, and it was subsequently deflated. This maneuver causes an increase in sheer stress exerted by the flow of blood over the surface of the endothelium in the brachial artery in the forearm circulation (10,11). The arterial blood sample was withdrawn from the radial artery catheter on the same side in 1 minute after the deflation of the cuff for the measurement of the eNO. NO-derived end products (NO2, NO3) were measured by triiodine/ozone-based chemiluminescence assay, described elsewhere (12).

Operative procedure

Both groups underwent sternotomy procedure. In the off-pump group, all patients underwent CABG without CPB. In this group patients were kept normothermic, heparin at a dose 300 U/kg was given intravenously and was reversed with protamine at a dose of 0.5 mg/300 units. In on-pump group, CABG with CPB was performed under hypothermia. Heparin was administered at a dose of 300 U/kg and it was reversed with protamine of 1 mg/300 units of heparin. Induction and maintenance of anesthesia were similar for all patients and it includes administration of intravenous weight-related doses of fentanyl, midazolam, and pancuronium bromide. Central venous catheterization and radial artery cannula insertion were completed before induction of anesthesia.

Statistical analysis

Statistical analysis SPSS (Chicago, IL, USA) for Windows 15.0 statistics package program was used for statistical analysis of the data. A Student's *t*-test for paired samples was used for variables with normal distribution. Independent sample t test, χ^2 test, Pearson correlation, and linear regression tests were

done. The data were expressed as mean ± standard deviation and the categorical variables as percentages. $P < 0.05$ was considered statistically significant.

The present clinical study was carried out in an academic institution and was approved by the Institutional Ethical Review Board. All subjects volunteered to participate in this study and gave informed consent after the objectives and method of the study had been explained. All patients had to anticipate having the same female sexual partner (vaginal intercourse was a required study activity) throughout the study for consistency in recording responses to efficacy questionnaires.

Main Outcome Measures

IIEF-5 scores were used for assessment of erectile function of the CAD patients before and after CABG surgeries. The measurement of plasma NO level was used in order to assess change in endothelial function.

RESULTS

Demographic characteristics of on-pump and off-pump groups were shown in Table-1. Based on the IIEF-5 scores, ED was present in 24 of the total 28 patients selected for the study. The degree of ED was determined as mild, mild to medium, medium and severe in 21.4, 35.7, 14.3 and 14.3% of patients, respectively. In four (14.3%) patients, there was no ED. The mean IIEF-5 score increased insignificantly over baseline from 14.9 to 15.8 ($p = 0.29$) and 12.4 to 14.3 ($p = 0.11$) after on-pump and off-pump CABG surgeries, respectively. Change in IIEF-5 scores was also statistically insignificant between two groups ($p = 0.46$). Comparison of IIEF-5 between on-pump and off-pump patients after surgery was shown in Table-2.

Baseline NO levels in on-pump were 18.16 ± 7.63 nmol/L, and in off-pump they were 21.76 ± 11.08 nmol/L ($p = 0.64$). Pre-operatively, after reactive hyperemia, the plasma NO levels were 22.14 ± 10.52 nmol/L in on-pump and 21.49 ± 9.13 in off-pump ($p = 0.96$). Two hours after the CPB, in both groups, baseline NO levels were 24.44 ± 12.31 in on-pump and 20.58 ± 6.74 nmol/L in off-pump ($p = 0.66$). The difference in the plasma NO levels in on-pump (3.98 ± 12.29) and off-pump (-1.62 ± 16.40) groups before surgery was not significant ($p = 0.51$).

Baseline NO level in patients without ED ($n = 4$) was 15.45 ± 1.46 nmol/L. Pre-operatively, after reactive hyperemia, the plasma NO levels was 19.46

Table 1 - *Demographic characteristics of on-pump and off-pump CABG.*

	On-pump (mean ± SD) (n = 12)	**Off-pump (mean ± SD) (n = 16)**	***p****
Age (years)	57.35 ± 7.65	59.30 ± 6.72	0.43
Ca-channel blocker (n,%)	3(25)	1(6.3)	0.19
Nitroglycerine (n,%)	10(83.3)	8(50)	0.19
ACE-inhibitor (n,%)	9(75)	4 (25)	0.06
Beta-blocker use (n,%)	12 (100)	7(43.8)	0.01*
Myocardial infarction (n,%)	7(58.3)	8 (50)	0.53
Hypertension (n,%)	8(66.6)	10 (62.5)	0.65
Lipid-lowering statin use (n,%)	12 (100)	16 (100)	0.73
Smoker (n,%)	10(83.3)	7(43.8)	0.08
Total cholesterol (mg/dL)	194.4 ± 28.2	157.7 ± 31.2	0.35
HDL cholesterol (mg/dL)	36.2 ± 11.5	39.7 ± 16.3	0.27

**: $p < 0.05$ statistically significant.*
SD: Standard deviation

Table 2 - *Comparison between on-pump and off-pump patients.*

	On-pump patients (n = 12)	Off-pump patients (n = 16)	All patients (n = 28)
IIEF-5 results before surgery			
Normal	2 (16.6%)	2 (12.5%)	4 (14.3%)
Mild ED (17-21)	1 (8.3%)	1 (6.3%)	2 (7.1%)
Mild-moderate ED (12-16)	2 (16.6%)	3 (18.8%)	5 (17.9%)
Moderate ED (8-11)	6 (50.0%)	7 (43.8%)	13 (46.4%)
Severe ED (5-7)	1 (8.3%)	3 (18.8%)	4 (14.3%)
IIEF-5 mean ± SD	14.9 ± 6.9	12.4 ± 7.1	
IIEF-5 results and change after surgery			
IIEF-5 mean ± SD	15.8 ± 5.3	14.3 ± 8.4	
No IIEF-5 change	7 (58.3%)	8 (50.0%)	15 (53.6%)
Increased IIEF-5	5 (41.6%)	7 (43.8%)	12 (42.9%)
Decreased IIEF-5	-	1 (6.3%)	1 (3.6%)

± 1.31 nmol/L. Two hours after the CPB baseline NO levels was 13.66 ± 6.15 nmol/L.

After reactive hyperemia, the NO levels were found as 35.55 ± 23.54 and 23.00 ± 15.40 nmol/L in on-pump and off-pump, respectively. Two hours after surgery, the difference of the plasma NO levels in on-pump (11.11 ± 22.02) and off-pump (2.42 ± 18.20) groups were not significantly different from each other ($p = 0.11$).

Pearson correlation analysis of change in preoperative and postoperative plasma NO levels and IIEF-5 scores of ED patients before and 3 months after the surgery were also not significant ($r = -0.07$; $p = 0.84$). Pearson correlation analysis of preoperative and postoperative plasma NO levels and parameters that include; preoperative beta-blocker use, calcium channel blocker use, angiotensin converting enzyme inhibitors, operation time, use of CPB were done and the only relation was found with preoperative nitroglycerine use ($r = 0.51$, $p = 0.001$).

DISCUSSION

The present study demonstrates that the patients, who were performed on-pump or off-pump CABG surgery, had similar change in IIEF-5 scores. ED which was based on IIEF-5 scores was found in 24 (85.7%) study group patients. Fifty percent (12/24) of the patients with ED had an insignificant increase in IIEF-5 scores. Although the number of our ED patients was higher than in the previous studies which investigated cardiac patients (13,14), it was found similar in patients who were candidate for CABG (15).

Outcomes of on-pump versus off-pump CABG surgery were examined in various studies on different topics (3,4,16). To assess midterm quality of life after off-pump CABG with that after on-pump CABG procedure, Immer et al. compared an age- and sex-matched standard population (3). Immer et al. demonstrated that the use of CPB allows CABG surgery to be performed with excellent results without impairment in neurocognitive outcome and quality of life in low-risk patients (3). Van Dijk et al. have recently published a randomized trial referring to the data of 281 patients looking at cognitive outcome and cardiac outcomes 5 years after on- or off-pump CABG surgery (16). They found that the avoiding the use of CPB had no effect on five-year cognitive or cardiac outcomes (16). In a meta- analysis study, Marasco et al. evaluated eight prospective randomized controlled trials to assess neurocognitive out-

comes after off-pump versus on-pump CABG (17). Marasco et al. concluded that there is no clinically relevant difference between two groups either early or late after surgery (17). According to the studies evaluating neurocognitive outcome, there was also no difference between on- or off-pump CABG surgery groups (3,16,17). In a large series during the 10-year follow-up, Puskas et al. found that on-pump and off-pump of CABG result in similar survival, regardless of gender (18).

Penile erection is a neurologically driven hemodynamic action. Erection is initiated by NO, a potent vasodilator, released from the nerve endings. Further production of NO depends on increased blood flow which is also known as shear stress (19). In most vascular beds, the NO is released by a stimulus that increases the shear stress over the endothelium. Shear stress over the brachial artery has been reported to induce activation of eNOS in the endothelium. Rassaf and his colleagues showed that up to 72 to 90% of circulating plasma NO is derived from eNOS activity (11).

Although it is well established that cardiovascular risk factors are associated with ED, once it is present there is mixed information on whether treating the risk factors will treat the ED (13). Recently, Mohamed et al. investigated the difference between the on pump and off-pump CABG surgery on the sexual function (15). The study design included subjective (IIEF-5 score) and objective (penile duplex ultrasonography) findings related to erectile function (15). The number of patients who reported post-operative improvement of their IIEF-5 score was found significantly higher in off-pump group. Nevertheless, there was no significant change in the duplex ultrasound data (peak systolic, end-diastolic velocities, and resistance index) after surgery between both groups (15). Although Mohammed et al. concluded that type of surgery can be considered a predictive factor of sexual function following CAB surgery, it was not clearly explained how it affects penile tissue without any change in vascular bed. Besides, previous studies demonstrated that NO-mediated erectile function fundamentally involves both nNOS and eNOS locally, whereby the former initiates the erectile response and the latter facilitates full erection (19).

In our study, we investigated whether CPB-induced transient pulmonary endothelial dysfunction result in decreased NO release that contributes to post-operative change in erectile function. Although twelve patients had improved IIEF-5 scores, this increase was found insignificant. We also demonstrated that there was no significant relation between postoperative plasma NO levels after reactive hyperemia following on and off-pump CABG. The current study implied that pre-operative nitroglycerine use was associated with increased plasma levels of NO after the on or off-pump CABG.

Limitations of our study are the relatively small number of patients, the lack of long-term follow-up data. A better study design for simultaneous evaluation of FMD and plasma NO levels is warranted for further studies.

CONCLUSIONS

This study demonstrates that in on- and off-pump CABG surgeries the IIEF-5 score and plasma NO levels did not reveal any significant difference in the early postoperative period.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Montorsi P, Ravagnani PM, Galli S, Salonia A, Briganti A, Werba JP, et al.: Association between erectile dysfunction and coronary artery disease: Matching the right target with the right test in the right patient. Eur Urol. 2006; 50: 721-31.
2. Beghetti M, Silkoff PE, Caramori M, Holtby HM, Slutsky AS, Adatia I: Decreased exhaled nitric oxide may be a marker of cardiopulmonary bypass-induced injury. Ann Thorac Surg. 1998; 66: 532-4.
3. Immer FF, Berdat PA, Immer-Bansi AS, Eckstein FS, Müller S, Saner H, et al.: Benefit to quality of life after off-pump versus on-pump coronary bypass surgery. Ann Thorac Surg. 2003; 76: 27-31.
4. Ivanov J, Borger MA, Tu JV, Rao V, David TE: Mid-term outcomes of off-pump versus on-pump coronary artery bypass graft surgery. Can J Cardiol. 2008; 24: 279-84.

5. Lee JD, Lee SJ, Tsushima WT, Yamauchi H, Lau WT, Popper J, et al.: Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. Ann Thorac Surg. 2003; 76: 18-25; discussion 25-6.
6. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Rand WM, Udelson JE, et al.: Peripheral vascular endothelial function testing as a noninvasive indicator of coronary artery disease. J Am Coll Cardiol. 2001; 38: 1843-9.
7. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999; 11: 319-26.
8. Wassmann S, Ribaudo N, Faul A, Laufs U, Böhm M, Nickenig G: Effect of atorvastatin 80 mg on endothelial cell function (forearm blood flow) in patients with pretreatment serum low-density lipoprotein cholesterol levels <130 mg/dl. Am J Cardiol. 2004; 93: 84-8.
9. Masumoto A, Hirooka Y, Hironaga K, Eshima K, Setoguchi S, Egashira K, et al.: Effect of pravastatin on endothelial function in patients with coronary artery disease (cholesterol-independent effect of pravastatin). Am J Cardiol. 2001; 88: 1291-4.
10. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al.: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002; 39: 257-65. Erratum in: J Am Coll Cardiol 2002; 39: 1082.
11. Rassaf T, Kleinbongard P, Preik M, Dejam A, Gharini P, Lauer T, et al.: Plasma nitrosothiols contribute to the systemic vasodilator effects of intravenously applied NO: experimental and clinical Study on the fate of NO in human blood. Circ Res. 2002; 91: 470-7.
12. Dejam A, Hunter CJ, Pelletier MM, Hsu LL, Machado RF, Shiva S, et al.: Erythrocytes are the major intravascular storage sites of nitrite in human blood. Blood. 2005; 106: 734-9.
13. Kloner RA, Mullin SH, Shook T, Matthews R, Mayeda G, Burstein S, et al.: Erectile dysfunction in the cardiac patient: how common and should we treat? J Urol. 2003; 170: S46-50; discussion S50.
14. Chew KK, Finn J, Stuckey B, Gibson N, Sanfilippo F, Bremner A, et al.: Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med. 2010; 7: 192-202.
15. Mohamed OA, Bennett CJ, Roaiah MF, Helmy T, Mahran A, Hamed HA: The impact of on-pump coronary artery bypass surgery vs. off-pump coronary artery bypass surgery on sexual function. J Sex Med. 2009; 6: 1081-9.
16. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, et al.: Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. JAMA. 2007; 297: 701-8.
17. Marasco SF, Sharwood LN, Abramson MJ: No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis. Eur J Cardiothorac Surg. 2008; 33: 961-70.
18. Puskas JD, Kilgo PD, Lattouf OM, Thourani VH, Cooper WA, Vassiliades TA, et al.: Off-pump coronary bypass provides reduced mortality and morbidity and equivalent 10-year survival. Ann Thorac Surg. 2008; 86: 1139-46; discussion 1146.
19. Burnett AL: Novel nitric oxide signaling mechanisms regulate the erectile response. Int J Impot Res. 2004; 16(Suppl 1): S15-9.

Submitted for publication:
January 10, 2011

Accepted after revision:
May 12, 2011

Correspondence address:
Dr. Onder Canguven
Sakacı sokak 34/5 Yildiz apt.
Kozyatagi, Kadikoy, 34738 Istanbul, Turkey
Fax: + 90 216 352 0083
E-mail: ocanguven@yahoo.com

Clinical Urology
International Braz J Urol
Vol. 37 (6): 739-744, November - December, 2011

PCNL - A comparative study in nonoperated and in previously operated (open nephrolithotomy/pyelolithotomy) patients - A single-surgeon experience

Rahul Gupta, Arti Gupta, Gursimran Singh, Abhineet Suri, Sandeep K Mohan, C.L.Gupta

Department of Surgery Government Medical College, Jammu and Kashmir, India

ABSTRACT

Purpose: Re-procedure in patients with history of open stone surgery is usually challenging due to the alteration in the retroperitoneal anatomy. The aim of this study was to determine the possible impact of open renal surgery on the efficacy and morbidity of subsequent percutaneous nephrolithotomy (PCNL).
Materials and Methods: From March 2009 until September 2010, 120 patients underwent PCNL. Of these, 20 patients were excluded (tubeless or bilateral simultaneous PCNL). Of the remaining 100, 55 primary patients were categorized as Group 1 and the remaining (previous open nephrolithotomy) as Group 2. Standard preoperative evaluation was carried out prior to intervention, Statistical analysis was performed using SPSS v. 11 with the chi-square test, independent samples t-test, and Mann-Whitney U test. A p-value < 0.05 was taken as statistically significant.
Results: Both groups were similar in demographic profile and stone burden. Attempts to access the PCS was less in Group 1 compared to Group 2 (1.2 + 1 2 vs 3 + 1.3 respectively) and this was statistically significant ($p < 0.04$). However, the mean operative time between the two groups was not statistically significant ($p = 0.44$). Blood transfusion rate was comparable in the two groups ($p = 0.24$). One patient in Group 2 developed hemothorax following a supra-11th puncture. Remaining complications were comparable in both groups.
Conclusion: Patients with past history of renal stone surgery may need more attempts to access the pelvicaliceal system and have difficulty in tract dilation secondary to retroperitoneal scarring. But overall morbidity and efficacy is same in both groups.

Key words: *calculi; kidney; outcomes*
Int Braz J Urol. 2011; 37: 739-744

INTRODUCTION

The prevalence of urolithiasis is approximately 2 to 3 percent in the general population, and the estimated lifetime risk of developing a kidney stone is about 12% (1). Over time, renal stone management has undergone a dramatic change, beginning from the era of open pyelolithotomy, to the first percutaneous lithotomy (PCNL) in 1976 (2,3). At present PCNL has become the procedure of choice for managing large renal calculi (4).

However, some authors have reported higher rate of treatment failures in those with past history of lumbotomy and others have implicated any preceding renal surgery as a confounding factor affecting the overall outcome (5,6).

Stone recurrence rate is up to 50% within 5 to 7 years (7), thus increasing the need for re-intervention. Re-operation following open renal surgery would be difficult due to the distortion of the pelvicaliceal anatomy and expected retroperitoneal scarring. The aim of our study was to evaluate the outcome of PCNL in patients with past history of open nephrolithotomy in comparison to those with primary cases.

MATERIALS AND METHODS

We reviewed the records of 120 PCNLs performed in our unit between March 2009 and September 2010. Of these, 20 patients who had undergone tubeless or bilateral simultaneous PCNL were excluded from the study. Of the remaining 100, 55 were primary patients were categorized as Group 1, and the remaining who had history of open nephrolithotomy/pyelolithotomy were categorized as Group 2. Table-1 compares the demographic profile of the two groups.

Table 1 - *Demographic profile of patients in both the groups.*

Parameters	Group 1 (n = 55)	Group 2 (n = 45)	P VALUE
Mean Age(years)	35.51 ± 11.1	40.64 ± 12.3	0.87
Males	65%	60%	-
BMI(kg/m^2)	21.1 ± 24	22.4 ± 25	0.65
Stone size(cm)	2.8 ± 1.5	3.0 ± 2.3	0.34
Stone Side(R:L)	0.8:1	1:1.25	0.39
Location Of Stone Calyceal	15 (27.27%)	13 (28.89%)	
Pyelocalyceal	25 (45.54%)	20 (44.44%)	0.76
Pelvic	15 (33.33%)	12 (26.67%)	

The indications for PCNL included a stone burden of greater than 1.5 cm in length and failure of SWL treatment. The stone burden was measured as the product of the two dimensions on plain radiographs. All patients were evaluated with renal function test, hemogram, coagulation profile, urine routine, urine culture sensitivity and ultrasonography. An intravenous urography (IVU) was carried out in all to assess function and plan the puncture. Urinary tract infections detected preoperatively were treated according to antibiotic sensitivity.

Technique

All PCNLs were performed by the same surgeon. The standard technique followed for the procedure is explained in brief. Following anesthesia, a retrograde catheter (5fr) was placed cystoscopically in the ipsilateral pelvicaliceal system (PCS) under fluoroscopy in lithotomy position. The patient was then placed in the prone position for percutaneous access. Transpapillary puncture was made preferably away from the previous incision site, using a three part needle (Angiomed 1.3mm (17.5G)) under fluoroscopy control after retrograde opacification of the pelvicaliceal system via ureteral catheter. An angle tip terumo wire (Radifocus; Terumo wire) was then positioned in the upper ureter. The tract was then dilated initially using serial Teflon dilators up to 10 Fr, followed by placement of Alken's rod. The subsequent dilation was achieved using serial Alken metal dilators (usually up to 26 Fr and occasionally 30 Fr depending on the pelvicaliceal dilation and stone burden) and an Amplatz sheath (Cook Surgical) of adequate caliber placed (28 Fr/32 Fr depending on dilation). The PCNL was then completed using Wolf nephroscope (24 Fr) and pneumatic lithotripsy. The fragmented calculi were removed using forceps or suction. On the table, complete clearance was ensured on fluoroscopy and direct nephroscopy. An adequate size nephrostomy was placed at the end of the procedure. Nephrostomy was removed on the second postoperative day after the check x-ray KUB. The nephrostomy tract site was the dressed with sterile dressing. Patient was then discharged with the instructions to remove the dressing after 72 hours and follow-up after one month if asymptomatic.

Data Analysis

Stone size (cm), attempts to access PCS, operating time in minutes, intraoperative and postoperative complications, stone-free rate, blood transfusions, duration of hospital stay were examined. Statistical analysis was performed using SPSS v. 11 with the chi-square test, independent samples t-test, and Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table-2 shows the overall outcome in the two groups. Both of the groups were comparable in terms of age, sex, side, BMI and stone burden. Mean operative time for Group 1 was shorter (78.24 ± 17.6 mints) compared to Group 2 (82.09 ± 28.23 min), but this was not statistically significant. The majority (42/45) of the patients in Group 2 had undergone one surgery in the past, except three (two of which had undergone open surgery twice and one three times). The average time from last open surgery to the present percutaneous procedure was 7 ± 2 years. Attempts to access the PCS was less in Group 1 compared to Group 2 (1.2 ± 1.2 vs 3 ± 1.3 respectively), and this was statistically significant ($P < 0.04$). We used a no. 21 knife blade for the sharp incision of the fascia and the scar tissue in previously operated patients to facilitate the subsequent dilation. We observed that when the approach in Group 2 was not from the incision site, the dilation was easy compared to access gained from the region of scar tissue. This also reduced the probability of guide wire kinking oraccess failure.

Table-2 also compares the complications within the two groups. Overall intraoperative bleeding was encountered in 6% (6/100). Nine percent (9/100) of the patients required blood transfusion. Bleeding responded to conservative measures. None of our patients developed pseudoaneurysms, injury to adjoining organs (Bowel). However, one patient in Group 2 developed hemothorax and required chest drain placement. This patient had undergone PCNL for a recurrent calculus by supracostal approach (supra-11th puncture). Eleven of 100 patients developed postoperative fever and that was attributed to pyelonephritis. These patients were treated conservatively with injectable antibiotics (first-generation cephalosporins and aminoglycoside) until they were afebrile and then switched over to oral therapy (oral quinolone) to complete two weeks of medication. Six of our patients developed a persistent nephrostomy site discharge (4 in Group 1 and 2 in Group 2). These patients were evaluated with local nephrostomy site biopsy and were found to have caseating granuloma. They were treated with the anti-tubercu-

Table 2 - *Results.*

Parameters	**Group 1(%) (N=55)**	**Group 2(%) (N=45)**	**p VALUE**
Mean Operative Time(minutes)	78.24 ± 17.616	82.09 ± 28.236	0.44
Average Drop In Hb(gm%)	1.1 ± 0.495	1.39 ± 0.590	0.12
Bleeding(Intra-op)	4 (7.2)	2 (4.4)	0.22
Blood Transfusion	5 (9.09)	4 (8.8)	0.24
Pseudoanurysm	0	0	-----
Hemothorax	0	1 (2.2)	0.31
Renal pelvic injury	1 (1.8)	1 (2.2)	0.15
Damage to adjoining organs	0	0	-----
Post Operative Fever	5 (9.09)	6 (13.33)	0.29
Stone Clearance	91.11%	93.33%	0.69
Hospital stay	3.11 ± 0.532	3.13 ± 0.548	0.84

lar treatment to which they responded well. Overall stone-free rate is comparable in both groups.

DISCUSSION

Percutaneous nephrolithotomy was introduced in 1976 but it was not until the 1990s that it became an established and preferred procedure for renal stone management (3,6). In the Indian scenario, though PCNL has established itself well in major cities but in the peripheral regions it is still not freely available. As a result, many patients with renal stones are still being treated conventionally with open surgery. With the recurrence rate for renal stones being high (up to 50% in 5-7 years (7)), these patients often need re-intervention.

Reports have claimed higher failure rates of PCNL in patients with prior open intervention or lumbotomy (5,6). In those series, PCNL failed in almost one-third of patients with a history of lumbotomy. Similar observations were made by Jones and associates (6) who reported a higher complication rate (24% vs. 13.6%), as well as a lower stone-free rate (51% vs. 92%), in those patients with a previous open nephrolithotomy. However, our study did not show any difference in the outcome of PCNL in such patients.

PCNL in the previously-operated patients may be hampered at various stages. At the outset (i.e at the time of puncture and dilation) perirenal fibrosis and retroperitoneal scarring, may cause a problem (8-10). This was depicted in our study too, as we had to make more attempts to access the PCS in previously-operated patients compared to primary cases. A similar observation was made by Margel et al. (8), who required 2.3 ± 1.9 vs. 1.2 ± 1.1 attempts in secondary vs. primary cases, thus stressing the fact that retroperitoneal scarring does hamper access to the kidney. Also, retroperitoneal and perinephric scarring make the dilation of the tract difficult. This may be attributed to the marginally longer operating time in case of previously operated cases despite patients having similar stone burden compared to primary cases. To avoid this problem some authors have even used Collings knife or optic urethrotome for tract dilation. However, this increased morbidity, so it is not used now (11,12). We have modified our technique by generously incising the expected tract site with a no. 21 knife blade. This we do by going parallel to the puncture needle under fluoro control so as not to damage the renal parenchyma. Additionally, puncturing the calyx of interest through the non-operated site (scar site) makes the dilation easy. At times (very sparingly) we have used the reverse end of the Alken rod to get an initial access to the PCS by guiding it over the prepositioned Terumo wire (specially, in cases of caliceal scarring). Later the rod is reversed and placed normally for further telescopic dilation. Difficulty in tract dilation has been observed by Kurtulus et al. (10) in their study where in successful tract formation with balloon dilation in one step could be obtained in 83% of primary cases while in patients with history of open surgery it was possible in only 50%. Moreover, in their series one patient required open surgery due to a failure to create tract despite using Amplatz and balloon dilators in tandem. We did not convert any case to open due to failure to create tract. The disadvantage of telescopic metal dilation reported in literature is the high incidence of pelvic perforation, but this is rare in experienced hands (13). In our series we had one patient in each of the two groups who had small pelvic perforations that responded well to conservative treatment. We feel that excessive force used for dilation should always be avoided (this can be facilitated by the incision of the fascia as discussed), and also the dilators should always be advanced gently under fluoroscopy to prevent this problem.

Some have recommended a preoperative CT scan so as to study the relationship between the adjoining viscera to the kidney following open surgery (8,10). However, this view is not shared by others (14,15). We did not do a CT scan in any of our patients. We prefer IVU as the initial imaging study to show the exact anatomy of the renal collecting system, which for us is important in planning the initial access. In addition, this helps to keep the cost of evaluation to minimum. None in our series developed injury to adjoining organs (bowel).

Margel et al. (8), in their study, recommend choosing upper-pole caliceal puncture to avoid the scar tissue coming in the way of the puncture needle. In our opinion, mere presence of scar should not guide upper calyx puncture as it has significant

morbidity. In our series, we encountered one hemothorax following a supracostal puncture in a previously operated patient. However, we agree with the fact that the previous incision site should be avoided if possible to facilitate puncture and ease dilation.

Retroperitoneal and caliceal scarring may fix the kidney thus reducing its mobility. In these cases intraoperative manipulation of nephroscope may torque the kidney and cause laceration with bleeding (14,16). Also, this hampers access to the intrarenal calyces affecting the overall clearance (8). Though we observed difficulty in the intrarenal manipulation, it that did not have a bearing on the overall clearance rate (91.1% vs. 93.33% respectively) or the overall transfusion rate in the two groups (9.09% vs. 8.8% respectively). The clearance rate and transfusion rate were comparable to those reported in literature (8,16,17).

CONCLUSIONS

Our single-surgeon experience has proved that PCNL in a patient with a history of open nephrolithotomy is safe and effective. It can be performed with no fear of higher risk of failure, excessive bleeding, or damage to adjoining organs. Difficulty in access and tract dilation can be overcome by preferably selecting the site of puncture away from the previous scar and a generous but controlled incision of the fibrous tract.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT: Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979; 16: 624-31.
2. James EL, Brian RM, Andrew PE: Surgical Management of Upper Urinary Tract Calculi, Chapter 44; In: Campbell-Walsh urology 9th (ed.), Philadelphia, Saunders. 2007; pp. 1431-508.
3. Fernström I, Johansson B: Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976; 10: 257-9.
4. Kim SC, Kuo RL, Lingeman JE: Percutaneous nephrolithotomy: an update. Curr Opin Urol. 2003; 13: 235-41.
5. Viville C: Percutaneous nephrolithotomy. Personal experience in 100 cases. J Urol (Paris). 1987; 93: 253-8.
6. Jones DJ, Russell GL, Kellett MJ, Wickham JE: The changing practice of percutaneous stone surgery. Review of 1000 cases 1981-1988. Br J Urol. 1990; 66: 1-5.
7. Parmar MS: Kidney stones. BMJ. 2004; 328: 1420-4.
8. Margel D, Lifshitz DA, Kugel V, Dorfmann D, Lask D, Livne PM: Percutaneous nephrolithotomy in patients who previously underwent open nephrolithotomy. J Endourol. 2005; 19: 1161-4.
9. Lojanapiwat B: Previous open nephrolithotomy: does it affect percutaneous nephrolithotomy techniques and outcome? J Endourol. 2006; 20: 17-20.
10. Kurtulus FO, Fazlioglu A, Tandogdu Z, Aydin M, Karaca S, Cek M: Percutaneous nephrolithotomy: primary patients versus patients with history of open renal surgery. J Endourol. 2008; 22: 2671-5.
11. Davis BE, Noble MJ, Mebust WK: Use of the Collings knife electrode for percutaneous access in difficult endourology cases. J Urol. 1991; 145: 257-61; discussion 261-2.
12. Tzai TS, Chang CL, Hwang IS: An alternative approach to tract dilation using optic urethrotome in percutaneous nephrolithotomy. J Urol. 1987; 137: 1110-2.
13. Lynch W, Doust B, Golovsky D: Percutaneous dilatation of difficult nephrostomy tracts. Br J Urol. 1992; 70: 455-6.
14. Lojanapiwat B: Does previous open nephrolithotomy affect the efficacy and safety of tubeless percutaneous nephrolithotomy? Urol Int. 2010; 85: 42-6.
15. Basiri A, Karrami H, Moghaddam SM, Shadpour P: Percutaneous nephrolithotomy in patients with or without a history of open nephrolithotomy. J Endourol. 2003; 17: 213-6.
16. Tugcu V, Su FE, Kalfazade N, Sahin S, Ozbay B, Tasci AI: Percutaneous nephrolithotomy (PCNL) in patients with previous open stone surgery. Int Urol Nephrol. 2008; 40: 881-4.
17. Gupta NP, Mishra S, Nayyar R, Seth A, Anand A: Comparative analysis of percutaneous nephrolithotomy in patients with and without a history of open stone surgery: single center experience. J Endourol. 2009; 23: 913-6.

Submitted for publication:
July 25, 2011

Accepted after revision:
August 23, 2011

Correspondence address:
Dr. Rahul Gupta
3D/D 2nd Extension Surgery
Government Medical College Jammu Green Belt Park,
Gandhinagar
Jammu, Jammu and Kashmir, 180004, India
Fax: + 91 979 622-1166
E-mail: rajaguptadr@rediffmail.com

Clinical Urology
International Braz J Urol
Vol. 37 (6): 745-750, November - December, 2011

Does the duration of infertility affect semen parameters and pregnancy rate after varicocelectomy? A retrospective study

Mohammed A. Al-Ghazo, Ibrahim Fathi Ghalayini, Rami S al-Azab, Ibrahim Bani-Hani, Mohammad S. Daradkeh

King Abdullah university Hospital, faculty of Medicine, Jordan University of Science and technology, Irbid-Jordan

ABSTRACT

Objectives: The most common indication for treatment of varicocele is still male subfertility. The aim of this study was to explore the effect of infertility duration on semen parameters and spontaneous pregnancy rate after varicocelectomy.
Materials and Methods: The medical records of 183 infertile patients with clinical varicocele were retrospectively reviewed. The patients were divided into three groups according to the duration of infertility (group I, 1-3 years, group II, 3-6 years and group III, > 6 years). Total sperm motility counts (TMCs) before and after varicocelectomy and spontaneous pregnancy rate among these groups were statistically compared.
Results: The greatest changes, regarding preoperative and postoperative TMCs and spontaneous pregnancy rate were noticed between group I and III. Preoperative TMCs in group I and III was 15.2 ± 1.2, 7.8 ± 1.4, respectively ($p < 0.05$). Postoperative TMCs in group I and III was 33.7 ± 2.5, 25.2 ± 1.9, respectively ($p < 0.05$). An overall spontaneous pregnancy rate of 34.4% was achieved after inguinal varicocelectomy. The greatest spontaneous pregnancy rate was achieved in Group I (37.3%), and the lowest pregnancy rate in Group III (26.3%) ($P < 0.05$).
Conclusions: Surgical varicocelectomy improves the total sperm motility counts especially in patients who have a TMCS more than 5 million and improves the spontaneous pregnancy rates. The improvement in the spontaneous pregnancy rates after varicocelectomy correlates negatively with the duration of infertility. Therefore, duration of infertility should be considered in treating a patient with a varicocele as a cause of infertility.

Key words: *infertility; spermatogenesis; varicocele; semen analysis*
Int Braz J Urol. 2011; 37: 745-750

INTRODUCTION

Infertility, defined as the inability to conceive after one year of unprotected intercourse, affects 15% of couples (1). The most common identifiable cause of male infertility (subfertility) is a varicocele, a condition of palpably distended veins of the pampiniform plexus of the spermatic cord (2,3). Varicoceles occur in approximately 15% of the general male population but are more common (25%-35% prevalence) in infertile men and are the most common physical abnormality in infertile men (3,4). Various mechanisms have been proposed to explain infertility in men with varicocele. These include hypoxia, stasis, testicular venous hypertension, elevated testicular temperature, increase in spermatic vein catecholamine, and increased oxidative stress (5). However, there have still been some undefined mechanisms of varicocele since some of the patients with varicocele have normal semen parameters (6). The most common indication for treatment of varicocele is still the male subfertility. The other possible indications are varicocele-related scrotal pain or swelling not relieved by conservative treatment. Duration and severity of varicocele may be a risk factor for infertility related with age

in patients with varicocele (7). The mean time for semen improvement and spontaneous pregnancy after surgery is approximately five to seven months, respectively (8). However, the aetiology of underlying infertility is especially uncertain in men whose semen parameters do not significantly improve or do not achieve pregnancy following varicocele surgery. Marcello et al. (9) reported that high-grade varicocele (grade III), normal FSH, total motility over 60% and total motile sperm count over 5 x10^6 (before surgery) are good prognostic factors of varicocele repair outcomes in infertile patients, while subclinical varicocele, presence of Y chromosome microdeletions, testicular atrophy and total motile sperm count less than 20 x 10^6 (after surgery) are poor prognostic factors. Zorba et al. (10) reported that the duration of infertility should be considered as another predictive factor for a positive seminal response to varicocelectomy and achieving pregnancy. It is uncertain the effect of varicocele surgery on the duration of infertility and outcome especially semen characteristics and pregnancy rate, only a limited number of studies have been reported and this subject is not completely understood.

The aim of this study is to evaluate the duration of infertility on postvaricocelectomy semen parameters and spontaneous pregnancy rates.

MATERIALS AND METHODS

Our institution's protocol review board approved this retrospective study.

From March 2003 to October 2009, we retrospectively reviewed the medical records of 183 patients, who underwent inguinal varicocelectomy because of infertility at King Abdullah University Hospital. Patients who were treated by other approaches such as high ligation, laparoscopic, or subinguinal microscopic surgery were excluded to avoid its effect on the results. The data collected included the following: age, period of infertility, spontaneous pregnancy, semen analysis before and after surgery, and complications and hormone profile. According to the period of infertility, 183 patients were divided into three groups. Group I 1-3 years, (n = 102); group II, 4-6 years (n = 43), and group III, > 6 years (n = 38). Diagnosis of varicocele was made by physical examination of all patients. Varicoceles are graded as subclinical (impalpable, detected by ultrasonography), grade I (palpable by Valsava manoeuvre when upright), grade II (palpable without Valsava manoeuvre when upright) , or grade III (visible) (11). Semen for analysis was obtained by masturbation after 3-5 days of sexual abstinence and was processed within one hour of ejaculation. All men had at least two semen analyses before and two semen analyses after surgery. We used the average data both preoperatively and postoperatively. All analyses were performed in the same laboratory by the same technicians. After liquefaction of semen, sperm concentration and motility were evaluated according to the World Health Organization (WHO) guidelines (12). The preoperative and postoperative total motile sperm counts (TMCs) were calculated by the following formula: TMC = ejaculate volume (mL) x concentration (x10^6 /mL) x motile fraction (13). –Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were determined before varicocelectomy. Patients with abnormal hormone levels were excluded from the study. The spouses of these men were evaluated by the gynaecologists for factors related to female infertility, and patients whose spouses might have had concomitant female factors for infertility were also excluded. The mean follow-up period was 38 months (range, 14 to 82). During the follow-up period, we focused on surgical complications, varicocele recurrence, seminal fluid parameters and spontaneous pregnancy. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 16.0.

Multivariate analysis was performed using age of the patient, grade of varicocele and duration of infertility in relation to spontaneous pregnancy rate. One-way analysis of variance and student's test were used to compare the preoperative and postoperative TMCs and pregnancy rates among the three groups. Probability (P) values < 0.05 were considered significant.

RESULTS

The mean age of patients included in this study was 28.4 ± 5.4 years (range 22-56). The mean age of patients in Groups I-III was 29.4 ± 5.2 (range

22-46), 31.2 ± 4.8 (range 26-51), and 32.4 ± 4.2 (range 25-55), respectively, with $p > 0.05$.

Patients with unilateral (left-sided) and bilateral varicocele and clinical grades who underwent varicocelectomy for treatment of infertility are shown in Figure-1.

Abnormality in the total sperm motility count (TMCs) and pregnancy rates in patients among the three groups is shown in Table-1.

A total of 23 patients had severe oligozoospermia < 5 mil/mL and seven had azoospermia. The number of patients with azoospermia in Groups I-III was 4, 2, and 1, respectively. None of these patients could father a child after varicocelectomy. One azoospermic patient in Group I showed few motile sperms in the ejaculate after surgery, but he refused assisted reproduction for religious reasons. The number of patients with severe oligozoosper-

Figure 1 - *Patents who underwent varicocelectomy for infertility treatment.*

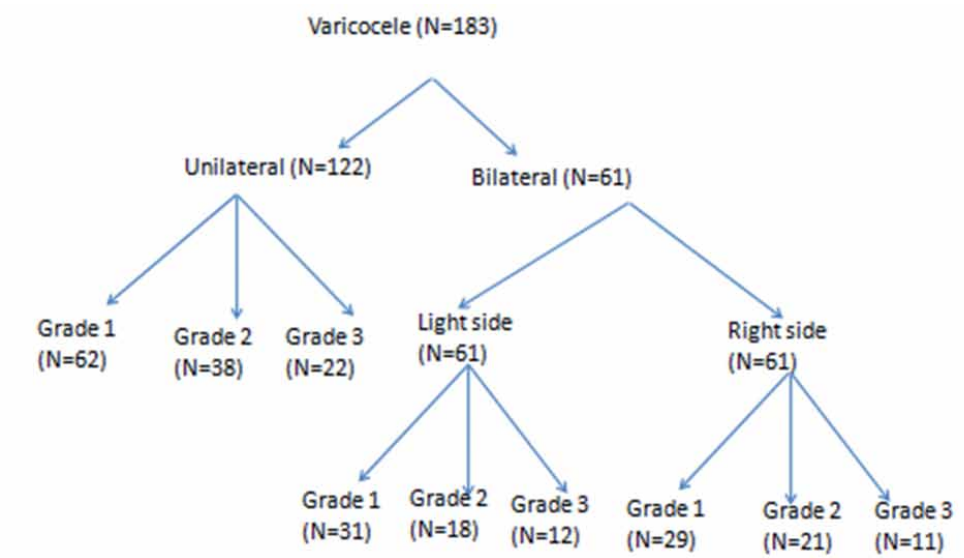


Table 1 - *Preoperative and postoperative mean total sperm motility count and pregnancy rate between the three groups of patients.*

Variable	Group I	Group II	Group III
Number of patients	102	43	38
Preoperative TMCs($X10^6$)	15.6±1.2	12.4±1.4	8.0±1.7*
Postoperative TMCs ($X10^6$)	33.7±2.5	29.6±3.2	25.2±1.9*
Increase in the mean TMCs($X10^6$)	18.1	17.3	16.5
Pregnancy rate%	37.3%	34.9%	26.3%*

** - Statistically significant difference between group 1 and 3*
Group I: duration of infertility 1-3 years, Group II: duration of infertility 3-6 years, Group III: duration of infertility > 6 years.

mia in Groups I-III was 12, 4, and 7, respectively. The pregnancy rate in these groups with severe oligospermia was 2, 0, and 0.

Changes in sperm motility rate in all groups before and after varicocelectomy are shown in Table-1. The greatest increase in motility rate after surgery was noted in group I ($17.2 \pm 1.4x10^6$), while patients in group III had the lowest increase in motility rate ($7.9 \pm 1.8x10^6$). The difference was statistically significant ($p < 0.05$).

Preoperative motility rate had the tendency to decrease with an increasing period of infertility. The difference was not significant between Groups I and II or between Groups II and III ($p > 0.05$), while it was significant between Group I and III ($p < 0.05$).

Spontaneous pregnancy was achieved in 63 out of 183 patients (34.4%) after an average of 11.2 ± 2.8 months after surgery (range 4-26 months). Most of these were achieved within the first year, in 57 of the 63 patients (90.5%). No significant difference ($p > 0.05$) was observed among the groups in the time elapsed after surgery to pregnancy state. Pregnancy rates were 37.3%. 34.9% and 26.32% in Groups I-III, respectively. The only statistically significant difference in spontaneous pregnancy rate was observed between Groups I and III ($p < 0.05$). Multivariate analysis revealed that the duration of infertility was the only significant factor affecting the pregnancy rate.

DISCUSSION

Varicocele, which is defined as an abnormal dilation of the testicular veins and pampiniform plexus, is the most frequent curable cause of male infertility (1). Deregulation of nitric oxide, reactive oxygen species, and regulators of apoptosis have been implicated in the pathophysiology of varicocele (11,14). Several mechanisms may be involved in the negative effect of varicocele on male infertility. These include elevated intrascrotal temperature, reflux of adrenal and renal metabolites through renal vein, hypoxia, and ischemia (15,16). A statistically significant deterioration in sperm count and motility throughout the follow-up period of untreated varicocele has been previously documented (17). More importantly, histological changes and atrophy have been demonstrated in the testes associated with varicocele (18). In this study, the difference in the preoperative sperm motility between Groups I and III was statistically significant ($p < 0.05$). Moreover, we noticed that the sperm parameters correlate negatively with the increased period of infertility. These findings are in agreement with the results of Chehval and Prucell (17) who demonstrated a decline in sperm parameters over time in men with untreated varicocele. Many prospective studies have shown that testicular volume either fails to increase or actually decreases in testes that are associated with varicoceles (19,20). Findings from previous studies provide strong evidence supporting the hypothesis that varicoceles exert a progressive deleterious effect on the testis during adolescence (17).

In the present study, we found a good response after varicocelectomy in the semen parameters in all patients with TMCs > $5 x10^6$ and the greatest improvement was found in patients in Group I, who had the greatest preoperative TMCs. On the other hand, patients with severe oligozoospermia and azoospermia showed a bad response. These findings are similar to the previously reported results (21). Also, we found that after varicocelectomy, the results of semen parameters correlated negatively with the duration of infertility which is in agreement with reported study (10).

In the present study, multivariate analysis revealed that varicocele grade effect on pregnancy rate was insignificant, which is in agreement with a previously published study (10). It was reported that varicocele size did not have an impact upon either semen improvement or pregnancy rate (22). In contrast, studies have shown that subclinical varicoceles are much more common, being present in 44% of fertile men and 60% of men attending infertility clinics (23). Despite the insignificant effect of varicocele size on pregnancy rate, we found that varicocele size had an adverse relationship with baseline semen parameters and direct relationship with potential improvement which is in agreement with previous findings (11).

In the present study, the difference in the postoperative TMCs between Groups I and III was statistically significant ($p < 0.05$). The greatest increase in TMCs in patients with primary infertility

was encountered in Group I and the pregnancy rate in this group was significantly higher than in Group III. Therefore, according to these results, we could assume that an increase in the TMCs after varicocelectomy is an indicator of pregnancy rate improvement. After varicocelectomy TMCs increased more than $18x10^6$ in all our patients provided the preoperative TMCs were more than $5x10^6$ and the pregnancy rate reached 34.4%. These findings were comparable to previously reported results (24). Marmar et al. (24) according to their conducted meta-analysis study including only randomized, controlled trials concluded that varicocelectomy is an effective method for improving spontaneous pregnancy rates in the infertile male who has poor semen quality and palpable varicocele. On the other hand, many authors are still not convinced of the positive effect of varicocelectomy on pregnancy rate. There are many approaches for varicocelectomy, such as high ligation (retroperitoneal), inguinal, laparoscopic and subinguinal microscopic approach. The Subinguinal microscopic approach described by Marmar et al. (24) was considered as a gold standard. In our study most of our patients underwent inguinal varicocelectomy. Therefore, patients who were treated by other approaches were excluded from the study in order not to have an impact upon our results.

Through multivariate analysis, including patient's age, varicocele grade, and infertility period, we found that the infertility period was the only independent factor affecting sperm motility and pregnancy rate, which is in agreement with reported series (10).

CONCLUSIONS

Varicocele remains a risk factor for abnormal semen parameters that affect spontaneous pregnancy. Surgical varicocelectomy was found to improve the total sperm motility counts even in patients with azoospermia and to improve the spontaneous pregnancy rates especially in patients who have a total motile sperm count more than five million. The duration of infertility correlates negatively with the improvement in the total sperm count and the spontaneous pregnancy rates after varicocelectomy. Therefore, duration of infertility should be considerd in treating a patient with a varicocele as a cause of infertility.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Kolettis PN: Evaluation of the subfertile man. Am Fam Physician. 2003; 67: 2165-72. Erratum in: Am Fam Physician. 2003; 68: 1266.
2. No authors listed: The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. Fertil Steril. 1992; 57: 1289-93.
3. Steckel J, Dicker AP, Goldstein M: Relationship between varicocele size and response to varicocelectomy. J Urol. 1993; 149: 769-71.
4. Hauser R, Paz G, Botchan A, Yogev L, Yavetz H: Varicocele: effect on sperm functions. Hum Reprod Update. 2001; 7: 482-5.
5. Marmar JL: The pathophysiology of varicoceles in the light of current molecular and genetic information. Hum Reprod Update. 2001; 7: 461-72.
6. Basar MM, Kisa U, Tuglu D, Kacmaz M, Basar H: The effect of varicocele on seminal plasma and serum inhibin-B levels in adolescent and adult men. Int Urol Nephrol. 2010; 42: 47-51.
7. Resorlu B, Kara C, Sahin E, Unsal A: The significance of age on success of surgery for patients with varicocele. Int Urol Nephrol. 2010; 42: 351-6.
8. Colpi GM, Carmignani L, Nerva F, Piediferro G, Castiglioni F, Grugnetti C, et al.: Surgical treatment of varicocele by a subinguinal approach combined with antegrade intraoperative sclerotherapy of venous vessels. BJU Int. 2006; 97: 142-5.
9. Cocuzza M, Cocuzza MA, Bragais FM, Agarwal A: The role of varicocele repair in the new era of assisted reproductive technology. Clinics (Sao Paulo). 2008; 63: 395-404.
10. Zorba UO, Sanli OM, Tezer M, Erdemir F, Shavakhabov S, Kadioglu A: Effect of infertility duration on postvaricocelectomy sperm counts and pregnancy rates. Urology. 2009; 73: 767-71.
11. Jarow JP: Effects of varicocele on male fertility. Hum Reprod Update. 2001; 7: 59-64.

12. World Health Organization (WHO) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge University Press, Cambridge 1992.
13. Cayan S, Erdemir F, Ozbey I, Turek PJ, Kadioglu A, Tellaloglu S: Can varicocelectomy significantly change the way couples use assisted reproductive technologies? J Urol. 2002; 167: 1749-52.
14. Sharma RK, Agarwal A: Role of reactive oxygen species in male infertility. Urology. 1996; 48: 835-50.
15. Zorgniotti AW, Macleod J: Studies in temperature, human semen quality, and varicocele. Fertil Steril. 1973; 24: 854-63.
16. Pintus C, Rodriguez Matas MJ, Manzoni C, Nanni L, Perrelli L: Varicocele in pediatric patients: comparative assessment of different therapeutic approaches. Urology. 2001; 57: 154-7.
17. Chehval MJ, Purcell MH: Deterioration of semen parameters over time in men with untreated varicocele: evidence of progressive testicular damage. Fertil Steril. 1992; 57: 174-7.
18. Saypol DC, Howards SS, Turner TT, Miller ED Jr: Influence of surgically induced varicocele on testicular blood flow, temperature, and histology in adult rats and dogs. J Clin Invest. 1981; 68: 39-45.
19. Haans LC, Laven JS, Mali WP, te Velde ER, Wensing CJ: Testis volumes, semen quality, and hormonal patterns in adolescents with and without a varicocele. Fertil Steril. 1991; 56: 731-6.
20. Sayfan J, Siplovich L, Koltun L, Benyamin N: Varicocele treatment in pubertal boys prevents testicular growth arrest. J Urol. 1997; 157: 1456-7.
21. Matkov TG, Zenni M, Sandlow J, Levine LA: Preoperative semen analysis as a predictor of seminal improvement following varicocelectomy. Fertil Steril. 2001; 75: 63-8.
22. Dubin L, Amelar RD: Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril. 1970; 21: 606-9.
23. Schlegel PN: Is assisted reproduction the optimal treatment for varicocele-associated male infertility? A cost-effectiveness analysis. Urology. 1997; 49: 83-90.
24. Marmar JL, Agarwal A, Prabakaran S, Agarwal R, Short RA, Benoff S, et al.: Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. Fertil Steril. 2007; 88: 639-48.

Submitted for publication:
January 05, 2011

Accepted after revision:
April 25, 2011

Correspondence address:
Dr. Mohammed A Al-Ghazo
Associate professor of Urology
Department of General Surgery and Urology,
Faculty of Medicine
Jordan University of Science and Technology
PO Box 3030, Irbid, 22110, Jordan
Fax: + 962 2 7200621
E-mail: alghazo@just.edu.jo

Surgical Technique
International Braz J Urol
Vol. 37 (6): 751-757, November - December, 2011

Intraoperative maximal urethral closing pressure measurement: a new technique of tape tension adjustment in transobturator sling surgery?

Myung Beum Kang, Hyeong Gon Kim, Sung Hyun Paick, Yong Soo Lho, Hyoung Keun Park

Department of Urology, School of Medicine, Konkuk University

ABSTRACT

Purpose: Tape tension adjustment is an essential procedure in mid-urethral sling surgery. The goal of this study was to determine if intraoperative maximal urethral closing pressure (MUCP) elevation could be used as a reference value for adequate tape tension adjustment and predict transobturator (TOT) sling surgery outcome.
Materials and Methods: A prospective study was performed using MUCP measurements just before tape insertion and just after tension adjustment during surgery. Clinical data including preoperative urodynamic results were collected. The cure rate was determined by questionnaire. Patients were divided into two groups. The MUCP elevation group included patients with a MUCP elevation of more than 10 cmH_2O before tape insertion; the others were regarded as the non-elevation group. The cure rate and pre- and postoperative clinical variables were compared between the two groups.
Results: A total of 48 patients had TOT surgery. The MUCP elevation group (n=19) and the non-elevation group (n=29) were similar with regard to patient characteristics and the preoperative parameters including age, mixed incontinence prevalence, Q-tip angle, peak flow rate, MUCP and the valsalva leak point pressure (VLPP). The mean follow-up period was nine months. The cure rate was significantly higher in the group with MUCP elevation than in the non-elevation group (84% vs. 52%, p = 0.02). There was no significant difference in the mean postoperative peak flow rate between the two groups and there was no retention episode.
Conclusions: MUCP elevation of more than 10 cmH_2O just after tape insertion was a prognostic factor.

Key words: *urinary incontinence; suburethral slings; treatment outcome; urodynamics*
Int Braz J Urol. 2011; 37: 751-757

INTRODUCTION

In 1996 a new surgical technique called the tension-free vaginal tape procedure was introduced by Ulmsten for stress urinary incontinence (SUI) (1). This procedure has become popular for treating SUI. Many studies have reported on a long-term success rate of more than 80% using both objective and subjective assessments (2,3). Although the success rate of the mid-urethral sling is high, there are also many failed procedures. Therefore, identifying the factors that are associated with persistent SUI after surgery is extremely important. Though controversial, the low valsalva leak point pressure (VLPP), low maximal urethral closing pressure (MUCP), the presence of intrinsic sphincter deficiency (ISD), presence of mixed incontinence, and the presence of a high grade cystocele are thought to be important prognostic factors (4,5).

However, among the studies on the prognostic factors, there is no study on the tape tension adjustment during surgery as a possible prognostic factor. Recently, the tape shortening technique using clips showed a 60-70% success rate in patients with recurrence after a sling operation (6,7). These studies suggest the importance of tape tension in sling surgery. In addition, a tension adjustable sling system, such as the Remeex readjustable sling, was

developed and widely used for repair of SUI (8). Therefore, providing the proper tension during surgery to render the patient continent, is now a focus of study.

Tape tension adjustment is essential for mid urethral sling surgery. However, there have been no methods developed to evaluate the degree of tape tension during surgery. In addition, there is no consensus on the appropriate amount of tension. The amount of tension adjustment has occasionally been determined by the subjective judgment of the surgeon.

We hypothesized that tape tension would influence urethral pressure,which could be measured as the MUCP level in urodynamic testing.

The goal of this study was to determine whether MUCP changes influence the surgical outcome. The MUCP changes were studied before and after placement of the tape and the outcomes were assessed as potential prognostic factors of TOT surgery.

MATERIALS AND METHODS

From October 2007 to November 2008, the MUCP was prospectively measured just before and after tape insertion in the operating room. A single surgeon performed all TOT operations. The preoperative protocol included a history and physical examination, urinalysis, urine culture, uroflowmetry, PVR urine measurement, Q-tip test, and multichannel urodynamic studies. Urethral hypermobility was defined as when the angle of Q tip test was more than 30 degrees. Written consent was obtained from all patients.

Patients were included in the study if they were female with SUI or MUI (mixed urinary incontinence) and older than age 18.Patients were excluded if they had any urinary tract infection, malignancy, or were pregnant

TOT procedures were performed as follows. The procedures were performed under spinal anesthesia. After incision and minimal dissection of the vaginal wall, a 6Fr two-channel flexible UPP catheter was inserted to measure the MUCP using a multichannel urodynamic study instrument (Medtronics Inc., Minneapolis, MI, USA). Then, after removal of the catheter, Transobturator tape (Monarc) needles were inserted through out-in technique. After filling the bladder with 250 mL physiological saline, cystoscopy was performed with the needles still in place.

After cystoscopy examination, a Monarc needle was connected to tape and pulled outside of the previous insertion site. The tension of the tape was adjusted and the catheter was re-inserted to measure the MUCP again. All measurements were completed and the vaginal wound was closed. Operator was blinded to intraoperative MUCP results and did not adjust the tension of the tape after second MUCP measurement.

Patients were discharged from the hospital the morning following the procedure, and were followed up with at one, six, and 12 months and then every year thereafter. The follow-up evaluation included a clinical history, physical examination with a stress test, uroflowmetry, and post-void residual (PVR) measurement.

Cure of incontinence after the procedure was defined as the absence of subjective leakage after coughing, laughing, or other abdominal-straining circumstances, and as the absence of objective leakage on stress cough tests when the patients felt a normal voiding sensation and other term was defined according to recent report (9).

All other cases were considered to be failures. The patients were divided into two groups by the change in the MUCP, i.e. the MUCP elevation group was defined as patients in whom the MUCP was elevated more than 10 cmH_2O after insertion of the tape compared to before insertion of the tape; the non-elevation group was shown by no change or elevation less than 10 cmH_2O. Cure rate in the MUCP elevation group was compared to the non-elevation group. In addition, the MUCP changes were compared in patients who had successful procedures and patients who had failed procedures to determine whether it was a possible predictive factor.

Statistical analysis was performed using the Student t-test for continuous data, as well as Fisher's exact test and the chi-square test. Variables that had a p-value less than 0.05 in the univariate analysis were included in the multivariate logistic model. A 5% level of significance was used for all statistical testing and all statistical tests were 2-sided. The statistical analyses were performed using SPSS® 11.0.

RESULTS

1. Patient demographics

A total of 48 patients, between 32 and 77 years of age (mean 50.3), underwent mid urethral sling surgery with the TOT technique by a single surgeon. No difference in the clinical characteristics was observed between the MUCP elevation group (n = 19) and the non-elevation group. Age, prevalence of mixed urinary incontinence, urethral hypermobility, peak flow rate, preoperative MUCP and leak point pressure were not significantly different between the two groups (Table-1).

Table 1 - *Preoperative clinical parameter between elevation group and non elevation group.*

	MUCP elevation group	Non elevation group	p- value
No. of patients	19	29	
Mean age (years)	49.7 ± 8.7	50.7 ± 9.9	0.72
Prevalence of urgency (%)	32	46	0.06
Prevalence of urge incontinence (%)	31	35	0.56
Prevalence of urethral hypermobility (%)	69	52	0.06
Prevalence of detrusor overactivity (%)	11	14	0.15
Mean MUCP (cmH_2O)	60 ± 24	66 ± 33	0.16
Mean VLPP (cmH_2O)	100 ± 15	95 ± 25	0.10
Mean peak flow rate (ml/sec)	25	26	0.70

MUCP: maximal urethral closing pressure; VLPP: valsalva leak point pressure

2. MUCP changes and cure rate

The overall cure rate was 65% (n = 35) and the mean follow-up period was nine months (6-15 months). The MUCP was elevated significantly from 36 ± 17 cmH_2O (before placement of the tape) to 42 ± 18 cmH_2O (after placement of the tape) in all patients (p = 0.04). The MUCP was significantly elevated in the MUCP elevation group (from 32 ± 15 cmH_2O to 51 ± 17 cmH_2O) but not in the non-elevation group (from 40 ± 18 cmH_2O to 35 ± 16 cmH_2O).

The overall cure rate was significantly higher in the MUCP elevation group compared to the non-elevation group (84% vs. 52%) (p = 0.02) (Figure-1).

In the group that was cured, the MUCP increased from 34 ± 17 cmH_2O to 41 ± 16 cmH_2O after placement of the tape; however, there was no difference in the group with a failed procedure (from 40 ± 18 cmH_2O to 42 ± 22 cmH_2O) (Figure-2).

3. Complications

De novo urgency or urge incontinence was present in one patient in the group with the MUCP elevation group and in seven patients in the non-elevation group. The bladder irritation symptoms were more severe in the MUCP elevation group; however, this difference was not significant. The postoperative peak flow rate and PVR was not significantly different in comparisons between the two groups. No patients developed urinary retention (defined as PVR greater than 100 mL or did not void) or vaginal erosion during the follow-up period (Table-2).

DISCUSSION

Since tension-free vaginal tape has been introduced and used widely, many clinical prognostic factors have been reported including ISD, low VLPP, presence of cystocele, and mixed incontinence (4,5). However, there has been little attention focused on the tension of the tape during surgery and the prognostic significance of the tape tension on the surgical outcome.

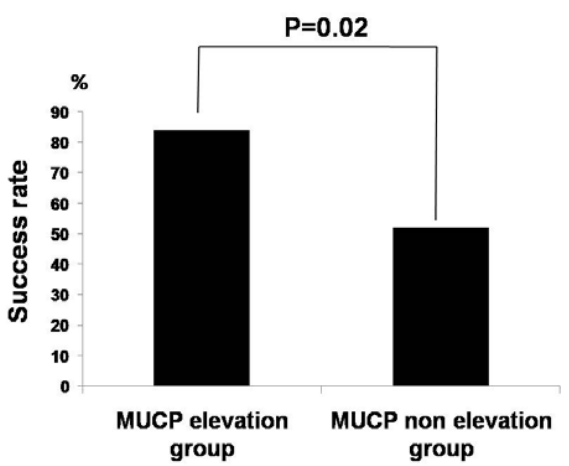
Initially, many surgeons thought it was unnecessary to provide tension on the tape. This was because the mechanism of the mid-urethral sling was

Table 2 - *Postoperative clinical parameter between MUCP elevation group and non elevation group.*

	MUCP elevation group	Non elevation group	P value
Success rate (%)	84	52	0.02
Mean MUCP change (cmH_2O)	19 ± 16	5 ± 17	0.03
No. of patients with de novo urgency and/or urge incontinence	1	7	0.17
Mean peak flow rate (mL/sec)	18.2 ± 8.8	19.7 ± 9.6	0.52
Mean post void residual (mL)	24 ± 29	29 ± 25	0.46
Episode of Urinary retention	0	0	
Episode of vaginal erosion	0	0	

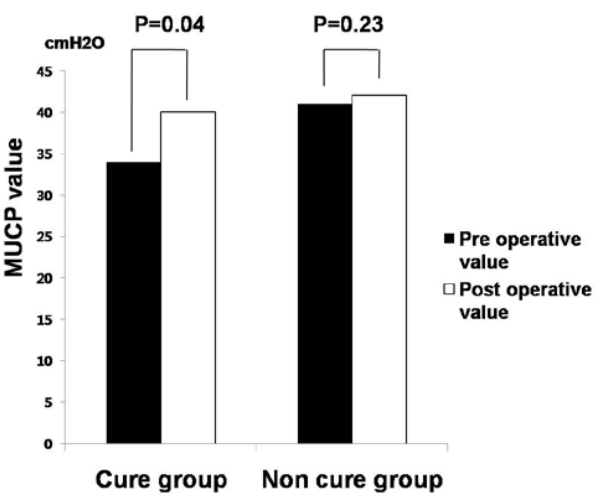
MUCP: maximal urethral closing pressure

Figure 1 - *Comparison of cure rate between MUCP elevation group and non elevation group.*



The overall cure rate was significantly higher in the MUCP elevation group compared to the non elevation group (84% vs. 52%) (p=0.02).

Figure 2 - *The comparison of MUCP change between the cure group and non cure group.*



The MUCP increased significantly in the group that was cured (p=0.04); however, there was no difference in the group with a failed procedure (p=0.23).

thought to be based on collagen fibers growing into the tape, which would then fix the tape with mid-urethral tissue rather than tension on the urethra (10).

However, with more experience, many surgeons thought proper tension was needed in the insertion of the tape and that the tension was associated with the surgical outcome. In the case of failed prior mid-urethral sling placement, the tape shortening technique, which shortened the tape to give more tension, had a 60-70% success rate (5-7). In addition, the Remeex system that allows for tape tension adjustments after surgery was introduced and widely used (8). The latter two methods were based on the concept that tape tension would produce positive outcomes on continence after sling surgery. Good results using these methods suggest the importance of tension adjustment. Although the tension of the tape has been accepted as an important factor, there has been no study addressing the measurement of the tension and its association with patient outcome.

As there is no standard method of tape tension adjustment, it is usually performed in accordance with the surgeon's experience and feeling. Some surgeons use the surgical scissors or right

angle clamp between the tape and urethra and others used a bechop clamp to fold the middle part of tape.

Therefore, the purpose of this study was to determine whether tape tension influences surgical outcome and to determine the reference value of proper tension adjustment. We hypothesized that tape tension would influence urethral pressure, which could be measured as the MUCP level in urodynamic testing. The degree of tension was assumed by the change in MUCP before and after placement of the tape using urodynamic studies in the operating room.

The results of this study showed that patients with an elevated MUCP had a higher cure rate compared to patients without an elevated MUCP. An elevated MUCP above 10 cmH_2O, after placement of the tape, was associated with a good outcome. Therefore, this factor might be used to help predict patient outcome.

In the non-elevation group, there were patients who showed a decrease in MUCP after tape implantation. So, the mean MUCP was slightly changed.

Similarly, one study reported significant postoperative changes of the MUCP (11). However, another study reported no difference in the MUCP between pre- and post-surgery measurements and no relationship between the outcome of surgery and the UPP (urethral pressure profile) parameters (12). However, in that study, although routine resting UPP had no added value, the postoperative MUCP was also significantly higher in patients with successful outcomes compared to those that had failed surgery (12).

Similarly, the results of this study showed that the mean postoperative MUCP did not differ between patients with successful procedures and failed procedures. The MUCP was decreased in some cases, which made the mean value more similar in the two groups. However, the MUCP was significantly increased in the group with a successful outcome. These findings suggest that the degree of increase in the MUCP rather than the absolute value is the important factor to evaluate during surgery.

The limitations of this study include the following. First, only the UPP and not the URP was measured. The URP may reflect the tension applied to the urethra and further study may show that the value of the URP is an important prognostic factor. In addition, the cut level of 10cmH_2O was decided by an analysis that showed a significant difference between the two groups; however, additional studies with more patients are needed to determine the optimal cut-off level.

The patients with MUCP elevation would be expected to have more obstructive symptoms; however, there was no difference in the peak flow rate or residual urine and irritation. One possible explanation is that there was no severe tension that caused residual urine or decreased uroflow in the two groups; even in the group with MUCP elevation. In addition, the number of patients that had urgency or urge incontinence was relatively small.

Although the clinical parameters between the two groups were not significantly different, the prevalence of urinary urgency (32% compared to 46%) was higher in the non-elevation group, and this difference might be clinically relevant.

However, p-value was 0.06, Also, the prevalence of urge incontinence and detrusor overactivity in the urodynamic study were similar between the two groups.

The operator was aware of the baseline MUCP results, and this factor could influence the surgeon's decision during the tape adjustment. However, between the elevation group and the non-elevation group, there is no difference in baseline MUCP. Furthermore, MUCP results before and after placement of the tape were blinded to the operator, and those results did not influence the tape adjustment.

Finally, we performed the operation under spinal anesthesia. The estimated MUCP discrepancy between what was measured during the MUS procedure under spinal anesthesia and the real pressure generated during outcome assessment is unknown. Spinal anesthesia may affect pressure difference during sling surgery. The pressure difference may be a result of the anesthesia utilized. In one study (13), URP was decreased after spinal anesthesia. Similarly, our study showed that the baseline MUCP under no anesthesia is higher than preoperative MUCP under spinal anesthesia. However, the point of our study is that the MUCP difference prior to and after tape insertion is an important prognostic factor, and this is the indirect support needed for proper tension during tape implantation.

Despite these limitations, this preliminary study shows several implications. First, to our knowledge, there is no study about tape tension influencing sling surgery outcome. Our study showed that tape tension, which was indirectly measured by MUCP elevation, is an important prognostic factor. This study suggests that the intraoperative MUCP measurement should be a useful method for deciding on the appropriate tension adjustment and introduces a method for the quantification of the tension using urodynamic studies.

The feasibility of performing urethral closure pressures pre-and intraoperatively may be questioned. However, intraoperative UDS measurement is not so difficult and it may only take few more minutes. We are convinced of the usefulness of the UDS study because the other known prognostic factors, such as low VLPP, cystocele, mixed incontinence, and other factors are almost uncorrectable. However, MUCP elevation can be measured during surgery and can therefore be adjusted.

In this study, the tape tension was not adjusted when MUCP was not elevated more than 10cm-H_2O. It is another topic and further prospective study will be needed to show the effect of tape tension on surgical outcome.

CONCLUSIONS

The overall cure rate was significantly higher in patients with MUCP elevation compared to patients without MUCP elevation. The change in the MUCP might be a prognostic factor for patient outcome. The intraoperative MUCP measurement was a useful method for deciding on the appropriate tension adjustment.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS:

ISD: intrinsic sphincter deficiency
MUCP: maximal urethral closing pressure
MUI: mixed urinary incontinence
PVR: post void residuals
SUI: stress urinary incontinence
TOT: transobturator tape
URP: urethral retro-resistance pressure
UPP: urethral pressure profile
VLPP: valsalva leak point pressure

ACKNOWLEDGEMENT

This work was supported by Konkuk University in 2011

REFERENCES

1. Ulmsten U, Henriksson L, Johnson P, Varhos G: An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7: 81-5; discussion 85-6.
2. Kim NS, Bae JH, Lee JG: Long-term follow-up of the tension free vaginal tape (TVT) procedure for treating female stress urinary incontinence. Korean J Urol. 2006; 47: 729-33.
3. Nazemi TM, Yamada B, Govier FE, Kuznetsov DD, Kodama K, Kobashi KC: Minimum 24-month followup of the sling for the treatment of stress urinary incontinence. J Urol. 2008; 179: 596-9.
4. Cetinel B, Demirkesen O, Onal B, Akkus E, Alan C, Can G: Are there any factors predicting the cure and complication rates of tension-free vaginal tape? Int Urogynecol J Pelvic Floor Dysfunct. 2004; 15: 188-93.
5. Koh JS, Kim HS, Kim HW, Lee YS, Kim SI, Lee KS, et al.: Comparison of secondary procedures for recurrent stress urinary incontinence after a transobturator tape procedure: shortening of the tape versus tension-free vaginal tape redo. Korean J Urol. 2007; 48: 1149-54.
6. Nam SB, Bae JH, Lee JG: Surgical considerations for recurrent stress urinary incontinence after the midurethral sling procedure: redo midurethral sling and shortening of the tape. Korean J Urol. 2007; 48: 527-35.
7. Lo TS, Wang AC, Liang CC, Long CY, Lee SJ: Treatment for unsuccessful tension-free vaginal tape operation by shortening pre-implanted tape. J Urol. 2006; 175: 2196-9; discussion 2199-200.
8. Sousa-Escandón A, Cabrera J, Mantovani F, Moretti M, Ioanidis E, Kondelidis N, et al.: Adjustable suburethral sling (male remeex system) in the treatment of male stress urinary incontinence: a multicentric European study. Eur Urol. 2007; 52: 1473-9.

9. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al.: An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010; 29: 4-20.
10. Petros PE, Ulmsten UI: An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993; 153: 1-93.
11. Wang AC: An assessment of the early surgical outcome and urodynamic effects of the tension-free vaginal tape (TVT). Int Urogynecol J Pelvic Floor Dysfunct. 2000; 11: 282-4.
12. Wadie BS, El-Hefnawy AS: Urethral pressure measurement in stress incontinence: does it help? Int Urol Nephrol. 2009; 41: 491-5.
13. Duckett RA, Grapsas P, Eaton M, Basu M: The effect of spinal anaesthesia on urethral function. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19: 257-60.

Submitted for publication:
January 10, 2011

Accepted after revision:
April 15, 2011

Correspondence address:
Dr. Hyoung Keun Park
Department of Urology,
College of medicine, Konkuk University
4-12 Hwayang-dong, Gwangjin-gu
Seoul, Korea 143-729
Fax: + 02 2030-5319
E-mail:drurol@naver.com

Neurourology
International Braz J Urol
Vol. 37 (6): 758-765, November - December, 2011

Elderly men's quality of life and lower urinary tract symptoms: an intricate relationship

Vitor Last Pintarelli, Lygia Ferreira Gomes Perchon, Fábio Lorenzetti, João Toniolo Neto, Miriam Dambros

Division of Geriatric Urology (VLP, LFGP, FL, MD), Division of Geriatrics and Gerontology (JTN), Federal University of São Paulo, Brazil

ABSTRACT

Purpose: To evaluate the impact of lower urinary tract symptoms (LUTS) on the quality of life (QoL) in a group of elderly men.
Materials and Methods: Observational clinical study contained 200 men recruited between March-September 2008 in the community and Urology and Geriatrics ambulatories. The data collected included health and sociodemographic conditions; the International Prostate Symptom Score (IPSS); an anxiety/depression inventory; the World Health Organization Quality of Life -Bref and -Old questionnaires (WHOQoL). Participants were classified according to IPSS: Group I (moderate/severe symptoms) and Group II (absence/mild symptoms) and 100 men were included in each group. Results: The groups were statistically similar in sociodemographic, morbidity, and anxiety/depression scores. Both QoL scales showed significant lower median scores in group I in all parameters, except the global subjective self-evaluation of QoL. The domains social and environmental relations presented the most significative differences ($p < 0.0005$) in both questionnaires, and final mean WHOQoL-Old score was lower in group I ($p < 0.0005$).
Conclusions: For elderly men, moderate to severe LUTS do significantly impact almost all parameters of QoL proposed by the WHO, especially social and environmental relations.

Key words: *Prostatic hyperplasia; aged; quality of life; questionnaires*
Int Braz J Urol. 2011; 37: 758-765

INTRODUCTION

The conditions leading to lower urinary tract symptoms (LUTS) are among the most prevalent diseases of elderly males, with potential impairment of quality of life (QoL) (1-11). Among elderly men, benign prostatic enlargement (BPE) is the main cause of LUTS, which can be evaluated by the International Prostate Symptom Score (IPSS) (1-3,12). Among elderly men, benign prostatic enlargement (BPE) is the main cause of LUTS. Despite criticisms about its discriminatory power to predict infravesical obstruction, the International Prostate Symptom Score (IPSS) is the most used instrument to evaluate LUTS in male patients (1-3,13). BPE, except in extreme cases, does not pose a major threat to one's physical integrity, but undermines QoL; for most mild and moderate-symptom patients, QoL impairment is the main parameter evaluated on whether treating BPE, and choosing therapeutic methods (1-13). Many articles attempting to evaluate the impact of LUTS and BPE on men's QoL have been published since the World Health Organization Consensus Committee recommended the association of the IPSS with QoL scales, but inappropriate interpretations of the concept of QoL in many of these studies have triggered criticisms (3,14-17). Furthermore, while BPE occurs predominantly in elderly men, and validated geriatric QoL scales do exist, no studies using such questionnaires to assess the impact of LUTS on elderly

populations have been published. This article aims to assess the role of LUTS on the QoL in a group of elderly men.

MATERIALS AND METHODS

This was an observational clinical study conducted between March-September 2008, approved by the institutional ethics committee.

The inclusion criteria were: male sex; 65-years aged or over; voluntary participation; understanding and signing the consent form. The exclusion criteria were: previous radical prostatectomy; use of bladder catheter; acute diseases; trauma, surgeries or hospitalizations during the preceding month; uncompensated chronic diseases; malignancies; neuropsychiatric diseases; alcoholism; drug abuse; use of psychotropics. Two hundred men (any race, schooling and social level) were selected from among Urology (90 patients) and Geriatrics (60) outpatients at a university hospital, these patient's companions (10), participants of community centers (20) and fitness programs for the elderly (20). The research protocol was composed of:

1. Sociodemographic and health conditions questionnaire;
2. International Prostate Symptom Score (IPSS) (14);
3. Hospital Anxiety and Depression Scale (HADS) (18);
4. WHOQoL-Bref questionnaire (19);
5. WHOQoL-Old questionnaire (20);

Four trained researchers conducted the interviews in private rooms, which lasted on average 40 minutes. Self-administration of questionnaires was preferred, but face-to-face interviews were conducted when the participants presented visual deficits, illiteracy or semi-illiteracy. Only 13 participants could not respond by themselves.

Sociodemographic information included age, race, marital status, schooling, religion, economic and employment status. Health conditions investigated included previous diagnoses of hypertension, diabetes and heart diseases; use of medications; practice of sports or physical activities (at least walking for 30 minutes, thrice a week).

The Hospital Anxiety and Depression Scale (HADS), also used to evaluate non-hospitalized patients and individuals without disease, has 14 items, seven focusing on anxiety assessment (HADS-A), and seven on depression (HADS-D). Each of its items can be scored from 0-3, giving a maximum score of 21 points for each scale. Values ≥ 9 positively detect the assessed symptom (18).

The questionnaires WHOQoL-Bref and WHOQoL-Old are generic instruments developed by the World Health Organization to evaluate quality of life (QoL) with cross-cultural validity and applicability. Both provide a comprehensive assessment of QoL through evaluating different parameters (termed domains and facets), such as physical health, psychological aspects, social relationships, among others. The questionnaire WHOQoL-Bref contains 26 multiple-choice questions, divided in four domains. The questionnaire WHOQoL-Old was especially developed to assess individuals aged 60-years or over, and contains 24 multiple-choice questions, divided in six facets. In both questionnaires, the scores from responses produce a profile of QoL, which can be split into individual scores, for each of the different domains and facets examined, scaled in a positive direction (higher scores indicate higher QoL); the average scores from items within each field are used to calculate the score for the whole field, and, for the questionnaire WHOQoL-Old, an overall score can be calculated (19,20).

The participants were divided into two groups, according to the IPSS results:

Group I: Scores 8-35 (moderate/severe symptoms).

Group II: Scores 0-7 (absence/mild symptoms).

The sample size was estimated from a pilot sample, composed of the first 50 participants in each group. The loss of, in mean, 1 point per facet of the WHOQoL-Old questionnaire was accepted as clinically significant; assuming a difference of 6.5 units as relevant, with standard deviation of 14, statistical analysis estimated that a sample of 100 participants per group would be needed for the detection of statistically significant differences between the mean total scores of WHOQoL-Old for the two groups (assuming a statistical power of 90% and a significance level of 5%), through a bilateral hypothesis test. For statistical evaluation,

the tests used were student's t, Brown-Mood, chi-square, and Fisher-Freeman-Halton exact test.

Every significant probability (p values) was recorded as the bilateral type, and values < 0.05 were considered statistically significant. The SAS 9.1 software (Statistical Analysis System, Cary, NC, USA) and Minitab 14.1 (State College, PA, USA) were used for the statistical analyses.

RESULTS

The results from the sociodemographic and health conditions data are described in Table-1.

Mean ages were 72.89 (± 5.96) and 73.41 (± 5.95) years, in groups I and II, respectively (p = 0.538). The distribution of proportions of race categories (p = 0.0932), schooling level (p = 0.1521), and diagnoses of hypertension (p = 0.099), diabetes (p = 0.5993), heart diseases (p = 0.6418) and sedentarism (p = 0.1543), marital status (p = 0.5127), religious denominations (p = 0.4079), monthly income (p = 0.9848), causes of inactivity (p = 0.9446) and use of medications (p = 0.4306) showed no difference.

With regard to HADS scores, the number of individuals who attained the anxiety and depression cutoff scores was exactly the same, 21 men in group

Table 1 *- Main socio-demographic and health conditions results.*

Socio-demographic and health data		Group I	Group II	Total
Age	65-69 years-old	35	30	65 (32.5%)
	70-79 years-old	48	50	98 (49.0%)
	≥ 80 years-old	17	20	37 (18.5%)
	Minimum	65	65	
	Maximum	88	89	
	Median	72.5	72.5	
	Mean (SD)	72.89 (± 5.96)	73.41 (± 5.95)	
Ethnicity / race	White	70	74	144 (72.0%)
	Non-white	30	26	56 (28.0%)
Marital status	Married	74	82	156 (78.0%)
	Widowed	13	11	24 (12.0%)
Religion	Catholics	75	71	146 (73.0%)
	Protestants	16	13	29 (14.5%)
Schooling	Primary school	78	66	144 (72.0%)
Monthly income	≤ 2 MW	48	44	92 (46.0%)
	2-5 MW	43	47	90 (45.0%)
Inactivity causes	Retirement	73	70	143 (71.5%)
	Still active	23	24	47 (23.5%)
Arterial hypertension		72	61	133 (66.5%)
Diabetes mellitus		22	19	41 (20.5%)
Heart diseases		31	28	59 (29.5%)
Anti-hypertensive drugs use		55	47	102 (46.0%)
Anti-diabetic drugs use		02	03	05 (2.5%)
Anti-hypertensive and anti-diabetic drugs use		17	14	31 (15.5%)
Sedentary		61	51	112 (56.0%)

SD: standard deviation; MW: minimum wages (About US$ 200.00).

I and 8 in group II, for each of these conditions, leading to no differences in the proportions of anxiety ($p = 0.0932$) and depression scores ($p = 0.0932$).

Groups I and II presented mean IPSS 15.83 (± 6.3) and 4.01 (± 2.12) respectively. The medians for IPSS-QoL were also different between the two groups ($p < 0.0001$).

The WHOQoL-Bref scores achieved for each question were transformed into a scale of one hundred points, in accordance with the syntax recommended in the manual. The statistical analysis on these responses was performed by gathering the questions relating to every QoL domain evaluated. Such results are presented in Tables 2 and 3.

The first two questions of the WHOQoL-Bref presented significant differences in responses only in the second question ($p < 0.0001$), however the means scores from each WHOQoL-Bref domain revealed differences between the scores of: physical health ($p = 0.007$), psychological aspects ($p = 0.001$), social relationships ($p < 0.0005$) and environment ($p < 0.0005$).

Table 2 *- WHOQoL-BREF Results Relative to the First Two Questions.*

Questions	Answers	Group I	Group II	Total	p
1. How would you rate your quality of life?	Very poor	01	01	02 (1.0%)	0.0814
	Poor	04	01	05 (2.5%)	
	Neither good nor poor	29	20	49 (24.5%)	
	Good	62	66	128 (64.0%)	
	Very good	04	12	16 (8.0%)	
	Total	**100**	**100**	**200 (100%)**	
2. How satisfied are you with your health?	Very dissatisfied	03	00	03 (1.5%)	< 0.0001
	Dissatisfied	20	05	25 (12.5%)	
	Neither satisfied nor dissatisfied	28	16	44 (22.0%)	
	Satisfied	41	58	99 (49.5%)	
	Very satisfied	08	21	29 (14.5%)	
	Total	**100**	**100**	**200 (100%)**	

Table 3 *- WHOQoL-BREF Results Relative to the Four Domains.*

Domain	Values	Group I	Group II	p
Physical health	Mean (SD)	56.5 (± 10.2)	60.32 (± 9.36)	0.007
	Standard error	1.0	0.94	
Psychological	Mean (SD)	56.2 (± 12.0)	61.5 (± 10.0)	0.001
	Standard error	1.2	1.0	
Social relationships	Mean (SD)	62.3 (± 16.5)	70.4 (± 14.4)	< 0.0005
	Standard error	1.7	1.4	
Environment	Mean (SD)	57.0 (± 12.2)	65.5 (± 12.7)	< 0.0005
	Standard error	1.2	1.3	

SD: Standard deviation

WHOQoL-Old scores were transformed in accordance with the syntax in the manual, to compare the mean scores of every facet and produce the overall WHOQoL-Old score. The results relating to WHOQoL-Old scores are presented in Table-4.

The analysis of mean scores of the questionnaire WHOQoL-Old revealed differences between the scores obtained by groups I and II for each of the six facets, and also for the final score: sensory functioning ($p = 0.003$), autonomy ($p = 0.003$), past, present and future activities ($p = 0.001$), social participation ($p < 0.0005$), dying and death ($p = 0.003$), intimacy ($p = 0.003$) and Old score ($p < 0.0005$).

DISCUSSION

The variety of backgrounds of participants was adopted to raise the epidemiological spectrum of the sample, so as not to restrict the investigation to patients undergoing outpatient medical care. However, it should be mentioned that this was not a true random sample of men, but patients were chosen for inclusion into the study, which allows the possibility of selection bias. The exclusion criteria were, essentially, prevalent clinical conditions that undermine QoL. Previous radical prostatectomy was an exclusion criterion because it is mainly used as treatment for prostate malignancies.

Users of bladder catheters were excluded because of the impossibility to assess LUTS through the IPSS. Previous transurethral resection of prostate, except for recent postoperative states, and the use of alpha-blockers and 5-alpha-reductase inhibitors, were not exclusion criteria, because neither prevent assessment of LUTS, nevertheless symptoms at the time of the interview could be different from those observed before such treatments.

The two groups were adequately matched to sociodemographic and health condition. Despite not statistically significant, a trend to increase in anxiety and depression scores was observed in group I. The median age was similar in the two groups (72.5 years); nevertheless it could seem a low indicator for a geriatric sample, it exceeds the 2006 WHO estimative of male population life-expectancy of this country (68.8 years), and overlaps in more than 12 years

Table 4 - *WHOQoL-OLD Results.*

Facet	Values	Group I	Group II	p
Sensory Functioning	Mean (SD)	14.71 (± 3.55)	15.68 (± 3.17)	0.003
	Standard error	0.35	0.32	
Autonomy	Mean (SD)	14.24 (± 2.68)	15.38 (± 2.58)	0.003
	Standard error	0.27	0.26	
Past, Present and Future Activities	Mean (SD)	14.03 (± 2.83)	15.26 (± 2.42)	0.001
	Standard error	0.28	0.24	
Social Participation	Mean (SD)	13.77 (± 2.69)	15.10 (± 2.44)	< 0.0005
	Standard error	0.27	0.24	
Dying and Death	Mean (SD)	14.49 (± 4.01)	16.12 (± 3.69)	0.003
	Standard error	0.40	0.37	
Intimacy	Mean (SD)	15.09 (± 2.94)	16.27 (± 2.67)	0.003
	Standard error	0.29	0.27	
Final global score OLD	Mean (SD)	86.3 (± 12.5)	93.8 (± 11.5)	< 0.0005
	Standard error	1.3	1.1	

SD: Standard deviation

the 60-year-old parameter, accepted in developing countries as demographic indicator for classification of elderly people.

Most of the studies performed to measure the impact of LUTS on men's QoL evaluate pharmacological and surgical treatments for BPO, and largely adopt expressions like "quality of life" and "health-related quality of life", since most of the authors believe that the impairment of QoL due to LUTS is a key measurement to assess the effectiveness of any treatment for BPO (1-11,17,21). However, criticisms have been made regarding the poor standardization of QoL scales, and the frequent inappropriate use of the term QoL (17). The use of a one-item scale to assess general QoL (the IPSS-QoL question, called "bother score"), and the misinterpretation of QoL as synonym of symptom-control, or perceived general health or functional status, are the most frequent reasons for such criticisms (1,9,17,21).

In the present study, two QoL scales validated by the WHO (one especially developed to assess the geriatric population) were used (19,20). Over the last ten years, despite descriptions of associations between LUTS and advancing age, with increasing discomfort, impairment of daily activities and perception of poor health, few texts were specifically focused on elderly men, and none adopted the WHOQoL-Old (3,5,22).

All domains and facets evaluated by both QoL questionnaires, with the exception of the first question of WHOQoL-Bref, reached results that differed statistically between the two groups, with lower QoL scores in group I. The items assessed by WHOQoL-Bref with lower p value ($p < 0.0005$) were observed in the domains "social relationships", "environment", and the question "self-satisfaction with his own health" ($p < 0.0001$). Among WHOQoL-Old results, the facet "social participation" and the Old score presented the lowest p values (< 0.0005). These results can be compared with the findings of two studies that applied the SF-36 questionnaire to men with LUTS and/or BPE. In the first study, the IPSS and SF-36 were used to evaluate 189 patients on the waiting list for surgical treatment for BPE, who presented worse perceptions of QoL than the general population of similar age, in direct relation to increasing severity of irritative symptoms (7). Social functioning was the parameter of best performance, and role-physical was the worst one. The second study employed the SF-36 and the American Urological Association Symptom Index, and the main losses of QoL were in energy and vitality, general health perception and overall physical dimension (10). Significant worsening of social functioning of individuals with LUTS was not identified, and the authors reasoned this result might have been due to inadequacy of the SF-36 for recognizing the social impact caused by LUTS. Besides such studies evaluated men whose mean age was 68.8 ± 6.9 and 61.9 ± 9.1 years, none was designed to evaluate a geriatric population.

Another study evaluated 480 men referred for urological consultation, using the WHOQoL-Bref and the IPSS (23). There was no exclusive selection of elderly patients, and the only QoL domain impaired by increasing LUTS was physical health. Such article concludes that WHOQoL-Bref would be too comprehensive to identify associations between specific symptom-related factors, and LUTS suggestive of BPE and LUTS-associated factors would not be important determinants of QoL.

The present study signals that older men are particularly sensitive to the impact of LUTS on their QoL, because all domains and facets of QoL analyzed by WHOQoL-Bref and WHOQoL-Old had significantly lower scores among moderate to severe-symptomatic patients. These findings corroborate for the existence of important QoL indicators for the elderly, which are not evaluated on general QoL scales for adults; studies that make no distinction between different age groups may be unable to recognize differences in QoL impairment related to age. Additionally, older men's perceptions of the impact of LUTS on their QoL extend not only to parameters straightly determined by urinary symptoms. Members of group I presented worse performances in sensory functioning and perception of death and dying, which do not seem to have any direct/causal relationship with LUTS. The psychological impact of LUTS on elderly men might lead to poor self-perception of QoL, and group I members did present lower scores in psychological domains, while LUTS-related psychological aspects have already been described elsewhere (24,25). However, in the present study, similar

scores for depression and anxiety were recorded for the two groups. Hence, whether self-depreciation of QoL is cause or consequence of LUTS-related psychological factors can not be described here.

Finally, this study leads to reflections on the importance of proper assessment of moderate LUTS men. Group I joined moderate and severe LUTS patients, but its mean IPSS was 15.83 (± 6.3), which suggests that the results could be extrapolated for moderate symptomatic patients. Surgical treatments are predominantly indicated for severe-symptomatic patients, and watchful waiting or conservative measures are indicated for patients with mild complaints (2,14,26). However, therapeutic choices for moderate cases are frequent source of doubts among urologists, especially in the presence of co-morbidities. Recognition of significant deterioration of QoL among moderate LUTS patients is an evidence for the need of treatment (as opposed to waiting approaches), and justification for early surgery (26).

The similarity of answers to the self-rated QoL question (WHOQoL-Bref n.1) only represents an apparent contradiction. The answers to 49 of 50 questions that compose the two QoL questionnaires presented lower scores in group I, besides around 90% of all participants declared that their QoL was "good" or "neither bad nor good". This inconsistency exemplifies that a single question for QoL assessment may not reflect the results obtained with comprehensive scales (17).

In regards to potential problems and limitations, the population studied was not a true random sample of elderly men, which allows the possibility of selection bias. The role of specific comorbities, the analysis of age subgroups, and clinical implications of the results obtained were not evaluated. Potential differences between moderate and severe LUTS patients could not be determined precisely, because they were joined in the same group.

CONCLUSIONS

Men aged 65-years or over with moderate/severe LUTS have worse QoL ratings for almost all evaluation parameters proposed by the World Health Organization, according to the WHOQoL-Bref and WHOQoL-Old instruments, especially social and environmental relationships, compared with mildly symptomatic or asymptomatic men in the same age group.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

BPE - Benign prostatic enlargement
CI - Confidence interval
HADS - Hospital Anxiety and Depression Scale
IPSS - International Prostate Symptom Score
LUTS - Lower urinary tract symptoms
MW - Minimum wages
QoL - Quality of life
SD - Standard deviation
WHO - World Health Organization
WHOQoL - World Health Organization Quality of Life

REFERENCES

1. Fitzpatrick JM: The natural history of benign prostatic hyperplasia. BJU Int. 2006; 97(Suppl 2):3-6; discussion 21-2.
2. Burnett AL, Wein AJ: Benign prostatic hyperplasia in primary care: what you need to know. J Urol. 2006; 175: S19-24.
3. Medina JJ, Parra RO, Moore RG: Benign prostatic hyperplasia (the aging prostate). Med Clin North Am. 1999; 83: 1213-29.
4. Girman CJ, Jacobsen SJ, Tsukamoto T, Richard F, Garraway WM, Sagnier PP, et al.: Health-related quality of life associated with lower urinary tract symptoms in four countries. Urology. 1998; 51: 428-36.
5. Trueman P, Hood SC, Nayak US, Mrazek MF: Prevalence of lower urinary tract symptoms and self-reported diagnosed 'benign prostatic hyperplasia', and their effect on quality of life in a community-based survey of men in the UK. BJU Int. 1999; 83: 410-5.
6. Bertaccini A, Vassallo F, Martino F, Luzzi L, Rocca Rossetti S, Di Silverio F, et al.: Symptoms, bothersomeness and quality of life in patients with LUTS suggestive of BPH. Eur Urol. 2001; 40 (Suppl 1): 13-8.

7. Salinas-Sánchez AS, Hernández-Millán I, Lorenzo-Romero JG, Segura-Martin M, Fernández-Olano C, Virseda-Rodriguez JA: Quality of life of patients on the waiting list for benign prostatic hyperplasia surgery. Qual Life Res. 2001; 10: 543-53.
8. Quek KF, Loh CS, Low WY, Razack AH: Quality of life assessment before and after transurethral resection of the prostate in patients with lower urinary tract symptoms. World J Urol. 2001; 19: 358-64.
9. Yoshimura K, Arai Y, Ichioka K, Terada N, Matsuta Y, Okubo K: Symptom-specific quality of life in patients with benign prostatic hyperplasia. Int J Urol. 2002; 9: 485-90.
10. Welch G, Weinger K, Barry MJ: Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. Urology. 2002; 59: 245-50.
11. Bobé Armant F, Buil Arasanz ME, Allué Buil AI, Morro Grau A, Maxenchs Esteban M, Gens Barberà M: Benign prostate hyperplasia. Need to evaluate quality of life in the therapeutic process]. Aten Primaria. 2006; 38: 387-91.
12. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992; 148: 1549-57; discussion 1564.
13. Rodrigues P, Meller A, Campagnari JC, Alcântara D, D'Império M: International Prostate Symptom Score--IPSS-AUA as discriminat scale in 400 male patients with lower urinary tract symptoms (LUTS). Int Braz J Urol. 2004; 30: 135-41.
14. Barry MJ, Mulley AG Jr, Fowler FJ, Wennberg JW: Watchful waiting vs immediate transurethral resection for symptomatic prostatism. The importance of patients' preferences. JAMA. 1988; 259: 3010-7.
15. Fowler FJ Jr, Wennberg JE, Timothy RP, Barry MJ, Mulley AG Jr, Hanley D: Symptom status and quality of life following prostatectomy. JAMA. 1988; 259: 3018-22.
16. Cockett AT, Aso Y, Denis L, Khoury S, Barry M, Carlton CE, et al.: World Health Organization Consensus Committee recommendations concerning the diagnosis of BPH. Prog Urol. 1991; 1: 957-72.
17. Haltbakk J, Hanestad BR, Hunskaar S: Use and misuse of the concept of quality of life in evaluating surgical treatments for lower urinary tract symptoms. BJU Int. 2003; 91: 380-8.
18. Marcolino JA, Mathias LA, Piccinini Filho L, Guaratini AA, Suzuki FM, Alli LA: Hospital Anxiety and Depression Scale: a study on the validation of the criteria and reliability on preoperative patients. Rev Bras Anestesiol. 2007; 57: 52-62.
19. [No authors listed]: The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998; 46: 1569-85.
20. Fleck MP, Chachamovich E, Trentini C: Development and validation of the Portuguese version of the WHOQoL-Old module. Rev Saude Publica. 2006; 40: 785-91.
21. O'leary MP: Validity of the "bother score" in the evaluation and treatment of symptomatic benign prostatic hyperplasia. Rev Urol. 2005; 7: 1-10.
22. Vela-Navarrete R, Alfaro V, Badiella LL, Fernández-Hernando N: Age-stratified analysis of I-PSS and QoL values in spanish patients with symptoms potentially related to BPH. Eur Urol. 2000; 38: 199-207.
23. Haltbakk J, Hanestad BR, Hunskaar S: How important are men's lower urinary tract symptoms (LUTS) and their impact on the quality of life (QOL)? Qual Life Res. 2005; 14: 1733-41.
24. Quek KF, Low WY, Razack AH, Loh CS: The psychological effects of treatments for lower urinary tract symptoms. BJU Int. 2000; 86: 630-3.
25. Quek KF, Razack AH, Chua CB, Low WY, Loh CS: Effect of treating lower urinary tract symptoms on anxiety, depression and psychiatric morbidity: a one-year study. Int J Urol. 2004; 11: 848-55.
26. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG: A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. N Engl J Med. 1995; 332: 75-9.

Submitted for publication:
August 27, 2010

Accepted after revision:
April 11, 2011

Correspondence address:
Dr. Vitor Last Pintarelli
R. Gabirobas, 12 / 54
Curitiba, PR, 81560-150, Brazil
Fax: +55 41 3253-4178
E-mail: vitorpintarelli@yahoo.com.br

International Braz J Urol
Vol. 37 (6): 766-772, November - December, 2011

Determining the variables associated to clean intermittent self-catheterization adherence rate: one-year follow-up Study

Marcia Eli Girotti, Sarita MacCornick, Humberto Perissé, Nelson S Batezini, Fernando G. Almeida

Division of Voiding Dysfunctions, Female Urology and Urodynamics - Department of Urology Paulista School of Medicine at Federal University of Sao Paulo, Sao Paulo, Brazil

ABSTRACT

Purpose: To determine adherence rate and variables associate with patients' adherence to Clean Intermittent Self Catheterization (CISC).
Materials and Methods: Patients refereed to CISC training program between July 2006 and May 2008, were prospectively evaluated with urodynamic, 3 days bladder diary (BD) and WHOQoL-bref questionnaire. After training to perform CISC, patients were evaluated at 2 weeks, monthly for 6 months and at 12 months with clinical visits and BD. Patients were considered adherent if they were performing at least 80% of the initial recommendation.
Results: Sixty patients (50.4 ± 19.9 years old) were trained to perform CISC (21 female and 39 male). Out of them, 30 (50%) had neurogenic and 30 (50%) had a non-neurogenic voiding dysfunction. The adherence rate at 6 and 12 months was 61.7%, 58%, respectively. Patients < 40 years old had adherence rate of 86%. Women and neurogenic patients had higher adherence rate than their counterparts ($p = 0.024$ and $p = 0.016$, respectively). In the WHOQoL-bref, patients that adhere to the program had a significant higher score on psychological and social relationships domains. There was not difference in pre and post training WHOQoL-bref scores. Educational background, marriage status, detrusor leak point pressure, Bladder Capacity, number of leakage episodes did not play a role on the adherence rate.
Conclusion: Patients in CISC program present a reasonable adherence after one year. Women, neurogenic voiding dysfunction and patients under 40 years old were significantly more adherents. The psychological and social relationship status seems to positively interfere on adherence. CISC did not affect patient's QoL evaluated by WHOQoL-bref.

Key words: *Intermittent Urethral Catheterization; quality of life; urinary bladder, neurogenic; urinary retention*
Int Braz J Urol. 2011; 37: 766-772

INTRODUCTION

Several conditions associated with incomplete bladder emptying, such as, bladder outlet obstruction without clinical conditions to surgical treatment, under or acontractile bladder and detrusor-sphincter dyssynergia have limited treatment options. One of the main alternatives is to perform clean intermittent self-catheterization (CISC), which has been described by Lapides in 1972 (1). CISC can be defined as intermittent catheter introduction through the urethral meatus up to the bladder, removing it immediately after urine drainage (2).

When appropriately established, the CISC program reduces bladder over distention, bladder ischemia, and urinary tract complications (3,4). Unfortunately, CISC is not the ideal method to empty the bladder. The main problems are the patient's adherence, the potential impact on quality of life, pain during the procedure, urinary infection, costs, urethral injury and it depend on patient's ability and some degree of cognition (5,6).

The World Health Organization defines adherence as the extent of which a person's behavior corresponds with agreed recommendations from a health care professional (7). There are a variety of

reasons for a patient does not adhere to CISC (8). Some patients report feeling worried, shocked or even depressed, especially those patients with non-neurological conditions, after being offered for the first time to perform CISC. Furthermore, patients that initiate the CISC may not completely follow the physician recommendation reducing the daily number of self-catheterization, similarly to any long-term treatments.

Patients requiring CISC who do not adhere or have a partial adherence may develop major urological complications. Thus, predicting which patient are more likely to adhere to CISC is very important, since it may interfere in the medical treatment decisions in order to prevent future complications. Attempts to determine which factors are associated with patient's adherence to CISC have been done. Age, gender, urethral sensitivity, pain, general health status, mobility and specialized training have been suggested to be predictive of patient's adherence (9). However, there is a lack of studies that clearly demonstrate which of those variables play a role on patient's adherence (10). In the present study, we sought to determine which variables are involved in the patient's acceptance and adherence to a CISC program.

MATERIALS AND METHODS

We performed a prospective study between July 2006 and May 2008. It was included all patients refereed to our CISC training program, except those patients with inability to follow the program due to motor, psychiatric or cognitive limitations. All patients were evaluated by means of urological and past medical history, urodynamic study (UDS), 3 days bladder diary and WHOQoL-bref (11). Patients with indwelling catheter had their catheter removed, urinalyses performed and antibiotics introduced as necessary. All patients were individually trained by the same specialized nurse in order to achieve the ability of self catheterization at home. A visual analogical scale (VAS) ranging from 0 to 10, where 0 was no pain at all and 10 was the worst scenario of pain was used to determine pain expectation (before performing the catheterization) and pain experience (after being trained and considered able to perform the catheterization). Patients were evaluated two weeks after have been trained, then monthly for 6 months and 1 year by means of clinical evaluation and 3 days bladder diary to determine the adherence to the program and the ability to self catheterization.

Patient's training consisted of theoretical explanation with regard to lower urinary tract and how to introduce the urethral catheter by means by means of verbal, visual (at the computer) and written orientations, including explanation regarding the lower urinary tract function and practical training, which was directly guided by a specialized nurse to access if the patient was able to perform the CISC or not. All patients receive the same instructions to perform clean intermittent self-catheterization using a 12 F gel lubricated. All patients were instructed to use the same catheter, which was provided by the hospital. After being trained, patient was sent home to perform the procedure alone and recommended to contact the responsible nurse in case of any difficult. After one week, patients' catheterization ability was evaluated. Those considered skillful were included in the program and those unable to perform the catheterization adequately were re-trained.

The 3 days bladder diary enabled the nurse to evaluate the CISC frequency and to adjust it as necessary based on the urodynamic information regard the bladder compliance and overactive bladder trigger volume. The bladder diary was also used to evaluate adherence to procedure. Patients were considered adherent to the program if they were performing at least 80% of the initial recommendation (10,12,13). The adherence rate was evaluated by patient´s report in the 3 days bladder dairy. Data were analyzed using mean comparisons (hypothesis tests), ANOVA, tabulation, frequency analysis. We used statistical confidence of 95% and significant level when $p < 0.05$.

RESULTS

Sixty three patients were refereed to the CISC program. Out of them 3 (4.3%) were excluded because they refuse to initiate the training after nurse explanation on how to perform CISC. We trained and included 60 patients in the study (Table-1). Of these patients, 21 (35%) were women and 39 (65%)

Table 1 *- Distribution of patients by gender and diagnosis.*

	Total	Female n = 21	Male n = 39
Neurogenic Bladder	30 (100%)	13 (43.3%)	17 (56.7%)
Bladder Sphincter Dyssynergia	11 (36.7%)	5	6
Under or acontractile Bladder	19 (63.3%)	7	12
Non-Neurogenic Bladder	30 (100%)	8 (24.7%)	22 (73.3%)
Under or acontratilite Bladder	26 (86.7%)	5	21
Bladder Outlet Obstruction	4 (13.3%)	3	1

were men, the mean age was 50.4 (range: 15 to 88 years old).

All 60 patients included in the study were able to perform the procedure as instructed. Fifty-five (92%) patients learned how to perform the CISC with only one training session and 5 (8%) patients needed 2 sessions to become skillful.

Out of the 60 patients, 30 (50%) had neurogenic voiding dysfunction and 30 (50%) had a non-neurogenic etiology. The main etiologies for neurogenic dysfunction was Parkinson's disease, cerebral vascular accident, multiple sclerosis, traumatic injury, tumors cerebral, infections with HTLV-1 and neuroschistosomiasis, causing neurological damage. The main etiologies for non-neurogenic dysfunction was diabetes mellitus, benign prostatic hypertrophy, pelvic surgery, and other dysfunction of idiopathic etiology that caused increased post voiding residual, and others dysfunctions (Table-2).

The adherence rate at 1, 6 months was 61.7% and at 12 months was 58%. Table-2 shows the adherence rate according to the gender. Women adhered more to the CISC program than their counterpart. We observed that the younger the patient, the greater the adherence. Patients with neurogenic bladder had a higher adherence rate than non-neurogenic bladder patients ($p = 0.016$) (Table-3).

A multivariate analysis including diagnosis (neurogenic/non-neurogenic), gender and age (≤ 40 y.o.; 41-60 y.o; and ≥ 61 y.o) showed that men ≥ 61 years old with non-neurogenic bladder dysfunction were less adherent to the program ($p = 0.003$) and women ≤ 40 years old with neurogenic bladder dysfunction were the most adherent to the CISC program ($p = 0.040$).

At 12 months follow-up, patients did not present major complications, such as bleeding, urethral traumatic lesion, urethral stenosis/erosion that

Table 2 - *Adherence to CISC by gender, age and diagnosis.*

	n	Adherent	Non Adherent	
Female	21	17 (81.0%)	4 (19.0%)	p = 0.024
Male	39	20 (51.3%)	19 (48.7%)	
< 40years-old	22	19 (86%)	3 (14%)	p < 0.0001
40-60 years-old	17	11 (64%)	6 (36%)	
> 60 years-old	21	7 (33%)	14 (77%)	
Neurogenic bladder	30	23 (76.7%)	7 (23.3%)	p = 0.016
Non Neurogenic bladder	30	14 (46.7%)	16 (53.3%)	

Table 3 - *Pain Visual Analog Scale (VAS) values in adherent and non adherent patients, before and after training.*

	Total	Adherent	Non Adherent	p
VAS pre training (Mean ± S.D.)	5.47 ± 2.90	6.49 ± 2.18	3.83 ± 3.19	p < 0.001
VAS post training (Mean ± S.D.)	2.34 ± 1.64	2.38 ± 1.62	2.29 ± 1.71	p = 0.742
p	p < 0.001	p < 0.001	p = 0.031	

Table 4 - *The WHOQoL-Bref score between adherent and non adherent patients to the program CISC.*

	Total	Adherent (N = 37)	Non adherent (N = 23)	p value
Physical	53.43	54.41	51.59	0.356
Psychological	64.18	66.30	60.18	0.043
Social relationships	61.54	63.73	57.41	0.022
Environment	55.67	54.85	57.71	0.181
Self evaluation quality of life	54.09	56.62	49.31	0.059

difficult CISC. The main complication was symptomatic lower urinary tract infection in 18 patients.

Educational background (p = 0.246), marriage status (p = 0.978), detrusor leak point pressure (p = 0.373), bladder capacity (p = 0.081), urinary leakage (p = 0.362), superior members limitations (p = 0.187) or inferior members limitations (p = 0.741), did not play a role on patient's adherence.

Overall, patients anticipated with higher pain expectation before training than they score the pain after experience the catheterization. Adherent patients had higher pain expectation before training, but after experience the catheterization they showed similar values (Table-4). Women reported higher pain expectation than men (p < 0.000). Interestingly, patients with neurogenic bladder reported higher pain expectation than non-neurogenic patients (p = 0.012). These differences were not observed in the post training VAS evaluation (Table-4).

Table-4 shows the results from WHOQoL-Bref. Higher scores are associated with better quality of life. Patients that adhered to the program had a significant higher score on psychological and social relationships domains.

DISCUSSION

In the present study, we evaluated 63 consecutive patients referred to initiate CISC. Five percent decline to initiate the training at the first visit, even after being previously instructed by their urologist. Sixty patients that concluded the CISC training were evaluated. After being trained, the overall adherence rate was 61.7%. We demonstrated that women, younger patients (≤ 40 years old) and neurogenic voiding dysfunction had the better adherence rate. Educational background, marriage status, bladder capacity, detrusor leak point pressure and daily leakage episodes did not play a role in adherence. Furthermore, pain did not play a role in patients' adherence. Performing CISC did not present any impact on patient's quality of life. However, adherent patients had better scores on social relationships and psychological domains as measured by WHOQol-bref questionnaire.

It is important to emphasize that performing CISC it is a simple procedure and can be learned even by elderly patients (35% of the patients were older than 60 years old). We found that 55 (92%)

patients were considered able to perform the CISC with only one training session and 5 (8%) patients needed no more than 2 sessions to become skillful. It demonstrates that performing the CISC is not a great technical challenge. On the other hand, some patients (5%) decline to initiate the training, even after being previously instructed by his doctor. It suggests that a small number of patients are greatly scared of passing a urethral catheter and may not even be referred to CISC.

Although all patients were able to perform the urethral catheterization, had understood the importance to perform the treatment due to their clinical condition and had precise indication to CISC, the adherence rate was 61.7%. Interestingly, the adherence rate was similar at 1, 6 months and 12 months follow-up. Demonstrating that once the patient adhere to the procedure and have an adequate instruction, health care support and follow-up, they maintain the CISC at least in the first year. We believe that performing monthly visits in the first 6 months after initiate the CISC was very important providing a positive feedback and re-assuring the importance to perform the procedure.

One possible explanation to patients' adherence to CISC is the possible distress, mostly pain, generated by passing a urethral catheter. To our knowledge, it has never been adequately studied. By assuming that pain is a problem to patients performing CISC, one possibly will believe that it would be less stressful to neurogenic patient with decrease urethral sensitivity and women due to their shorter urethra. Indeed, pain is a great concern to those patients referred to CISC. Just before initiate the CISC training patients had a great pain expectation (score = 5.4 in a scale raging from 0 to 10). However, after passing the urethral catheter the observed pain was considerably less than what they expected (score = 2.3). Furthermore, our data demonstrates that the pain during urethral catheterization was similar for men and women, adherents and non-adherents and neurogenic and non-neurogenic patients. It demonstrates that pain is not the main factor to determine if a patients will or will not adhere to CISC. Interestingly, those patients with greater pain expectation before initiate training were those who shown higher adherence rate, suggesting that patients with CISC indication should, at least, undertake an initial trial before decide if they would be able to continue with such therapy.

Patients with better perception of the severity of their disease show higher rates of adherence, even in longer treatments (14). Usually, patients with neurological problems have a chronic health condition that demands more intensive care and, in turn, motivates a better understanding of their pathology. It seems to be a more reasonable explanation to our finding that neurogenic patients had higher adherence rate than their counterparts ($p = 0.016$), rather than thinking that this population had a great adherence because they present less pain during urethral catheterization.

Age seems to be a very important variable to consider when planning a CISC recommendation. Establishing CISC in elderly can be complex, because this group of patients may present little capacity for self-care, lack of motivation, decreased ability to deal with new situations, decreased visual acuity, decreased motor dexterity and preconceptions regarding manipulate their genitals (15). We found that the adherence rate for patients older than 60 years old was only 33%. On the other hand, the adherence rate for patients under 40 years old was 86%.

A major concern with the institution of treatment with CISC is the impact this may have on the daily routine, their social and sexual relationship, economic factors, and the lives of patients who begin the program of CISC (16-20). Performing urethral catheterization four times a day seems to adversely affect QoL, especially for those patients that did not leak urine. In the present study, we search for the CISC impact on QoL by using the WHOQoL-bref questionnaire. We observed that the CISC had neither positive nor negative impact on quality of life. The main difference found on QoL evaluation was between adherent and non-adherent patients. Those patients that adhere to CISC had significant better scores in psychological and social relations domains. It may be associated with a better support and motivation from relatives and friends, which help patients to have a better acceptance and understanding regard their condition.

The adherence rate evaluation is a very important issue. It is a very important variable to de-

termine the treatment success and the health system efficiency. There are few studies aiming to determine the CISC adherence rate and the variables related to it. Van Achterberg et al. (10) performed a study with 20 patients to determine the important factors in patient's long-term adherence. They were not able to find a significant variable to correlate with patient's adherence and concluded that it would be important to perform a more specific study to evaluate the adherence rate to CISC.

CONCLUSIONS

The present study demonstrates that CISC has not a significant impact on the quality of life evaluated by WHOQoL-bref and that gender; age and neurogenic voiding dysfunction play a significant role on patient's adherence. These findings will help physicians to decide which patients would be better candidates to CISC and to define the best treatment strategy for each individual patient with voiding dysfunction.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

CISC - Clean intermittent self-catheterization
VAS - Pain visual analogical scale
UDS - Urodymanic study
QoL - Quality of Life
BD - Bladder diary
WHOQol-brief questionnaire: World Health Organization Quality of Life brief questionnaire

REFERENCES

1. Lapides J, Diokno AC, Silber SJ, Lowe BS: Clean, intermittent self-catheterization in the treatment of urinary tract disease. J Urol. 1972; 107: 458-61.
2. Chai T, Chung AK, Belville WD, Faerber GJ: Compliance and complications of clean intermittent catheterization in the spinal cord injured patient. Paraplegia. 1995; 33: 161-3.
3. Wyndaele JJ, Maes D: Clean intermittent self-catheterization: a 12-year followup. J Urol. 1990; 143: 906-8.
4. Wyndaele JJ: Complications of intermittent catheterization: their prevention and treatment. Spinal Cord. 2002; 40: 536-41.
5. Vaidyanathan S, Soni BM, Dundas S, Krishnan KR: Urethral cytology in spinal cord injury patients performing intermittent catheterisation. Paraplegia. 1994; 32: 493-500.
6. Perrouin-Verbe B, Labat JJ, Richard I, Mauduyt de la Greve I, Buzelin JM, Mathe JF: Clean intermittent catheterisation from the acute period in spinal cord injury patients. Long term evaluation of urethral and genital tolerance. Paraplegia. 1995; 33: 619-24.
7. Woodward S, Rew M: Patients' quality of life and clean intermittent self-catheterization. Br J Nurs. 2003; 12: 1066-74.
8. WHOQoL GROUP: The development of the World Health Organization quality of life assessment instrument (the WHOQoL). In: Orley J, Kuyken W, (ed.), Quality of life assessment: international perspectives. Heigelberg: Springer Verlag; 1994. pp. 41-60.
9. Oh SJ, Ku JH, Lim SH, Jeon HG, Son H: Effect of a 'centralized intensive education system' for clean intermittent self-catheterization in patients with voiding dysfunction who start catheterization for the first time. Int J Urol. 2006; 13: 905-9.
10. van Achterberg T, Holleman G, Cobussen-Boekhorst H, Arts R, Heesakkers J: Adherence to clean intermittent self-catheterization procedures: determinants explored. J Clin Nurs. 2008; 17: 394-402.
11. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al.: Application of the Portuguese version of the abbreviated instrument of quality life WHOQoL-bref. Rev Saude Publica. 2000; 34: 178-83.
12. Quirino JS: Household treatments based on sociocultural classifications of disease. J Clin Epidemiol. 1999; 52(Suppl 1): J-8S.

13. Leite SN, Vasconcellos MPC: Adesão à terapêutica medicamentosa: elementos para discussão de conceitos e pressupostos adotados na literatura. Ciência e Saúde Coletiva, 2003: 8: 775-82.
14. Borg C, Hallberg IR, Blomqvist K: Life satisfaction among older people (65+) with reduced self-care capacity: the relationship to social, health and financial aspects. J Clin Nurs. 2006; 15: 607-18.
15. Silvestre Busto C, Ramalle-Gómara E, Arnáez García R, Flor-Serrano A, García-Fernández J, Ramil Pernas H, et al.: Multicenter study of children's compliance to antibiotic treatment in primary care. Aten Primaria. 2001; 27: 554-8.
16. Alpert SA, Cheng EY, Zebold KF, Kaplan WE: Clean intermittent catheterization in genitally sensate children: patient experience and health related quality of life. J Urol. 2005; 174: 1616-9; discussion 1619.
17. Consortium for Spinal Cord Medicine: Bladder management for adults with spinal cord injury: a clinical practice guideline for health-care providers. J Spinal Cord Med. 2006; 29: 527-73.
18. Bakke A, Brun OH, Høisaeter PA: Clinical background of patients treated with clean intermittent catheterization in Norway. Scand J Urol Nephrol. 1992; 26: 211-7.
19. Bennett CJ, Diokno AC: Clean intermittent self-catheterization in the elderly. Urology. 1984; 24: 43-5.
20. Pilloni S, Krhut J, Mair D, Madersbacher H, Kessler TM: Intermittent catheterisation in older people: a valuable alternative to an indwelling catheter? Age Ageing. 2005; 34: 57-60.

Submitted for publication:
November 25, 2010

Accepted after revision:
June 22, 2011

Correspondence address:
Dr. Fernando Gonçalves Almeida
R. dos Otonis 683, Vila Clementino
São Paulo, SP, 04025-002, Brazil
Fax:+ 55 11 5576-4086
E-mail: fernandourologia@hotmail.com

Neurourology
International Braz J Urol
Vol. 37 (6): 773-780, November - December, 2011

Phasic or terminal detrusor overactivity in women: age, urodynamic findings and sphincter behavior relationships

Françoise A. Valentini, Brigitte G. Marti, Gilberte Robain, Pierre P. Nelson

ER6 (FAV, GR, PPN), Université Pierre et Marie Curie (Paris 06), Service de MPR (FAV, GR, PPN), Hôpital Rothschild and Service de Rééducation (BGM), Hôpital Saint Antoine. Paris, France

ABSTRACT

Objectives: To search for relationships between phasic (P) and terminal (T) DO with age, urodynamic findings and sphincter behavior during involuntary detrusor contraction in woman.
Materials and Methods: Urodynamic studies (triple lumen catheter 7F, seated position) of 164 successive women referred for LUTS with diagnosis of DO were reviewed. Patients were stratified in 4 sub-groups: pre- (18-44 y), peri- (45-54 y), post-menopause (55-74 y) and oldest old (≥ 75 y). The urethral sensor was positioned at the level of the maximum urethral closure pressure for sphincter behavior analysis. A variation of at least 5 cm H_2O in pressure (detrusor or urethra) was chosen to assert DO or sphincter response. Sphincter response was classified as relaxation (re) before or during DO, or steady (st).
Results: Occurrence of P and TDO was similar: 77 P and 87 T. The PDO group was significantly younger ($p = 0.0003$). TDO was more frequent in patients with a history of neurological disease.
The percentage of PDO remained almost constant in age groups, while that of TDO increased with age from 6.7% to 23.2% ($p = 0.0013$).
Uninhibited contraction occurred at a smaller bladder volume in the P group: 149 ± 95 vs. 221 ± 113 mL ($p < 0.0001$).
Steady sphincter predominated in the TDO subgroup: 45.9% vs. 32.1% and increased significantly in each DO sub-group of ≥ 75 y.
Conclusion: Steady sphincter during both P and TDO, and occurrence of TDO appear as specific of aging. The last result could be related to structural changes in the detrusor muscle with aging.

Key words: *Urinary bladder, overactive; urinary incontinence; Women; Urodynamics*
Int Braz J Urol. 2011; 37: 773-780

INTRODUCTION

Detrusor overactivity (DO) is a frequent urodynamic diagnosis in women with urge syndrome with or without incontinence. DO is characterized by involuntary detrusor contraction (IDC) during the filling phase and can be idiopathic when there is no defined cause (IDO) or neurogenic when there is a relevant neurological condition (NDO) (1). According to the ICS recommendations, it is usual to distinguish phasic (P) (wave(s) with or without leakage) from terminal (T) DO (single involuntary detrusor contraction occurring at cystometric capacity, which cannot be suppressed, and results in incontinence, usually resulting in bladder emptying) (1). To make a distinction between P and TDO is sometimes difficult: high vesical pressure or/and pain during cystometry might lead to stop the filling and to under-estimate DO. Distinction of TDO from decreased bladder compliance needs to repeat the cystometry at lower filling rate to assert or to invalidate DO.

As DO is believed to underlie overactive bladder (OAB) symptoms, most studies focus on relationships between OAB and DO (2-6). If, the impact of DO on bladder function in women has

been widely studied (7-11), few studies have been conducted to analyze the relationships between each type of DO with age, history of neurological disease, urodynamic findings including sphincter behavior during IDC (2, 12-14).

Our purpose was to look for relationships between P or TDO and these conditions or findings.

MATERIALS AND METHODS

Between June 2005 and December 2007, 684 women were referred in our outpatient clinic for investigation of lower urinary tract (LUT) dysfunction. Nineteen were excluded (complete spinal cord injury, severe dementia (mini mental state < 20) and grade ≥ 2 prolapse). Among the 665 eligible women, the urodynamic diagnosis of DO was made in 164; of these, 72 had a history of neurological disease (Table-1). The DO population was then stratified in 4 age groups: pre- (18-44y), peri- (45-54y), postmenopause (55-74y) and oldest old (≥ 75y).

All patients had evaluation including medical history and usual medication, bladder diary for at least 48 hours including voiding times and voided volumes during day- and night-time, physical examination and dipstick urinalysis.

Cystometry was performed with a triple lumen catheter 7F at a filling rate of 50 mL/min in seated position using a Dorado® unit from Laborie.

Pressures were zeroed to atmosphere with the transducers placed at the level of the upper edge of the symphisis pubis. For urethral pressure recording, the catheter eye was positioned at the level of the maximum urethral closure pressure (located from a urethral profilometry bladder empty). Abdominal pressure was recorded using a punctured intra-rectal balloon catheter.

The urethral sensor was positioned at the level of the maximum urethral closure pressure (MUCP) for sphincter behavior analysis.

To avoid instrumental errors, we considered that there was an episode of DO when the detrusor pressure increased of at least 5 cmH_2O in pressure; in the same way, a variation of ± 5 cmH_2O in urethral pressure was chosen to evaluate the sphincter response. In case of rhythmic rectal contractions, the change in vesical pressure was considered. Shifting of the urethral transducer during filling and non rhythmic rectal activity during IDC were criteria for exclusion.

One voiding cycle was recorded during each cystometry. For 18 patients a second cystometry at a lower filling rate of 20 mL/min was performed to conclude between decreased bladder compliance and DO.

Sphincter response was classified as relaxation (re) before or during IDC, or remaining steady (st).

Recordings were reviewed independently by three investigators; good agreement occurred in up to 88% of the files. In the remaining 12%, an additional interpretation was made jointly to reach a single conclusion.

Table 1 - *Description of the DO population with a history of neurological disease. In each age-group, the number of patients is presented as total (a) and in parentheses bP and cT DO: a(bP+cT).*

	18-44 y	**45-54 y**	**55-74 y**	**≥ 75 y**	∑
Encephalic lesion (stroke, meningioma)	1 (P)	5(1P+4T)	9(3P+6T)	7(1P+6T)	22(6P+16T)
Parkinson's disease	0	1(T)	1(P)	4(1P+3T)	6(2P+4T)
Multiple sclerosis	8(4P+4T)	7(4P+3T)	6(3P+3T)	1(T)	22(11P+11T)
Supra-sacral spinal cord lesion	4(2P+2T)	4(1P+3T)	8(3P+5T)	4(1P+3T)	20(7P+13T)
Sub-sacral and Peripheral	1(P)	1 (P)	0	0	2(2P)
∑	14(8P+6T)	18(7P+11T)	24(10P+14T)	16(3P+13T)	72

This study was conducted in accordance with the declaration of Helsinki. According to the local practice of our Ethics Committee, there is no formal Institutional Review Board approval required for retrospective studies.

STATISTICAL ANALYSIS

Data are presented as mean ± SD and range. The Wilcoxon signed rank test was used for comparison of related samples, analysis of variance (ANOVA), the t-test and the Chi 2 test to compare unrelated samples. Statistical analysis was performed using SAS, version 5.0 (SAS Institute, Inc., Cary, NC). All statistical results were considered significant at $p < 0.05$.

RESULTS

In the whole DO population, there were 77 (46.9%) PDO and 87 (53.1%) TDO, with 28 and 44 women respectively who had a history of neurological disease (Table-1). A history of neurological disease was not significantly different (n.s.) between the DO sub-groups.

Main LUT symptoms were urgency with or without incontinence (118 patients) and frequency (35 patients). Other symptoms were 5 stress urinary incontinence, 3 bedwetting and 3 incomplete retention. Incontinence was the main complaint for 123 (75%) of the patients.

Table-2 shows the distribution in the different of both populations with DO (PDO or TDO) and without DO.

Age incidence (Table-2):

Comparing the four age groups, there was no significant incidence of age on occurrence of DO. TDO was more frequent than PDO with aging ($p = 0.006$).

In the DO population, PDO was predominant in the 18-44 y age group ($p = 0.008$), and TDO in the ≥ 75 y one ($p < 0.0001$) with a ratio 3/1, while in the 45-54 y and 55-74 y age groups the ratio was close to 1.

In the entire population, increase of TDO was significant with aging between age ($p = 0.0036$) while the decrease of PDO was not significant.

The PDO group was significantly younger (52 ± 19) than the TDO group (63 ± 16) ($p = 0.0003$).

There was no significant difference in age between women with or without neurological disease in DO subgroups.

Table 2: *Number of women in each age group. No difference in age between the 3 groups: PDO, TDO and no DO whatever the neurological history.*

age group	History of neurological disease	18-44 y	45-54 y	55-74 yr	≥ 75 y	Σ	mean age y
No pts with **P**DO		28	13	24	12	77	52 ± 19
	No	20	6	14	9	49	51 ± 18
	Yes	8	7	10	3	28	53 ± 21
No pts with **T**DO		10	18	29	30	87	63 ± 16
	No	4	7	14	13	38	60 ± 16
	Yes	6	11	15	17	49	66 ± 17
No pts without DO		110	92	212	87	501	57 ± 17
	No	83	66	155	63	367	58 ± 17
	Yes	27	26	57	24	134	57 ± 17

PDO was less frequent than TDO in advanced age ($p = 0.006$). PDO frequency did not change with ageing (n.s.) while TDO frequency increased ($p = 0.0013$).

History of neurological disease (HND) (Table-3)

For women without HND, occurrence of each kind of DO was significantly different with age ($p = 0.0114$) with a decrease of PDO and an increase of TDO; for women with HND, no difference was observed.

In the PDO sub-group, HND was predominant in the peri- and post-menopausal age groups (53.8 and 41.6%), while in the pre-menopause and the oldest groups the percentage of HND was close to that observed in the eligible population (28.5 and 25% vs. a mean value of 26.7%). The frequency of HND was very high (60.0 and 61.1%) in the pre- and peri-menopausal age groups with TDO and remained at a significant level in the other age groups (48.3 and 43.3%).

In the NDO population, neurological disorder secondary to supra-pontine (SP) lesions (encephalic lesion and Parkinson's disease) was observed in 8/28 (28%) of the PDO group and 20/44 (45%) of the TDO group. The distribution of SP lesions showed an increase with ageing in the TDO group.

Urodynamic findings

The bladder volume of occurrence of the first IDC in P group was smaller than that at the IDC in the T group: 144 ± 95 vs. 219 ± 114 mL ($p < 0.0001$); the functional bladder capacity in group P (296 ± 105 mL) was significantly higher than that in the T group (246 ± 121 mL) ($p = 0.0045$). The functional capacity in the population without DO was 391 ± 149 mL ($p < 0.0001$).

The detrusor pressure (p_{det}) was 37 ± 25 cm H_2O at the onset of flow (when intubated flow was obtained) in the PDO population and 35 ± 19 cmH_2O at the onset of leakage in the **T** DO population (n.s.). In each DO sub-group, there was no significant difference between patients without (39 ± 29 cm H_2O) and those with HND (31 ± 14 cm H_2O); the same result was observed in each age group. There was no significant effect of aging on p_{det}.

Table 3 - *Ratio of women with neurological disease (N) in each sub group of DO and in each age group.*

age group	18-44 y	45-54 y	55-74 y	≥ 75 y
% PNDO/ (PDO)	28.5	53.8	41.6	25.0
% TNDO/ (TDO)	60.0	61.1	48.3	43.3
% N/entire population	24.3	28.4	26.8	27.3

The maximum urethral closure pressure (MUCP) decreased with aging but was most often found normal or higher (Table-4) compared with the value expected for age [(110 - age) ± 20% in cm H_2O] (15). Mean expected value was 62.8 ± 22.3 cm H_2O when the mean observed value was 69.9 ± 37.4 cm H_2O ($p = 0.0021$).

IDC characteristics in the PDO population (Table-5)

The number of IDC varied from 1 to > 5 with 12 leakage-micturitions during the last IDC in

Table 4: *Comparison of the maximal urethral closure pressure (MUCP) with the expected value for age in each DO group (women with or without a history of neurological disease (HND)).*

	P			T		
MUCP	with HND	without HND	Σ	with HND	without HND	Σ
Low	4	6	10(12.9%)	1	7	8 (9.2%)
Normal	7	17	24(31.2%)	20	19	39(44.8%)
High	17	26	43(55.8%)	23	16	39(44.8%)

Table 5 - *Spatio-temporal characteristics of the successive IDC in the PDO population; comparison between women with or without history of neurological disease (HND).*

	Duration (s)	Time to maximum (s)	Amplitude (cm H_2O)
Pts without HND	14.9 ± 1.7	6.6 ± 0.5	11.1 ± 3.3
Pts with HND	16.1 ± 1.8	7.5 ± 1.1	14.3 ± 1.9
p	n.s.	n.s.	n.s.

the NDO sub-group and 16 in the IDO sub-group.

Characteristics of the IDC are given in the Table-3. There was no significant variation in the duration, time to maximum and amplitude whatever the neurological status.

Recorded sensation (desire to void) showed mainly an occurrence of the first IDC before or at the first desire to void (FDV) (p = 0.033) (Table-6). That behavior was independent of a HND.

Sphincter behavior (Table-7)

Steady sphincter was predominant in the TDO subgroup: 45.9% vs. 32.1% (n.s.). In each DO sub-group, the ratio of steady sphincter increased in the ≥ 75 y sub-group (P: 50.0% vs. 32-33-36%; T: 65% vs. 40-35-34%); in the same way, the ratio of sphincter relaxation before IDC decreased in the ≥ 75 y sub-group (P: 0% vs. 29-42-23%; T: 17% vs. 33-29-34%).

DISCUSSION

The distinction between IDO and NDO has been frequently studied (16,17), but scarce data exist regarding the conditions underlying occurrence and expression of P or TDO. Occurrence of TDO has been related to aging and particularly to elderly patients with neurological lesions such as cerebrovascular accident (3,12,18). In his study, Tong (14) reported a high incidence of TDO with abnormal bladder sensation and unfelt PDO in men with benign prostatic hyperplasia.

Our purpose was to search for a condition which could be an indicator for occurrence of P or TDO. The first idea was to test aging because it is well known that LUT function changes in elderly patients. Because about half of the population (44%) had DO and a history of neurological disease, that last condition was also analyzed. Finally, because DO is a urodynamic diagnosis, some urodynamic parameters (p_{det} at the onset of flow for PDO, or at the onset of leakage for TDO, MUCP and sphincter behaviour during IDC) have been investigated. In their paper, Romanzi et al. (19) compared patients (men and women) according to the main presenting symptom and the neurological status and concluded that the characteristics of the cystometric tracing during IDC were not distinct to aid in differential diagnosis but might have prognostic and therapeutic significance.

Occurrence of TDO is significantly associated with aging; an inversion of the ratio PDO/TDO from 3:1 to is also observed. That result is consistent with an association between TDO and changes in LUT function due to aging. TDO would more probably due to alteration in detrusor function or abnormal micturition reflex than to sphincter incompe-

Table 6 - *Recorded sensation on UDS at occurrence of the first IDC in the PDO group (FDV: first desire to void; NDV: normal desire to void; SDV: strong desire to void). The first IDC occurs significantly before or at the first desire to void (FDV) (p = 0.033).*

Age group 1rst IDC	18-44 y	45-54 y	55-74 y	≥ 75 y	Σ
Up to FDV	14 (50%)	4 (31%)	11(46%)	7 (58%)	36
> FDV to NDV	7	2	5	1	15
> NDV to SDV	7	7	8	4	26

Table 7 - *Relationship between sphincter behavior and a history of neurological disease (HND) at IDC in each DO group. Sphincter relaxation before or during IDC is significantly observed in PDO women without HND (p = 0.0045).*

	PDO			TDO		
Sphincter behavior	With HND	Without HND	Σ	With HND	Without HND	Σ
Relaxation before IDC	4	14	18 (24.33%)	12	11	23 (27.05%)
Relaxation during IDC	8	21	29 (34.52%)	13	10	23 (27.05%)
Steady during IDC	15	12	27 (32.14%)	19	20	39 (45.88%)

tence because, in the oldest group, p_{det} at leakage is significantly lower than MUCP ($p < 0.0001$). With regard to aging-related DO, a characteristic structural pattern (20) and age-related changes in muscarinic receptor functions have been reported (21) but not related to each kind of DO.

The percentage of women with PDO is significantly higher than that of TDO in the 18-44 y subgroup ($p = 0.008$). A hypothesis to explain that result could be a high incidence of spinal lesions (spina bifida, multiple sclerosis) in younger. Unfortunately, in this age group the number of spinal lesion is the same in P and TDO groups.

Among the whole population, occurrence of DO was higher in the group with history of neurological disease (44% vs. 18%) as it has been previously reported (17-22). It has been verified that there was no bias of recruitment, as the percentage of patients with a neurological disease was similar in the different age groups: 26.8 ± 1.3%. Aging and history of neurological disease appear to be conditions for occurrence of TDO; consequently, the role of encephalic lesions (stroke, meningioma and Parkinson's disease) which frequency increases with ageing is a question. Unfortunately, that sub-group comprises only nine women, which is too small a group to conclude.

As expected, the functional bladder capacity (FBC) is lower in the DO population for which main motive for urodynamics is urge or mixed incontinence compared to the population without DO.

Comparing P and TDO patients, FBC is significantly higher in the PDO group. That result is consistent with the ability of PDO patients to counterbalance the increase in detrusor pressure and to prevent voiding. p_{det} does not differ at the onset of flow for PDO women and at the onset of leakage for TDO women. That result confirms the inability to abort IDC for TDO women. For our female population, the values of p_{det} at IDC are lower than the values reported by Romanzi et al. (19) whose study included men with urethral obstruction leading to detrusor hypertrophy.

MUCP decreases with aging but its value remains normal and higher the value expected for the age which can be the consequence of long-lasting DO and unconscious reinforcement of the striated sphincter.

An intuitive proposal that the larger the amplitude of the IDC, the more severe DO has been invalidated by Miller et al. (23), as it is severely confounded by the urethral sphincter function. That result is consistent with our findings; we do not observe differences between duration, time to maximum, and amplitude in successive IDC whatever the neurological status, and in addition, MUCP is normal or higher than the expected value for age. An unexplained result is the value of detrusor pressure generated during IDC which is much lower than the values reported by Romanzi et al. (19). In his paper (2), P Abrams suggests that PDO tends to be characterized by contractions of increasing amplitude as the bladder volume increases and that this pattern is seen in most IDO of middle age men and women. We don't observe any increase of the IDC amplitude with bladder filling. The number of IDC in the PDO group is lower for the NDO group (only 28% had 3 IDC vs. 43% in the IDO group); that result could be a limitation of the comparison between characteristics (duration, time to maximum, and amplitude) of the IDC between NDO and IDO but in this study there is no significant difference between these parameters during the first and second IDC.

In the PDO group, the first IDC is mainly observed up to first desire to void, which could imply abnormal intrinsic bladder reflexes (24) to bladder filling.

Incidence of steady sphincter in the oldest old group might be the consequence of aging on urethral function, as the threshold of urethral sensation increased in the elderly (3). The same conclusion can be proposed for the decrease of sphincter relaxation before IDC with aging.

In the population with a history of neurological disease, one observes a higher occurrence of a steady sphincter during IDC in the PDO group and a lower occurrence of sphincter relaxation before IDC when the neurological condition is an incomplete spinal cord injury.

Our study has several limitations, including its retrospective nature as well as the limited number of patients in each type of neurological lesion; its merit is that it is to be the first report assessing to find characteristics for each kind of DO.

CONCLUSIONS

Steady sphincter during non-inhibited detrusor contraction for both P and TDO, and occurrence of TDO appear as specific of aging. In the elderly, occurrence of a steady sphincter may be associated with loss of sensory nerve function in the urethra and occurrence of TDO could be related to the structural changes in the detrusor muscle with aging. Looking at a history of neurological disease, there is a trend of increase for both P and TDO with aging, except in the oldest group where TDO predominates.

ABBREVIATIONS:

DO = Detrusor Overactivity
FBC = Functional Bladder Capacity
FDV = First Desire to Void
HND = History of Neurological Disease
IDC = Involuntary Detrusor Contraction
IDO = Idiopathic Detrusor Overactivity
LUT = Lower Urinary Tract
MUCP = Maximum Urethral Closure pressure
NDO = Neurogenic Detrusor Overactivity
NDV = Normal Desire to Void
OAB = Overactive Bladder
$\mathbf{p_{det}}$ = Detrusor pressure
PDO = Phasic Detrusor Overactivity
STV = Strong Desire to Void
TDO = Terminal Detrusor Overactivity

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al.: The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002; 21: 167-78.
2. Abrams P: Describing bladder storage function: overactive bladder syndrome and detrusor overactivity. Urology. 2003; 62(5 Suppl 2): 28-37; discussion 40-2.
3. Guralnick ML, Grimsby G, Liss M, Szabo A, O'Connor RC: Objective differences between overactive bladder patients with and without urodynamically proven detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct. 2010; 21: 325-9.
4. Hashim H, Abrams P: Overactive bladder: an update. Curr Opin Urol. 2007; 17: 231-6.
5. Schaefer W: Re: Is the bladder a reliable witness for predicting detrusor overactivity? H. Hashim and P. Abrams. J Urol, 175: 191-195, 2006. J Urol. 2006; 176: 1255-7; author reply 1256-7.
6. Andersson KE: Mechanisms of Disease: central nervous system involvement in overactive bladder syndrome. Nat Clin Pract Urol. 2004; 1: 103-8.
7. Pfisterer MH, Griffiths DJ, Schaefer W, Resnick NM: The effect of age on lower urinary tract function: a study in women. J Am Geriatr Soc. 2006; 54: 405-12.
8. Kayigil O, Metin A, Atmaca AF: Obstructive urodynamic findings in idiopathic detrusor overactivity. Int Urol Nephrol. 2007; 39: 445-8.
9. Garnett S, Swithinbank L, Ellis-Jones J, Abrams P: The long-term natural history of overactive bladder symptoms due to idiopathic detrusor overactivity in women. BJU Int. 2009; 104: 948-53.
10. Serati M, Salvatore S, Cattoni E, Soligo M, Cromi A, Ghezzi F: Ultrasound measurement of bladder wall thickness in different forms of detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct. 2010; 21: 1405-11.

11. Lee SR, Kim HJ, Kim A, Kim JH: Overactive bladder is not only overactive but also hypersensitive. Urology. 2010; 75: 1053-9.
12. Kessler TM, Madersbacher H: Urodynamic phenomena in the aging bladder. Urologe A. 2004; 43: 542-6.
13. Schaefer W, Tadic S, Griffiths DJ, Resnick NM: Overactive bladder and detrusor overactivity: but what does the sphincter do? J Urol 2007;177(suppl 4):556. #abstract 1677.
14. Tong YC: Comparisons of urodynamic findings and voiding habits in patients with concomitant benign prostatic hyperplasia and detrusor overactivity presenting with or without the symptom of urgency. Urol Int. 2007; 78: 219-25.
15. Constantinou CE: Urethrometry: considerations of static, dynamic, and stability characteristics of the female urethra. Neurourol Urodyn. 1988; 7: 521-39.
16. Defreitas GA, Lemack GE, Zimmern PE, Dewey RB, Roehrborn CG, O'Suilleabhain PE: Distinguishing neurogenic from non-neurogenic detrusor overactivity: a urodynamic assessment of lower urinary tract symptoms in patients with and without Parkinson's disease. Urology. 2003; 62: 651-5.
17. Lemack GE, Frohman EM, Zimmern PE, Hawker K, Ramnarayan P: Urodynamic distinctions between idiopathic detrusor overactivity and detrusor overactivity secondary to multiple sclerosis. Urology. 2006; 67: 960-4.
18. Geirsson G, Fall M, Lindström S: Subtypes of overactive bladder in old age. Age Ageing. 1993; 22: 125-31.
19. Romanzi LJ, Groutz A, Heritz DM, Blaivas JG: Involuntary detrusor contractions: correlation of urodynamic data to clinical categories. Neurourol Urodyn. 2001; 20: 249-57.
20. Elbadawi A, Yalla SV, Resnick NM: Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility. J Urol. 1993; 150: 1657-67.
21. Andersson KE: Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol. 2011; 59: 377-86.
22. Ashok K, Wang A: Detrusor overactivity: an overview. Arch Gynecol Obstet. 2010; 282: 33-41.
23. Miller KL, DuBeau CE, Bergmann M, Griffiths DJ, Resnick NM: Quest for a detrusor overactivity index. J Urol. 2002; 167: 578-84; discussion 584-5.
24. Fowler CJ: Integrated control of lower urinary tract--clinical perspective. Br J Pharmacol. 2006; 147(Suppl 2): S14-24.

Submitted for publication:
January 04, 2011

Accepted after revision:
April 05, 2011

Correspondence address:
Dr. Françoise A. Valentini
Université Pierre et Marie Curie (Paris 6)
4 Place Jussieu, 75005 Paris, France
Fax: + 33 1 4959-4697
E-mail: favalentini@gmail.com

Radiology Page
International Braz J Urol
Vol. 37 (6): 781-782, November - December, 2011

HASTE MRU In the Evaluation of Acute Flank Pain

Jeffrey Mullins, Michelle J. Semins, Mark E. Bohlman, Brian R. Matlaga

Departments of Urology and Radiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

A 20 year old, otherwise healthy, G2PO, 21 week pregnant female presented to the emergency department with a one day history of left flank pain, nausea, and vomiting. She denied a history of fevers, chills, or dysuria. Physical examination revealed left costovertebral angle tenderness. Laboratory evaluation was significant for leukocytosis (14,000), normal creatinine (0.6), and unremarkable urinalysis. Renal ultrasound demonstrated mild left hydroureteronephrosis without evidence of stone. Subsequent HASTE magnetic resonance urography (MRU) revealed a 3mm left ureteral stone, mild hydronephrosis, and a forniceal rupture (Figure-1). The patient was managed conservatively with hydration and oral narcotics.

Urolithiasis is not an uncommon finding in pregnancy with an estimated incidence of 1/1,500 pregnancies (1). Although pregnancy does not confer an increased risk of urolithiasis, a shift in stone profile in pregnant patients has been observed. Specifically, there is an increased incidence of calcium phosphate stones as opposed to calcium oxalate stones most commonly observed in non-pregnant females. Reasons for this shift in stone composition include an absorptive hyercalciuria and relatively alkaline urine pH that occur in this population (2). Despite the common occurrence of stone disease in pregnancy, safe and accurate diagnosis remains a dilemma.

When subjecting pregnant patients to diagnostic imaging studies the potential impact to the fetus must be considered. Computed tomography (CT), the gold standard for stone diagnosis, exposes the pa-

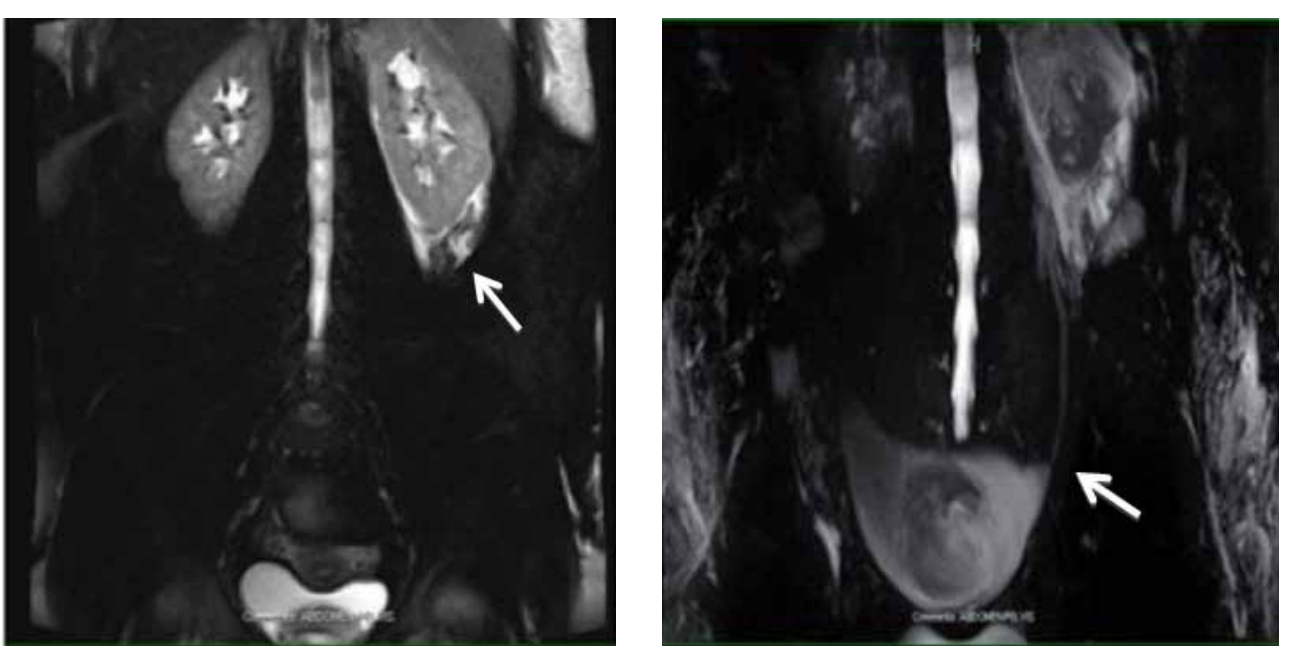


Figure 1 - *Magnetic resonance urogram demonstrating A: Forniceal rupture with fluid within Gerota's fascia (arrow). B: Forniceal rupture and fluid within Gerota's fascia again demonstrated as well as a 3 mm distal ureteral calculus (arrow).*

tient and fetus to ionizing radiation. The amount of radiation exposure to the fetus depends on both the gestational age as well as scanning parameters. On average, a typical pelvic CT scan will expose the fetus to 0.024 Gy in the first trimester and 0.046 Gy in the third trimester (3). While these doses are less than levels which are considered "dangerous", there nonetheless exists concern regarding potential teratogenic and carcinogenic risks to the fetus.

Alternative diagnostic imaging studies imposing no risk to the fetus have been historically limited to ultrasound. This modality, however, has limitations in diagnosing ureteral calculi. HASTE MRU has recently emerged as a safe, highly accurate means of diagnosing ureteral calculi. HASTE MRU utilizes a heavily T2 weighted image that does not require the administration of intravenous contrast agents, which are potentially hazardous to the pregnant patient. In a study by Spencer et al., MRU was utilized to evaluate painful hydronephrosis in pregnancy. The authors were able to successfully diagnose all cases of ureteral stones. They also describe the "double kink" sign indicative of distal ureteral obstruction (4). Regan et al. directly compared the ability of spiral CT and MRU to diagnose acute ureteral obstruction secondary to ureteral calculi. The authors concluded that MRU was able to diagnose acute ureteral obstruction secondary to ureteral calculi with similar accuracy to spiral CT. While ultrasound remains the initial diagnostic modality of choice in pregnant patients with suspected ureteral calculi, MRU appears to be an accurate alternative diagnostic tool in this patient population.

REFERENCES

1. Meria P, Hadjadj H, Jungers P, Daudon M; Members of the French Urological Association Urolithiasis Committee: Stone formation and pregnancy: pathophysiological insights gained from morphoconstitutional stone analysis. J Urol. 2010; 183: 1412-6.
2. Chen MM, Coakley FV, Kaimal A, Laros RK Jr: Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008; 112: 333-40.
3. Spencer JA, Chahal R, Kelly A, Taylor K, Eardley I, Lloyd SN: Evaluation of painful hydronephrosis in pregnancy: magnetic resonance urographic patterns in physiological dilatation versus calculous obstruction. J Urol. 2004; 171: 256-60.
4. Regan F, Kuszyk B, Bohlman ME, Jackman S: Acute ureteric calculus obstruction: unenhanced spiral CT versus HASTE MR urography and abdominal radiograph. Br J Radiol. 2005; 78: 506-11.

Correspondence address:
Dr. Brian R. Matlaga
James Buchanan Brady Urological Institute
The Johns Hopkins University School of Medicine
600 North Wolfe Street
Baltimore, MD 21287, USA
Fax: + 1 410 502-7711
E-mail: bmatlaga@jhmi.edu

International Braz J Urol Vol. 37 (6): 783-801, November - December, 2011

UROLOGICAL SURVEY

Athanase Billis
State University of Campinas
Campinas, SP, Brazil

Andreas Böhle
Helios Agnes Karll Hospital
Bad Schwartau, Germany

Sean P. Elliott
University of Minnesota
Minneapolis, MN, USA

Fernando J. Kim
Univ Colorado Health Sci Ctr
Denver, Colorado, USA

Ricardo Miyaoka
State University of Campinas
Campinas, SP, Brazil

Manoj Monga
University of Minnesota
Edina, MN, USA

Adilson Prando
Vera Cruz Hospital
Campinas, SP, Brazil

Leonardo O. Reis
State University of Campinas
Campinas, SP, Brazil

M. Chad Wallis
University of Utah
Salt Lake City, Utah, USA

STONE DISEASE

Percutaneous nephrolithotomy of caliceal diverticular calculi: a single center experience

M Ndez-Probst CE, Fuller A, Nott L, Denstedt JD, Razvi H
Division of Urology, Department of Surgery, The University of Western Ontario, London, Ontario, Canada
J Endourol. 2011; 25: 1741-5

Abstract Background and Purpose: Caliceal diverticula are rare renal anomalies present in approximately 0.6% of the population. They are associated with calculi in 50% of cases. Therapeutic options include several minimally invasive techniques. We report a retrospective review of outcomes and complications from our series of patients who were treated with a percutaneous approach.
Patients and Methods: A database of outcomes related to percutaneous nephrolithotomy (PCNL) has been maintained at our institution since 1992. Data on all patients with caliceal diverticular stones who underwent PCNL during a 17-year period from 1992 to 2009 were reviewed retrospectively. Our preferred approach to PCNL in these patients is to puncture directly into the diverticulum and to try to advance a guidewire through the infundibular neck. In cases where the caliceal neck could not be intubated, we performed a transdiverticular approach with creation of a neoinfundibulum as a salvage procedure. We evaluated the two techniques with regard to stone-free rates and early postoperative complications.
Results: Seventy-six procedures were performed. The mean age was 43 years (range 17-72y). The mean stone area was 583mm (2). The surgical approach was direct puncture in 47, transdiverticular in 20, retrograde in 8, and unknown in 1 patient. Eight patients underwent lining fulguration. The average duration of surgery was 75 minutes (23-169min) with an average hospital stay of 4.7 days. There were a total of 23 complications, of which 11 necessitated additional intervention. The overall stone-free rates were 77% and 89% for direct puncture and transdiverticular approaches, respectively.
Conclusions: The percutaneous management of caliceal diverticular calculi is highly effective and can be accomplished with low morbidity.

Editorial Comment

For patients who failed direct puncture, a transdiverticular neoinfundibular approach was successful in only 60% of patients. Retrograde ureteroscopy was utilized as a salvage procedure. One might propose that retrograde ureteroscopy be considered as a primary procedure, in particular as 2/3rds of patients in this study had upper pole diverticulae. The upper pole location is more amenable to a ureteroscopic approach, and is at higher risk for pulmonary complications from a percutaneous approach. Indeed, the complication rate in this study was 30%, with 90% of the complications being pulmonary. Interestingly, contrary to what one might anticipate, there was no increased risk of hemorrhagic complication with the transdiverticular neoinfundibulotomy approach.

Dr. Manoj Monga
Director, Stevan B. Streem Center for
Endourology & Stone Disease
Glickman Urological & Kidney Institute
The Cleveland Clinic
Cleveland, Ohio, USA
E-mail: endourol@yahoo.com

Perioperative patient radiation exposure in the endoscopic removal of upper urinary tract calculi

Jamal JE, Armenakas NA, Sosa RE, Fracchia JA
Department of Urology, Lenox Hill Hospital , New York, New York

J Endourol. 2011; 25: 1747-51

Abstract Background and Purpose: The efficacy of computed tomography (CT) in detailing upper urinary tract calculi is well established. There is no established acceptable annual recommended limit for medical exposure, yet the global accepted upper limit for occupational radiation exposure is < 50 millisieverts (mSv) in any one year. We sought to appreciate the CT and fluoroscopic radiation exposure to our patients undergoing endoscopic removal of upper tract calculi during the periprocedure period.
Patients and Methods: All patients undergoing upper urinary endoscopic stone removal between 2005 and 2009 were identified. To calculate the cumulative radiation exposure, we included all ionizing radiation imaging performed during a periprocedure period, which we defined as ≤ 90 days pre- and post-therapeutic procedure.
Results: A total of 233 upper urinary tract therapeutic patient stone procedures were identified; 127 patients underwent ureteroscopy (URS) and 106 patients underwent percutaneous nephrolithotomy (PCNL). A mean 1.58 CTs were performed per patient. Ninety (38.6%) patients underwent ≥ 2 CTs in the periprocedure period, with an average number in this group of 2.49 CT/patient, resulting in approximately 49.8mSv of CT radiation exposure. Patients who were undergoing URS were significantly more likely to have multiple CTs (P = 0.003) than those undergoing PCNL. Median fluoroscopic procedure exposures were 43.3mGy for patients who were undergoing PCNL and 27.6mGy for those patients undergoing URS.
Conclusions: CT radiation exposure in the periprocedure period for patients who were undergoing endoscopic upper tract stone removal is considerable. Added to this is the procedure-related fluoroscopic radiation exposure. Urologic surgeons should be aware of the cumulative amount of ionizing radiation received by their patients from multiple sources.

Editorial Comment

It is interesting that the authors excluded patients with a prior indwelling ureteral stenting - indeed these present a decision-making challenge as conventional imaging may have difficulty identifying residual ureteral calculi, leaving the patient and physician faced with the dilemma of stent removal or ureteroscopy. New modalities such as dual-energy CT scan imaging may prove helpful in this subset of patients, as one would anticipate that the risk of negative ureteroscopy would be higher in this group.

The average time from CT scan to ureteroscopy was 55 days in this study. It is unclear from the study what follow-up occurred during this time period. Did patients strain their urines to identify stone passage? Was any re-imaging performed on any of these patients in the interval between diagnosis and surgery? What drove the decision to proceed with ureteroscopy - did the patients have persistent colic? These questions would help delineate the significance of the findings of this study.

Only 1/3rd of patients received medical expulsive therapy - suggesting that the risk of a negative URS would be even higher than the 10% reported in this study in areas where medical expulsive therapy has become standard practice. This study highlights the need to emphasize to patients the importance of straining their urine to monitor for stone passage. Not only does this minimize the risk for repeat imaging, but also

would likely decrease the risk of unnecessary anesthesia. For patients who cannot reliably strain their urine, reimaging with a low-dose CT pelvis should be seriously considered for those patients with distal ureteral calculi ≤ 5mm in size.

Dr. Manoj Monga
Director, Stevan B. Streem Center for
Endourology & Stone Disease
Glickman Urological & Kidney Institute
The Cleveland Clinic
Cleveland, Ohio, USA
E-mail: endourol@yahoo.com

ENDOUROLOGY & LAPAROSCOPY

Natural orifice transluminal endoscopic radical prostatectomy: initial perioperative and pathologic results

Humphreys MR, Sauer JS, Ryan AR, Leslie KO, Castle EP, Lingeman JE, Andrews PE
Mayo Clinic, Phoenix, Arizona
Urology. 2011; 78: 1211-7

Objective: To describe the first clinical experience, pathologic, and perioperative outcomes of natural orifice transluminal endoscopic surgery (NOTES) radical prostatectomy. NOTES represents the evolution of minimally invasive surgery. The conceptual feasibility has been shown in careful laboratory and animal studies, but a scarcity of information regarding clinical applications exists.
Methods: After institutional review board approval, 2 patients agreed to undergo NOTES radical prostatectomy for localized prostate cancer. The prostate was radically resected using a 26F resectoscope, 550-µm laser fiber, and holmium laser. The prostate was delivered into the bladder and removed at the conclusion of the procedure through a suprapubic cystotomy for histopathologic analysis. The vesicourethral anastomosis was completed using a cannula scope, urethral-vesical suturing device, and titanium knot applier. Cystograms were taken immediately postoperatively and at catheter removal.
Results: Both patients tolerated the procedure without operative complications. All intraoperative cystograms showed watertight anastomoses. The pathologic examination revealed Gleason score 3 + 3 and Stage pT2aNxMx for 1 patient and Gleason score 3 + 4 and Stage pT2cNxMx for 1 patient, with negative margins for both. No blood transfusions were required. Patient 2 experienced some left-sided gluteal and suprapubic pain postoperatively.
Conclusion: NOTES radical prostatectomy appears to be a safe and feasible option for the management of carefully selected, organ-confined prostate cancer. The perioperative and pathologic outcomes show promise with this new technique; however, the high standards of oncologic and functional outcomes demand close and longer follow-up before adoption into the surgical armamentarium can be recommended.

Editorial Comment

The authors must be congratulated for their pioneer work. The advancement of minimally invasive urological surgery has pushed the technology and surgical instruments industry to collaborate with surgeons allowing better care of our patients.

Although the idea of transurethral radical prostatectomy has been studied by others previously (Kavoussi et al.); this report of 2 patients with localized prostate cancer with negative margins using this novel NOTES approach may have been possible due to the great experience of the authors with laser prostate enucleation and new instrumentation for suturing endoscopically.

I am certain longer follow-up will determine the validity of this novel technique but undoubtedly, this innovating work has to be recognized as breaking ground.

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med. Ctr.
Associate Professor, Univ. Colorado Health Sci. Ctr.
Director of Minimally Invasive Urol. Oncology, UCHSC
Denver, Colorado, USA
E-mail: fernando.kim@dhha.org

Comparison of Laparoendoscopic Single-site Donor Nephrectomy and Conventional Laparoscopic Donor Nephrectomy: Donor and Recipient Outcomes

Afaneh C, Aull MJ, Gimenez E, Wang G, Charlton M, Leeser DB, Kapur S, Del Pizzo JJ
Department of Surgery, Division of Transplantation Surgery, New York Presbyterian Weill Cornell Medical College, New York, New York
Urology. 2011; 78: 1332-7

Objective: To present a comparison of perioperative donor outcomes and recipient graft function in a series of patients undergoing laparoendoscopic single-site donor nephrectomy (LESS-DN) versus conventional laparoscopic donor nephrectomy (LDN).

Methods: Data were collected for 50 consecutive LESS-DN patients and a matched cohort of 50 LDN patients. The donor outcomes analyzed included operative time, estimated blood loss, complications, visual analog pain scores, and recovery time. The recipient outcomes analyzed included serum creatinine at discharge and follow-up and the incidence of delayed graft function.

Results: The mean total operative time was shorter in the LDN group than in the LESS-DN group ($P < 0.0001$). Linear regression analysis of the LESS-DN operative times relative to case number showed a significant decrease in the operative time with increasing case number ($r(2) = 0.19$, $P = 0.002$). No statistically significant differences were found in estimated blood loss, warm ischemia time, length of stay, or visual analog pain scores between the 2 groups. However, the surgical incision was significantly smaller in the LESS-DN group ($P < 0.0001$). After discharge, the patient-reported time to complete recovery was faster in the LESS-DN group ($P = 0.01$). The incidence of complications was similar in both groups; however, major complications only occurred in the LDN group. No differences were found in the recipient serum creatinine values or the incidence of delayed graft function.

Conclusion: Our initial experience with LESS-DN is encouraging. This retrospective matched-pair comparison between LESS-DN and LDN suggests that the single-port approach might be associated with quicker convalescence. Longer operative times in the LESS-DN group could simply represent the learning curve of a novel procedure.

Editorial Comment

Laparoscopic live donor nephrectomy (LDN) has become the standard of care at most major academic centers. The benefits of laparoscopic over open donor nephrectomy have extensively been demonstrated since the first report by Kavoussi et al. Recently, the LESS Urological procedures are gaining popularity.

The authors studied 50 consecutive LESS-DN patients versus a matched cohort of 50 LDN patients. They demonstrated that LESS-DN patients recovered faster and complications were comparable with equal graft function and warm ischemia time. This report is valuable since convalescence and recovery is pivotal variables that may influence the decision to become a kidney donor increasing the pool of donors for the current high demand. The Gelport was used in this study that may also facilitate the learning curve compared to other single ports.

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med. Ctr.
Associate Professor, Univ. Colorado Health Sci. Ctr.
Director of Minimally Invasive Urol. Oncology, UCHSC
Denver, Colorado, USA
E-mail: fernando.kim@dhha.org

IMAGING

Characterization of adrenal masses with diffusion-weighted imaging

Sandrasegaran K, Patel AA, Ramaswamy R, Samuel VP, Northcutt BG, Frank MS, Francis IR
Department of Radiology, Indiana University School of Medicine, Indianapolis, 46202, USA
AJR Am J Roentgenol. 2011; 197: 132-8

Objective: The purpose of this article is to assess the role of diffusion-weighted MRI in characterizing adrenal masses.
Materials and Methods: A retrospective review of the MRI database from August 2007 to July 2009 was performed. The MRI examinations of 48 patients, with 49 lesions, were reviewed independently and blindly by two experienced abdominal radiologists who measured the signal intensities on in-phase and opposed-phase T1-weighted imaging and apparent diffusion coefficient (ADC). ADC measurements and quantitative parameters of chemical shift imaging (signal intensity index and adrenal-to-spleen ratio) were assessed separately and in combination. Lesions with indeterminate signal intensity index (< 16.5%) were considered benign if ADC was greater than or equal to 1.0 × 10(-3) mm(2)/s and malignant if ADC was less than 1.0 × 10(-3) mm(2)/s. Stepwise logistic regression analysis and receiver operating characteristic curves analysis were performed.
Results: There were 12 malignant and 37 benign lesions. On multivariate analysis, the only significant predictors of lesion status were signal intensity index from reviewer 2 (p = 0.05) and lesion size (p = 0.04); ADC values were not found to be useful. On receiver operating characteristic curve analysis, there was no significant difference in area under the curve for ADC, signal intensity index, adrenal-to-spleen ratio, or the combined signal intensity index and ADC assessment. For lesions that were indeterminate according to signal intensity index, ADC values greater than 1.50 × 10(-3) mm(2)/s were found only in benign lesions, and nine of 11 lesions with ADC less than 1.0 × 10(-3) mm(2)/s were malignant.

Conclusion: In general, ADC values are not useful in differentiating adrenal lesions. However, when ADC values are applied to lesions that are indeterminate on signal intensity index, they may help in differentiating a subset of benign and malignant lesions.

Editorial Comment

Adrenal incidentalomas are found in about 6% of patients submitted to abdominal computed tomography. Based on distinct radiologic criteria classified as morphologic (size, shape, rate of growing), histologic (lipid content of the mass on CT without contrast or on chemical-shift imaging on MRI without contrast) and physiologic (absolute washout of contrast on CT), the vast majority of adrenal incidentalomas are adequately characterized as a benign or malignant. Lipid rich adrenal adenoma loses signal intensity when protons from water and fat are on opposed-phase in comparison with imaging when these protons are in-phase. Signal intensity index higher than 16.5% is usually found in benign adenomas. Indeterminate adrenal lesion represents a lesion with signal intensity index below 16.5%. In such situation, the authors showed that use of ADC values obtained with diffusion-weighted imaging (DWI) might be useful in differentiating benign from malignant adrenal lesions.

Although in our protocol for DWI of adrenal masses we use a different "b-value" (b-factor of 1000), we have found no utility of DWI even in this selected group of patients with indeterminate lesion on CSI. Actually we have seen two out of 13 adrenal adenomas showing the lowest ADC values. As pointed out by the authors, the different proportion of lipid-poor adenomas and fat-containing adrenal metastases may explain distinct results with DWI.

Dr. Adilson Prando
Head, Department of Radiology and
Diagnostic Imaging, Vera Cruz Hospital
Campinas, São Paulo, Brazil
E-mail: adilson.prando@gmail.com

Characterization of small solid renal lesions: can benign and malignant tumors be differentiated with CT?

Millet I, Doyon FC, Hoa D, Thuret R, Merigeaud S, Serre I, Taourel P
Department of Radiology, CHU Lapeyronie, 371 Ave du Doyen Gaston Giraud, 34295 Montpellier, France
AJR Am J Roentgenol. 2011; 197: 887-96

Objective: The purpose of this study was to evaluate the diagnostic performance of CT in determining whether a small solid renal enhancing mass is benign or malignant.
Materials and Methods: Ninety-nine biopsies of enhancing solid renal masses 4 cm or smaller without fat on CT scans were performed under CT fluoroscopic guidance. The growth pattern, interface with parenchyma, presence of a scar and segmental inversion enhancement, unenhanced CT histogram, and pattern and degree of enhancement on triphasic MDCT images were independently evaluated by two radiologists. Biopsy and pathology reports were used as the reference standard, and imaging follow-up of benign lesions was performed for at least 1 year. Statistical analysis was performed to determine the significance of CT criteria in differentiating malignant from benign lesions.
Results: Of the 99 lesions, 74 (75%) were malignant at biopsy, and 25 (25%) were benign. Lesions with gradual enhancement were more likely to be benign. No significant correlation was found between other CT

features and a malignant or benign diagnosis. The sensitivity, specificity, and positive and negative predictive values of progressive enhancement for a diagnosis of benignity were 60%, 73%, 43%, and 84%.
Conclusion: In the evaluation of enhancing small solid renal lesions without fat, no CT criteria were of substantial help in differentiating malignant from benign lesions.

Editorial Comment

Pre-operative characterization of small solid enhancing renal lesion containing no macroscopic fat is a difficult task. Although the CT characteristics of benign solid renal lesion overlap with those of renal cell carcinoma, we encourage radiologists from our institution to narrow the differential diagnosis whenever it is possible. The pre-operative radiologic impression of renal tumor histology is of particular value when affects therapeutic management. During the nephrographic (90-100 seconds) and excretory phase (180 seconds), some renal tumors subtypes demonstrate significant different degrees of enhancement. Clear cell of renal carcinoma can be suggested by the presence of strong and heterogeneous contrast enhancement and rapid washout. Papillary renal cell carcinoma is usually homogeneously hipovascular similarly to the rare benign metanephric adenoma. Solid homogeneously hypervascular renal mass can be observed in oncocytoma and angiomyolipoma without macroscopic fat. Thus, depending on the clinical scenario, percutaneous biopsy is performed particularly when its results will influence therapeutic management

Dr. Adilson Prando
Head, Department of Radiology and
Diagnostic Imaging, Vera Cruz Hospital
Campinas, São Paulo, Brazil
E-mail: adilson.prando@gmail.com

PATHOLOGY

Identification of Gleason pattern 5 on prostatic needle core biopsy: frequency of underdiagnosis and relation to morphology

Fajardo DA, Miyamoto H, Miller JS, Lee TK, Epstein JI
Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
Am J Surg Pathol. 2011; 35: 1706-11

The presence of a Gleason pattern 5 prostatic adenocarcinoma is associated with a worse outcome. This study assesses the accuracy of grading a tumor as having Gleason pattern 5 and the potential factors contributing to its undergrading. From the consultation service of one of the authors, we identified 59 consecutive needle biopsy cases comprising 138 parts that, upon review, were graded as having Gleason pattern 5. All cases were reported as the final diagnosis by the outside pathologist. They were sent for a second opinion at the behest of clinicians or patients and not because the pathologist was seeking a second opinion. Considering the highest Gleason score in a given multicore specimen as the overall Gleason score, Gleason pattern 5 was missed in 34 of 59 (57.6%) cases by the outside pathologist. Compared with the outside pathologist's diagnosis, the Gleason score rendered at the second opinion was increased in 101 of 138 (73.2%) parts, was decreased in 5 of 138 (3.6%) parts, and remained unchanged in 32 of 138 (23.2%) parts. Gleason pattern 5 was not identified by the initiating pathologist in 67 of 138 (48.6%) of the evaluated parts. The architectural patterns of pattern 5

were as follows: single cells (n = 104, 75.3%); solid sheets (n = 69, 50%); cords (n = 62, 44.9%); and comedonecrosis (n = 3, 2.2%). Pattern 5 was missed more frequently when it was not the primary pattern. The most common Gleason pattern 5 architectural type was single cells and the least common was comedonecrosis. None of the architectural patterns appeared to be more correctly identified than the others; however, the most accurate grading was when the primary pattern was 5 and was composed mostly of solid sheets. Owing to the important prognostic and therapeutic implications of Gleason pattern 5, pathologists must be attuned to its varied patterns and to the fact that it may often represent a secondary or tertiary component of the carcinoma.

Editorial Comment

Gleason pattern 5 is associated with a worse outcome following radical prostatectomy. There are several architectural types for pattern 5: single cells, solid sheets, cords and comedocarcinoma. The latter architectural type is the least common.

The consensus meeting by the International Society of Urological Pathology (ISUP) on Gleason grading held during the USCAP Congress in San Antonio in 2005, established that the tertiary pattern on a needle biopsy should be incorporated in the final score whenever is higher than the secondary pattern (1). This may be one of the reasons why general pathologists do not consider pattern 5 in the final Gleason score.

The study from Johns Hopkins, compared how often pattern 5 was missed by outside pathologists in cases that were reviewed by Epstein at the study Institution. Considering the highest Gleason score in a given multicore specimen as the overall Gleason score, Gleason pattern 5 was missed in 34 of 59 (57.6%) cases by the outside pathologist. Compared with the outside pathologist's diagnosis, the Gleason score rendered at the second opinion was increased in 101 of 138 (73.2%) parts, was decresed in 5 of 138 (3.6%) parts, and remained unchanged in 32 of 138 (23.2%) parts.

The study emphasizes that owing to the important prognostic and therapeutic implications of Gleason pattern 5, pathologists must be attuned to its varied patterns and to the fact that it may often represent a secondary or tertiary component of the carcinoma.

References

1. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005; 29: 1228-42.

Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

Evolution of the clinical presentation of men undergoing radical prostatectomy for high-risk prostate cancer

Pierorazio PM, Ross AE, Han M, Epstein JI, Partin AW, Schaeffer EM
Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA
BJU Int. 2011 Aug 22; doi: 10.1111/j.1464-410X.2011.10514.x. [Epub ahead of print]

Study Type - Prognosis cohort series (multi-centre) Level of Evidence 4 What's known on the subject? and What does the study add? Men with high-risk prostate cancer experience recurrence, metastases and death at a higher rate in the prostate cancer population. This study adds greater than 20-year data regarding the continued evolution of high-risk prostate cancer toward high-Gleason disease as the sole determinant of high-risk status prior to radical prostatectomy. It validates the accumulation of multiple-risk factors as a poor prognostic indicator in a radical prostatectomy population and demonstrates long-term cancer specific outcomes, extending the findings demonstrated by previous publications.
Objective: To investigate the outcomes and potential effect of improved longitudinal screening in men presenting with high-risk (advanced clinical stage [> T2b], Gleason score 8-10 or prostate-specific antigen [PSA] level > 20ng/mL) prostate cancer (PC).
Patients and Methods: The Institutional Review Board approved, Institutional Radical Prostatectomy Database (1992-2010) was queried for men with high-risk PC based on D'Amico criteria. Year of surgery was divided into two cohorts: the Early PSA Era (EPE, 1992-2000) and the Contemporary PSA Era (CPE, 2001-2010). PC features and outcomes were evaluated using appropriate comparative tests.
Results: In total, 667 men had high-risk PC in the EPE and 764 in the CPE. In the EPE, 598 (89.7%) men presented with one high-risk feature; 173 (29.0%) men had a Gleason score of 8-10 on biopsy. In the CPE, 717 (93.9%) men presented with one high-risk feature (P = 0.004) and 494 (68.9%) men had a Gleason score of 8-10. At 10 years, biochemical-free survival (BFS) was 44.1% and 36.4% in the EPE and CPE, respectively (P = 0.04); metastases-free survival (MFS) was 77.1% and 85.1% (P = 0.6); and PC-specific survival (CSS) was 83.3% and 96.2% (P = 0.5). BFS, MFS and CSS were worse for men with more than one high-risk feature in both eras.
Conclusions: Over the PSA era, an increasing percentage of men with high-risk PC were categorized by a biopsy Gleason score of 8-10. The accumulation of multiple high-risk features increases the risk of biochemical recurrence, the development of metastases and death from PC. BFS, MFS and CSS are stable over the PSA era for these men. The balance between a greater proportion of men having high Gleason disease and a greater proportion with small, less advanced tumours may explain the stability in MFS and CSS over time.

Editorial Comment

High-risk prostate cancer includes advanced clinical stage (> T2), Gleason score 8-10 or PSA level > 20ng/mL. Men with high-risk prostate cancer experience recurrence, metastases and death at a higher rate in the prostate cancer population.

The study from Johns Hopkins, compared the frequency of Gleason score 8-10 on biopsy in two cohorts: the early PSA era from 1992 to 2000, and the contemporary era from 2001 to 2010. In the early era, 29.0% patients had a Gleason score of 8-10 on biopsy, and in the contemporary era 68.9%. In spite of this significant difference, considering all high-risks, at 10 years the biochemical-free survival, the metastases-free survival, and prostate cancer-specific survival were stable comparing the two eras.

The authors conclude that the balance between a greater proportion of men having high Gleason disease and a greater proportion with small, less advanced tumours may explain the stability in survival.

Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

RECONSTRUCTIVE UROLOGY

Low yield of early postoperative imaging after anastomotic urethroplasty
Terlecki RP, Steele MC, Valadez C, Morey AF
Department of Urology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA
Urology. 2011; 78: 450-3

Objectives: To evaluate the necessity and clinical effect of posturethroplasty imaging.
Methods: We reviewed our database of all urethroplasties performed by a single surgeon at our referral center during a 2-year period. The patients underwent voiding cystourethrography at a mean of 24 days postoperatively. The data analyzed included patient history and demographics, operative details, imaging results, and clinical outcomes.
Results: From 2007 to 2009, 210 patients underwent urethral reconstruction at our center. The patients undergoing meatoplasty or staged repairs were excluded, leaving 156 patients with postoperative imaging studies for analysis. Of 110 anterior urethroplasties, 59 (54%) consisted of excision and primary anastomosis, 28 (25%) an augmented anastomotic procedure, and 23 (21%) a pure ventral onlay with a flap or graft. All 46 posterior urethroplasties were performed with scar excision and primary anastomosis. Of the 156 patients, only 4 (3%) had extravasation on postoperative voiding cystourethrography (2 after posterior urethroplasty, 1 after augmented anastomosis, and 1 after ventral onlay)--all were successfully managed with catheter replacement and removal at a mean of 8 days afterward. None of the 59 men undergoing excision and primary anastomosis demonstrated extravasation.
Conclusions: Extravasation on posturethroplasty voiding cystourethrography is rare after approximately 3 weeks of catheter drainage. Imaging can be omitted after uncomplicated excision and primary anastomosis urethroplasty.

Editorial Comment

Urethral imaging after urethroplasty is performed in order to rule out extravasation. If extravasation is seen then the catheter is replaced in order to divert the urine until the extravasation is healed. Such imaging is commonly done as either a peri-catheter retrograde urethrogram or a voiding cystourethrogram after catheter removal. The authors demonstrate that when removing the catheter at a mean of 3.5 weeks after surgery, the incidence of extravasation is extremely low. Furthermore, in anastomotic urethroplasties there were no instances of extravasation. The suture line is shorter in anastomotic urethroplasties so it is intuitive that these would have a lower risk of prolonged extravasation.

Others have pushed for early catheter removal but have admitted a higher chance of urinary extravasation.

I think what is clear from this article is that surgeons have a choice - they can leave the catheter in for a long period of time and not perform imaging or they can try to remove the catheter early but should perform imaging if they do so. With prolonged catheterization comes increased risk of urinary tract infection and patient discomfort. With early catheter removal comes the risk that about 1 in 5 will need the catheter replaced for another week or two due to extravasation on imaging. It would seem that for patients who live close to a reconstructive center, early catheter removal with imaging and a chance of catheter replacement may be preferable. For those who live far from their reconstructive surgeon or who want to minimize extra visits, a longer period of catheterization without subsequent imaging would be appropriate.

Dr. Sean P. Elliott
Department of Urology Surgery
University of Minnesota
Minneapolis, Minnesota, USA
E-mail: selliott@umn.edu

Long-term results of permanent urethral stent Memotherm implantation in the management of recurrent bulbar urethral stenosis

Sertcelik MN, Bozkurt IH, Yalcinkaya F, Zengin K
Ankara Diskapi Yildirim Beyazit Training and Research Hospital 1. Urology Clinic, Ankara, and Department of Urology, Karaman State Hospital, Karaman, Turkey
BJU Int. 2011; 108: 1839-42. doi: 10.1111/j.1464-410X.2011.10230.x.

Study Type - Therapy (case series) Level of Evidence4 What's known on the subject? and What does the study add? Milroy reported 84% success at a mean of 4.5 years follow-up by usage of a permanently implantable "urolume" spent in 1993. Study Type - Therapy (case series) Level of Evidence Memotherm was developed later, especially for urologic use. Our study is one of the largest in this urea, with a high number of patients and a long follow-up period.

Objective: To evaluate the effectiveness and long-term results of permanent urethral stent (Memotherm) implantation in the treatment of recurrent bulbar urethral stricture.

Patients and Methods: In all, 47 patients with a history of previous unsuccessful treatment for bulbar urethral stricture were treated using Memotherm bulbar urethral stents between 1998 and 2002. Long-term follow-up data was analysed and discussed.

Results: At the end of the 7-year period 37 of 47 patients (78.7%) had been treated successfully. Post-micturition dribbling incontinence lasting up to 3 months after stent placement occurred in 32 (68.1%) patients, but this was reduced to only seven patients (14.9%) by the 7-year follow-up. There was stress incontinence of various severities in nine (19.2%) patients at the 1-year follow-up. These patients were those who had stenosed urethral segments adjacent to the external sphincter. At the long-term follow-up < 10% of the patients had stress incontinence complaints.

Conclusion: Memotherm is a good treatment option in patients with recurrent bulbar urethral stricture of any cause.

Editorial Comment

We do not yet have a urethral stent that is ready for broad application. The authors describe their experience with Memotherm. This is a stent that contracts in cold water and expands after being placed in the urethra at body temperature. Removing it is fairly easy after irrigating the urethra with cold water. This is a big improvement over the Urolume stent which is very difficult to extract. Still the results reported herein show that there is still much room for improvement in the design of urethral stents, or that stents hold limited promise in urethral stricture management. Approximately half of the patients required secondary procedures for restenosis or "hyperplastic ingrowth" inside the stent. The true future of stents likely lies in drug-eluting stents or temporary stents acting as scaffolds for engineered tissue ingrowth.

Dr. Sean P. Elliott
Department of Urology Surgery
University of Minnesota
Minneapolis, Minnesota, USA
E-mail: selliott@umn.edu

NEUROLOGY & FEMALE UROLOGY

Long-term subjective results of tension-free vaginal tape operation for female urinary stress incontinence

Glavind K, Glavind E, Fenger-Grøn M
Department of Gynecology and Obstetrics, Aalborg Hospital, 9000, Aalborg, Denmark
Int Urogynecol J. 2011; 18. [Epub ahead of print]

Introduction and Hypothesis: The aim of the study was to evaluate the subjective outcome between 1 and 5 years after tension-free vaginal tape (TVT) operation and the need for follow-up.
Methods: A prospective questionnaire study was performed including questions about incontinence, urinary tract infection, emptying problems, the wish for a clinical control and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF).
Results: One hundred seventy-three patients were included. There were more patients with subjective recurrent stress incontinence over the years, but ICIQ-SF was unchanged. There was no rise in patients reporting urge incontinence over the years. Only 11.4% of the patients wished for a clinical control at some time.
Conclusion: The TVT operation showed a slight degree of subjective deterioration between 1 and 5 years after the operation; however, the ICIQ-SF was unchanged. There seems to be no need for long-term follow-up at the operating department.

Editorial Comment

This is an interesting paper by Glavind et al. aiming to show sustained results after TVT operation for treating female stress urinary incontinence (SUI) from 3 months up to 5 years of follow-up. Their idea is to question the need for such long follow-up.

They analyzed 173 patients and present an increase from 12.2% to 26.7% in recurrent SUI comparing 3 mo x 5 years results with an odds ratio (OR) of 1.38. A similar finding occurred for subjective complaints regarding difficulty to empty the bladder (8.6% to 26.7% for 3 mo and 5 years, respectively, with a yearly OR of 1.57). However, the drop out rate of 38% during long term follow-up seems unacceptably high (81 x 51 patients at 3 mo and 5 years). Despite this it is interesting to note that ICIQ-SF scores did not rise throughout time and only 11% of patients requested a clinical control over time. The authors conclude suggesting no need

for clinical control or postal questionnaires after a normal visit at 3 mo after surgery; as no patient presented a major complication or need for surgical revision following long term clinical control. I would point out this should be seen with caution as slow flow was reported by half of patients at 1 and 5 years of follow up and no objective exam was performed to diagnose a possible obstructive flow. Also, ICIQ-SF does not take this matter into account.

Dr. Ricardo Miyaoka
State University Campinas
Campinas, SP, Brazil
E-mail: rmiyaoka@uol.com.br

Are commonly used psychoactive medications associated with lower urinary tract symptoms?
Hall SA, Maserejian NN, Link CL, Steers WD, McKinlay JB
New England Research Institutes, 9 Galen St., Watertown, MA, 02472, USA
Eur J Clin Pharmacol. 2011; 4. [Epub ahead of print]

Purpose: Lower urinary tract symptoms (LUTS) such as urinary frequency and urgency are bothersome and associated with reduced quality of life. Atypical antipsychotics (AAPs) have been implicated in increasing the risk of urinary incontinence. In a large community-based sample of men and women, we examined the associations of AAP and selective serotonin reuptake inhibitor (SSRIs) use with LUTS.
Methods: Data were collected (2002-2005) from a generalizable sample of Boston, MA, USA, residents aged 30-79 (N = 5503). LUTS were assessed using the American Urologic Association Symptom Index (AUA-SI). The prevalence of clinically-significant LUTS was estimated using a cutoff AUA-SI score of 8+ to indicate moderate-to-severe symptoms. Confounder-adjusted odds ratios (ORs) and 95% confidence intervals (CI) were calculated from multivariate logistic regression to estimate the associations for psychoactive drugs used in the previous month (SSRIs, AAPs, both) and LUTS.
Results: Among women, AAP users had a higher prevalence of LUTS (46.2%) compared with SSRI users (23.5%) and those with depressive symptoms not using SSRIs or AAPs (26.3%). Corresponding prevalence estimates among men were 32.7%, 29.8%, and 33.3%. In multivariate models, AAP use was significantly associated with LUTS among women when used either with (OR = 2.72, 95% CI:1.45-5.10) or without (OR = 3.05, 95% CI:1.30-7.16) SSRIs, but SSRI use without AAP use was not associated with LUTS compared with non-users without depressive symptoms. No associations were observed among men.
Conclusions: In our study, AAPs but not SSRIs were associated with increased prevalence of LUTS among women only. Further prospective research is needed to determine time sequence and cause and effect.

Editorial Comment

The study by Hall and cols. aimed to analyze lower urinary tract symptoms (LUTS) in a restricted cohort establishing a possible influence of depressive symptoms and psychoactive drugs (namely antipsychotics and serotonin reuptake inhibitors- SSRIs). The analysis was controlled for age, gender, race/ethnicity, socioeconomic status, comorbidities and the presence of symptoms of depression. They conclude only atypical antipsychotic (AAP) agents show a correlation with LUTS and exclusively affecting women. It is suggested by authors that women may suffer a different psychological impact from depressive symptoms

and also may present a diverse metabolism than men. But whilst the reason why AAPs correlates with LUTS in women only remain obscure it is interesting to notice that SSRIs do not. As such, women under SSRIs treatment who present LUTS should be further investigated instead of having their therapy discontinued.

Dr. Ricardo Miyaoka
State University Campinas
Campinas, SP, Brazil
E-mail: rmiyaoka@uol.com.br

GERIATRIC UROLOGY

Prostate cancer in the elderly: Frequency of advanced disease at presentation and disease-specific mortality

Scosyrev E, Messing EM, Mohile S, Golijanin D, Wu G
Department of Urology, University of Rochester Medical Center, Rochester, New York
Cancer. 2011; 17. doi: 10.1002/cncr.26392. [Epub ahead of print]

Background: The objectives of this study were to determine the frequency of metastatic (M1) prostate cancer (PC) at presentation in different age groups, to examine the association of age with PC-specific mortality, and to calculate the relative contribution of different age groups to the pool of M1 cases and PC deaths.

Methods: Records from 464,918 patients who were diagnosed with PC from 1998 to 2007 were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. The patients were categorized according to age into groups ages < 50 years, 50 to 54 years, 55 to 59 years, 60 to 64 years, 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years, 85 to 89 years, and ≥ 90 years. The cumulative incidence of death from PC was computed using the Gray method.

Results: The frequency of M1 PC at presentation was 3% for the group aged < 75 years, 5% for the group ages 75 to 79 years, 8% for the group ages 80 to 84 years, 13% for the group ages 85 to 89 years, and 17% for the group aged ≥ 90 years. The 5-year cumulative incidence of death from PC was 3% to 4% for all patients with PC in any category aged < 75 years, 7% for patients ages 75 to 79 years, 13% for patients ages 80 to 84 years, 20% for patients ages 85 to 89 years, and 30% for patients aged ≥ 90 years. Although patients aged ≥ 75 years at PC diagnosis represented just over a quarter (26%) of all PC cases, they contributed almost half (48%) of all M1 cases and more than half (53%) of all PC deaths.

Conclusions: Compared with younger patients (aged < 75 years), older patients were more likely to present with very advanced disease, had a greater risk of death from PC despite higher death rates from competing causes, and contributed more than half of all PC deaths. Awareness of this issue may improve future outcomes for elderly patients with PC.

Editorial Comment

The recognition of the substantial contribution of older age groups to the pool of M1 cases and prostate cancer (PC) deaths is fundamental to advancement of its treatment and handling. In the presented study, although older patients did not lose as many years of life as younger patients because of shorter remaining life expectancy in the elderly, the proportion of remaining life lost in the elderly still was very high. While it is known that the death rates from competing causes are higher in the elderly, the absolute risk of death from PC increased with age.

In this scenario of cancer time line paralleling the human aging process there are many irrefutable biases acting on the numbers coming from population based studies such as lead time and selection biases, adding to those for treatment or tumor characteristics.

It is obvious that people that score higher ages are selected from population when they fail of perishing from many other conditions. Authors have speculated more aggressive disease (e.g., faster growing tumors) in the elderly and/or less frequent use of PSA testing and further diagnostic evaluation (such as biopsy for an elevated PSA) in older men compared with younger men. Furthermore, among a compilation of possible biases, two mechanisms were well recognized: 1) over diagnosis of nonaggressive PC in younger patients and 2) delay in diagnosis of aggressive disease in the elderly.

Until nowadays, PC natural history is complex and unpredictable in a large number of cases. The aging process will naturally culminate with death, and it is not surprisingly that virtually all cause of death will increase with age considering the cumulative co-morbidities and the innately decreasing functional status.

While it should be viewed with caution, better understandings of the aging process as well as prostate cancer natural history will add to the understanding of the illustrated scenario.

Dr. Leonardo Oliveira Reis
Assistant Professor of Urology
University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: reisleo@unicamp.br

Clinically relevant fatigue in men with hormone-sensitive prostate cancer on long-term androgen deprivation therapy

Storey DJ, McLaren DB, Atkinson MA, Butcher I, Frew LC, Smyth JF, Sharpe M
Edinburgh Cancer Research UK Centre, University of Edinburgh, Edinburgh
Ann Oncol. 2011; 17. [Epub ahead of print]

Background: The purpose of the study was to determine the prevalence and associations of clinically relevant fatigue (CRF) in men with biochemically controlled prostate cancer on long-term androgen deprivation therapy (ADT).

Patients and Methods: One hundred and ninety-eight men were surveyed and the prevalence of CRF (Brief Fatigue Inventory score > 3) determined. Associations with other measures (Hospital Anxiety and Depression Scale; International Prostate Symptom Score; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; Brief Pain Inventory worst pain; clinical and demographic information) were explored in univariate and multivariate analyses.

Results: Eight-one per cent (160 of 198) of questionnaires were analysable. CRF prevalence was 43% (68 of 160). CRF associations included moderate/severe urinary symptoms, anxiety and medical co-morbidities; the strongest associations were depression [odds ratio (OR) 9.8, 95% confidence interval (CI) 4.3-22.8] and pain (OR 9.2, 95% CI 4.0-21.5). After controlling for other factors, the independent associations were depression (OR 4.7, 95% CI 1.6-14.0) and pain (OR 3.1, 95% CI 1.0-8.9). There was no association with age, disease burden or treatment duration.

Conclusions: Two-fifths of men with biochemically controlled prostate cancer on long-term ADT report CRF that interferes with function. Management aimed at improving CRF should address depression and pain.

Editorial Comment

This study though based on a cross-sectional survey with small patient numbers restraining its power, adds to the limited literature concerning clinically relevant fatigue (CRF) in men with biochemically controlled prostate cancer on long term GnRH-based ADT.

The main findings were as follows:

- CRF prevalence in the sample was 43% (95% CI 35% to 50%) and the difference in scores between those with and without CRF far exceeded the 20 points described as a 'large' clinically significant;
- CRF was associated with moderate/severe pain, depression, anxiety, concurrent co-morbidities and moderate/severe urinary symptoms but the only independent associations of CRF were depression and pain.

Fatigue may be attenuated optimizing depression and pain treatments.

Dr. Leonardo Oliveira Reis
Assistant Professor of Urology
University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: reisleo@unicamp.br

PEDIATRIC UROLOGY

Surgical outcome in children undergoing hypospadias repair under caudal epidural vs penile block

Kundra P, Yuvaraj K, Agrawal K, Krishnappa S, Kumar LT
Department of Anaesthesiology & Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research (J.I.P.M.E.R), Pondicherry, India Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research (J.I.P.M.E.R), Pondicherry, India Department of Paediatric surgery, Jawaharlal Institute of Postgraduate Medical Education and Research (J.I.P.M.E.R), Pondicherry, India

Paediatr Anaesth. 2011; 29. doi: 10.1111/j.1460-9592.2011.03702.x. [Epub ahead of print]

Aim and Objective: To evaluate the effect of penile block vs caudal epidural on the quality of analgesia and surgical outcome following hypospadias repair.

Background: Intraoperative penile engorgement because of caudal epidural may result in tension on surgical sutures and alter surgical outcome.

Methods: Fifty-four ASA I and II children were randomly allocated to group P (penile block, 0.25% bupivacaine, 0.5 mg·kg (-1); n = 27) and group C (caudal epidural, 0.25% bupivacaine, 0.5 mL·kg (-1); n = 27), respectively. Quality of analgesia was assessed by visual analog scale (VAS) score recorded at 0, 0.5, 3, 6, 12, 24 h, and once a day for the next 4 days. Duration of analgesia was calculated from the institution of block to the first analgesic demand by child or VAS > 5. Total morphine consumption in the first 48 h and oral paracetamol consumption till 5th day were recorded. Children were regularly followed up in their respective outpatient clinic for early or late complications.

Results: In group P, lower mean VAS scores were seen from 0.5 h after surgery till day 3 and analgesia lasted for significantly longer duration (82 min) when compared with caudal epidural, $P < 0.001$. Incidence of urethral fistula formation after primary hypospadias repair was 19.2%, and all had received caudal epidural. An increase of 27% in penile volume from baseline value was observed 10 min after caudal epidural placement, $P < 0.05$.

Conclusion: Penile block provided better analgesia when compared with caudal epidural in children undergoing primary hypospadias repair. Postoperative urethral fistula formation was more likely in children who received caudal epidural.

Editorial Comment

This is a prospective randomized controlled trial comparing penile block with a caudal block for children undergoing hypospadias repair. They had 27 children in each group. Their patient population was older than most contemporary series with ages ranging from 4-12 years. Penile measurements were taken before and 10 minutes after the block in both groups. Breakthrough fentanyl was given for patients with increase in mean arterial pressure (MAP) or heart rate greater than 15% from baseline. Visual analogue scores were measured at various intervals over the course of 4 days. The authors found that pain scores were significantly worse in the group receiving the caudal block. In addition, changes in MAP and heart rate were significantly higher in the caudal group. This resulted in increased use of narcotics for the caudal block group. Five patients developed urethrocutaneous fistula. All of these patients were in the caudal group. The authors speculated that this may be due to the increase in penile volume that was seen in the caudal group but not observed in the penile block group.

Both penile and caudal blocks are used routinely for hypospadias repair. There is very limited data comparing the two in a prospective fashion as these authors have done. The decision of which type of regional anesthesia to perform is often based on the preference of the surgeon or anesthesiologist involved and over time a particular type of block simply becomes part of the culture of each individual institution. The authors only included patients with midshaft to distal hypospadias. Their fistula rate of nearly 20% seems high for a primary repair in such patients. It is interesting that all of these fistulas occurred in the caudal group. More prospective studies with greater numbers of patients would be helpful to improve our care for a common procedure.

Dr. M. Chad Wallis
Division of Pediatric Urology
University of Utah
Salt Lake City, Utah, USA
E-mail: chad.wallis@hsc.utah.edu

Effects of botulinum toxin type a in the bladder wall of children with neurogenic bladder dysfunction: a comparison of histological features before and after injections

Pascali MP, Mosiello G, Boldrini R, Salsano ML, Castelli E, De Gennaro M
Department of Nephro-Urology, Bambino Gesù Pediatric and Research Hospital, Piazza S. Onofrio 4, Rome, Italy
J Urol. 2011; 185(6 Suppl): 2552-7

Purpose: Botulinum toxin type A has gained popularity in urology. Most reported studies have been in adults at urology centers and most have addressed long-term safety. Since botulinum toxin type A treatment for neurogenic bladder dysfunction requires repeat injections, verifying that such treatment does not induce fibrosis in children seems essential.

Materials and Methods: The study was approved by the institutional review board and patients were enrolled after we obtained written consent. Patients with neurogenic bladder dysfunction not responding to conventional treatment (anticholinergics and clean intermittent catheterization) were treated with 10 IU/kg botulinum toxin type A up to a maximum of 300 IU. Endoscopic cold cup biopsies were obtained from the posterolateral bladder wall 1.5 to 2 cm above the ureteral orifice. Bladder wall findings were categorized into 3 groups, including inflammatory infiltration, edema and fibrosis. Each criterion was then graded as mild or severe and analyzed by Fisher's exact test ($p < 0.05$).

Results: A total of 46 bladder wall biopsies were obtained from 40 patients 2 to 18 years old. Biopsies were evaluated in groups 1 and 2, including group 1-20 from patients with no botulinum toxin type A injection and group 2-20 after botulinum toxin type A injection. Group 2 was subdivided into group 3-10 biopsies after 1 injection and group 4-10 after multiple injections. Six patients underwent biopsy twice, that is before the first and second treatments. Histological changes were present in all biopsies. When comparing groups 1 and 2, there was no statistically significant difference in inflammation and edema. However, there was a significant difference in fibrosis between groups 1 and 4 ($p < 0.05$) with apparently decreased fibrosis after multiple injections.

Conclusions: In our experience repeat botulinum toxin type A injections into the detrusor in children do not lead to increased fibrosis in the bladder wall. This study confirms the long-term safety of botulinum toxin type A in the pediatric population.

Editorial Comment

The use of Botox to manage neurogenic bladder dysfunction in the pediatric population has gained ground in recent years as a minimally invasive alternative to bladder augmentation. Much of our information about the use of Botox comes from studies in adult populations whose bladder pathology often differs from the congenital conditions seen in the pediatric population. Concerns have been raised about the long-term use of Botox and the possibility of inducing fibrosis due to repeated injections. The authors in this study performed biopsies in pediatric patients with neurogenic bladder dysfunction both before and after Botox injections. They excluded patients with prior bladder surgery, vesicoureteral reflux, or those with a symptomatic urinary tract infection in the three months prior to biopsy. They biopsied 40 patients total. 20 of these were biopsied prior to a Botox injection and 20 at the time of repeat injection, 10-14 months later. In the second group half of them were biopsied after having received multiple injections (up to 4). Follow-up was performed at three-month intervals following treatment.

In biopsies performed prior to any injection of Botox, the authors found that patients already had evidence of edema and inflammation as well as some baseline fibrosis. This was typically mild in nature. There were no statistically significant changes noted in the biopsies after injection of Botox. They did note that in the patients who were biopsied after multiple injections there did seem to be a decrease in the severity of fibrosis.

This is a small study with short-term follow-up, but it is certainly encouraging for those seeking an alternative to augmentation cystoplasty, at least in the short term. Questions still remain regarding long-term efficacy and side effects, particularly in the pediatric population. Further studies like this with longer follow-up and a greater number of patients will be valuable in clinical decision-making and counseling of patients and families.

Dr. M. Chad Wallis
Division of Pediatric Urology
University of Utah
Salt Lake City, Utah, USA
E-mail: chad.wallis@hsc.utah.edu

Video
International Braz J Urol
Vol. 37 (6): 802-803, November - December, 2011

Complex vesico-vaginal fistula repair with posterosuperior bladder flap

Enrique Rijo, Oscar Bielsa, J.A. Lorente, J.M. Gil-Vernet, Lluís Fumadó, Albert Francés, Octavio Arango

Department of Urology, Hospital del Mar, Barcelona - Universitat Autonòma de Barcelona, Spain

ABSTRACT

Introduction: Vesicovaginal fistulae (VVF) remain one of the most challenging problems in modern female urology.
VVF are classified as simple and complex. Complex fistulae are fistulae of large size (greater than or equal to 3 cm in diameter); those recurring after prior attempts at closure; those associated with a history of prior radiation therapy or with malignancy; those occurring in a compromised operative field owing to poor healing or host characteristics and those involving the trigone, bladder neck and/or urethra.
Materials and Methods: From November 1985 to September 2010, 58 cases of VVF were repaired at our institution with the Gil-Vernet technique, without the necessity of interposition of any autologous or heterologous material.
We present the case of a 44-year old woman with a previous history of cesarean, who presented with vaginal urine leakage after bladder injury with an initial attempt of primary closure during laparoscopic hysterectomy for uterine myoma.
This video describes the VVF repair using a autoplasty closure with posterosuperior vesical flap "The Gil-Vernet technique**.**
Results: In 99.41% cases closure of the fistula was achieved at the first surgical attempt.
Conclusion: In our experience, the Gil-Vernet technique has been successful in most cases and we recommend this technique for repair of complex VVF.

Int Braz J Urol. 2011; 37 (Video #6): 802_3
Available at: www.brazjurol.com.br/videos/november_december_2011/Rijo_802_803video.htm

Correspondence address:
Dr. Enrique Rijo
Universitat Autònoma de Barcelona
Department of Urology. Hospital del Mar
Passeig Maritim 25-29. Barcelona. Spain
Email: erijo@parcdesalutmar.cat

EDITORIAL COMMENT

In the video by Rijo et al., the authors highlight a specific procedure (Gil-Vernet Technique) for the repair of a vesicovaginal fistula (VVF) within a single institution case series. VVF is a subtype of female urogenital fistula (UGF) in which an abnormal fistulous tract extends between the bladder and the vagina with the continuous involuntary discharge of urine into the vaginal vault. In addition to the potential medical sequelae of such fistulas, they often have a profound effect on the patient's emotional well-being and quality of life. Hence, VVF's pose a significant source of morbidity for affected women, highlighting the importance of managing this pathology using a highly successful and ideally minimally invasive technique. Techniques used to repair VVF have been well described within the peer reviewed scientific literature and the current video focuses on a contemporary approach. The authors submit a video pertaining to one of their cases treated in this fashion. The video is comprehensive and highlights the major pivotal points critical in a successful repair. This video nicely depicts how this surgical procedure can be conducted with successful correction of the underlying pathology.

Dr. Rafael E. Carrion
Associate Professor of Urology
Department of Urology
USF Health College of Medicine
Tampa, Florida, USA
E-mail: rcarrion@health.usf.edu

International Braz J Urol

REVIEWERS - YEAR 2011

The Editors of the International Braz J Urol acknowledge in deep the following 204 experts, from 34 different countries, who contributed to the peer-review process, reviewing articles and/or making editorial comments during the year 2011.

1. Friedrich Aigner, (Austria)
2. Fernando Gonçalves de Almeida, (Brazil)
3. Ronaldo Alvarenga Álvares, (Brazil)
4. João Luiz Amaro, (Brazil)
5. Sero Andonian, (Canada)
6. Alberto Azoubel Antunes, (Brazil)**
7. M. H. Ather, (Pakistan)
8. Riccardo Autorino, (Italy)
9. Marcio Averback, (Brazil)***
10. Ubirajara Barroso Jr., (Brazil)*
11. Kurdo Barwari, (The Netherlands)
12. Lucas Teixeira Batista, (Brazil)
13. Ricarda M. Bauer, (Germany)*
14. Antonio Lopez-Beltran, (Spain)
15. Milton Berger, (Brazil)
16. Eduardo Bertero, (Brazil)
17. José de Bessa Jr., (Brazil)
18. AthanaseBillis, (Brazil)***
19. Andreas Boehle, (Germany)***
20. Edson Borges Jr., (Brazil) *
21. Francisco Botelho, Portugal
22. Stefan Candefjord, (Sweden)
23. Onder Canguven, (Turkey)
24. Serge Carrier, (Canada)
25. Arlindo Monteiro de Carvalho Jr., (Brazil)*
26. João P. Martins de Carvalho, (Brazil)
27. Marcelo F. Cassini, (Brazil)
28. Lísias Nogueira Castilho, (Brazil)*
29. Andre Guilherme Cavalcanti, (Brazil)
30. K. Ceylan, (Turkey)
31. Benjamin Challacombe, (United Kingdom)
32. Michael Chancellor, (USA)
33. David Y. Chen, (USA)
34. Liang Cheng, (USA)
35. Boris Chertin, (Israel)
36. Ben Chew, (Canada)
37. Anthony NG Chi-fai, (Hong Kong)
38. Kazim R. Chohan, (USA)
39. Otávio Clark, (Brazil)**
40. Jose Jaime Correa, (Colombia)*
41. Alexandre Crippa, (Brazil)
42. Marcos F. Dall'oglio, (Brazil)**
43. Marco De Sio, (Italy)**
44. Francisco Tibor Dénes, (Brazil)
45. Aderivaldo Cabral Dias Filho, (Brazil)
46. Pasquale Ditonno, (Italy)
47. Sean P. Elliott, (USA) ***
48. Ahmed I. El-Sakka, (Egypt)
49. J. I. Epstein, (USA)
50. Fernando Facio, (Brazil)
51. Eliney Ferreira Faria, (Brazil)*
52. Sandro Faria, (Brazil)*
53. Fábio Tadeu Ferreira, (Brazil)***
54. Alexandre Fornari, (Brazil)**
55. Renato Fraietta, (Brazil)**
56. Ferdinand Frauscher, (Austria)
57. Marcos Freire, (Brazil)*
58. Mark Frydenberg, (Australia)
59. E. García-Cruz, (Spain)
60. Ibrahim Fathi Ghalayini, (Jordan)
61. Peter Gilling, (New Zealand)
62. Stefano Giuliani, (USA)
63. A. Gomelsky, (USA)
64. Cristiano Mendes Gomes, (Brazil)
65. Stavros Gravas, (Greece)**
66. Tulio Grazziotin, (Brazil)
67. Philippe Grise, (France)
68. Ethan D. Grobera, (Canada)
69. Shilpa Gupta, (USA)
70. T. Hajdinjak, (Slovenia)*

71. Jorge Hallak, (Brazil)
72. Noboru Hara, (Japan)
73. Giles O. Hellawell, (United Kingdom)
74. Flavio Luís O. Hering, (Brazil)
75. Christiaan F. Heyns, (South Africa)
76. Sarah A. Hosgood, (United Kingdom)
77. Kenneth Iczkowski, (USA)
78. Efthimiou Ioannis, (Greece)*
79. Steven Joniau, (Belgium)
80. Ates Kadioglu, (Turkey)
81. Abdol-Mohammad Kajbafzadeh, (Iran)
82. Wassim Kassouf, (Canada)*
83. Chris Keto, (USA)
84. Ozgur Kilickesmez, (Turkey)
85. Fernando J. Kim, (USA)***
86. Wachira Kochakarn, (Thailand)
87. Paul J. Kokorowski, (USA)
88. Stamatiou Konstantinos, (Greece)
89. Walter Krause, (Germany)
90. Rodrigo Krebs, (Brazil)
91. Hann Chorng Kuo, (Taiwan)
92. Francisco G. La Rosa, (USA)
93. D. Dirk Lang, (Canada)
94. Erich K. Lang, (USA)**
95. Massimo Lazzeri, (Italy)*
96. Angus T. Lecuona, (South Africa)
97. Kátia Ramos Moreira Leite, (Brazil)**
98. Salvador Vilar Correia Lima, (Brazil)*
99. Bannakij Lojanapiwat, (Thailand)
100. Fábio Lorenzetti, (Brazil)
101. Nicolaas Lumen, (Germany)
102. Antonio Macedo Jr., (Brazil)*
103. João Pádua Manzano, (Brazil)
104. Aaron D. Martin, (USA)
105. Eduardo Mastalir, (Brazil)
106. Hitoshi Masuda, (Japan)*
107. Edward D. Matsumoto, (Canada)
108. Jane Mattei, (USA)
109. Evangelos M. Mazaris, (Greece)*
110. Mohammad Mohsen Mazloomfard, (Iran)
111. Eduardo Mazzucchi, (Brazil)
112. Fernando Meyer, (Brazil)
113. V. A. Mezentsev, (United Kingdom)*
114. Roberto Miano, (Italy)
115. Andrea Minervini, (Italy)*
116. Valérie Mitchell, (France)
117. Anuar Ibrahim Mitre, (Brazil)
118. Ricardo Miyaoka, (Brazil)***
119. Chinedu Mmeje, (USA)
120. Wilson Molina, (USA)
121. Manoj Monga, (USA)***
122. Dan Moreira, (USA)
123. Teemu J. Murtola, (Finland)**
124. Kurt G. Naber (Germany)
125. William Nahas, (Brazil)
126. Ricardo Akiyoshi Nakamura, (Brazil)
127. Ricardo Natalin, (Brazil)*
128. Armando Luis Negri, (Argentina)
129. M. Neuman, (Israel)
130. Hiep T. Nguyen, (USA)
131. Vladimir Novotny, (Germany)
132. Valerie Odero-Marah, (USA)
133. Antonio A. Ornellas, (Brazil)*
134. Valdemar Ortiz, (Brazil)
135. Cristiano Paiva, (Brazil)
136. Athanasios Papatsoris, (United Kingdom)
137. Dong Soo Park, (South Korea)
138. Anup Patel, (United Kingdom)*
139. Stephen E. Pautler, (Canada)
140. Renato Nardi Pedro, (Brazil)*
141. Antonio Cassio Assis Pellizzon, (Brazil)
142. Vitor Pintarelli, (Brazil)
143. Cristiane Paim Pires, (Brazil)
144. P. Nick Plowman, (United Kingdom)
145. Antonio Pompeo, (Brazil)
146. Steven P. Petrou, (USA)***
147. Adilson Prando, (Brazil)***
148. J. Puig, (Spain)
149. David E. Rapp, (USA)
150. Hassan Razvi, (Canada)
151. Rodolfo Borges dos Reis, (Brazil)
152. Leonardo Oliveira Reis, (Brazil)***
153. Y. Reisman, (The Netherlands)*
154. Mesut Remzi, (Austria)
155. S. Resim, (Turkey)
156. Ernani Rhoden, (Brazil)**
157. Jonathan C. Routh, (USA)
158. Mauricio Rubinstein, (Brazil)*
159. Aly Saber, (Egypt)
160. Marcos V. Sadi, (Brazil)*

REVIEWERS - YEAR 2011

161. Julio Pow Sang, (USA)
162. Marair Sartori, (Brazil)
163. Daniel Seabra, (Brazil)*
164. Silvia Secco, (Italy)
165. Avishay Sella, (Israel)
166. Selim Serter, (Turkey)
167. Wade J. Sexton, (USA)**
168. Hiroki Shima, (Japan)
169. Avraham Shtricker, (Israel)
170. Grahame H. H. Smith, (Australia)
171. Philippe E. Spiess, (USA)**
172. Roberto Soler, (Brazil)
173. José Carlos Stumpf Souto, (Brazil)
174. Shalom J. Srirangam, (United Kingdom)
175. Yoshiki Sugimura, (Japan)
176. José Tadeu Nunes Tamanini, (Brazil)**
177. F. Cahit Tanyel, (Turkey)
178. Seppo Taskinen, (Finland)
179. Heidar Tavilani, (Iran)**
180. David D. Thiel, (USA)
181. Hsu Ting, (China)
182. Marcos Tobias-Machado, (Brazil)**
183. Claudemir Trapp, (Brazil)
184. José Carlos Truzzi, (Brazil)**
185. Matvey Tsivian, (USA)
186. Rainy Umbas, (Indonesia)**
187. Robert Guy Uzzo, (USA)
188. George Vaos, (Greece)
189. Vijaya Vemulakonda, (USA)
190. Charles Alberto Villacorta, (Brazil) ***
191. Carlos Villanueva, (USA)
192. Geert M. Villeirs, (Belgium)
193. M. Chad Wallis (USA)***
194. C. Wang, (USA)
195. Andreas H. Wille, (Germany)*
196. Henry H. Woo, (Australia)
197. Marcelo Wroclawski, (Brazil)
198. Sérgio Ximenes, (Brazil)
199. Claire C. Yang, (USA)
200. Asif Yildirim, (Turkey)
201. M. Youssif, (Egypt)
202. Alon Zadokweizer, (USA)*
203. Stefan Zastrow, (Germany)
204. Stênio de Cássio Zequi, (Brazil)*

The names marked with asterisks refer to the most active reviewers. Reviewers with one asterisk (*) reviewed three or more manuscripts or made Editorial Comments, reviewers with two asterisks (**) reviewed five or more manuscripts, and reviewers with three asterisks (***) reviewed more than eight manuscripts during the year 2011.