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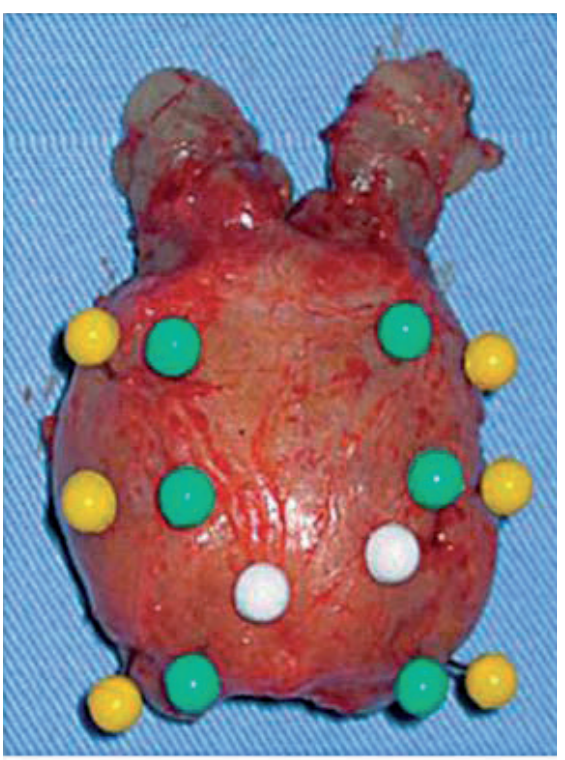

Extended prostate biopsy on the bech (Page 565)

XXXI Brazilian Congress of Urology
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EDITOR'S COMMENT

Extended Prostate Biopsy

The September – October 2008 issue of the International Braz J Urol presents interesting contributions from many different countries, and as usual, the editor's comment highlights some papers.

Doctor Nesrallah and co-workers, from University of Sao Paulo Medical School, Brazil, compared on page 563 the advantage of performing prostate biopsy with a greater number of cores using the classic sextant procedure. The authors obtained 100 prostates from consecutive radical prostatectomies performed by the same surgeon. Fourteen cores were obtained on the bench following surgery using an automatic pistol with an 18-gauge needle. Six of these cores were obtained according to the sextant technique, as classically described, and additionally three lateral cores from each lobe and one from the bilateral transition zone were also obtained. An analysis of the frequency of the cancers identified in the cores of the sextant and the extended biopsies was undertaken by the same pathologist and the results were evaluated comparatively. The authors found that when 6 cores were removed, the positive cancer rate was 75%, which was increased to 88% when 14 cores were obtained ($p < 0.001$). They concluded that extended biopsy, with the removal of 14 cores, is more efficient than the sextant procedure in improving the rate of prostate cancer detection. Dr. Brian J. Moran, from Chicago Prostate Center, Westmont, Illinois, USA, provided editorial comment on this article.

Doctor Navai and colleagues, from Northwestern University, Chicago, Illinois, USA, presented on page 594 a single institutional experience of intra and postoperative complications following urethral reconstructive surgery, and the impact of these complications on overall results. After 153 consecutive urethral reconstructive procedures performed on 128 patients by the same surgeon, the complication rates were determined. Overall, the authors found in 23 of 153 cases (15%) an intra or postoperative complication with a mean follow-up time of 28.3 months. They concluded that complications following reconstructive surgery for urethral stricture disease were mostly related to infection or repair breakdown in the immediate postoperative period. It does not appear that an intra or postoperative complication following urethral reconstructive surgery impacts the chance of eventual stricture recurrence at intermediate follow-up. Dr. Antonio Macedo Jr, from Federal University of São Paulo, Brazil and Dr. Sean P. Elliott, from University of Minnesota, Minneapolis, MN, USA, provided critical editorial comments on this article.

Doctor Mousavi, from Mazandaran University of Medical Sciences, Sari, Iran, presented on page 609 his experience with tubularized incised plate (TIP) urethroplasty in re-operative hypospadias repairs or repair in circumcised children. After reviewing 17 children referred for hypospadias re-operation, he found 4 (30.7%) complications of TIP re-operation, being 2 meatal stenosis, one stenosis with small fistula and one dehiscence. Re-operation was necessary in only one patient. The author concluded that TIP urethroplasty is

a suitable method for treating primary and re-operative cases. It can also be used successfully in patients, who do not have a healthy skin flap and in circumcised patients when there is a lack of foreskin. Interesting editorial comments on this work were provided by Dr. Marco Castagnetti, from University Hospital of Padova, Italy, Dr. Alchiede Simonato & Dr. Matteo Orlandini, from University of Genoa, Italy, Dr. Kimihiko Moriya, from Hokkaido University Graduate School of Medicine, Sapporo, Japan, and Dr. Maike Beuke, from Asklepios-Klinik Harburg, Germany.

Doctor D. Kyriazis and collaborators, from University Hospital of Heraklion, Greece, and Freie Universitaet Berlin, Germany, reviewed and evaluated on page 617 the anatomical definitions of perinatal extravaginal torsion (EVT) of the testis. They made an extensive review of the literature and analyzed the appearance of twisted testes obtained during surgery for 14 cases of EVT. They found that the most commonly accepted suggestions describe an EVT within dartos muscle that includes all layers of spermatic cord or an EVT outside parietal layer of tunica vaginalis within internal spermatic fascia. However, both of them were found inadequately documented, while a large volume of controversial data has been accumulated, that raises doubts regarding the validity of such definitions. The gross appearance of twisted testes failed to confirm both an EVT including all layers of the spermatic cord and also an EVT outside tunica vaginalis as possible mechanisms of torsion. Dr. Francisco Tibor Dénes, from University of Sao Paulo, Brazil, Dr. Feilim Murphy, from St George's Hospital, London, UK and Dr. Ahmed H. Al-Salem, Maternity and Children Hospital, Dammam, Saudi Arabia, provided interesting editorial comments on this manuscript.

Doctor Hendlin and Monga from University of Minnesota, Minneapolis, MN, USA, analyzed on page 546 the ability of percutaneous balloons to expand under different radial constrictive forces. Three 30F nephrostomy balloons were tested: Bard X-Force™, Boston Scientific Microvasive Amplatz Tractmaster™, and Cook Ultraxx™. With a super stiff guidewire in place, the balloon tip was secured by elevated vice grips on either side of the balloon. The authors found that all balloons were unable to reach 90% of their expected diameter with larger constrictive loads. Only the Bard and Cook balloons reached at least 90% of the expected diameter. Our reviewers provided editorial comments on this on the bench work.

Doctor Basok and colleagues, from Istanbul Goztepe Training and Research Hospital, Turkey, evaluated on page 577 the outcome of bipolar energy by using PlasmaKinetic™ cystoscope instruments in the treatment of urethral stricture and bladder neck contracture. After studying 22 male patients with urethral stricture and 5 with bladder neck contracture treated by endoscopic bipolar vaporization, they found a success rate of 77% for urethral stricture at mean follow-up time of 14.2 months and 60% for bladder neck contracture with a mean follow-up time of 12.2 months. They conclude that it could be considered as a new therapeutic option for the endoscopic treatment of urethral stricture and bladder neck contracture. Dr. A. Abou-Elela, from Cairo University, Nasr City, Egypt and Dr. Massimo Lazzeri, from Casa di Cura Santa Chiara, Firenze, Italy, provided balanced editorial comment on this article.

Francisco J.B. Sampaio, M.D.
Editor-in-Chief

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Radial Dilation of Nephrostomy Balloons: A Comparative Analysis

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ABSTRACT

Purpose: The dynamics of percutaneous balloon expansion may differ with increasing extrinsic compressive forces and increasing inflation pressures. This study compares the ability of percutaneous balloons to expand under different radial constrictive forces.
Materials and Methods: Three 30F nephrostomy balloons were tested: Bard X-Force™, Boston Scientific Microvasive Amplatz Tractmaster™, and Cook Ultraxx™. With a super stiff guidewire in place, the balloon tip was secured by elevated vice grips on either side of the balloon. A string was wrapped around the balloon center once, and incremental increases in load were added (2g, 42g, 82g, and 122g) to represent increasing extrinsic compression. The balloon was inflated with a contrast agent and circumference changes were measured at increments of 4 ATM, 10 ATM, and burst pressure. Balloons were tested in triplicate for each load.
Results: All balloons were unable to reach 90% of their expected diameter with larger constrictive loads (122g) at low (4 ATM) and nominal (10 ATM) inflation pressures. Only the Bard and Cook balloons reached at least 90% of the expected diameter with a coefficient of variance (CV) less than 10% at burst pressure under the larger constrictive load (122g), 94.3% ± 6.7%, CV 7.1% and 96.3% ± 2.9%, CV 3.0% respectively. All balloons performed well under low constriction forces and reached at least 80% of the expected diameter by 10 ATM under all constrictive loads.
Conclusions: The Bard X-Force and Cook Ultraxx percutaneous nephrostomy balloons achieved the most reliable radial dilation against large constrictive forces simulating fascial or retroperitoneal scar tissue.

Key words: *balloon dilation; percutaneous nephrolithotomy; renal calculi*
Int Braz J Urol. 2008; 34: 546-54

INTRODUCTION

Percutaneous renal access is an important component of many complex procedures including stone extraction, antegrade endopyelotomy, and resection of transitional cell carcinoma of the upper urinary tract. The choice of nephrostomy tract dilation technique is significant in minimizing the risk of complications such as blood loss and perforation of the collecting system. Approaches to percutaneous nephrostomy tract dilation have included serially introduced, progressive fascial dilators, Amplatz dilator sets, metal coaxial dilators and high pressure balloons. Balloon systems have recently become the instrument of choice as they allow for one-step dilation, minimized total operative and fluoroscopic time, and reduced risk of hemorrhage in comparison to other methods of tract dilation (1-3). It has been proposed that the lateral compressive forces produced by the balloons are less traumatic and thereby minimize complications in comparison to the angular shearing forces exerted by successive dilation methods (1,4).

The dynamics of percutaneous balloon expansion may differ with increasing extrinsic compressive forces and increasing inflation pressures. This study

Table 1 *– Percutaneous nephrostomy balloons tested.*

Balloon	**Inflated Diameter** (mm)	**Length** (cm)	**Burst Pressure** (ATM)
Bard X-Force™	10	15	30
Cook Ultraxx™	10	15	20
BSM TractMaster™	10	12	17

compares the ability of several percutaneous balloons to expand under different radial constrictive forces.

MATERIALS AND METHODS

Three 30 Fr nephrostomy balloons were tested: Bard X-Force™ (Bard, Covington, GA) Boston Scientific Microvasive Amplatz Tractmaster™ (Boston Scientific, Natick, MA), and Cook Ultraxx™ (Cook Urological, Spencer, IN) (Table-1). Testing methods used were the same as those used to test commercially available ureteral balloons (5). The initial circumference, prior to any inflation, was measured at the balloon center. With a super stiff guidewire in place, the balloon tip was secured by elevated vise grips on either side of the balloon (Figure-1). A small plastic bag for adding radial load was attached to a string, which was wrapped around the balloon once and then secured so that the bag was hanging between the vice grips and centered beneath the balloon. A ruler measuring 1/100th of an inch was secured vertically to the ledge directly behind the center of the balloon. Contrast solution was mixed in a 1:1 ratio with water. A Cook inflation device (Patent no. 5,860,955) was used to inject contrast solution into the balloon inflation port. Pressure was increased and the change in balloon circumference was recorded at pressures of 4 ATM, 10 ATM and burst pressure. Balloons were tested three times consecutively for each radial load of 2g, 42g, 82g, and 122g. These loads were selected to evaluate balloon performance through a range of simulated constrictive forces. These constrictive forces have previously been demonstrated to be effective at eliciting differences in balloon performance for ureteral balloons (5). Statistical comparisons were performed using 95% confidence intervals, ANOVA, and one-sample t-tests compared to 100% inflation diameter per manufacturer. A p value < 0.05 was considered statistically significant. Results were reported as coefficient of variance (%), mean (%) ± standard deviation (%).

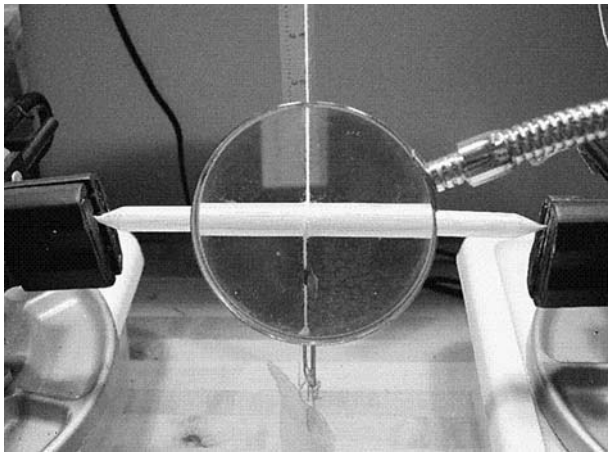

Figure 1 *– Test set-up.*

RESULTS

All balloons were unable to reach 90% of their expected diameter with larger constrictive loads (122g) at low (4 ATM) and nominal (10 ATM) inflation pressures (Figure-2 and Figure-3). Only the Bard X-Force™ and Cook Ultraxx™ balloons reached at least 90% of the expected diameter with a coefficient of variance (CV) less than 10% at burst pressure under the larger constrictive load (122g), (94.3% ± 6.7%, CV 7.1% and 96.3%% ± 2.9%, CV 3.0% respectively) (Figure-4) (Table-2).

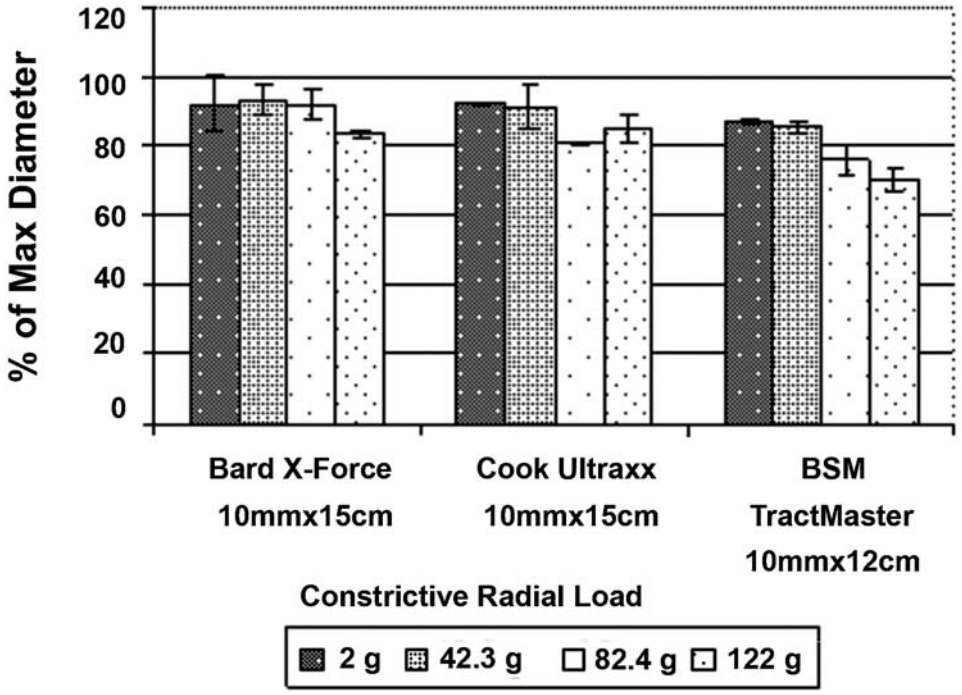

Figure 2 *– Balloon dilation at 4 ATM.*

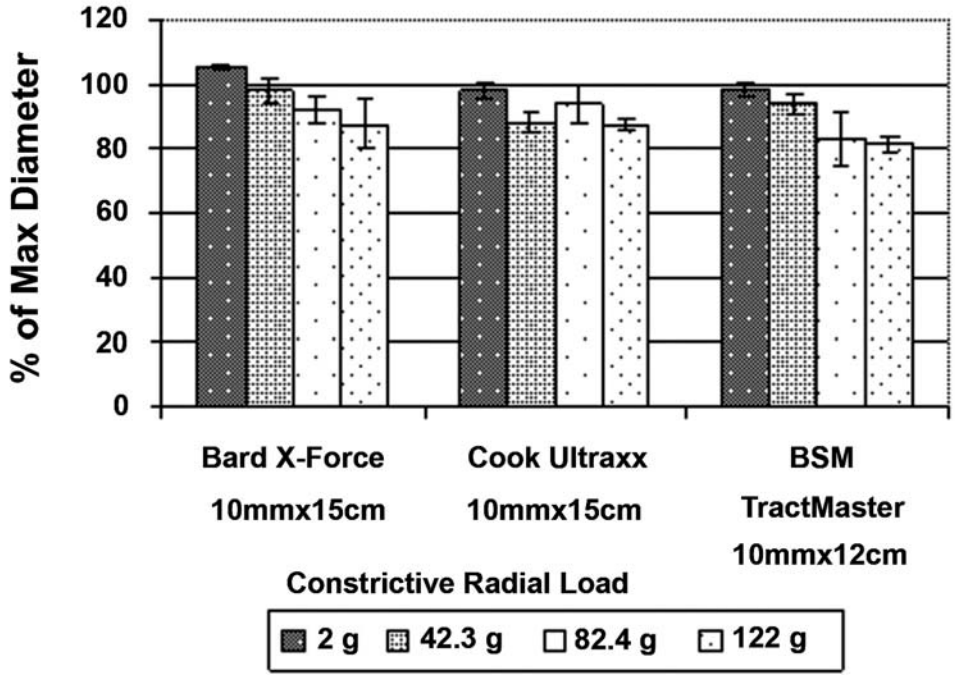

Figure 3 *– Balloon dilation at 10 ATM.*

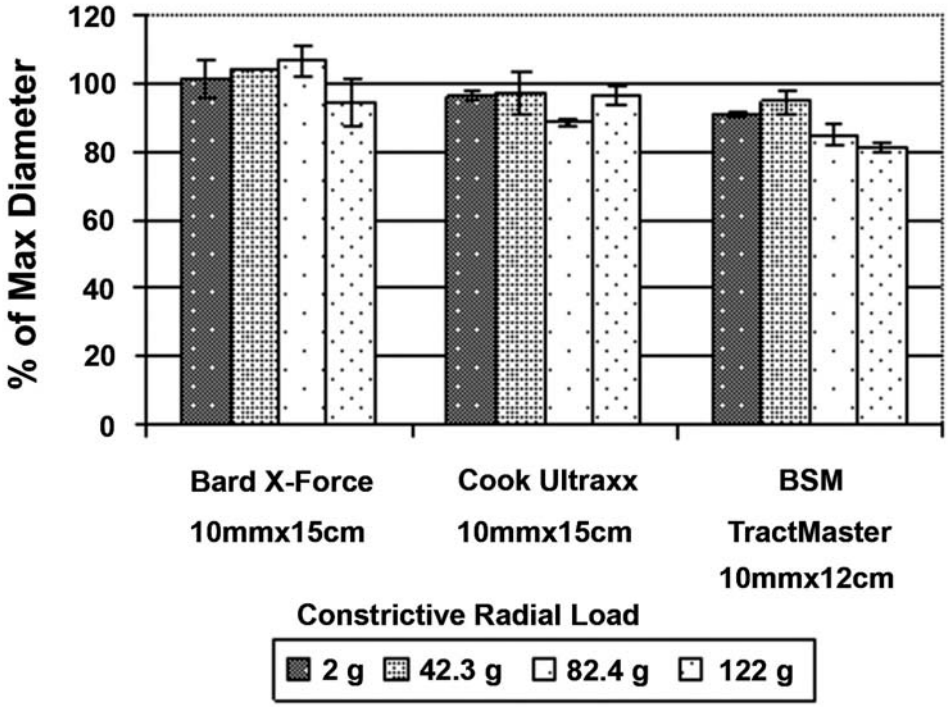

Figure 4 – *Balloon dilation at burst pressure.*

All balloons performed well under low constriction forces and reached at least 80% of the expected diameter by 10 ATM under all constrictive loads. Overall, the 95% confidence intervals for each pressure over all loads were not significantly different (Table-3). The ANOVA comparisons between the 3 balloons for each pressure and load were not statistically significant (Table-2). When compared to the anticipated inflated balloon diameter as stated per the manufacturer, all balloons performed radial dilation notably less than expected for all constrictive loads at low pressure, 4 ATM, $p < 0.02$. However, radial dila-

Table 2 – *Average coefficient of variance (CV, %) at 4 ATM, 10 ATM and burst pressure for each constrictive load and ANOVA comparisons.*

	Coefficient of Variance (%)											
	4 ATM				10 ATM				Burst Pressure			
Balloon	2g	42.3g	82.3g	122g	2g	42.3g	82.3g	122g	2g	42.3g	82.3g	122g
Bard X-Force™ 10mm x 15cm	8.40	4.45	4.39	1.12	0.80	4.12	4.40	8.58	5.60	0.00	4.37	7.13
Cook Ultraxx™ 10mm x 15cm	0.50	6.89	0.58	4.75	2.40	3.69	6.34	2.13	1.50	6.30	1.39	3.03
BSM TractMaster™ 10mm x 12cm	0.90	1.97	5.32	4.77	2.10	3.11	10.19	3.19	0.90	3.24	3.84	1.52
ANOVA (p Value)	0.70	0.67	0.95	0.95	0.94	0.85	0.68	0.59	0.85	0.82	0.97	0.91

Table 3 *– Average 95% confidence intervals for each pressure across all loads.*

	95% Confidence Intervals	
4 ATM	Average Lower	Average Upper
Bard X-Force™ 10mm x 15cm	78.1	104.3
Cook Ultraxx™ 10mm x 15cm	78.8	95.9
BSM TractMaster™ 10mm x 12cm	72.3	87.4
10 ATM	Average Lower	Average Upper
Bard X-Force™ 10mm x 15cm	83.5	108.5
Cook Ultraxx™ 10mm x 15cm	81.8	102.3
BSM TractMaster™ 10mm x 12cm	77.0	101.4
Burst Pressure	Average Lower	Average Upper
Bard X-Force™ 10mm x 15cm	89.5	115.7
Cook Ultraxx™ 10mm x 15cm	85.8	103.5
BSM TractMaster™ 10mm x 12cm	81.7	94.4

tion was significantly closer to the projected inflated balloon diameter at 10 ATM under lower constrictive forces (2 and 42.3g, $p > 0.5$) but not for higher constrictive forces (82.4-122g, $p < 0.04$). All balloons were best able to reach the expected inflated balloon diameter for all constrictive forces at burst pressure, $p > 0.05$.

COMMENTS

The ability to obtain optimal percutaneous access is critical with respect to percutaneous nephrolithotomy (PCNL)-related complications including blood loss. Overall, technical success rates have been shown to be higher with fewer complications when access is obtained by a urologist versus an interventional radiologist (6). In particular, loss of tract access and pelviocalyceal tears can lead to excessive bleeding and blood transfusion. While most PCNL-related bleeding can be managed conservatively, up to 6% of patients require a blood transfusion (6).

Clinical and animal studies have shown similar blood loss, renal damage, and chronic renal function changes when comparing Amplatz and balloon dilation systems under a single puncture setting (2,7). Moreover, histological similarities between the acute and chronic effects on the renal parenchyma suggest that the choice of dilatation can be based on physician preference (8). However, each method has potential benefits. Balloon systems can be accurately placed minimizing the risk of creating a false passage, are quick to use, and provide compressive hemostasis (2,3,7-10). Balloon dilation is considered to be the safest method of percutaneous tract dilation with proper placement and use (1-3,7,11). Radial dilation results in less renal movement away from the surgeon compared to longitudinal shearing forces as seen with other methods of track dilation. In addition, the minimization of tissue trauma and the pressure tamponade effect of the balloon may decrease blood loss.

However, balloon dilation is not able to create sufficient renal access in all patients. Joel et al. found balloon failure to occur in 17% of patients overall, including a 25% risk of failure in patients with a history of prior renal surgery compared to 8% of patients with no prior history (12). In addition, stone burden, patient body mass index (BMI), and history of pyelonephritis were not shown to be predictors for balloon failure (12).

Manual balloon inflation allows for controlled incremental changes in pressure; yet, this does not correlate with proportional changes in balloon diameter as we have shown in our study. Pressures of 4 to 5 ATM are typically sufficient to dilate a nephrostomy tract in patients with no prior renal surgery while higher pressures are necessary

to achieve full dilation in those with a history of renal surgery due to retroperitoneal scar tissue (13). During balloon inflation, a characteristic "waist" will appear in areas of high resistance such as the renal capsule or a previous operative scar (14). The amount of force required to eliminate the waist will vary according to the degree of resistance and must exceed the resistance according to Newton's second law. Even so, this limiting force threshold may not be obtainable at full inflation. The uniaxial nature of the applied force during balloon inflation maximizes the net force in the direction of radial dilation in comparison to other dilator systems where dispersion of forces limit effectiveness under the same net force and are also subject to a friction force, or drag.

In this situation of significant perirenal or renal fibrosis or scarring, Metal Alken dilators and fascial dilators tend to be more effective than high pressure balloons (13-15). It is feasible that the newly developed balloon dilators with a burst pressure of 30 ATM may be successful in these situations. Other potential downsides to using balloon dilation include high cost, fixed length, and lack of effectiveness in the face of dysmorphic body habitus or severe fibrosis (14).

During our previous years of experience with the Boston Scientific Trackmaster™ we had noted that in approximately 5-10% of procedures, we would need to convert to use of an Amplatz dilator set due to persistent waisting of the balloon after full-inflation. Since completing this study, we have successfully performed 60 PCNL procedures with the use of the Bard X-Force™ without any failures.

CONCLUSIONS

From the individual percutaneous balloons tested, the Bard X-Force™ and Cook Ultraxx™ percutaneous balloons were found to be superior to the Boston Scientific Amplatz Tractmaster™ balloon with regards to radial dilation consistently closer to the expected diameter of the inflated balloon and better able to achieve reliable radial dilation against large constrictive forces simulating fascial or retroperitoneal scar tissue. However we note that intra-balloon variation in performance was not tested in this study. In vitro testing such as this may help select the appropriate clinical tool.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Davidoff R, Bellman GC: Influence of technique of percutaneous tract creation on incidence of renal hemorrhage. J Urol. 1997; 157: 1229-31.
2. Kukreja R, Desai M, Patel S, Bapat S, Desai M: Factors affecting blood loss during percutaneous nephrolithotomy: prospective study. J Endourol. 2004; 18: 715-22.
3. Safak M, Gögüş C, Soygür T: Nephrostomy tract dilation using a balloon dilator in percutaneous renal surgery: experience with 95 cases and comparison with the fascial dilator system. Urol Int. 2003; 71: 382-4.
4. Goharderakhshan RZ, Schwartz BF, Rudnick DM, Irby PB, Stoller ML: Radially expanding single-step nephrostomy tract dilator. Urology. 2001; 58: 693-6.
5. Hendlin K, Lund B, Dockendorf K, Ramani A, Monga M: Radial dilation of ureteral balloons: comparative in vitro analysis. J Endourol. 2005; 19: 575-8.
6. Lashley DB, Fuchs EF: Urologist-acquired renal access for percutaneous renal surgery. Urology. 1998; 51: 927-31.
7. Clayman RV, Elbers J, Miller RP, Williamson J, McKeel D, Wassynger W: Percutaneous nephrostomy: assessment of renal damage associated with semi-rigid (24F) and balloon (36F) dilation. J Urol. 1987; 138: 203-6.
8. Al-Kandari AM, Jabbour M, Anderson A, Shokeir AA, Smith AD: Comparative study of degree of renal trauma between Amplatz sequential fascial dilation and balloon dilation during percutaneous renal surgery in an animal model. Urology. 2007; 69: 586-9.
9. Stoller ML, Wolf JS Jr, St Lezin MA: Estimated blood loss and transfusion rates associated with percutaneous nephrolithotomy. J Urol. 1994; 152: 1977-81.
10. Roth RA, Beckmann CF: Complications of extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy. Urol Clin North Am. 1988; 15: 155-66.
11. Zagoria RJ, Dyer RB: Do's and don't's of percutaneous nephrostomy. Acad Radiol. 1999; 6: 370-7.

12. Joel AB, Rubenstein JN, Hsieh MH, Chi T, Meng MV, Stoller ML: Failed percutaneous balloon dilation for renal access: incidence and risk factors. Urology. 2005; 66: 29-32.
13. McDougall EM, Liatsikos EN, Dinlenc CZ, Smith AD: Percutaneous Approaches to the Upper Urinary Tract. In: Alan M, Retik B, Darracott Vaughan JE, Wein J (ed.), Campell's Urology, 8th ed, Vol. 4. Philadelphia, WB Saunders. 2002; pp. 3320-60.
14. Press SM, Smith AD: Dilation of the Nephrostomy Tract: Use of Plastic Malleable Dilators - Amplatz System. In: Smith AD (ed.), Controversies in Endourology. Philadelphia, Pennsylvania. 1995; pp. 51-9.
15. Miller NL, Matlaga BR, Lingeman JE: Techniques for fluoroscopic percutaneous renal access. J Urol. 2007; 178: 15-23.

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EDITORIAL COMMENT

The authors compare the characteristics of three balloon dilators used to achieve tract dilation in percutaneous nephrostolithotomy from three different manufacturers. An elegant experimental model was used to check the variation in balloon circumference with different pressures against constrictive loads that simulated fascial resistance. It has been extensively shown that balloon fascial dilation is less time consuming and results in less renal parenchyma damage and bleeding when compared to mechanical dilators (e.g. Amplatz and Alken dilators) (1,2). Disadvantages include high cost, failure in performing access in obese patients and in those who have undergone previous open or percutaneous stone removal. In this study all of the balloon dilators were unable to reach 90% of their expected diameters with larger constrictive loads at low (4 ATM) and nominal (10 ATM) inflation pressures and two of them reached 90% of the expected diameter at their burst pressure. This interesting finding corroborates the idea that urologists may select a balloon with a higher pressure rating when treating multi-operated patients. Unfortunately balloons are expensive and a 25% failure rate to create adequate renal access in patients with a history of prior renal surgery has been reported (3); probably in such cases using mechanical dilators can be more cost effective especially in developing countries.

REFERENCES

1. Traxer O, Smith TG 3rd, Pearle MS, Corwin TS, Saboorian H, Cadeddu JA: Renal parenchymal injury after standard and mini percutaneous nephrostolithotomy. J Urol. 2001; 165: 1693-5.
2. Davidoff R, Bellman GC: Influence of technique of percutaneous tract creation on incidence of renal hemorrhage. J Urol. 1997; 157: 1229-31.
3. Joel AB, Rubenstein JN, Hsieh MH, Chi T, Meng MV, Stoller ML: Failed percutaneous balloon dilation for renal access: incidence and risk factors. Urology. 2005; 66: 29-32.

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EDITORIAL COMMENT

Choice of nephrostomy tract dilation technique is significant in minimizing the risk of complications such as blood loss and perforation of the collecting system.

Among other choices, Balloon systems have typically been the instrument of choice for many surgeons as they allow for one-step dilation, minimized total operative and fluoroscopic time and reduced risk of hemorrhage in comparison to other methods of tract dilation. It has been proposed that the lateral compressive forces produced by the balloons are less traumatic and thereby minimize complications in comparison to the angular shearing forces exerted by successive dilation methods (1).

The potential downsides to using balloon dilation include high cost, fixed length, and lack of effectiveness in the face of dysmorphic body habitus or severe fibrosis (2).

The ideal site of percutaneous puncture should be selected to maximize the use of rigid instruments, minimize the risk of complications and obtain stone-free status.

This study compares the ability of several percutaneous balloons to expand under different radial constrictive forces.

All balloons were unable to reach 90% of their expected diameter with larger constrictive loads (122g) at low (4 ATM) and nominal (10 ATM) inflation pressures. Balloon systems can be accurately placed minimizing the risk of creating a false passage, are quick to use and provide constant hemostasis.

REFERENCES

1. Miller NL, Matlaga BR, Lingeman JE: Techniques for fluoroscopic percutaneous renal access. J Urol. 2007; 178: 15-23.
2. Al-Kandari AM, Jabbour M, Anderson A, Shokeir AA, Smith AD: Comparative study of degree of renal trauma between Amplatz sequential fascial dilation and balloon dilation during percutaneous renal surgery in an animal model. Urology. 2007; 69: 586-9.

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EDITORIAL COMMENT

The balloon dilation used in percutaneous access for kidney surgery represents a very effective method for accessing the urinary tract. It is faster and less traumatic than other kinds of dilators as discussed by the authors. However, some details might be considered like: 1. It is necessary to have some space in the urinary tract for the tip of the balloon dilator, in order to dilate all the way from the skin to the urinary tract; 2. The accessed calyx should be a posterior one, otherwise during the dilation the balloon becomes straight and could leave the calyx; 3. The balloon should be dilated uniformly to permit the smoothly introduction of the Amplatz sheet over it to the urinary tract.

It becomes expensive and extremely undesirable when an irregularity of the balloon occurs (as a figure eight) which will not permit the introduction of the Amplatz sheet. It generally happens by muscle fascia or fibrous tissue resistance around the balloon. Then, the urologist has to dispose off his balloon dilator and use another kind. This paper accurately analyses the third condition above with practical application for surgeons at the moment of choosing the dilator in a percutaneous surgery. It is of great importance to choose the reliable dilators that will accomplish their task. It can also be considered as

an appeal for producers in order to improve their products. However, we may question if only three dilators of each brand represent a true performance profile. Additionally, there are other not considered aspects of each product that may have an influence on the preference of the surgeon.

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EDITORIAL COMMENT

Percutaneous surgery has firmed its place as gold standard treatment for large and/or complex kidney stones; and access to the collecting system is the key-factor for a successful and safe procedure.

The present manuscript translates the unlimited benefits of coupling medicine with engineering in optimizing surgical instruments, medical tools and consequently surgical procedures. The University of Minnesota's urology team has great experience in testing endourological devices and has granted the medical literature with another interesting and useful manuscript.

Dilating balloon catheters have met with the acceptance of urologists as they save time and simplify the percutaneous surgery. The authors have compared the performance of different brands of dilating balloons in artificially reproduced case scenarios. Interestingly, devices showed different performances on similar testing settings and it was even more significant at higher compressive forces (simulating a stricture for example). This information is of particular importance for endourologists who depend on the efficiency of instruments to successfully treat a patient.

Another message one can take from the study is that one should anticipate the difficulties of a procedure and choose the right tool to deal with them.

Body mass index (BMI) could be another indication for nephrostomy balloons.

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The Effects of Lovastatin on Conventional Medical Treatment of Lower Urinary Tract Symptoms with Finasteride

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ABSTRACT

Objective: To explore whether or not statins have any impact on the progression of components of benign prostatic hyperplasia (lower urinary tract symptoms severity, prostate volume and serum prostate specific antigen (PSA) when combined with other agents inhibiting growth of prostate cells.
Materials and Methods: This was a preliminary, clinical study. Eligible patients were aged > 50 yrs, with International Prostate Symptom Score (IPSS) between 9 and 19, total prostate volume (TPV) > 40 mL, and serum PSA > 1.5 ng/mL. Patients were divided in two groups: those with and those without lipidemia. After selection, eligible BPH patients with lipidemia (n = 18) were prescribed lovastatin 80 mg daily and finasteride 5 mg daily, while eligible patients without lipidemia (n = 15) were prescribed only finasteride 5 mg daily. IPSS, TPV and serum PSA were evaluated at end point (4 months).
Results: There was no difference between the two groups on the primary end point of mean change from baseline in IPSS (p = 0.69), TPV (p = 0.90) and PSA (p = 0.16) after 4 months of treatment.
Conclusions: Short-term lovastatin treatment does not seem to have any effect on IPSS, TPV and PSA in men with prostatic enlargement due to presumed BPH.

Key words: *prostate; benign prostate hyperplasia; volume; PSA; statins; finasteride*
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INTRODUCTION

The etiology of benign prostatic hyperplasia (BPH) is still largely unresolved. Multiple partially overlapping and complementary systems (nerve, endocrine, immune, vascular) and local factors are likely to be involved (1), and therefore, several etiologic factors for BPH have been proposed to date (2). Primary interest has been focused on the steroid hormones, especially testosterone estrogen and their metabolites (3). Of the currently used BPH pharmacotherapeutic treatments, only the 5a-reductase inhibitors have been demonstrated to modify the underlying pathology (4).

A competitive inhibitor of the enzyme, type-II 5a-reductase, blocks the reduction of serum testosterone to the more active dihydrotestosterone (DHT). In fact, DHT and not testosterone is the major intraprostatic androgen (5,6). As a result, intraprostatic DHT levels decrease by 80-90% while serum testosterone levels remain unchanged. Although the role of these agents is not fully defined, a regression of the epithelial component of BPH causing a reduction of prostate volume (approximately 30%) (7) and a decrease in the 'static' component of bladder outlet obstruction resulting in improvements in lower urinary tract symptoms (LUTS) and urinary flow have been documented in flow rates, symptom

scores and imaging studies (8). The best results have occurred in men with large prostates (> 40 grams), while all the 5a-Reductase Inhibitor's (5ARI) effect takes approximately 3 to 6 months to occur (9). To our knowledge, of the currently used BPH pharmacotherapeutic interventions only the 5a-RI's have been shown to modify the underlying pathology.

Statins are commonly prescribed agents to lower cholesterol and the associated risks of vascular events. They act by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Stimulation of liver low-density lipoprotein (LDL) receptors by inhibition of this enzyme in the liver results in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels.

Since cholesterol is a required intermediate in sex steroid synthesis, a decrease in blood cholesterol levels results in a decrease in sex steroid synthesis. Indeed, epidemiological studies have demonstrated that alteration of hormonal levels results in modifications of hormonal activity in the prostate gland (10). Although the multiple interactions in the biochemical pathways and the molecular signaling of steroid hormones and its impact in the development of BPH in cellular level are poorly understood, it could be assumed that alteration of sex steroid synthesis leads to changes in local networks of epithelial, stromal and luminal factors necessary for the BPH development (11). Under those circumstances, it is possible that statins influence BPH development through effects on steroid hormone through interference of the 5a-RI's molecular mechanisms. Experimental studies have demonstrated that steroid hormones contain characteristic effects on prostatic smooth muscle cells (12) which can be altered by statins (13). Although the exact mechanism is not known, the impact of statins on hypertrophic prostate cells growth could be attributed to the apoptotic properties of statins. Effects of statins in both prostate stromal and epithelial cells could be also attributed to the anti-oxidative properties of statins. In fact, there is increasing evidence that oxidative stress might play a role in the induction of prostate cells growth and thus contribute to the pathogenesis of BPH (14,15).

Since most patients with symptomatic BPH are aging men and are likely to use additional drugs for the treatment of concomitant diseases, the identification of those which may interfere with BPH molecular mechanisms and enhance the efficacy of conventional BPH treatment would be useful to patients following conservative treatment alone. Given that the efficacy of 5aRI's in treating LUTS suggestive of BPH is limited (9), statins probably represent the perfect candidate.

The aim of the present study was to explore an approach to the treatment of men with LUTS and prostatic enlargement that involves simultaneous management of serum lipid levels, by evaluating the impact of lovastatin on conventional treatment with finasteride in men with BPH.

MATERIALS AND METHODS

Patients complaining of lower urinary tract symptoms who presented at the outpatient Department of Urology at the General Hospital of Thebes from June 2006 to February 2007 were asked to complete the International Prostate Symptom Score (IPSS). In collaboration with the Department of Cardiology, they underwent a serum total cholesterol, HDL and LDL examination. The only criterion for classifying a man as lipidemic, was a fasting serum low-density lipoprotein level > 100 mg/dL in two consecutive measurements. Inclusion criteria were as follows: age > 50 yrs., IPSS between 9 and 19, total prostate volume (TPV) > 40 mL, and serum prostate specific antigen (PSA) > 1.5 ng/mL at baseline. Patients who met the inclusion criteria were considered eligible for this study independently of their lipidemic status. Exclusion criteria were previous medical history, evidence, or suspicion of prostate cancer; history of urologic surgery or procedures that may have altered prostate anatomy/architecture cystoscopy, prostate biopsy or catheterization within 15 days of study entry, urinary tract infection; chronic prostatitis, bladder stone, severe infection or major surgical operation within 3 mo prior to study entry. Subjects with clinically significant impaired hepatic or renal function; clinically significant elevation in serum creatinine phosphokinase or TG levels were excluded from the study.

The study was approved by the local ethics committee and was performed in accordance with

the International Conference on Harmonization Guidelines for Good Clinical Practice (1996), which represents the international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve participation of human subjects.

Study Design

Preliminary, clinical study in men with BPH and LUTS. Both study group and controls were regular patients who presented at the outpatient department of the General Hospital of Thebes. Eligible patients were aged > 50 yrs., with an IPSS between 9 and 19, TPV > 40 mL, and serum prostate-specific antigen (PSA) > 1.5 ng/mL. They were selected among first time-diagnosed patients with BPH who were scheduled to receive the appropriate treatment. Study medication was only prescribed to those patients who were found to suffer from LUTS suggestive of BPH and lipidemia. After a nine-month screening period, selected patients were divided into two groups accordingly to their lipidemic status. In order to reduce potential bias, both groups were consisted of selected patients with similar demographics who met the same selection criteria.

Outcome Measures

The mean changes from baseline of IPSS, TVP and PSA as efficacy parameters were defined. Efficacy evaluations were performed at baseline and at four month of treatment. A GE 2000 ultrasound device was used to determine total prostate volume measurements. The TPV was calculated by using the formula for a prolate ellipse (width x length x height x 0.52). Symptom improvement was assessed using the International Prostate Symptom Score Questionnaire, whereas lipidemia was monitored through fasting low-density lipoprotein measurements..

RESULTS

The screening period was between June 2006 and February 2007. Eligible patients were divided in the two study groups between April and June 2007 (baseline) according to the lipidemic status. The remaining patients were prescribed the appropriate treatment accordingly to the bothersome of LUTS and the levels of serum LDL. Of 98 patients initially screened only 37 meeting the inclusion criteria had similar demographics: There was no statistically significant difference between the two groups regarding median age, body height, total cholesterol and LDL level at baseline. Patients with lipidemia (serum low-density lipoprotein > 100 mg/dL at baseline) were prescribed lovastatin 80 mg daily and finasteride 5 mg daily, while patients without lipidemia were prescribed only finasteride 5 mg daily. Two of the selected patients however did not receive treatment; one patient left the study due to adverse events, while another patient discontinued the study. Finally, 33 patients (18 with lipidemia and 15 without lipidemia), completed the study in October 2007.

The change in mean IPSS from baseline (14) to end point (7.5) was considered statistically significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean IPSS from baseline (14.8) to end point (8.7) was considered statistically significant ($p = 0.00$) in patients without lipidemia (finasteride group) also.

The change in mean TPV from baseline (58.7) to end point (46.8) was statistical significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean TPV from baseline (57.2) to end point (44.7) was considered statistically significant ($p = 0.00$) in patients without lipidemia (finasteride group).

The change in mean PSA from baseline (2.87) to end point (1.89) was considered statistically significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean PSA from baseline (3.09) to end point (2.37) was not considered of statistical significance ($p = 0.2$) in patients without lipidemia (finasteride group).

There was no difference between the two groups on the primary end point of mean change from baseline in IPSS ($p = 0.69$), TPV ($p = 0.90$) and PSA ($p = 0.16$) after 4 months of treatment (Table-1).

COMMENTS

The fact that both BPH and metabolic syndrome are very common conditions - particularly

Table 1 – *Patient demographics.*

	Patients Without Lipidemia (finasteride group)	**Patients With Lipidemia** (statin-finasteride group)
Mean age	65.7	66.2
Mean weight	78.2	80.8
Mean IPSS (baseline)	14.8 (3.27)	14 (3.18)
Mean IPSS (end point)		7.5 (2.95)
Mean TPV (baseline)	57.2 (18.01)	58.72 (16.92)
Mean TPV (end point)		46.69 (14.74)
Mean PSA (baseline)	3.067 (1.92)	2.87 (1.58)
Mean PSA (end point)	2.37 (2.09)	1.89 (1.1)

IPSS = International Prostate Symptom Score; PSA = prostate specific-antigen; TPV = total prostate volume (standard deviations are in parentheses)

among older men- and the observation that most BPH patients share similar metabolic abnormalities as patients with the metabolic syndrome, have led several investigators to point out a relationship between those two conditions (16,17). Although the specific mechanism is not clearly understood it could be assumed that it involves an interplay between several hormonal pathways: since lipids impact both on cardiovascular disease development and the production of sexual hormones, it is plausible that they might affect the risk for BPH development through the increase of DHT levels (18). Epidemiologic data demonstrated a significantly higher prevalence of cardiovascular diseases and dyslipidemia in men with BPH (3,19) and studies linking dyslipidemia with the rate of benign prostatic growth and with LUTS (20,21) further support the above-mentioned hypothesis. In confirmation of the above, an experimental study demonstrated that a high cholesterol diet, and subsequently high serum cholesterol levels, led to histological changes in the rat prostate that resembled prostatic hyperplasia (22) while, recently, statins have been proven to affect circulating androgens (23).

Only two clinical trials (24,25) to date have addressed the potential use of statins in the treatment of men with LUTS and BPH. In the study of Marino et al., simvastatin was used along with mepartricin, a polyene macrolide antibiotic with unknown composition, for the treatment of symptomatic BPH in a small sample of patients. In contrast Mills et al., assessed the efficacy of atrovastatin in the treatment of LUTS and prostate enlargement in a large, double blind, placebo-controlled trial. The results of these previous studies are controversial; while treatment with simvastatin achieved a 38-40% clinical response in the first study (24), treatment with atrovastatin did not show an effect on urinary symptoms, flow rate, quality of life, or prostate size and morphology and PSA in the second (25). Given the similarities in the pharmacological profile between simvastatin and atrovastatin it could be easily assumed that the effects on observed in the study of Marino et al., are more likely to be attributed to the mepartricin whose efficacy in the treating of BPH related symptoms was further investigated (26-28). Although a potential role of mepartricin in decreasing estrogen plasmatic levels and their concentration in the prostate has been proposed (29), it is more likely to be attributed to its antibacterial action. Indeed, a reduction in prostate size has not been achieved in any of these studies, while more recent studies linked the mepartricin induced LUTS improvement in cases of chronic nonbacterial prostatitis/chronic pelvic pain syndrome (30).

None of the previous studies, however, has evaluated the efficacy of BPH treatment with statins in combination with a 5a-reductase inhibitor. Currently,

it is still not clear which effect of 5ARIs is responsible for their benefits; current evidence suggests a apoptotic process restricted to epithelial cells (31). To our knowledge, BPH is caused by an increase in prostate epithelial and stromal cells, especially the latter. The observation that statins have pro-apoptotic effects in prostate stromal cells (32,33), justified the rationale for the complementary use of statins in the treatment of BPH: since BPH stromal cells have a long life span and are not very responsive to androgen withdrawal (32), pharmacologically inducing apoptosis in these cells could probably lead to a further reduction of hypertrophic prostate volume and to a consequent improvement of LUTS. Unfortunately, similar to the previous studies, statins did not show any effect of on IPSS, nor boosted the 5ARI's effect on TPV. However, serum PSA values seemed to be generally lower in the statin/finasteride arm compared to finasteride arm alone. This finding is interesting, as statins have been previously reported to decrease serum PSA (34). It could be assumed that statins also impact on the growth of prostate epithelial cells through an intervention in the pathway of androgen synthesis (35). Although, data suggest that treatment with statins may lower serum PSA with time, results must be confirmed in a larger study population while controlling for potential confounders. Finally, our finding of a non statistically significant change in mean PSA from baseline to end point in patients without lipidemia (finasteride group) could be probably attributed to the relatively low sample as well as to the relatively low duration of the study. In fact, it is not uncommon for therapies to not impact LUTS objective measures (prostate volume, PSA, flow rate) but still result in real patient improvement in IPSS scores (as in pde5i inhibitors).

CONCLUSION

Since the study period was very short, any long-term effects could not be discussed based on these results. It is probable that no effect of statins on IPSS, TPV and PSA would have been detected even if the study had lasted over a longer period of time. However, it is also possible the statins would have had an effect via metabolic pathways or atherosclerotic mechanisms only after max finasteride effect had occurred (minimum of 6 months f/u). Against a background of increased interest on the impact of steroid hormones in the development of BPH current knowledge is limited and no data indicate whether or not statins independently from their impact on circulating androgen levels does influence the natural history of BPH.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Untergasser G, Madersbacher S, Berger P: Benign prostatic hyperplasia: age-related tissue-remodeling. Exp Gerontol. 2005; 40: 121-8.
2. Guess HA: Benign prostatic hyperplasia: antecedents and natural history. Epidemiol Rev. 1992; 14: 131-53.
3. Bravi F, Bosetti C, Dal Maso L, Talamini R, Montella M, Negri E, et al.: Macronutrients, fatty acids, cholesterol, and risk of benign prostatic hyperplasia. Urology. 2006; 67: 1205-11.
4. Marberger M: Drug Insight: 5alpha-reductase inhibitors for the treatment of benign prostatic hyperplasia. Nat Clin Pract Urol. 2006; 3: 495-503.
5. McConnell JD: Prostatic growth: new insights into hormonal regulation. Br J Urol. 1995; 76 (Suppl 1): 5-10.
6. Bartsch G, Rittmaster RS, Klocker H: Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia. World J Urol. 2002; 19: 413-25.
7. Carson C 3rd, Rittmaster R: The role of dihydrotestosterone in benign prostatic hyperplasia. Urology. 2003; 61 (4 Suppl 1): 2-7.
8. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL, et al.: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med. 1998; 338: 557-63.
9. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al.: The long-term

effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003; 349: 2387-98.
10. Beutel ME, Wiltink J, Hauck EW, Auch D, Behre HM, Brähler E, et al.: Correlations between hormones, physical, and affective parameters in aging urologic outpatients. Eur Urol. 2005; 47: 749-55.
11. Schaffner GP: Effect of Cholesterol-Lowering Agents. In: Hinman F. Jr (ed.), Benign Prostatic Hypertrophy. New York, Springer-Verlag. 1983; pp. 280.
12. Zhang J, Hess MW, Thurnher M, Hobisch A, Radmayr C, Cronauer MV, et al.: Human prostatic smooth muscle cells in culture: estradiol enhances expression of smooth muscle cell-specific markers. Prostate. 1997; 30: 117-29.
13. Padayatty SJ, Marcelli M, Shao TC, Cunningham GR: Lovastatin-induced apoptosis in prostate stromal cells. J Clin Endocrinol Metab. 1997; 82: 1434-9.
14. Berger AP, Kofler K, Bektic J, Rogatsch H, Steiner H, Bartsch G, et al.: Increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia. Prostate. 2003; 57: 57-65.
15. Ghafar MA, Puchner PJ, Anastasiadis AG, Cabelin MA, Buttyan R: Does the prostatic vascular system contribute to the development of benign prostatic hyperplasia? Curr Urol Rep. 2002; 3: 292-6.
16. Bourke JB, Griffin JP: Hypertension, diabetes mellitus, and blood groups in benign prostatic hypertrophy. Br J Urol. 1966; 38: 18-23.
17. Giovannucci E, Rimm EB, Chute CG, Kawachi I, Colditz GA, Stampfer MJ, et al.: Obesity and benign prostatic hyperplasia. Am J Epidemiol. 1994; 140: 989-1002.
18. Howie BJ, Shultz TD: Dietary and hormonal interrelationships among vegetarian Seventh-Day Adventists and nonvegetarian men. Am J Clin Nutr. 1985; 42: 127-34.
19. McVary KT: BPH: epidemiology and comorbidities. Am J Manag Care. 2006; 12 (5 Suppl): S122-8.
20. Hammarsten J, Högstedt B: Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur Urol. 2001; 39: 151-8.
21. Rohrmann S, Smit E, Giovannucci E, Platz EA: Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). Int J Obes (Lond). 2005; 29: 310-6.
22. Mitropoulos D, Ploumidou K, Kyroudi-Voulgari A, Perea D, Kittas C, Karayannacos P: Hypercholesterol diet (HD) alters serum lipid profile and ventral prostate structure in rats. Eur Urol. 2003; 2 (Suppl): 20.
23. Hall SA, Page ST, Travison TG, Montgomery RB, Link CL, McKinlay JB: Do statins affect androgen levels in men? Results from the Boston area community health survey. Cancer Epidemiol Biomarkers Prev. 2007; 16: 1587-94.
24. Marino G, Pugno E, Cevoli R, Griffa D, Pastorini S, Cocimano V: Pharmacologic treatment of benign prostatic hypertrophy (BPH): a combination of mepartricin and simvastatin. Analysis and results. Minerva Urol Nefrol. 1991; 43: 279-82.
25. Mills IW, Crossland A, Patel A, Ramonas H: Atorvastatin treatment for men with lower urinary tract symptoms and benign prostatic enlargement. Eur Urol. 2007; 52: 503-9.
26. Prezioso D, Fabrizio F, Russo A, Lotti T: Mepartricin in BPH. A new dosage approach. Minerva Urol Nefrol. 1996; 48: 117-20.
27. Prajsner A, Szkodny A, Duda W, Szurkowski A, Tkocz M: Mepartricin (Ipertrofan) in the treatment of BPH patients. Urologia Polska. 1992; 45: 4.
28. Denis L, Pagano F, Nonis A, Robertson C, Romano P, Boyle P: Double-blind, placebo-controlled trial to assess the efficacy and tolerability of mepartricin in the treatment of BPH. Prostate. 1998; 37: 246-52.
29. Barbero R, Badino P, Odore R, Galmozzi MR, Cuniberti B, Zanatta R, et al.: Mepartricin long-term administration regulates steroid hormone and adrenergic receptor concentrations in the prostate of aged rats. J Vet Pharmacol Ther. 2006; 29: 289-97.
30. De Rose AF, Gallo F, Giglio M, Carmignani G: Role of mepartricin in category III chronic non-bacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. Urology. 2004; 63: 13-6.
31. Bozec A, Ruffion A, Decaussin M, Andre J, Devonec M, Benahmed M, et al.: Activation of caspases-3, -6, and -9 during finasteride treatment of benign prostatic hyperplasia. J Clin Endocrinol Metab. 2005; 90: 17-25.
32. Padayatty SJ, Marcelli M, Shao TC, Cunningham GR: Lovastatin-induced apoptosis in prostate stromal cells. J Clin Endocrinol Metab. 1997; 82: 1434-9.
33. Parsons JK, Bergstrom J, Barrett-Connor E: Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men. BJU Int. 2008; 101: 313-8.
34. Cyrus-David MS, Weinberg A, Thompson T, Kadmon D: The effect of statins on serum prostate

specific antigen levels in a cohort of airline pilots: a preliminary report. J Urol. 2005; 173: 1923-5.

35. Barnard RJ, Kobayashi N, Aronson WJ: Effect of diet and exercise intervention on the growth of prostate epithelial cells. Prostate Cancer Prostatic Dis. 2008; 19. Epub ahead of print

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EDITORIAL COMMENT

Stamatiou and colleagues are to be lauded on presenting this "negative results" study. The conclusions of the study are reasonable based on the given preliminary data. However, additional assessment of the study's endpoints at the one year mark and beyond while on therapy is crucial. As the authors mention, the maximum effect of finasteride is often not seen until 6 months of therapy has been utilized; this study yields data after only 4 months of intervention. Perhaps more importantly, determination of any synergistic effect of lovastatin with finasteride on LUTS via either metabolic syndrome or a pelvic atherosclerosis mechanism (both long term processes) would likely also require a more robust length of follow-up to note a significant difference between the study's treatment arms.

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EDITORIAL COMMENT

Finasteride, a 5α-reductase inhibitor is currently an established part of medical management of benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS). Inhibition of 5α-reductase lowers serum levels of dihydrotestosterone, the active androgen metabolite. This leads to reduction in prostate volume and serum prostate specific-antigen (PSA) values.

Experimental studies have reported that statins, a widely used group of cholesterol-lowering drugs, can reduce proliferation of prostate stromal and epithelial cells in vitro (1). This effect seems to

be at least partly mediated by inhibition of the enzyme HMG-CoA reductase that, in addition to precursors of cholesterol, also produces isoprenoids essential in control of cell cycle and apoptosis. However, also other mechanisms of action have been proposed (1).

Thus, it is within possibilities that statins could be effective in treatment of LUTS due to BPH. In this issue of the International Braz J Urol, Stamatiou et al. report results from a clinical experiment, in which they recruited 33 men with BPH, and treated hypercholesterolemic men with combination of finasteride and lovastatin (2), while normolipidemic men were treated conventionally with finasteride only.

The study setting is interesting. As the mechanisms for action in the prostate tissue are likely separate for lovastatin and finasteride, they could in theory have a synergistic effect in BPH treatment.

However, the observed decrease in clinical parameters of BPH was similar for both groups. After four months treatment there was no significant difference in prostate volume, serum PSA or IPSS symptom score between the study groups, i.e. there was no advantage for combining lovastatin with finasteride. Still, the PSA level was lower among hypercholesterolemic men both at the base line and after four months treatment, which suggests that serum cholesterol level could also affect PSA.

This is among the first clinical studies on this subject. The results in general concur with previous studies (2). Thus, based on the present evidence, the answer for the title question seems to be "no". Lovastatin does not enhance the effect of finasteride treatment for lower urinary tract symptoms or prostate volume, and statins cannot be currently endorsed for treatment of LUTS.

However, the follow-up time in this study was only four months, and thus long-term effects cannot be ruled out. While lovastatin does not appear to have any immediate treatment effect in BPH (based on the absence of synergistic effect with finasteride), it still remains unclear whether lovastatin could reduce progression of BPH. Due to slowly progressing nature of BPH this kind of treatment effect would take years, instead of months, to become evident in a clinical study.

Additionally, the two study groups differed systematically according to their lipidemic status. Serum cholesterol affects prostate growth (3), and it is possible that this difference could have changed the treatment response between the study groups.

In spite of these uncertainties, the study by Stamatiou et al. shows that, despite the drug's beneficial cardiovascular effects, lovastatin does not seem to have any short-term effect against BPH and does not bring any benefit over the conventional medical management of the condition. Thus, based on the current evidence, we cannot recommend lovastatin to patients for treatment of BPH and LUTS.

REFERENCES

1. Murtola TJ, Visakorpi T, Lahtela J, Syvälä H, Tammela TLj: Statins and prostate cancer prevention: where we are now, and future directions. Nat Clin Pract Urol. 2008; 5: 376-87.
2. Stamatiou K, Zaglavira P, Skolarikos A, Sofras F: The effects of lovastatin on conventional medical treatment of lower urinary tract symptoms with finasteride. Int Braz J Urol. 2008; (this issue)
3. Solomon KR, Freeman MR: Do the cholesterol-lowering properties of statins affect cancer risk? Trends Endocrinol Metab. 2008; 19: 113-21.

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The Role of Extended Prostate Biopsy on Prostate Cancer Detection Rate: A Study Performed on the Bench

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ABSTRACT

Introduction: The aim of this prospective study was to compare the advantage of performing prostate biopsy with a greater number of cores using the classic sextant procedure, with the aim of reducing false negative results.
Materials and Methods: 100 prostates were acquired from consecutive radical prostatectomies performed by the same surgeon. Fourteen cores were obtained on the bench following surgery using an automatic pistol with an 18-gauge needle. Six of these cores were obtained according to the sextant technique, as described by Hodge et al.; with the addition of a further three lateral cores from each lobe and one from the bilateral transition zone. The whole gland and the fragments were assessed by the same pathologist. An analysis of the frequency of the cancers identified in the cores of the sextant and the extended biopsies was undertaken and the results evaluated comparatively. The chi-square test was used for the comparative analysis of the cancer detection rate, according to the technique used.
Results: When 6 cores were removed, the positive cancer rate was 75%, which was increased to 88% when 14 cores were ($p < 0.001$). The withdrawal of 14 cores resulted in a significant 13% (95% CI [5%-21%]) increase in the positive rate of cancer detection.
Conclusion: Extended biopsy, with the removal of 14 cores, is more efficient than the sextant procedure in improving the rate of prostate cancer detection.

Key words: *prostatic neoplasm; biopsy needle; pathology; diagnosis*
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INTRODUCTION

Prostate cancer is the most common non-cutaneous malignant tumor in men. In the United States, it accounts for 33% of all new cancer cases and it is estimated that 218,890 men will be diagnosed in 2006, 91% of which will be discovered at a localized or regional stage. Moreover, it is estimated that 27,050 men will die of the disease (1).

A great challenge for the early diagnosis of prostate cancer is that in its initial phase, the tumor is asymptomatic and only detected by the alterations in the digital rectal examination, abnormal increase in the plasma level of the prostate specific antigen (PSA) or by means of transrectal ultrasound revealing hyperechoic and hypervascularized areas. When any of these alterations is found, it becomes necessary to perform a transrectal ultrasound-guided prostate biopsy.

In 1989, Hodge and colleagues proposed the undertaking of routine sextant biopsy and demonstrated the superiority of the method compared to the digitally guided biopsy directed to nodules or suspected areas. This method has become the gold standard for the diagnosis of prostate cancer (2).

A study with a mathematical laboratory model showed that sextant biopsy could detect the tumor in 36%, 44% and 100% of the cases in which

the lesion occupied 2.5%, 5% and 20%, respectively, of the gland volume (3). However, the sextant biopsy has led to false negative results in 15% to 34% of men (4-7). Furthermore, the general sensitivity of the sextant biopsy was only 60% in patients with normal prostatic DRE (8).

For these reasons, various modifications of the technique have been proposed, some of which suggested the acquisition of cores in a more lateral region (9) or an increase in the number of cores obtained (10-13). There seems to be a consensus in the literature as to the superiority of the techniques that involve the withdrawal of a larger number of cores for the diagnosis of adenocarcinoma of the prostate (10,12,14). However, the number of cores to be obtained varies significantly among the various studies published, with no overall consensus. In reviewing the subject, we found only one prospective and randomized study that compared 6 and 12-core biopsies obtained in a significant number of patients (14). This study did not demonstrate any significant difference between the two procedures in the detection of prostate cancer.

Curiously, recent analyses have shown that in the United States and the United Kingdom, traditional sextant biopsy continues to be used in 20% to 70% of the diagnostic centers, demonstrating a general uncertainty as to the ideal number of cores to be obtained in prostate biopsy (15-17). In the studies that show advantages from the removal of more than 6 cores, the comparison of sextant with extended biopsy was performed in groups of patients suspected of having of prostate cancer. To examine the true incidence of false negative results, it would be necessary to obtain the biopsy on patients known to be bearers of the disease (i.e., those with a previous positive biopsy). Further, the withdrawal of a large number of cores could lead to an increase in the diagnosis of tumors of no clinical importance and requiring no treatment. This question could only be answered if the entire prostate were examined histologically and completely, thus permitting the definition of the pathological characteristics of the tumor.

This study compares the rates of prostate cancer detection by means of the withdrawal of 6 or 14 cores in order to determine the cancer detection rates of the two techniques.

MATERIALS AND METHODS

The study comprised of a prospective and controlled analysis of prostate glands obtained by radical prostatectomy of one hundred consecutive patients with clinically localized prostate cancer during the period of August 2000 to March 2001. The project was approved by the Ethics in Research Committee of the hospital.

All the operations were performed by the same surgeon (MS), in accordance with the surgical technique previously described.

The inclusion criteria were the presence of adenocarcinoma of the prostate in clinical stages T1-T2 and recommendation of radical prostatectomy. Patients with a previous history of radiotherapy, hormone therapy or transurethral removal of the prostate were excluded.

All the surgical specimens were subjected to biopsy on the bench, immediately after their removal with an 18-gauge needle and an automatic pistol. Six cores were obtained from the peripheral zone, one from each sextant, according to Hodge et al. and were identified and analyzed under the label sextant biopsy (2). An additional 8 cores were then removed, three from the peripheral zone of the most lateral edge of the prostate and one core from the transitional zone of each lobe (Figures-1 and 2). These cores were analyzed together with the first 6 (a total of 14 cores) and were labeled as extended biopsy. All the cores were stored in separate flasks and sent, together with the surgical specimens, for pathological analysis. The histological reading of all the slides was carried out by the same pathologist (KRL).

The biopsy cores and the surgical specimens were fixed in 10% formalin for a period of 4 to 16 hours. All the glands were submitted to histological study in accordance with the recommendations previously described (18).

Both the biopsy cores and the surgical specimens were investigated for the presence of adenocarcinoma, as classified in accordance with Gleason's criteria (19).

The chi-square test was used for the comparison of the frequency of the positive results in both the sextant and the extended biopsies, employing a 95% confidence interval (95% CI) for each value. A

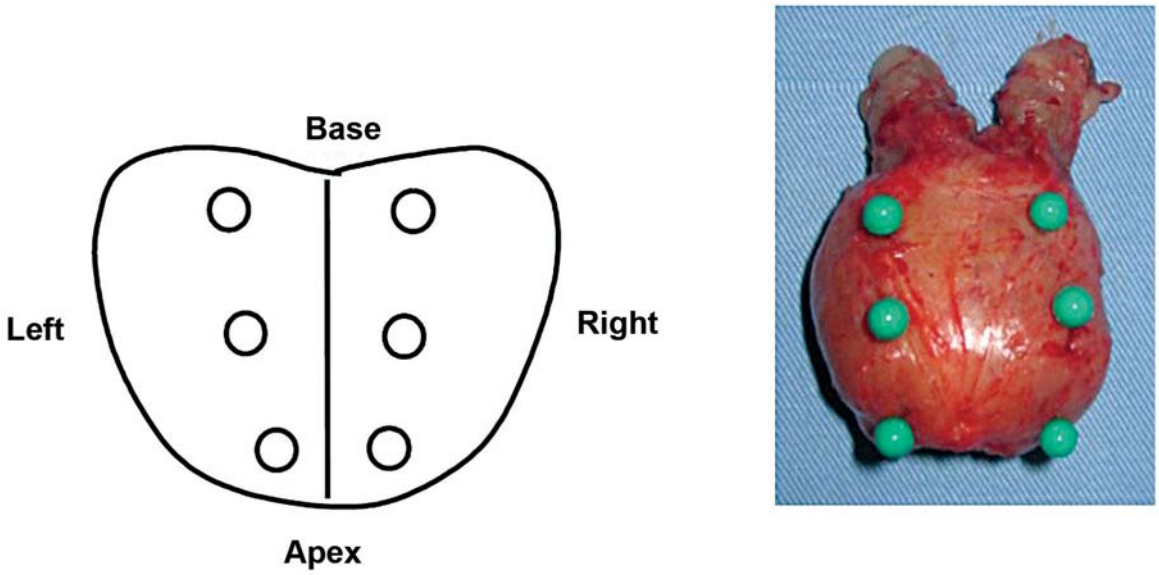

Figure 1 *– Sextant biopsy.*

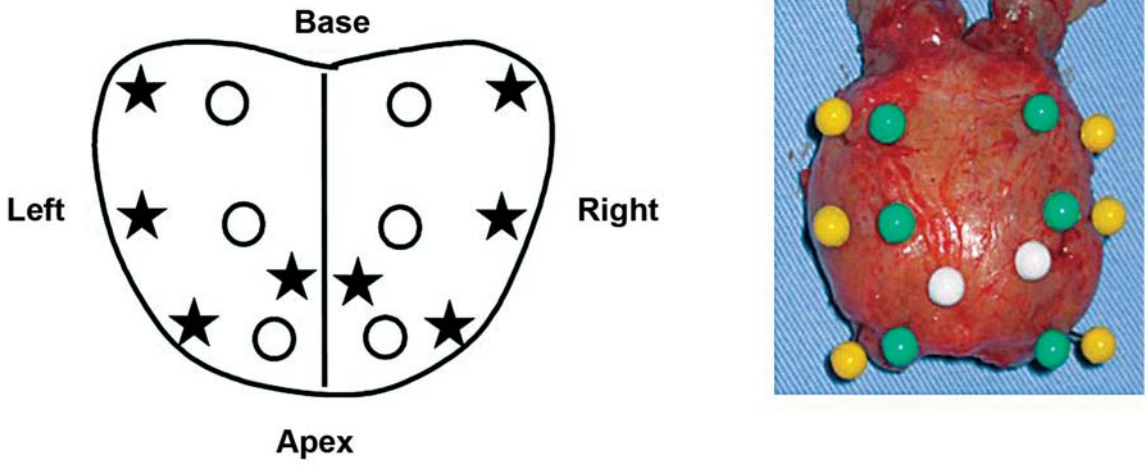

Figure 2 *– Extended biopsy.*

5% significance level ($p < 0.05$) was adopted for the rejection of the null hypothesis.

RESULTS

The determined positive cancer rate was compared between the groups of the sextant and extended biopsies. Each of the specimens assessed was considered to be positive when at least one positive core was found in the sample. Table-1 shows the joint distribution of the 100 assessed specimens when six and 14 cores were analyzed.

It may be observed from Table-1 that when 6 cores were removed the positive cancer rate was of 75%, compared to a rate of 88% when 14 cores were removed. Results of McNemar`s chi-squared test showed that there was a difference in the positive detection rate between these two techniques ($p < 0.001$). Thus, when 14 cores were removed there was a significant increase in the positive cancer detection rate (Figure-3), estimated at 13% (95% CI [5% - 21%]).

Cancer detection in each group increased as PSA increased but there was no significant difference between the groups (Table-2).

COMMENTS

Transrectal ultrasound-guided biopsy is the procedure of choice for the diagnosis of prostate cancer when the disease is suspected due to alterations in the PSA levels and/or alterations perceived by the DRE. This method has been modified, as there has recently been a tendency to obtain more than 8 cores, despite a lack of standardized literature on the subject. Regardless of recent studies demonstrating that extended biopsy fails less often in the diagnosis of prostate adenocarcinoma compared to the classic sextant biopsy proposed by Hodge et al., a large number of clinics still prefer the sextant technique. Although no data on this subject has been reported, we observed that the majority of clinics continue to follow the sextant method and biopsy only 6 cores. In our study, we were able to demonstrate that 6 cores

Table 1 – *Distribution of the 100 surgical specimens assessed by biopsy.*

		Sextant (6 cores)		**Total**
		Positive	**Negative**	
Extended	Positive	75	13	88
(14 cores)	Negative	0	12	12
	Total	75	25	100

Table 2 – *Cancer detection rates stratified by total PSA.*

	PSA (ng/mL)			
	≤ 4	**4.1 a 10**	**> 10**	**Total**
6 cores	6 (54.5%)	52 (83.9%)	16 (66.7%)	74 (76.3%)
14 cores	9 (81.8%)	58 (93.5%)	19 (79.2%)	86 (88.7%)
	p = 0.250	p = 0.061	p = 0.250	

PSA = prostate specific antigen

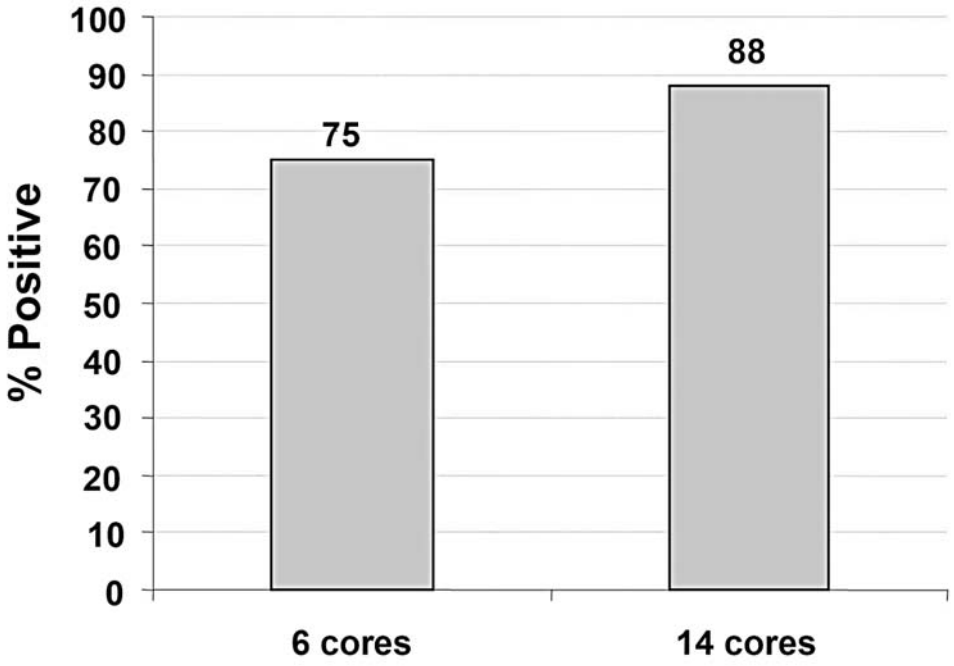

Figure 3 *– Percentage of positive detection following assessment of either 6 or 14 cores isolated from 100 prostate specimens.*

biopsy fails in 25% of the cases, while taking 14 cores decreases the failure rate to 12%, i.e. it detects 50% more.

When the 25 prostates, where the sextant biopsy was negative, were further analyzed, it was observed that the tumor was confined in 72% of them. Although no tumors were found in any of the cores, the disease was already extraprostatic in 28% of the cases. Conversely, in those cases where no tumor was found in the 14-core biopsy, only 8.3% of the specimens showed non-localized disease.

The fact that the present study was undertaken on 100 prostates acquired from consecutive radical prostatectomies not only eliminates any possible bias in the selection of cases, but also allowed us to compare the results of the two different methods applied to the same specimens. This differentiates this study from previous reports, all of which compared the findings of sextant biopsy with those of extended biopsy, undertaken "in vivo", and therefore, on different patients. Another advantage in using surgical specimens on the bench is that the procedure permits the acquisition of cores of better quality from more precise locations, as well as being undertaken by the same investigator, which is in contrast to the published studies in which the biopsy may be taken by different doctors, introducing a possible bias. Another strength of this study is that all the operations were carried out by the same surgeon, as well as all the pathological evaluation was performed by the same uropathologist, thus avoiding the inter-observer differences that are well-known in the literature.

Because it is intuitive, it is easy to accept that an increase in the number of cores obtained in a prostate biopsy will result in an improvement in the detection rate for prostate cancer. However, there is only indirect evidence and that expectation has not yet been completely proven by scientific studies. For example, the same author suggests opposite results. Naughton and colleagues first showed that 44% of cancer diagnoses require a biopsy from 7 to 13 cores, in a retrospective analysis (20). Later in a prospective study these authors showed that there was no statistically significant difference in the diagnosis of prostate

adenocarcinoma when 6 and 12-core biopsies were compared (14). Studies undertaken on Japanese men showed a much smaller improvement of 7.7% to 13.8% when 12 cores were obtained, as compared to those demonstrated by western studies (21,22). In a prospective study, in which 6 and 12-core biopsies by transperineal approach were compared, no significant difference was found when a palpable nodule or lesion suspected by transrectal ultrasound existed, except in situations in which there was an increase in the level of PSA with no alteration in the DRE or ultrasound, when the 12-core biopsy demonstrated an advantage (23). One variable that may affect the results of the biopsy is the volume of the prostate. Cancer detection in prostates less than 50 cc was 38%, whereas prostates more than 50 cc have a lower detection rate (23%) (24). One randomized prospective study investigated the influence of the increase in the number of cores as a function of prostate volume. In patients with no palpable nodule but increased PSA levels, the cancer detection rate doubled when using biopsies of 10 to 14 cores compared to the sextant technique (25). This correlation involving the need to increase the number of biopsy cores in accordance with the volume of the prostate has also been found in a Turkish study, in which the authors suggest that the sextant biopsy was not reliable even in small prostates. The study further recommended that prostates of more than 35 cc should have 10 cores removed, and that in smaller glands only 8 cores need to be obtained (26). The same author had previously demonstrated, though without relating the number of cores to prostate volume, that when 10 cores were obtained the cancer detection rate increased by 25.5% as compared with the classic 6-core biopsy (27). In the present study the average weight of the prostates was of 42.4 cc, the standard deviation was 23.9 cc, and the increase in tumor detection was of 13% when 14 cores were used compared with a 6-core biopsy.

In another study of 179 consecutive patients who underwent radical prostatectomy, it was observed that a 12-core biopsy detected 31.3% more cancer than the sextant technique (28). A group from the University of Vienna working with Athenian urologists in the attempt to validate a nomogram to define the ideal number of biopsy cores based on the age and prostate volume of the patient, submitted 502 men to biopsy on the basis of the criteria of the nomogram. The results were then compared with those of a control group of 1,051 patients who had previously had octant biopsy and re-biopsy when the former was negative. The disease was found in 36.7% of the patients when the Vienna nomogram was used, compared with 22% at the first octant biopsy and 10% on re-biopsy (29). This group confirmed that the sextant biopsy should only be used on patients of more than 70 years of age, who have a prostate volume of less than 40 mL. After excluding that group of patients, the techniques that used at least 8 core samples was preferred, with the number of samples increasing in accordance with the increased weight of the gland and as the age of the patient diminished.

More recently, the possibility of using the so-called saturation biopsies, which involve the withdrawal of more than 18 cores, has been analyzed. In one study, 24 cores were each acquired from 139 selected men and the procedure was performed by two surgeons. The results were compared with a group of 87 patients who had previously undergone the 10-core technique. No significant difference was found in the detection of the disease between these two groups. The authors concluded that a 10- or 12-core biopsy should be the method of choice for the first investigation in the early detection of prostate cancer (30). This type of strategy was also confirmed more recently in a systematic review of the literature, by which the present authors arrived at the conclusion that an investigation into prostate cancer using the 12-core biopsy should be considered (31).

On the basis of our findings and also on those reported in the literature, the authors suggest that there is no longer any justification, in practice, for the continued use of the sextant biopsy. Even with the extended technique, we still find an unacceptable number of biopsies with false negative results (12%, according to our data). In a future study we intend in to compare the extended with the saturation biopsy on the bench, which involves the acquisition of more than 18 cores, in an attempt to discover whether there is any advantage in this latter method in the detection of adenocarcinoma of the prostate.

CONCLUSION

Extended biopsy, with the removal of 14 cores, could be considered more effective than the sextant procedure in improving the prostate cancer detection rate.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ: Cancer statistics, 2007. CA Cancer J Clin. 2007; 57: 43-66.
2. Hodge KK, McNeal JE, Terris MK, Stamey TA: Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989; 142: 71-4; discussion 74-5.
3. Feneley MR, Parkinson MC: Biopsy diagnosis of prostatic cancer--current areas of concern. J Clin Pathol. 1997; 50: 265-6.
4. Chen ME, Troncoso P, Johnston DA, Tang K, Babaian RJ: Optimization of prostate biopsy strategy using computer based analysis. J Urol. 1997; 158: 2168-75.
5. Ellis WJ, Brawer MK: Repeat prostate needle biopsy: who needs it? J Urol. 1995; 153: 1496-8.
6. Keetch DW, Catalona WJ, Smith DS: Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. J Urol. 1994; 151: 1571-4.
7. Norberg M, Egevad L, Holmberg L, Sparén P, Norlén BJ, Busch C: The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer. Urology. 1997; 50: 562-6.
8. Terris MK: Sensitivity and specificity of sextant biopsies in the detection of prostate cancer: preliminary report. Urology. 1999; 54: 486-9.
9. Stamey TA: Making the most out of six systematic sextant biopsies. Urology. 1995; 45: 2-12.
10. Eskew LA, Bare RL, McCullough DL: Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol. 1997; 157: 199-202; discussion 202-3.
11. Levine MA, Ittman M, Melamed J, Lepor H: Two consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate for the detection of prostate cancer. J Urol. 1998; 159: 471-5; discussion 475-6.
12. Presti JC Jr, Chang JJ, Bhargava V, Shinohara K: The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: results of a prospective clinical trial. J Urol. 2000; 163: 163-6; discussion 166-7.
13. Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, et al.: A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. J Urol. 2000; 163: 152-7.
14. Naughton CK, Miller DC, Mager DE, Ornstein DK, Catalona WJ: A prospective randomized trial comparing 6 versus 12 prostate biopsy cores: impact on cancer detection. J Urol. 2000; 164: 388-92.
15. Davis M, Sofer M, Kim SS, Soloway MS: The procedure of transrectal ultrasound guided biopsy of the prostate: a survey of patient preparation and biopsy technique. J Urol. 2002; 167: 566-70.
16. Patel HR, Lee F, Arya M, Masood S, Palmer JH, Sheriff MK: A national survey of transrectal ultrasound-guided prostatic biopsies: time for a national guideline. Int J Clin Pract. 2003; 57: 773-4.
17. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J: Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol. 2006; 175: 1605-12.
18. Bostwick DG, Foster CS: Examination of Radical Prostatectomy Specimens: Therapeutic and Prognostic Significance. In: Foster CS, Bostwick DG (eds.) Pathology of Prostate. Philadelphia, WB Saunders. 1998; pp. 172.
19. Gleason DF: Histologic grading of prostate cancer: a perspective. Hum Pathol. 1992; 23: 273-9.
20. Naughton CK, Smith DS, Humphrey PA, Catalona WJ, Keetch DW: Clinical and pathologic tumor characteristics of prostate cancer as a function of the number of biopsy cores: a retrospective study. Urology. 1998; 52: 808-13.
21. Matsumoto K, Satoh T, Egawa S, Shimura S, Kuwao S, Baba S: Efficacy and morbidity of transrectal ultrasound-guided 12-core biopsy for detection of prostate cancer in Japanese men. Int J Urol. 2005; 12: 353-60.
22. Kojima M, Hayakawa T, Saito T, Mitsuya H, Hayase Y: Transperineal 12-core systematic biopsy in the detection of prostate cancer. Int J Urol. 2001; 8: 301-7.
23. Emiliozzi P, Scarpone P, DePaula F, Pizzo M, Federico G, Pansadoro A, et al.: The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. J Urol. 2004; 171: 197-9.

24. Uzzo RG, Wei JT, Waldbaum RS, Perlmutter AP, Byrne JC, Vaughan ED Jr: The influence of prostate size on cancer detection. Urology. 1995; 46: 831-6.
25. Mariappan P, Chong WL, Sundram M, Mohamed SR: Increasing prostate biopsy cores based on volume vs the sextant biopsy: a prospective randomized controlled clinical study on cancer detection rates and morbidity. BJU Int. 2004; 94: 307-10.
26. Eskicorapci SY, Guliyev F, Akdogan B, Dogan HS, Ergen A, Ozen H: Individualization of the biopsy protocol according to the prostate gland volume for prostate cancer detection. J Urol. 2005; 173: 1536-40.
27. Eskicorapci SY, Baydar DE, Akbal C, Sofikerim M, Günay M, Ekici S, et al.: An extended 10-core transrectal ultrasonography guided prostate biopsy protocol improves the detection of prostate cancer. Eur Urol. 2004; 45: 444-8; discussion 448-9.
28. Singh H, Canto EI, Shariat SF, Kadmon D, Miles BJ, Wheeler TM, et al.: Improved detection of clinically significant, curable prostate cancer with systematic 12-core biopsy. J Urol. 2004; 171: 1089-92.
29. Remzi M, Fong YK, Dobrovits M, Anagnostou T, Seitz C, Waldert M, et al.: The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. J Urol. 2005; 174: 1256-60; discussion 1260-1; author reply 1261.
30. Jones JS, Patel A, Schoenfield L, Rabets JC, Zippe CD, Magi-Galluzzi C: Saturation technique does not improve cancer detection as an initial prostate biopsy strategy. J Urol. 2006; 175: 485-8.
31. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J: Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol. 2006; 175: 1605-12.

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EDITORIAL COMMENT

It is commonly accepted that traditional sextant transrectal biopsy may underestimate the true tumor burden within the prostate after a whole mount specimen is available. Today as technology continues to evolve, it is imperative that clinicians have the most accurate and comprehensive information available upon which to base their recommendations. We know from large retrospective series of radical prostatectomies that traditional sextant biopsy may underestimate the true tumor extent by as much as 46.6% when the whole mount specimen is examined (1). The authors are to be commended on this prospective analysis of 100 consecutive radical prostatectomy specimens performed by the same surgeon and pathology reviewed by the same pathologist. Previous investigators have demonstrated an increased yield of malignant diagnoses in vivo using extended systematic sextant biopsy of twelve cores versus traditional sextant biopsy (2). To my knowledge this study is unique, based on the fact that the needle core biopsies were obtained from the RP specimen on the bench.

Clearly, the author's data demonstrate a statistically significant increased yield of malignant diagnoses of 13% when additional lateral cores were

obtained from each lobe and bilateral transition zone. These results further support the current trend of extended systematic sextant biopsy of 12-14 cores.

There is a subset of patients that will have negative biopsies even with the additional lateral and transitional cores, yet the PSA level may continue to rise. This particular scenario presents a diagnostic dilemma to the clinician and anxiety for the patient. In this setting, our approach is to perform stereotactic transperineal prostate biopsy (STPB). Similar to a prostate brachytherapy procedure, the prostate is positioned on the implant grid. Specimens are obtained according to x, y, and z coordinates from eight equal octants with pathology reported accordingly. Using this technique, we have consistently achieved a 39% positive biopsy rate. There was a significant difference in detection rates with the apex having a higher incidence of malignancy than the base of the prostate gland ($p = 0.000$). Furthermore, the anterior apex harbored significantly more adenocarcinoma when compared to the posterior apex ($p = 0.026$) (3).

As our knowledge of biopsy techniques become more sophisticated, it will be possible to map malignant versus benign regions of the prostate; whether or not targeted focal therapy results from this remains to be determined.

REFERENCES

1. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, Yoshida H: Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. Pathol Int. 2001; 51: 364-70.
2. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW: Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol. 2003; 169: 125-9.
3. Moran BJ, Braccioforte MH, Conterato DJ: Re-biopsy of the prostate using a stereotactic transperineal technique. J Urol. 2006; 176: 1376-81; discussion 1381.

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Patient's Reactions to Digital Rectal Examination of the Prostate

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ABSTRACT

Objective: In recent years, there has been a rise in the incidence of prostate cancer (PCa), and routine screening for the disease has become a well accepted clinical practice. Even with the recognized benefit of this approach, some men are still reluctant to undergo digital rectal examination (DRE). For this reason, we designed the present study in order to better understand men's reactions about this method of screening. The aim was to identify possible drawbacks that could be overcome to increase DRE.
Materials and Methods: We randomly selected 269 patients that were enrolled in an institutional PCa screening program. They were first asked to answer a question regarding their preferred position to undergo the examination. Following this step, they answered a questionnaire in which physical and psychological reactions regarding the DRE were presented. Finally, we used a visual analogical scale (VAS) to analyze the perception of pain during DRE.
Results: The supine position was preferred for most patients (53.9%). Before DRE, about 59.4% of patients felt that the exam would be acceptable. After DRE, this figure increased to 91.5% ($p < 0.001$). Mean VAS score during DRE was 1.69 on a scale with a range between 0 and 10 (0 = no pain; 10 = extreme pain).
Conclusion: Patient expectations about DRE were negative before examination and changed significantly following the exam. Pain during examination was negligible, contrary to the prevalent belief. These two findings must be clearly presented to patients in order to improve PCa screening acceptance.

Key words: *prostatic neoplasms; digital rectal examination; diagnosis*
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INTRODUCTION

Despite a certain degree of imprecision, digital rectal examination (DRE) still represents a useful method to identify prostate cancer (PCa) cases (1,2). Among the available diagnostic tools, this method is the fastest, cheapest, and most accessible to patients. However, a great number of men still refuse to undergo DRE (3), with reasons for this behavior varying from lack of knowledge about the disease to cultural prejudice related to the examination (3).

Despite some advantages, DRE has some limitations (4), most of them are related to determination of the prostate volume and the initial detection of PCa cases (5). Furthermore, its sensitivity depends on the expertise of the physician, and if there is a large amount of inter-observer variability.

Community studies analyzing the reason why men refuse to undergo DRE are of pivotal importance to the development of public health strategies aimed at PCa screening. The objectives of the present study are to analyze patients' preferred examination position, to analyze the patients' expectations and reactions regarding DRE before and after the examination, to analyze the level of pain felt during the exam, and finally, to define the acceptance of PCa screening performed annually.

MATERIALS AND METHODS

Among 1070 men who participated in a PCa screening program, 269 (25.14%) were randomly chosen to participate the study. The ages of the patients assessed varied from 45 to 86 years, and all men were interviewed by undergraduate medical students under the supervision of experienced urologists. All patients underwent blood analysis for measurement of prostate specific antigen (PSA), urinalysis, and DRE in the supine position by experienced urologists. Patients also completed questionnaires related to quality of life, urinary symptoms, and sexual function.

Following these steps, patients answered the questions presented in Figure-1. The first question concerned the preferred position for DRE. The options were standing up, kneeling while resting on the elbows, supine, and left lateral positions. The second question concerned the subjects' expectations of how it was going to be. Figure-2 included 3 questions about patient's reactions after examination. The first question concerned the subjects' expectations on how it was. The second question concerned the acceptance of the annual screening procedure and the third the perception of pain related to the exam on a score from 0 to 10 according to a visual analogical scale (VAS).

The impression of patients regarding the DRE was classified according to the answer about the expectation before and the reactions after DRE. Patients who answered normal or not comfortable were considered to have a good impression about the examination; conversely, those who responded humiliating or painful were considered to have a bad impression about the examination.

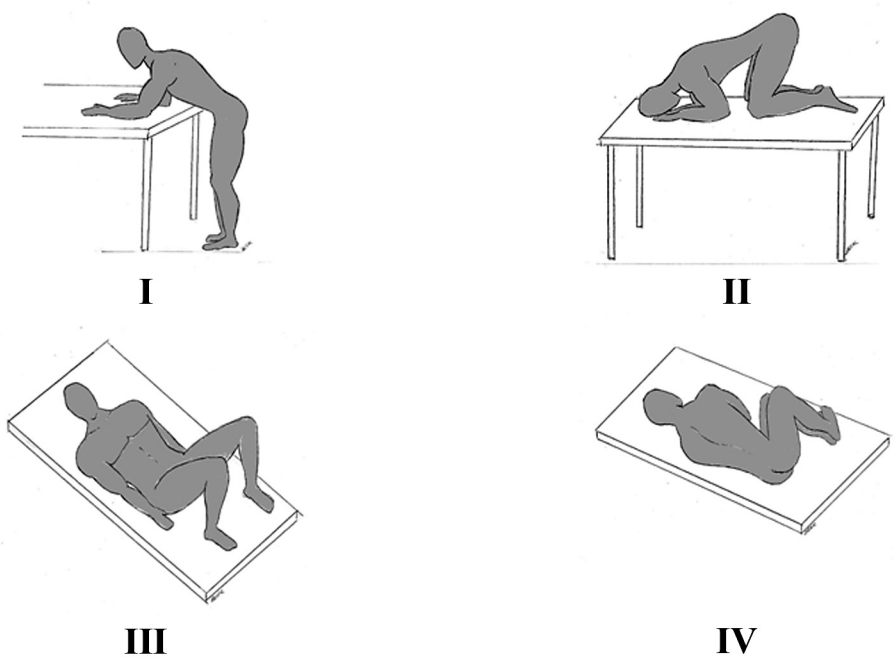

Figure 1

1) In which position would you rather be examined?

2) Before the exam, what was your impression about digital rectal examination?
- □ *Painful*
- □ *Humiliating*
- □ *Not comfortable*
- □ *Normal*

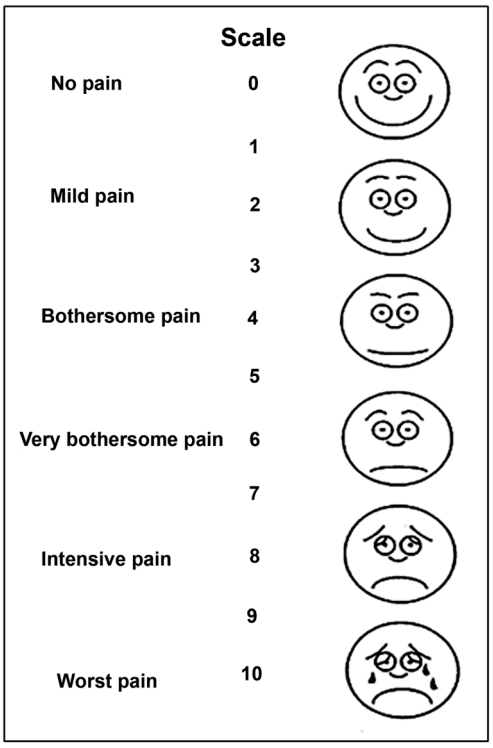

Figure 2

1) After the exam, what is your impression about DRE?
- □ *Painful*
- □ *Humiliating*
- □ *Not comfortable*
- □ *Normal*

2) Would you repeat this exam annually?
- □ *Yes*
- □ *No*

3) How do you classify pain in during this exam?

For statistical analysis we used the McNeman Chi-squared test. Statistical analysis was performed using the SPSS 12.0 for Windows software and significance was set as $p \leq 0.05$.

RESULTS

Table-1 shows the results of the patients' answers when questioned about the position they would choose to undergo DRE. More than half of the patients preferred the supine position, and kneeling while resting on the elbows was the least attractive.

Figure-1 illustrates the patients' expectations about DRE. Notably, before undergoing the exam, 54% of patients imagined that it would be painful, humiliating, or bothersome. After the exam, 137 (50.9%) patients maintained their answer, while 132 (49.1%) changed their answer and expressed a good impression about the exam. Also, before the exam, 160 of the 269 patients (59.5%) imagined that the exam would not cause discomfort. After DRE, 246 out of 269 patients (91.4%) had a good impression ($p < 0.001$) (Figure-2).

When the men were asked if they would be willing to repeat the examination annually, with the aim of screening for PCa, only five patients answered negatively. The other 264 (98.1%) patients said that they would repeat the exam without foreseeing any problem.

The mean pain score related to DRE as reported on the VAS was 1.68 (median 1).

COMMENTS

The present study analyzed the reactions of men regarding DRE who had never previously undergone this examination. To justify this study, it is necessary to consider that because of their pervasive heterosexual culture, for many decades Latin-Americans have been extremely hesitant to undergo this kind of examination.

Table 1 – *Patients' preferred position for digital rectal examination.*

Position	N	(%)
Standing up	76	28.25
Kneeling while resting on the elbows	19	7.07
Supine	145	53.90
Left lateral	29	10.78
Total	269	100

In the post-PSA era, there was a great advance when patients' wives and girlfriends became supportive of the urologists' cause, convincing patients that a man's prostate examination had the same significance as a woman's preventive gynecologic examination. With this example and with a great appeal from the medical community, there was a large amount of support for men to adhere to PCa screening programs. The extent of this cultural revolution could be proven by the fact that in only one day of attending PCa screening, we found 1070 men who were subsequently included in this study.

Based on the data of the present study, the expectations before the examination showed that half of the men were not worried because they imagined that the examination would be non-traumatic; this expectation was not only confirmed but increased after DRE.

One hundred nine patients did not have a favorable previous impression about the examination, but after the exam, only 23 men maintained this impression. It is important to point out that the level of pain reported when they underwent the exam was extremely low, 1.69 on a scale from 0 to 10, demonstrating numerically what specialists have been repeating continuously to patients.

In the medical literature, we found only one reference in which the authors compared two methods of prostate examination, with better acceptance of the standing position, with the body bending forward and supported by the elbow, than of the left lateral position (5). In the present report, the supine position was the preference of more than half of the patients. The majority of assistant physicians, seniors or juniors, also preferred the supine position, which allows a better impression of the prostate characteristics.

Scientifically unmasking the DRE, as we have shown, supplies important information to the physicians who are dedicated to PCa screening and to public health care problems. Our data clearly demonstrate that DRE is far from being a humiliating or painful exam. These figures indicate that when candidates for PCa screening are properly advised and treated with the humanistic principles that govern good medical practice, almost 100% of them promise to return annually to undergo the examination.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Srougi M: Cancer da Próstata. In: Srougi M, Simon SD (ed.), Câncer Urológico. São Paulo, Platina. 1996; pp. 281-359.
2. Tenke P, Horti J, Balint P, Kovacs B: Prostate cancer screening. Recent Results Cancer Res. 2007; 175: 65-81.
3. Nijs HG, Essink-Bot ML, DeKoning HJ, Kirkels WJ, Schröder FH Why do men refuse or attend population-based screening for prostate cancer? J Public Health Med. 2000; 22: 312-6.
4. Fournier G, Valeri A, Mangin P, Cussenot O: Prostate cancer: Diagnosis and staging. Ann Urol (Paris). 2004; 38: 207-24.
5. Frank J, Thomas K, Oliver S, Andrews S, Choong S, Taylor R, et al.: Couch or crouch? Examining the prostate: a randomized study comparing the knee-elbow and the left-lateral position. BJU Int. 2001; 87: 331-3.

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EDITORIAL COMMENT

The authors have analyzed one aspect of digital rectal examination (DRE) that, at first glance only, could be considered insignificant. In fact, we have to consider that the screening program was conducted in a geographic area where the predominant Latin-Americans have a great hesitation to undergo this kind of exam due to cultural and religious reasons. I fully agree that the results of this study should support the urologists and the general physicians to convince the patient that this type of exam is far from being humiliating and painful. If the cultural revolution continues on this course, DRE can be considered in the mind of the general population at the same level of a woman's preventive gynecologic exam. Unfortunately, many physicians are still reluctant to perform a DRE due to the lack of experience or due to culture reasons. Moreover, it should be remembered that the positive predictive value of DRE is limited as predictor of prostate cancer diagnosis (1), and an effective program of prostate cancer prevention has to be accompanied by a PSA examination.

REFERENCES

1. Issa MM, Zasada W, Ward K, Hall JA, Petros JA, Ritenour CW, et al.: The value of digital rectal examination as a predictor of prostate cancer diagnosis among United States Veterans referred for prostate biopsy. Cancer Detect Prev. 2006; 30: 269-75.

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EDITORIAL COMMENT

Digital rectal examination (DRE) is clearly not an ideal general screening tool for prostate cancer (if one believes that it should be done at all). Nevertheless, proposing DRE to his male patients the urologist raises their awareness of prostate diseases, and provided sufficient explanation is given, it should certainly be included in regular check-ups. The authors should be commended for demystifying DRE.

In addition I feel that this paper is a good illustration of an excellent clinical paper, tackling a single question, designing a well conducted study and providing a straight answer and conclusion.

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Can Bipolar Vaporization be Considered an Alternative Energy Source in the Endoscopic Treatment of Urethral Strictures and Bladder Neck Contracture?

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ABSTRACT

Objective: We evaluated the outcome of bipolar energy by using PlasmaKinetic™ cystoscope instruments in the treatment of urethral stricture and bladder neck contracture.

Materials and Methods: Twenty-two male patients with urethral stricture and five with bladder neck contracture were treated by endoscopic bipolar vaporization. The most common etiology for stricture formation was iatrogenic (85.2%) and the mean stricture length was 12.2 mm. All patients were evaluated with urethrography and uroflowmetry one month and 3 months after surgery. Urethroscopy was routinely performed at the end of the first year. Preoperative mean maximum flow rate (Q max) was 4.9 mL/s for urethral stricture and mean Q max was 3.4 mL/s for bladder neck contracture. The results were considered as "successful" in patients where re-stenosis was not identified with both urethrography and urethroscopy. Minimum follow-up was 13.8 months (range 12 to 20).

Results: Tissue removal was rapid, bleeding was negligible and excellent visualization was maintained throughout the vaporization of the fibrotic tissue. Postoperative mean Q max was 14.9 mL/s and the success rate was 77.3% for urethral stricture at mean follow-up time of 14.2 months. The success rate was 60% with a mean follow-up time of 12.2 months for bladder neck contracture and the mean Q max was 16.2 mL/s, postoperatively.

Conclusions: The study suggests that bipolar vaporization is a safe, inexpensive and reliable procedure with good results, minimal surgical morbidity, negligible blood loss, and thus, it could be considered as a new therapeutic option for the endoscopic treatment of urethral stricture and bladder neck contracture.

Key words: *urethra; urethral stricture; endoscopy; vaporization; bipolar energy*

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INTRODUCTION

The management of urethral stricture and bladder neck contracture include periodic dilatation, blind internal urethrotomy, optical urethrotomy with or without monopolar electrocautery or various laser treatment and definitive open urethroplasty. Although long term results of open urethroplasty surgery are excellent, open urethroplasty surgery can be challenging and time-consuming.

A recent survey of stricture management in the United States showed that most urologists (57.8%) do not perform urethroplasty, while 31% to 33% would continue to manage the stricture by minimally invasive means despite predictable failure. Many urologists have selected the use of endoscopic procedure as primary approach, but, currently, this approach is no longer justified based on studies reported in the literature (1-3).

Although internal urethrotomy continues to be the most commonly used procedure, the optimal

management is still widely debated, because the recurrence rates range between 75% and 80% in the long term (1-3). As an alternative energy source, the first bipolar device for endourological procedures was Gyrus device using PlasmaKinetic™ Endourology System (Gyrus PlasmaKinetic™ System, Medical, Maple Grove, MD). Bipolar energy enables an instant incision and vaporization of the stricture, and contributes to decreased recurrent scar tissue formation (4-6). Thus, current prospective pilot study was conducted to evaluate efficacy and safety of PlasmaKinetic™ cystoscope instruments in the treatment of urethral strictures and bladder neck contractures.

MATERIALS AND METHODS

Between May 2004 and December 2005, twenty-seven male patients 29 to 74 years old (mean age 56.3) with urethral strictures or bladder neck contractures underwent endoscopic bipolar vaporization using PlasmaKinetic™ cystoscope instruments: Plasma-Cise™ and Plasma-Cut™ (Figure-1). The study was performed in accordance with the Helsinki Declaration of the World Medical Association, and written informed institutional research consent was obtained from all patients. The strictures were localized in the urethra and the bladder neck in 22 and 5 patients, and treated with Plasma-Cise™ and Plasma-Cut™ in 16 and 11 patients, respectively. The most common cause of stricture was iatrogenic (85.2%), followed by trauma (14.8%). The location of the stricture was penile, bulbar and membranous urethra in 4, 15 and 3 patients, respectively (Table-1). Four of bladder neck contractures were detected after radical retropubic prostatectomy and one after ileal neobladder.

The stricture length was measured by both uroradiography and urethroscopy using a ureteric catheter after excising the scar tissue. The average length of the strictures was 12.2 mm. (range 10 to 25 mm). Twenty-two patients had untreated strictures and the remaining were previously treated by cold-knife urethrotomy in three and urethroplasty in two. There was single stricture in 23 and multiple in 4 patients.

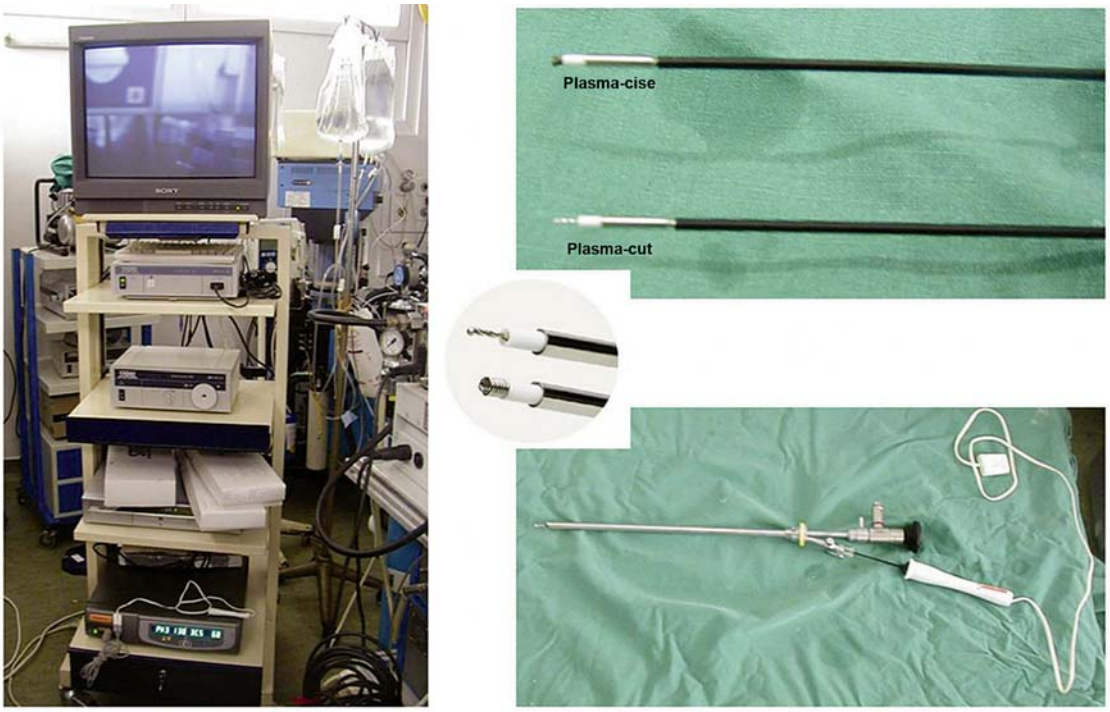

Figure 1 *– Gyrus PlasmaKinetic™ Endourology System and cystoscope instruments: Plasma-Cise™ and Plasma-Cut™.*

Table 1 – *Site and etiology of the stricture.*

	N Patients (%)
Site	
Urethra	22 (81.5)
Penile	4 (14.8)
Bulbar	15 (55.6)
Membranous	3 (11.1)
Bladder neck	5 (18.5)
Etiology	
Iatrogenic	23 (85.2)
TURP	13 (48.2)
TUR-BT	2 (7.4)
RP	3 (11.1)
RRP	4 (14.8)
Ileal neobladder	1 (3.7)
Traumatic	4 (14.8)

TURP = transurethral resection of prostate; TUR-BT = transurethral resection of bladder tumor; RP = retropubic simple prostatectomy; RRP = retropubic radical prostatectomy.

All patients were evaluated preoperatively based on previous medical history, physical examination, urine culture, ultrasound of the upper tract, urethrography and uroflowmetry. Combined antegrade and retrograde urethrography was performed in two patients with previously placed suprapubic tube. Any active urinary tract infection was treated and routine prophylactic antibiotics were administered before surgery. All patients received general or spinal anesthesia. For safety purposes, a guidewire or 5F ureteral catheter was passed through the stricture whenever possible (Figure-2). Core-through vaporization was performed for obliterative strictures in two patients with suprapubic tube. The procedure was performed by using a 19F cystoscope and PlasmaKinetic™ cystoscope instruments were easily passed through the 5F working channel of the cystoscope (Figure-1).

Vaporization was performed at 12 o'clock for urethral strictures and at 4 and 8 o'clock for bladder contractures using 60 watt vaporization power setting and 0.9% sodium chloride solution for irrigation. No desiccation was done. An 18 Fr. urethral catheter was left in the bladder for 24 hours after the procedure.

Uroflowmetry and urethrography were performed one month after surgery and repeated every 3 months. All patients were evaluated using urethroscopy 12 months after the procedure to assess the outcome. During the follow-up, if maximum flow rate (Q max) was < 15 mL/s, urethroscopy was performed to exclude recurrent stricture. The results

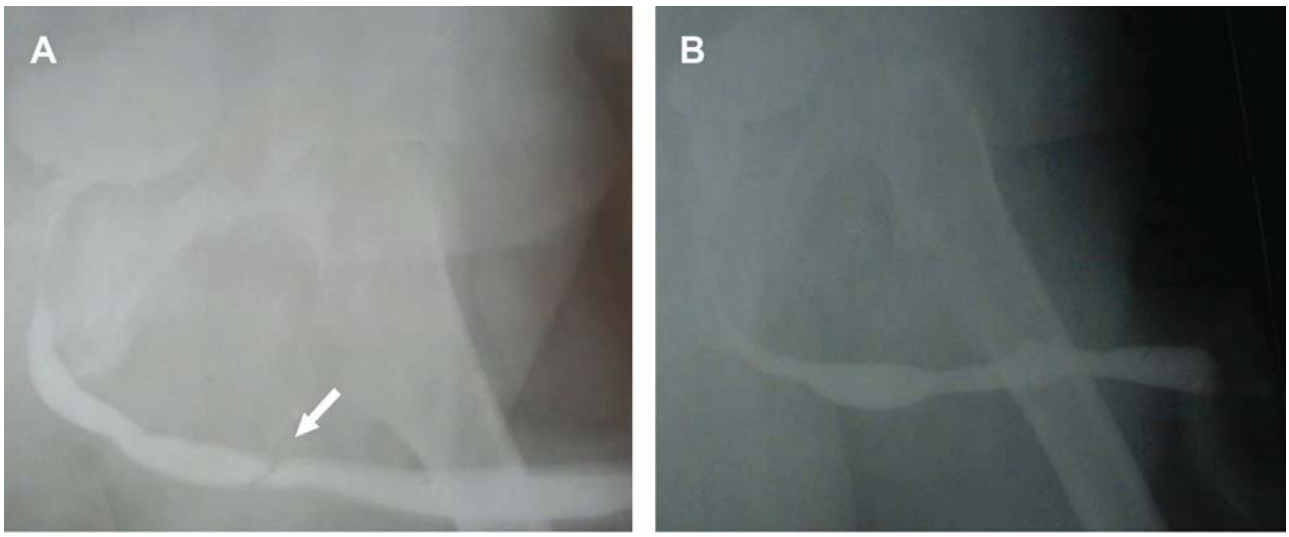

Figure 2 – *A)- Preoperative urethrography showing urethral stricture (arrowhead). B)- Postoperative urethrography showing widely patent urethra after bipolar vaporization.*

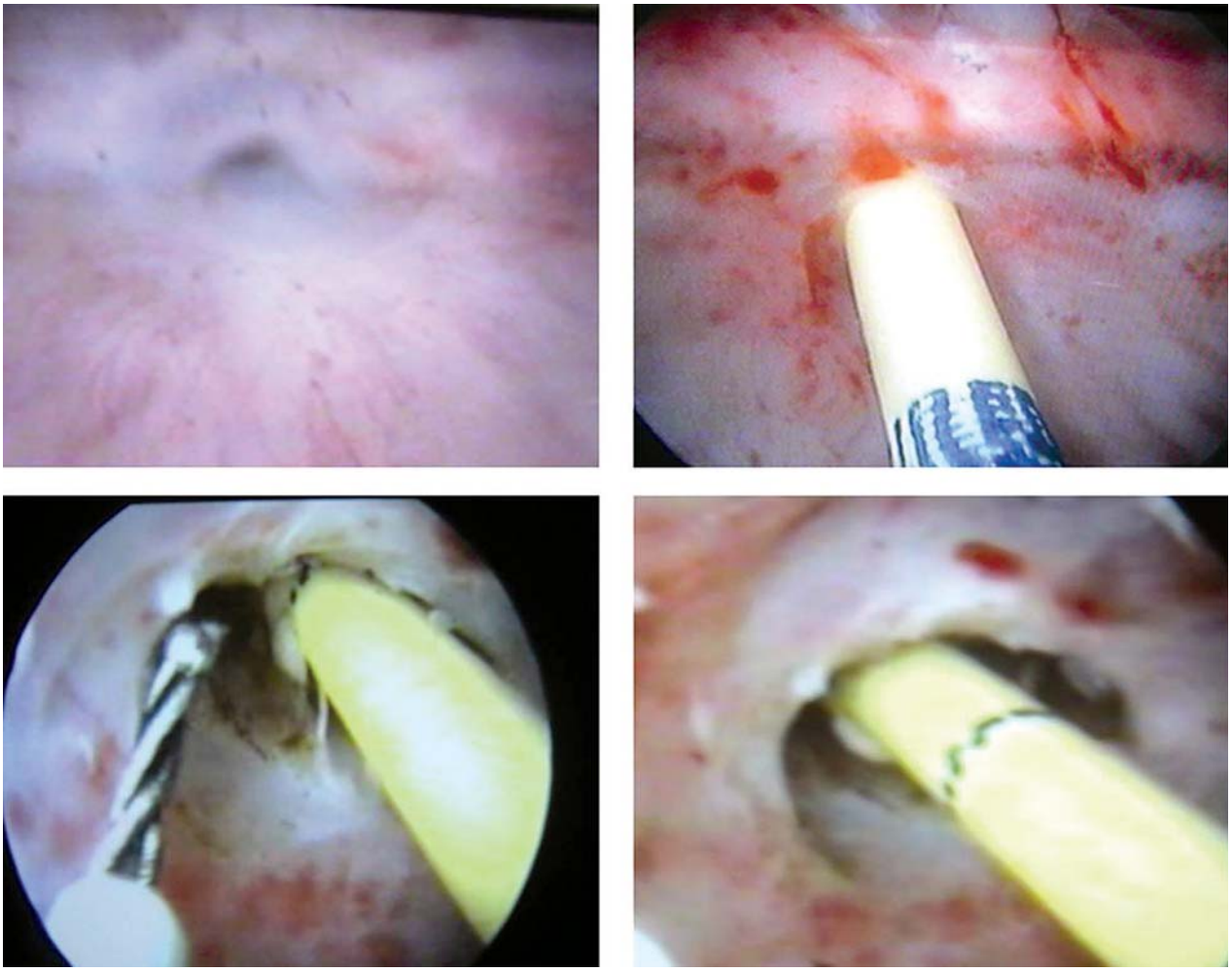

Figure 3 – *A guide-wire was passed through the stricture whenever possible and vaporization was performed.*

were considered as "successful" in patients in whom the Q max was ≥ 15 mL/s without any obstructive symptoms and with no evidence of recurrent stricture with urethrography or urethroscopy (Figure-3) (7). The outcome was defined as a "failure" if the patient needed any intervention after initial treatment due to re-stenosis (7). The follow-up was 12 to 20 months (mean 13.8 months). Preoperative mean Q max was 4.9 mL/s (range 0 to 9) in 22 patients who had urethral stricture and 3.4 mL/s (range 0 to 5) in 5 patients who had bladder neck contracture. The overall mean Q max was 4.6 mL/s (range 0 to 9) before surgery in 27 patients.

Statistical analysis was carried-out using the NCSS-PASS 2007. Differences between the preoperative and postoperative mean Q max values of patients were analyzed by the Wilcoxon test. Differences were considered significant for $p < 0.05$.

RESULTS

In 25 patients, we passed a guidewire or 5 Fr. ureteral catheter without any technical difficulty. Core-through vaporization was applied in two cases with obliterative strictures, successfully. Blood loss was negligible and excellent visualization was maintained throughout the procedure. The average operative time was 15 minutes (range 8 to 30). All patients were continent after removing the catheter and able

Table 2 *– Mean Q max of patients that did not require a subsequent procedure depending on location of the stricture.*

Location	N Pts	Preoperative Q max	Postoperative Q max
Urethra	22	4.9 mL/s	14.9 mL/s
Bladder neck	5	3.4 mL/s	16.2 mL/s

to void, satisfactorily. Postoperative Q max ranged between 6 to 25 mL/s (mean 15.2 mL/s) in 27 patients. Twenty patients without any evidence of recurrence on urethrography voided with a mean Q max of 17.2 mL/s (range 15 to 25) at the end of the first month.

In 22 patients with urethral stricture, at a mean follow-up time of 14.2 months (range 12 to 20 months) and the postoperative Q max ranged between 6 to 24 mL/s (mean 14.9 mL/s) ($p < 0.0001$) (Table-2). Seventeen of these patients with urethral stricture had no signs or symptoms to suggest recurrence after urethrography and uroflowmetry examinations, and the post-operative Q max ranged between 16 to 24 mL/s (mean 16.8 mL/s). Recurrent stricture was found in 5 (22.7%) cases, 3 of which underwent urethroplasty (Q max was 6 mL/s in all cases) and 2 were on urethral dilation (Table-3). The Q max was 11 mL/s and 13 mL/s in two patients who required urethral dilation. After urethral dilation, the Q max of these patients was improved to 15 mL/s and 17 mL/s, respectively. In all 5 patients, urethroscopy was performed to confirm recurrent urethral stricture. We had no evidence of voiding dysfunction in these patients, and therefore we did not use urodynamic study in the evaluation.

Of the 5 cases with bladder neck contracture, 3 were cured with a mean follow-up time of 12.2 months (range 12 to 14). The mean Q max was 16.2 mL/s (range 7 to 25), postoperatively ($p = 0.043$) (Table-2). One patient with a Q max of 7 mL/s required a second vaporization of the contracture and the other improved with frequent urethral dilation (Q max was increased from 10 mL/s to 17 mL/s) (Table-3).

The success rate was 77.3% (17/22) for urethral stricture and 60% (3/5) for bladder neck contracture. A total of 20 out of 27 patients were cured

Table 3 *– Outcome of bipolar vaporization and subsequent procedures.*

	N Pts	N (%) Pts Without Recurrence	N (%) Pts With Recurrence	N Pts With Subsequent Procedures		
				Urethroplasty	Dilation	Vaporization
Site						
Urethra	22	17 (77.3)	5 (22.7)	3	2	
Bladder neck	5	3 (60)	2 (40)		1	1
Etiology						
Iatrogenic	23	18 (78.3)	5 (21.7)			
TURP	13	11 (84.6)	2 (15.4)	1	1	
TUR-BT	2	2 (100)				
RP	3	2 (66.7)	1 (33.3)		1	
RRP	4	2 (50)	2 (50)			1
Ileal neobladder	1	1 (100)			1	
Traumatic	4	2 (50)	2 (50)	2		

TURP = transurethral resection of prostate; TUR-BT = transurethral resection of bladder tumor; RP = retropubic simple prostatectomy; RRP = retropubic radical prostatectomy.

(74%) after the procedure during a mean follow-up of 13.8 months (range 12 to 20 months).

COMMENTS

Iatrogenic causes, which result in strictures anywhere in the urethra, are the most common cause in current clinical practice and the optimal management still remains widely debated. Though urethroplasty has a high success rate, endoscopic treatment is still preferred by the majority of urologists (74%) because of its safety and simplicity (2, 8-10).

The low success rates of cold knife urethrotomy prompted us to search for different therapeutic alternatives, and various types of lasers were attempted for this purpose. The reason for using lasers instead of cold knife depends on the basis of decreased formation of scar tissue. Primary experience with lasers have shown success rates ranging between 36% and 50%. Some of the recent reported studies have shown promising success rates of up to 93% with contact Nd:YAG laser and Ho:YAG laser (1,11,12). Because of its high cost, laser treatments have not gained wide popularity for routine use. Therefore, we conducted this study to confirm if the vaporization could be an alternative energy source for the treatment of urethral strictures and bladder neck contractures.

The intended use of bipolar vaporization using PlasmaKinetic™ cystoscope instruments is to perform vaporization of fibrous tissue. Two types of tip design are available; braided-tip (Plasma-Cut™) for finer fibrous tissue, and spring-tip (Plasma-Cise™) for more aggressive fibrous tissue removal in stricture or bladder neck incisions. The mechanism of the bipolar energy depends on a vapor ball that is located around the end of the device where energy is passed. The high-frequency energy passes through the 0.9% sodium chloride solution that is in contact with the scar tissue from the active to the return tip of the instrument. The irrigation solution forms a thin layer to convert into vapor plasma containing energy charged particles. When these high energy charged particles come in contact with the tissue, they cause disintegration through molecular dissociation (4-6,13,14). This leads to lower temperatures at the treatment site, so that the depth of the thermal damage of the surrounding tissue is less than 1 mm. In recent studies, the depths of the vaporization ranged from 118μm to 163μm compared with 287μm for the monopolar energy (4,15). The depth of penetration of Ho:YAG laser, which is known to be as shallow, is 0.5 mm (11,16).

The main difference between the bipolar energy and cold-knife procedures is that the fibrotic tissue is not only incised but also evaporated with the vaporization. Thus, the recurrence of scar tissue can be decreased (4-6,15). As in laser therapy, we observed that the tissue removal was rapid and bleeding was minimal with the vaporization, and surgical field was visually clearer than the cold knife urethrotomy.

However, the abundant corpus spongiosum around the bulbar urethra renders endoscopic treatment more successful than the bladder neck, cold-knife urethrotomy is limited for short strictures in the bulbar urethra. This technique has high failure rates especially when the stricture is longer or is associated with significant spongiofibrosis. As a common concept, urethroplasty is the ideal first-line therapy in younger patients with traumatic strictures (8,10). We believe that bipolar vaporization can be considered an alternative treatment before performing more invasive procedure such as urethroplasty in older patients, the majority of which with longer and fibrotic iatrogenic urethral strictures and bladder neck strictures. If the bipolar technique is eventually selected in order to achieve lower rates of spongiofibrosis, bipolar vaporization can also be used effectively in younger patients with short traumatic strictures in the bulbar urethra.

The success rates of cold-knife urethrotomy at 5 years is less than that of urethroplasty (50% vs. 83%) and it is well accepted that bipolar PlasmaKinetic™ technology has a slightly greater failure rate compared with urethroplasty (9,17). However, failure of the procedure does not affect a second repeated procedure. Indeed, this technique was successful in 77.3 % of patients and spared the cases from a far more invasive procedure such as urethroplasty. Nevertheless, we believe that if vaporization fails, repeat attempts at endoscopic correction of urethral stricture should be abandoned in favor of definitive urethroplasty.

The results of core-through urethrotomy have ranged from 58% to 100% as reported by various investigators. A high recurrence rate (40% to 50%)

has been a cause of concern, especially after the use of cold knife (16,18). The key to successful treatment of obliterative urethral strictures is not only to incise the hard fibrotic tissue but also to excise the fibrosis to prevent re-stenosis. For this reason, bipolar energy can be used to incise, excise and vaporize during the core-through procedure, lowering the risk of re-scarring and re-stenosis by eliminating the need for coagulation (4-6).

In current study, we reported the first clinical experience with bipolar energy and our cure rate was 77.3% for urethral stricture and 60% for bladder neck contracture. As we compare success rates of bipolar energy with cold knife urethrotomy (range 60% to 70%) and laser therapy (range 59% to 93%) for the treatment of urethral strictures, our results seems to be as effective as laser treatment, and better than cold knife (1,19,20). Furthermore, as regards the cost-effectiveness of the treatment, vaporization of the scarred tissue using bipolar energy by PlasmaKinetic™ cystoscopic instruments has an obvious advantage over laser therapies with good results for urethral strictures and bladder neck contractures.

There may be some limitations of this study, such as the inadequacy of the sample size, the lack of a questionnaire for the assessment of urinary symptoms, and the heterogeneity of the patients.

CONCLUSION

In the present study, short operative time, minimal surgical morbidity, negligible blood loss and satisfactory success rate cast new light on the endoscopic treatment of urethral stricture. Our results indicate that bipolar vaporization of urethral strictures is a safe and cost-effective procedure.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Kamal BA: The use of the diode laser for treating urethral strictures. BJU Int. 2001; 87: 831-3.
2. Peterson AC, Webster GD: Management of urethral stricture disease: developing options for surgical intervention. BJU Int. 2004; 94: 971-6.
3. Bullock TL, Brandes SB: Adult anterior urethral strictures: a national practice patterns survey of board certified urologists in the United States. J Urol. 2007; 177: 685-90.
4. Rassweiler J, Schulze M, Stock C, Teber D, De La Rosette J: Bipolar transurethral resection of the prostate--technical modifications and early clinical experience. Minim Invasive Ther Allied Technol. 2007; 16: 11-21.
5. Alschibaja M, May F, Treiber U, Paul R, Hartung R: Recent improvements in transurethral high-frequency electrosurgery of the prostate. BJU Int. 2006; 97: 243-6.
6. Smith D, Khoubehi B, Patel A: Bipolar electrosurgery for benign prostatic hyperplasia: transurethral electrovaporization and resection of the prostate. Curr Opin Urol. 2005; 15: 95-100.
7. Micheli E, Ranieri A, Peracchia G, Lembo A: End-to-end urethroplasty: long-term results. BJU Int. 2002; 90: 68-71.
8. Greenwell TJ, Castle C, Andrich DE, MacDonald JT, Nicol DL, Mundy AR: Repeat urethrotomy and dilation for the treatment of urethral stricture are neither clinically effective nor cost-effective. J Urol. 2004; 172: 275-7.
9. Mandhani A, Chaudhury H, Kapoor R, Srivastava A, Dubey D, Kumar A: Can outcome of internal urethrotomy for short segment bulbar urethral stricture be predicted? J Urol. 2005; 173: 1595-7.
10. Rourke KF, Jordan GH: Primary urethral reconstruction: the cost minimized approach to the bulbous urethral stricture. J Urol. 2005; 173: 1206-10.
11. Matsuoka K, Inoue M, Iida S, Tomiyasu K, Noda S: Endoscopic antegrade laser incision in the treatment of urethral stricture. Urology. 2002; 60: 968-72.
12. Perkash I: Ablation of urethral strictures using contact chisel crystal firing neodymium: YAG laser. J Urol. 1997; 157: 809-13.
13. Eaton AC, Francis RN: The provision of transurethral prostatectomy on a day-case basis using bipolar plasma kinetic technology. BJU Int. 2002; 89: 534-7.
14. Starkman JS, Santucci RA: Comparison of bipolar transurethral resection of the prostate with standard transurethral prostatectomy: shorter stay, earlier catheter removal and fewer complications. BJU Int. 2005; 95: 69-71.
15. Wendt-Nordahl G, Häcker A, Reich O, Djavan B, Alken P, Michel MS: The Vista system: a new bipolar resection device for endourological procedures:

comparison with conventional resectoscope. Eur Urol. 2004; 46: 586-90.
16. Dogra PN, Nabi G: Core-through urethrotomy using the neodymium: YAG laser for obliterative urethral strictures after traumatic urethral disruption and/or distraction defects: long-term outcome. J Urol. 2002; 167: 543-6.
17. Barbagli G, Palminteri E, Bartoletti R, Selli C, Rizzo M: Long-term results of anterior and posterior urethroplasty with actuarial evaluation of the success rates. J Urol. 1997; 158: 1380-2.
18. Thomas MA, Ong AM, Pinto PA, Rha KH, Jarrett TW: Management of obliterated urinary segments using a laser fiber for access. J Urol. 2003; 169: 2284-6.
19. Pansadoro V, Emiliozzi P: Internal urethrotomy in the management of anterior urethral strictures: long-term followup. J Urol. 1996; 156: 73-5.
20. Albers P, Fichtner J, Brühl P, Müller SC: Long-term results of internal urethrotomy. J Urol. 1996; 156: 1611-4.

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EDITORIAL COMMENT

This study reminds us that the field of bipolar energy is moving forward and wider to treat urethral strictures besides transurethral resection of prostate. The endoscopic technology in the 21st century is running, not walking, towards reduction in the use of irrigation volume, bleeding, catheter, and hospital time. Urologist should not be left behind while the winds of endoscopy are blowing.

A limitation of this study is the small number of patients recruited at its current status. This limitation greatly implicates the interpretation of the complication findings. The use of statistics to decide clinical relevance of these findings at this stage is premature; hence, they must be viewed cautiously. Their statistical significance or insignificance may not reflect a true clinical relevance. A double-blind randomized comparison and accrual of a larger pool of patients with a longer follow-up period will definitely provide a more accurate picture that may prove the difference between bipolar energy, cold knife urethrotomy and laser therapy. More data will be needed for the comparison of different devices and for the further assessment of complications.

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EDITORIAL COMMENT

In this issue of International Braz J Urol, Basok and co-workers report their preliminary experience in the treatment of urethral stricture and bladder neck contracture using bipolar energy by PlasmaKinetic™ cystoscope instruments. They enrolled 22 male patients with urethral stricture and 5 with bladder neck contracture. In 22 patients with urethral stricture, postoperative mean Q_{max} was 14.9 mL/s and the success rate was 77.3% at mean follow-up time of 14.2; in the 5 cases with bladder neck contracture, the success rate was 60% with a mean Q_{max} of 16.2 mL/s at a mean follow-up time of 12.2 months. Authors conclude that bipolar vaporization is a safe, inexpensive and reliable procedure with good results, minimal surgical morbidity and negligible blood loss. They suggest that this new technique can be considered favorably as a new therapeutic option for the endoscopic treatment of urethral stricture and bladder neck contracture.

Each new technique is thought to be better than the old one, but it can be asserted only after a well design study with an adequate follow-up. Unlike new drugs, such as antimuscarinic agents or botulinum toxin for the treatment of overactive bladder, which require a substantial amount of research and assessment before licensing, new surgical procedures have often found their way into clinical practice with little and imperfect evidence. This has also been the case in Urology. Examples may be the widespread use of several and different sets of mid-urethral sling for the treatment of stress urinary incontinence or different techniques, using mesh, for pelvic organ prolapse repair. As concerns results, it generally seems that many of the new surgical approaches have not been developed gradually using adequate health-technology-assessment systems. This topic was primarily addressed by the Interventional Procedures Program of the UK's National Institute for Health and Clinical Excellence (NICE), which has published guidelines regarding the efficacy and safety of over 250 procedures since 2002. These guidelines primarily apply to the UK but are also used as a source of information for other countries (1).

Recently Barbagli and Lazzeri addressed the issue of performing randomized controlled studies on urethral reconstructive surgery (2). They realized that the evidence for new surgical techniques has often been poor, and typically included small numbers of patients with inadequate length and completeness of follow-up (3). The question is what has history taught us as regards who is dealing with new urethral reconstructive surgeries?

Most of the evidence usually comes from case series, whereas evidence from randomized trials is sparse and meta-analyses of these trials are extremely rare. One of the outstanding examples of that it is the introduction of oral mucosa as a substitute material. Currently, oral mucosa has become the most popular substitute material in the treatment of urethral strictures, as it is readily available and easily harvested from the cheek, lip or tongue, allowing for a concealed donor site scar with low oral morbidity (4). All the papers that have contributed to the widespread use of the oral mucosa graft are retrospective, not prospective, nor are they randomized, controlled trials.

Lack of good evidence for new techniques or new approaches to urethral strictures may represent challenges for many of us. It is a challenge for urologists who want to offer potential benefits of new treatments to suitably selected patients, for patients who need good information when making choices and for government and private health-care funding bodies in deciding whether new procedures should be introduced into use and reimbursed. Thus, caution should be reserved for any new techniques before introducing them in clinical practice. Registers for collection of data for all patients undergoing a new procedure might represent a valuable tool regarding efficacy and safety, when evidence from randomized trials is lacking.

REFERENCES

1. National Institute for Health and Clinical Excellence. Interventional procedures: issued guidance. 2007 http://www.nice.org.uk/guidance/index.jsp?action=byType&type=3&status=3&bId=t (accessed May 12, 2008).
2. Barbagli G, Lazzeri M: Can Reconstructive Urethral Surgery Proceed Without Randomised Controlled Trials? Eur Urol. 2008; in press.

3. Orandi A: One-stage urethroplasty. Br J Urol 1968;40: 717-9.

4. Cavalcanti A: Editorial comment on: Combined dorsal plus ventral double buccal mucosa graft in bulbar urethral reconstruction. Eur Urol. 2008; 53: 90.

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Epidemiologic Study on Penile Cancer in Brazil

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ABSTRACT

Objectives: To assess epidemiologic characteristics of penile cancer in Brazil.
Materials and Methods: From May 2006 to June 2007, a questionnaire was distributed to all Brazilian urologists. Their patients' clinical and epidemiological data was analyzed (age, race, place of residence, history of sexually transmitted diseases, tobacco smoking, performance of circumcision, type of hospital service), as well as the time between the appearance of the symptoms and the diagnosis, the pathological characteristics of the tumor (histological type, degree, localization and size of lesion, stage of disease), the type of treatment performed and the present state of the patient.
Results: 283 new cases of penile cancer in Brazil were recorded. The majority of these cases occurred in the north and northeast (53.02%) and southeast (45.54%) regions. The majority of patients (224, or 78.96%) were more than 46 years of age while only 21 patients (7.41%) were less than 35 years of age. Of the 283 patients presenting penile cancer, 171 (60.42%) had phimosis with the consequent impossibility to expose the glans. A prior medical history positive for HPV infection was reported in 18 of the 283 cases (6.36%). In 101 patients (35.68%) tobacco smoking was reported. The vast majority of the cases (n = 207; 73.14%) presented with tumors localized in the glans and prepuce. In 48 cases (16.96%) the tumor affected the glans, the prepuce and the corpus penis; in 28 cases (9.89%) the tumor affected the entire penis. The majority of the patients (n = 123; 75.26%) presented with T1 or T2; only 9 patients (3.18%) presented with T4 disease.
Conclusion: Penile cancer is a very frequent pathology in Brazil, predominantly affecting low income, white, uncircumcised patients, living in the north and northeast regions of the country.

Key words: *penile cancer; epidemiology; phimosis*
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INTRODUCTION

Penile cancer is an aggressive and mutilating disease that deeply affects the patient's self-esteem. Penile cancer is a rare neoplasia with low incidence in developed countries. One of the highest world incidence is found in India with rates of 3.32/100,000 inhabitants, and the lowest incidence is in Jewish men born in Israel with rates close to zero (1). In the United States, the incidence rate is 0.2 cases for each 100,000 inhabitants whereas in Brazil the incidence rate of penile cancer is 2.9 - 6.8/100,000 inhabitants, resulting in this country having one of the world's highest incidence rates for this neoplasia (2).

There are many proposed etiologies underlying the development to penile cancer however many aspects of the pathophysiology of this disease are still poorly elucidated. What is known is that there is a strong association between the presence of the prepuce and the development of the disease (3). The risk of developing this neoplasia was studied by Maden et al. (4) in three groups of individuals. In those that had never been circumcised, the risk was 3.2 times higher than in those that were circumcised at birth and 3 times higher than the ones who were circumcised during the neonatal period. Similarly, Paymaster and Gangadharan (5) reported an incidence of 3.3% among non circumcised individuals and 0% in those circumcised after birth.

Furthermore, among those with phimosis or excess prepuce, a low socioeconomic level of the patients and poor personal hygiene were the most important risk factors for the development of penile cancer (6). The importance of the association of these three risk factors is well established; nevertheless in the work of Frisch et al. (7), a low incidence of penile cancer was observed in Scandinavia, even though the population studies reported from this geographical area showed a low incidence of circumcisions.

Also smegma has been implied in the carcinogenesis of penile cancer. Experiments have demonstrated that cancer of the uterine cervix can be induced in female rats through the local application of smegma (8); however the specific carcinogenicity of this substance has yet to be defined (3). A common risk factor for penile cancer includes a clinical history of sexually transmitted diseases such as gonorrhea, Chlamydia, and/or syphilis, even though there is no evidence of a causality relationship between these infectious pathogens and the development of this neoplasia (4).

There is an association between Human Papilloma Virus (HPV) infection and penile cancer in 30 to 50% of cases, primarily HPV 16 (9), although the exact role of the infection in the genesis of this neoplasia has not yet been entirely clarified (10).

Prospective epidemiological studies about penile cancer are rare. In Brazil there are no multicenter epidemiological studies regarding this neoplasia. The aim of this study was to prospectively evaluate the epidemiological characteristics of penile cancer in Brazil, assessing the presence of predisposing factors, the places where the incidence of the disease is higher, the age of the manifestation and the clinical characteristics of the disease.

MATERIALS AND METHODS

Over the period from May 2006 to June 2007, an epidemiological study was conducted among Brazilian urologists to further elucidate the incidence, risk factors, and patient characteristics of newly diagnosed penile cancer patients within Brazil. Each urologist treating a newly diagnosed penile cancer was asked to complete a patient directed questionnaire with no patient identifiers provided in order to maintain patient confidentiality. These questionnaires were sent back to our institution and the results were entered into a prospectively collected database.

The patient's clinical and epidemiological data was assessed in the questionnaire: age, race, place of residence, degree of education, history and type of sexually transmitted diseases, presence of phimosis (patients with incapacity to expose the glans), presence of HPV, age the circumcision was performed (childhood, adolescence and adulthood), tobacco smoking, type of hospital service (public or private network).

Also assessed were: the time between the appearance of the symptoms and the diagnosis of penile cancer; the presence of pre-neoplasic diseases (balanitis xerotica obliterans, Bowen's disease or erythroplasia of Queyrat); the anatomical pathological characteristics of the tumor, such as the histological type, degree, localization of the lesion (glans, prepuce, corpus, shaft or the entire penis); size of the lesion; presence of palpable inguinal lymph nodes; stage of the disease; presence and localization of metastasis and the type of treatment performed, if surgical (partial penectomy, radical penectomy, lymphadenectomy) or palliative (chemotherapy, radiotherapy).

All patients filled out an informed consent form to be included in the sample. The present study was approved by the Bioethics Committee of our institution.

RESULTS

Study accrual and analysis was performed from May 2006 to August 2007. During this study period, 283 questionnaires were received containing 283 new cases of penile cancer. We observed that the majority of the cases (149 cases - 53.02%) were reported in the north and northeast regions of the country with the lowest human development index. The region with fewer reports of cases was the Southern region, a region with a high human development index presenting less than 2 cases (0.71%).

The age range of the patients affected by the disease is shown in Table-1. We can observe that the vast majority of the patients (n = 224; 78.96%) were

***Table 1** – Distribution of the cases of penile cancer in relation to age.*

Age Range	N of Cases (%)
< 26 years	10 (3.53)
27-35 years	11 (3.88)
36-45 years	34 (12)
46-55 years	53 (18.72)
56-65 years	60 (21.2)
> 66 years	111 (39.22)
Total	283 (100)

older than 46 years of age, while only 21 patients (7.41%) were less than 35 years of age. Of the 283 patients with penile cancer, 214 (75.61%) were Caucasian, 63 (22.26%) were Black and only 6 (2.12%) were Oriental.

Of the 283 patients presenting with penile cancer, 171 (60.42%) presented with severe phimosis not allowing the possibility of exposing the glans and 37 (13.07%) had a circumcision. Of these 37 patients, only 1 underwent the procedure in childhood, 4 during adolescence and 32 in adulthood. The patients that had a circumcision in childhood or adolescence presented a low grade penile tumor (Grade 1 - 3 patients, Grade 2 - 2 patients). Of the 32 patients who had a circumcision in adulthood, 28 presented low grade tumors and 4 (12.5%) presented high grade tumors. Of all 37 patients that had a circumcision, only 5 (all belonging to the group of those who underwent circumcision while adults) presented a tumor affecting the corpus penis.

***Table 2** – Staging of 283 cases of penile cancer studied.*

Staging	N of Cases (%)
Tis	7 (2.47)
T1	102 (36.04)
T2	111 (39.22)
T3	44 (15.54)
T4	9 (3.18)
Total	283 (100)

A history of HPV was reported in 18 of the 283 cases (6.36%). In 101 patients (35.68%) there was a report of tobacco smoking. The number of cigarettes per day that the patients consumed tobacco was not reported, nor was the length of time those patients had been tobacco smokers preventing further statistical analysis to be conducted. Of the 101 tobacco smoking patients, 87 (86.13%) presented with a low grade tumor and 14 (13.86%) presented with a high grade tumor.

The vast majority of cases (n = 207; 73.14%) presented with tumors localized in the glans penis and prepuce. In 48 cases (16.96%), the tumor affected the glans, prepuce, and corpora cavernosa of the penis; in 28 cases (9.89%) the tumor affected the entire penis. The frequency distribution of newly diagnosed penile cancer cases stratified by stage of disease is shown in Table-2. The majority of the patients 213 (75.26%) presented stage T1 or T2 tumors; only 9 patients (3.18%) presented stage 4 tumors.

COMMENTS

Brazil is a country with one of the highest incidences of penile cancer in the world; the frequency of this neoplasia is variable depending on the region considered, and is directly related to the local socioeconomic conditions. The overall relative incidence was 2.1% of the male neoplasias, reaching 5.7% in the Northeast region, 5.3% in the North region, 3.8% in the Center-east region, 1.4% in the Southeast region and 1.2% in the Southern region (11). According to the data from the Brazilian Ministry of Health, there is an estimated 850 partial or complete penile surgical procedures performed in the context of malignancy yearly within Brazil, with approximately 50% of these procedures being performed in the North and Northeast regions of the country. In our study we observe a predominance of reports of penile cancer in the North and Northeast (53.02%), which are regions with lower human development indexes.

The age range where penile cancer is more frequent is in the sixth decade of life (1,12). This sample included 78.96% of patients older than 45 years of age. However, 7.41% of the patients were less than 35 years of age. The occurrence of this neoplasia

in a younger age range serves as an alert that research of penile neoplasia in young non circumcised patients with suspected lesions is important (13).

There is very limited data in the scientific literature regarding the preponderance of penile cancer among various racial ethnicities. Busby and Pettaway (14) reports that the probability of Africo-American patients developing more aggressive penile cancer is higher than Caucasians; however, this article does not discuss socioeconomic factors that could influence these indexes, i.e. early medical assistance. In our sample the vast majority of the patients (75.61%) were Caucasian. Only 22.26% of the patients were Black and 2.12% Oriental. Since more than 90% of the patients originated from the public service network, this disease tends to affect poorer, non-circumcised patients with precarious hygiene habits. Race does not seem to be a determinant risk factor for the occurrence of this type of tumor.

The most important risk factor for the development of penile cancer is phimosis (4). Men who do not undergo neonatal circumcision have a 3.2 times higher risk to develop penile cancer than patients submitted to the removal of the prepuce after birth (37 patients (13.07%), who had a postectomy compared to 32 who had to the procedure in adulthood and 5 in childhood or adolescence. Only 4 (12.5%) of the 37 patients who had a circumcision presented with a high grade tumor. These data are interesting and may suggest that circumcision prevents the occurrence of penile cancer only if performed in the perinatal period, despite the fact that the patients that had circumcision in their majority (more than 87%) tended to develop low grade tumors.

An important epidemiological study conducted in 244 patients presenting penile cancer with a control group of 232 patients without penile cancer demonstrated that tobacco smoking is a risk factor for the development of penile cancer (15). Of the 283 patients in our study, 101 were tobacco smokers (35.65%). Of the tobacco smoking patients, 87 (86.13%) presented with a low grade and 14 (13.86%) with a high grade penile tumor. This correlation between tobacco smoking and the grade of penile cancer has not previously been reported. Our study, even though it does not offer a control group, demonstrates that more than one third of the patients presenting with penile cancer were tobacco smokers, suggesting that tobacco smoking is one of the risk factors for the development of this neoplasia. More than 85% of the tobacco smoking patients presenting with penile cancer had a low grade tumor.

Our study underlines the fact that even within the context of a contemporary series of penile cancer patients, 58% of patients were diagnosed with advanced disease (Grade T2 or higher). This finding is of concern because it is well established that the advanced stage is strongly correlated with degree of invasion and probability of regional and systemic metastases suggesting a worse prognosis for these patients (16-18).

These data suggest that patients delay in their search for medical care either because of fear or ignorance, or find it difficult to get access to specialized services. Independently from this, a national campaign to alert the greater public about this presently poorly known disease is fundamental. This campaign should also serve as an alert to the Brazilian authorities about the high incidence of this malignancy within our society.

CONCLUSION

Penile cancer is a very frequent pathology in Brazil, predominantly affecting low income, non-neonatal circumcised males, Caucasian patients living in North and Northeast regions of the country where there may be a delay in obtaining specialized medical assistance.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Solsona E, Algaba F, Horenblas S, Pizzocaro G, Windahl T: European Association of Urology. EAU Guidelines on Penile Cancer: Eur Urol. 2004; 46: 1-8.
2. Burgers JK, Badalament RA, Drago JR: Penile cancer. Clinical presentation, diagnosis, and staging. Urol Clin North Am. 1992; 19: 247-56.

3. Schoen EJ, Oehrli M, Colby C, Machin G: The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics. 2000; 105: E36.
4. Maden C, Sherman KJ, Beckmann AM, Hislop TG, Teh CZ, Ashley RL, et al.: History of circumcision, medical conditions, and sexual activity and risk of penile cancer. J Natl Cancer Inst. 1993; 85: 19-24.
5. Paymaster JC, Gangadharan P: Cancer of the penis in India. J Urol. 1967; 97: 110-3.
6. Dagher R, Selzer ML, Lapides J: Carcinoma of the penis and the anti-circumcision crusade. J Urol. 1973; 110: 79-80.
7. Frisch M, Friis S, Kjaer SK, Melbye M: Falling incidence of penis cancer in an uncircumcised population (Denmark 1943-90) BMJ. 1995; 311: 1471.
8. Plaut A, Kohn-Speyer AC: The Carcinogenic Action of Smegma. Science. 1947; 105: 391-392.
9. Villa LL, Lopes A.: Human papillomavirus DNA sequences in penile carcinomas in Brazil. Int J Cancer. 1986; 37: 853-5.
10. Bezerra AL, Lopes A: Landman G, Alencar GN, Torloni H, Villa LL: Clinicopathologic features and human papillomavirus dna prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol. 2001; 25: 673-8.
11. Brumini R: Câncer no Brasil: Dados histopatológicos: 1976-80, Ministério da Saúde - Campanha Nacional de Combate ao Câncer, 1982.
12. Ornellas AA, Seixas AL: Marota A, Wisnescky A, Campos F, de Moraes JR: Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. J Urol. 1994; 151: 1244-9.
13. Culkin DJ, Beer TM: Advanced penile carcinoma. J Urol. 2003; 170: 359-65.
14. Busby JE, Pettaway CA: What's new in the management of penile cancer? Curr Opin Urol. 2005; 15: 350-7.
15. Hellberg D, Valentin J, Eklund T: Nilsson S: Penile cancer: is there an epidemiological role for smoking and sexual behaviour? Br Med J (Clin Res Ed). 1987; 295: 1306-8.
16. Pizzocaro G, Piva L, Bandieramonte G, Tana S: Up-to-date management of carcinoma of the penis. Eur Urol. 1997; 32: 5-15.
17. Horenblas S: Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int. 2001; 88: 473-83.
18. Stancik I, Höltl W: Penile cancer: review of the recent literature. Curr Opin Urol. 2003; 13: 467-72.

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EDITORIAL COMMENT

The authors present an epidemiologic study including 283 patients with penile carcinomas. A questionnaire was distributed to all the Brazilian urologists and epidemiological data was analyzed. Penile cancer is an uncommon tumor with a significantly higher incidence in some areas of underdeveloped countries. Unfortunately, delay on the part of the physician in initiating diagnosis may be considerable and many patients are referred to treatment after developing advanced disease. There is a large volume of data on penile cancer in Brazil. Losing patients to follow-up is common and in some areas of the country, penile

cancer accounts for 17% of all malignancies in men (1). In these less developed areas, penile carcinoma represents one of the most important health problems. In Brazil, it is very difficult to get access to specialized services and unfortunately, in this article it was not possible to discuss socioeconomic factors that could influence the indexes analyzed by the study. This epidemiological study and another sponsored by the Brazilian Society of Urology (SBU) gave us an idea about the complexity of the problem (2). For example, the highest incidence rates of penile carcinoma were found in Maranhão and São Paulo. Maranhão is situated in an underdeveloped area and São Paulo is the richest state of the country. An explanation for this contradiction is the large migration of the poor from underdeveloped areas to São Paulo.

The SBU and the federal government are now waging a campaign to increase early diagnosis and improve health measures in order to eradicate the disease in the future. The authors are to be congratulated for their national campaign to alert the Brazilian urologists and the greater public about this poorly known disease.

REFERENCES

1. Brunini R, Torloni H, Henson DE, Gotlieb SL, De Souza JM: In: Cancer in Brazil: Histopathological Data, 1976-1980. Rio de Janeiro, Ministério da Saúde, 1982; pp. 480.
2. Nardi AC, Glina S, Favorito LA: I estudo epidemiológico sobre câncer de pênis no Brasil. Int Braz J Urol. 2007; 33 (Suppl 1): 1-7.

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EDITORIAL COMMENT

Penile cancer is a rare malignancy in most countries however Brazil has one of the highest incidences of this malignancy. The present study offers a unique opportunity to better define the socio-epidemiological characteristics of this patient population within Brazil. Several important conclusions can be made from this study that I would like to highlight. Firstly, the study illustrates that 283 newly reported cases of penile cancer were treated by Brazilian urologists over a one year period clearly representing one of the highest incidences of this malignancy worldwide. Furthermore, most newly identified cases of penile cancer were treated in 3 distinct parts of the country (north, northeast, and southeast) and most patients (79%) were more than 46 years of age. This study better defines the relative contribution of risk factors for penile cancer carcinogenesis within Brazil, particularly phimosis, previous HPV infection, and a history of tobacco smoking. Furthermore, the study as well highlights that most patients (58%) present with advanced disease (T2 or higher) clearly emphasizing the importance for better patient education and accessibility to early medical services. In this reviewer's opinion, studies such as this are important as they help better define the socioeconomic characteristics of those affected with penile cancer whereby the specific patient population at increased risk of this malignancy can be targeted for education on the signs and symptoms of penile cancer. Furthermore, the study brings attention to the high incidence of advanced disease at diagnosis and need for improved accessibility to early treatment diagnosis and intervention (raising question of the potential role of screening in high-risk populations like some regions of Brazil) in an attempt to optimize the treatment related outcomes for this highly aggressive tumor phenotype.

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EDITORIAL COMMENT

This study attempts to get grip on epidemiological data regarding penile cancer. This is a laudable attempt as penile cancer has a high incidence in Brazil. These basic data are essential for health strategies not only for the male population in Brazil but also for females. It is sobering to realize that the incidence of cervical cancer in Brazil ranks also as one of the highest in the world.

Some findings are remarkable.

The association of phimosis and penis cancer is well known amongst urologist. Is it equally known among other doctors and laymen? It is time to spread the gospel. This is unique opportunity for preventive medicine. Physiologic phimosis after the age of 6 year is not physiologic anymore. All involved in primary and pediatric medicine (health authorities, primary health care workers, general practitioners, gynecologists, pediatricians etc.) should be on the alert for this condition. Moreover, the public should be informed as well.

It is a riddle why circumcision done at a later stage than shortly after birth, does not have the same protective properties anymore. It is reasonable to assume that sexarche and the risk of acquiring high-risk HPV has a profound effect on the etiology of penile cancer. Could factors even before the start of sexual activity play a role?

It is remarkable that tumors arising after circumcision in adulthood seem to have a different biological make up (the majority are well differentiated).

This study has nevertheless some shortcomings. Considering the fact that according to the authors, more than 800 cases of penile cancer are treated in Brazil and considering the fact that some 200 + cases are described in this study, selection has occurred. It is unclear what sort of selection took place. Also we are not informed on the response rate after sending the questionnaires.

Restricting their epidemiological data to the clinical stage of the primary only and not expanding their data to the clinical stage of regional lymph nodes is a missed opportunity to have more insight in the incidence of lymph node invasion.

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Complications Following Urethral Reconstructive Surgery: A Six Year Experience

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ABSTRACT

Purpose: We present a single institutional experience over 6 years of intra and postoperative complications following urethral reconstructive surgery, and the impact of these complications on overall results.
Materials and Methods: From June 2000 through May 2006, 153 consecutive urethral reconstructive procedures were performed on 128 patients by one surgeon (CMG). Complication rates were determined, and subgroups were categorized based on stricture etiology, patient age, length of stricture, location of stricture, type of repair, and presence of various co-morbid conditions.
Results: Overall, 23 of 153 cases (15%) had an intra or postoperative complication with a mean follow-up time of 28.3 months (range 3 to 74). The most common complications were related to infection (n = 9). Other complications included repair breakdown (n = 4), bleeding (n = 4), fistulae (n = 3), thromboembolic (n = 2), positioning-related (n = 2), and Foley catheter malfunction (n = 1). Complication rates for anastomotic and substitution urethroplasty were 9.1% (4/44) and 17% (19/109), respectively. The number of patients with at least one year of follow-up who had a complication and eventual stricture recurrence was 20% (4/20), while only 7.4% (7/95) of those who did not have a complication recurred (p = 0.08).
Conclusions: Complications following reconstructive surgery for urethral stricture disease were mostly related to infection or repair breakdown in the immediate postoperative period. It does not appear that an intra or postoperative complication following urethral reconstructive surgery impacts the chance of eventual stricture recurrence at intermediate follow-up.

Key words: *urethral stricture; urethroplasty; complications; recurrence*
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INTRODUCTION

Reconstructive urethral surgery has been shown to be an effective treatment for urethral stricture disease with durable results (1-4). However, there are few major studies specifically analyzing complications following or during urethral reconstruction surgery. In a series of 60 patients, Al-Qudah et al. reported complication rates as high as 48%, though most of these events were classified as minor (5). In one of the largest reconstructive series to date, Andrich et al. reported that complications following reconstructive surgery have ranged from as low as 7% for excision and primary anastomosis to as high as 33% following substitution urethroplasty (1).

We assessed our experience with 153 consecutive urethral reconstructive cases over a 6-year period by a single surgeon within the same institution. A retrospective review of all urethral reconstructions, complications and recurrences over a 6-year period was performed. Our purpose was to determine the overall incidence and specific type of complications

that can occur during or after a variety of urethral reconstructive procedures, along with the impact these associated complications may have on disease recurrence. Specific patient demographics, co-morbid conditions, stricture characteristics, and reconstructive techniques were analyzed for complication rates.

MATERIALS AND METHODS

We evaluated patients who underwent urethral reconstructive surgery by a single surgeon (CMG) from June 2000 through May 2006. Follow-up was through July 2006 to ensure at least 60 days of follow-up per patient. All research activities met the approval of the Institutional Review Board. A total of 128 patients underwent 153 consecutive urethral reconstructive procedures during this period. Patients who underwent two-staged repairs account for the discrepancy between the number of reconstructive procedures and the number of patients. Patient characteristics, type of surgical procedure, stricture location, stricture length, stricture recurrence, patient age, complications, and presence of co-morbid conditions were prospectively entered into a database. Additionally, all inpatient and outpatient records were retrospectively analyzed to confirm the findings. The type of reconstructive procedure was determined by the surgeon after preoperative radiographic and endoscopic evaluation of the stricture, and ultimately after surgical evaluation of the stricture extent. Procedures were either done in dorsal lithotomy, supine or in exaggerated lithotomy. To prevent neurologic complications in patients placed in the exaggerated lithotomy position we utilized Yellofins® stirrups (Allen Medical Systems), and a 1 L saline bag wrapped in a blue towel to support the lumbar spine. Following urethral reconstruction a Foley catheter was routinely maintained indwelling for 3 weeks in those patients undergoing substitution urethroplasty with a graft or flap, and for 2 weeks in those men undergoing primary anastomosis, including those undergoing repair for urethral erosions. We made no distinction between perceived minor or major complications. Complications were classified as infection-related, bleeding, thromboembolic (deep vein thrombosis and pulmonary embolism), positioning-related, surgical repair breakdown, fistula formation, and Foley malfunction. Stricture recurrence rates were also evaluated, which we defined as the endoscopic identification of the urethral lumen at the repair site of less then 18 F in diameter.

All postoperative patients were screened for recurrence through assessment of subjective voiding symptoms, ultrasound post-void residual, and urine culture. Routine invasive monitoring with cystoscopy and retrograde urethrogram was not performed. Sexual dysfunction was not included as a complication in our study. Specific co-morbid conditions evaluated in this study included neurogenic bladder, prior renal or pancreas transplantation (enteric or bladder drained), penile or urethral lichen sclerosis including balanitis xerotica obliterans, previous hypospadias repair, and diabetes mellitus. Additionally, the etiology of stricture disease was recorded if it could be determined from the patient's initial history or previous medical record. Those strictures with no known etiology were classified as idiopathic. All patients received intravenous ampicillin (clindamycin or vancomycin if penicillin allergic) and gentamicin (ciprofloxacin if renal failure or insufficiency) peri-operatively, and all urine cultures were confirmed negative prior to surgery. For deep venous thrombosis prevention, compression stockings and sequential compression devices were used for patients in the supine and low lithotomy position, with only compression stockings used for those in the exaggerated lithotomy position.

RESULTS

Table-1 shows the distribution of types of repair and their associated complication rates. Mean patient age was 41.5 years (15 to 79 SD 14.5 years), with a mean follow-up of 28.3 months (SD 19.1 months). The average stricture length was 5.5 cm (1 to 22 SD 3.7 cm). Table-2 shows the distribution of stricture length by type of repair. Grafts and flaps used were as follows; 74 buccal grafts, 4 posterior auricular grafts, 2 scrotal skin grafts, 1 abdominal wall skin graft, 4 penile skin grafts, 5 circular fasciocutaneous flaps, 3 penile skin flaps, and 65 cases were done without the use of flap or graft. The total number of grafts

Table 1 – *Complication rate by type of urethral stricture repair.*

Type of Repair	Total Procedures	Procedures with Complications (%)
Anterior urethral excision and primary anastomosis (EPA)	33	2 (6)
Posterior urethral EPA	8	1 (13)
Diverticulum EPA	3	1 (33)
Bulbar urethral repair with buccal mucosa graft	38	5 (13)
Two-staged repair	36	7 (19)
Penile one-staged with graft or flap	23	5 (22)
Distal one-staged	6	1 (17)
Panurethral	3	1 (33)
Fistula repair	3	0

EPA = excision and primary anastomosis.

used in all cases exceeded the number of procedures secondary to the use of multiple grafts and /or flaps for long segment stricture repair.

Of the 153 cases, 23 cases had complications (15%). Two of these cases had multiple complications for a total of 25 recorded adverse events. There were no perioperative deaths. The most common type of complication was infection-related. Five of these were wound complications, including a scrotal abscess and a necrotizing glans penis infection in a patient with insulin dependent diabetes. Three of the infection-related complications were asymptomatic urinary tract infections, and there was one incident of postoperative urosepsis in a patient with a neurogenic bladder. Bleeding complications occurred in 4 patients, including one episode of excessive intraoperative bleeding requiring transfusion. Of the 3 complications that did not receive transfusions, 2 patients a developed perineal hematoma postoperatively and one had an episode of excessive bleeding from the buccal mucosa harvest site, which was managed conservatively with epinephrine-soaked packing. Four patients that underwent urethral erosion repairs secondary to chronic indwelling Foley catheter use suffered partial repair breakdown distally with an additional 3 patients developing a postoperative urethrocutaneous fistula; 2 of these spontaneously healed with Foley catheter drainage after one week. There were 2 thromboembolic events, including one patient with a deep vein thrombosis and another with a pulmonary embolism, which were related to a previously undiagnosed prothrombin gene mutation.

Table 2 – *Stricture length by type of surgical repair.*

Procedure Code	Total	Minimum Length (cm)	Maximum Length (cm)	Average Length (cm)
Excision and primary anastomosis	44	1.5	5	2.8
Two-staged	36	4	14	7.9
Distal one-staged	6	2	4	2.7
Penile one-staged	23	2	17	6.9
Bulbar w/ graft or flap	38	3	7	5.0
Long segment	3	11	22	18
Fistula repair	3	1	12	5.3

Of the 89 patients who underwent reconstruction in the high lithotomy position, only 2/89 (2.2%) had a complication related to positioning. In one of the first cases completed in this series, a young man suffered a severe femoral neuropathy most likely as a result of an operative time in the exaggerated lithotomy position in excess of five hours. The other patient had a temporary lateral foot paresthesia, which resolved spontaneously after three days. There were no positioning-related complications in patients who underwent repair in the dorsal lithotomy (n = 15) or supine positions (n = 49).

Table-3 shows the distribution of overall complications for the anastomotic and substitution urethral reconstructive cases. There was a complication rate of 9% (4/44) associated with anastomotic urethroplasty which included bulbar urethroplasty, membranous urethroplasty, and diverticulum repair when primary anastomosis was feasible. Substitution urethroplasty cases were found to have a complication rate of 17% (19/109). Chi-squared analysis was performed on these data, and although there was a trend towards more complications in the substitution urethroplasty subset, statistical significance was not achieved (p = 0.19). Table-4 shows complication data, which was stratified by patient characteristics, including age, stricture location, stricture etiology, and the presence of co-morbid conditions. These factors did not appear to impact upon the overall complication rate; however, given the limited number of complications within each subgroup, statistical analysis could not be made in most cases. To assess if complications during or following surgery impacted upon eventual stricture recurrence, we evaluated all men with at least one year of follow-up in this series. These men experienced an overall complication rate of 17% (20/115 cases), with an overall recurrence rate of 10.9% (11/101 men). The mean time to stricture recurrence for these men was 130 days (17 to 287, SD 134 days) with an average overall follow-up time of 35 months (12 to 74, SD 17 months). Strictures repaired with excision and primary anastomosis had a 7.7% (2/26) recurrence rate, whereas those repaired with substitution urethroplasty had a 10.1% (9/89) recurrence rate. Overall, 20% (4/20) of patients that suffered postoperative complications of any type had stricture recurrence, while only 7.4% (7/95) of those who did not have a complication recurred. Chi-squared analysis of these two groups showed a nonsignificant trend towards more recurrences in patients with complications (p = 0.08).

COMMENTS

We sought to elucidate and describe complications following 153 consecutive reconstructive pro-

Table 3 *– Types of complications for anastomotic and substitution repairs.*

Complication Code	Anastomotic	Substitution	Total
None	40	90	130
Infectious	2	7	9
Positioning-related	1	1	2
Bleeding	1	3	4
Thromboembolic	0	2	2
Fistula	0	3	3
Breakdown	0	4	4
Foley catheter malfunction	0	1	1
Total cases with complications	4	19	23
Total complications	4	21	25
Total cases	44	109	153
Complication rate	9% (4/44)	17% (19/109)	p = 0.19

Table 4 – *Complication rate by age, etiology of stricture, co-morbid disease, and stricture location.*

Age Group (years)	**Total Patients**	**Complications** (%)
< 20	5	1 (20)
21-30	32	4 (13)
31-40	40	6 (15)
41-50	37	3 (8)
51-60	20	4 (20)
> 60	19	5 (26)
Etiology of stricture		
Idiopathic	73	9 (12)
Infectious	6	4 (67)
Erosion	7	1 (14)
Instrumentation	15	4 (27)
Lichen sclerosis	9	1 (11)
Hypospadias	20	2 (10)
Prior urethroplasty	9	2 (22)
Trauma	13	0
Other	1	0
Co-morbid disease		
None	95	12 (13)
Neurogenic bladder	12	2 (17)
Transplant	8	4 (50)
Lichen sclerosis / BXO	8	0
Hypospadias	24	4 (17)
Both transplant and neurogenic bladder	1	0
Diabetes mellitus	5	1 (20)
Stricture location		
Fossa navicularis	8	1 (13)
Penile	58	12 (21)
Bulbar	79	9 (11)
Membranous	5	0
Panurethral	3	1 (33)

BXO = balanitis xerotica obliterans.

cedures for urethral stricture disease and the impact of these events on disease recurrence. With recent studies lending credence to broadening the use of formal urethral reconstruction (6,7) we believe a more complete understanding of complications following the multitude of available procedures for stricture disease is necessary for appropriate patient counseling.

Additionally, for the purposes of this study, we defined a complication as any adverse event or inadvertent deviation from the standard of care either during or after urethral reconstructive surgery. Our intention was to include all complications, however minor, without discrimination. Thus, we did not differentiate between perceived major and minor complications.

Postoperative sexual dysfunction was not included in this analysis as we have previously reported on these data from this same series (8).

The complication rate for anastomotic and substitution urethroplasty in this series was 9% and 17%, respectively. A comparison of these two groups did not reach a statistical difference ($p = 0.19$); however, a similar trend of complications following primary anastomosis and substitution urethroplasty has been previously reported at 7% and 33%, respectively (1). It is unclear why there were more complications in the substitution urethroplasty group as compared to the anastomotic group despite grouping posterior urethroplasty cases into the primary anastomosis group; however, contributing factors such as increased length of stricture and the need for harvest and interposition of graft tissue in the substitution urethroplasty group may factor into these findings. We also analyzed the number of complications related to one-stage 6/29 (21%) versus two-stage 7/36 (19%) procedures involving the penile urethra and fossa navicularis. Despite the fact that most of the strictures requiring two-stage procedures were more complex in etiology (i.e. hypospadias failure, failed prior reconstruction), no significant difference between the two groups was found ($p = 0.90$).

The high lithotomy position for urethral reconstructive surgery has been associated with complication rates between 10-16% (9-12). In our study, complications related to the high lithotomy position were limited and only occurred in two (2.2%) of the 89 cases performed. Major factors responsible for the limited number of positioning-related complications in this series included the self imposed limit of having the patient in exaggerated lithotomy for less than five hours, the use of specialized stirrups, lower back support, and high patient volume. Positioning-related complications in the supine and dorsal lithotomy position did not occur in this series.

The majority of complications in our series were related to infection. Despite the administration of peri-operative antibiotics, and a negative preoperative urine culture, wound-related infections accounted for 5/153 (3.2%) cases. Despite the relative frequency of these occurrences in this series, these data are comparable to wound infection rates reported for similar procedures including perineal prostatectomy (1.6%), circumcision (1.3%) and hydrocele repair (4%) (13-15).

Finally, we attempted to evaluate whether a complication following urethral reconstructive surgery increased the chance of eventual stricture recurrence. In order to avoid underestimation of recurrence, all men with less then one year of follow-up in this series were excluded. A recurrence rate of 10.9% was found in these men, which is similar to that of previously reported data (16,17). Although 20% of men with a complication eventually experienced a recurrence at a mean follow-up time of just less than three years, a statistically significant difference could not be found between those without a complication and those with an eventual recurrence. Long-term data are needed to confirm these findings at intermediate follow-up.

One of the major limitations of this study was the inability to perform statistical analysis on some of the subgroups due to the limited number of complications. We pooled similar subgroup for analysis when applicable; however, because of the relatively low number of events, meaningful statistical analysis could not be performed in some subgroups. Multi-institutional studies would be helpful in providing the appropriate statistical power necessary to determine if some of these potential co-morbidities may predispose a patient to a complication, thus allowing the employment of appropriate preventative measures. Nonetheless, to the best of our knowledge, this is one of the largest series of complications reported in consecutive patients undergoing urethral reconstruction surgery for stricture disease.

CONCLUSION

Complications following reconstructive surgery for urethral stricture disease were minor and mostly related to infection and repair breakdown in the postoperative period. Positioning-related and bleeding complications were relatively rare. It does not appear that intra or postoperative complications following urethral reconstructive surgery significantly impact the chance of eventual stricture recurrence at intermediate follow-up.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Andrich DE, Dunglison N, Greenwell TJ, Mundy AR: The long-term results of urethroplasty. J Urol. 2003; 170: 90-2.
2. Andrich DE, Mundy AR: Urethral strictures and their surgical treatment. BJU Int. 2000; 86: 571-80.
3. Barbagli G, Palminteri E, Bartoletti R, Selli C, Rizzo M: Long-term results of anterior and posterior urethroplasty with actuarial evaluation of the success rates. J Urol. 1997; 158: 1380-2.
4. Santucci RA, Mario LA, McAninch JW: Anastomotic urethroplasty for bulbar urethral stricture: analysis of 168 patients. J Urol. 2002; 167: 1715-9.
5. Al-Qudah HS, Santucci RA: Extended complications of urethroplasty. Int Braz J Urol. 2005; 31: 315-23; discussion 324-5.
6. Rourke KF, Jordan GH: Primary urethral reconstruction: the cost minimized approach to the bulbous urethral stricture. J Urol. 2005; 173: 1206-10.
7. Wright JL, Wessells H, Nathens AB, Hollingworth W: What is the most cost-effective treatment for 1 to 2-cm bulbar urethral strictures: societal approach using decision analysis. Urology. 2006; 67: 889-93.
8. Erickson BA, Wysock JS, McVary KT, Gonzalez CM: Erectile function, sexual drive, and ejaculatory function after reconstructive surgery for anterior urethral stricture disease. BJU Int. 2007; 99: 607-11.
9. Bildsten SA, Dmochowski RR, Spindel MR, Auman JR: The risk of rhabdomyolysis and acute renal failure with the patient in the exaggerated lithotomy position. J Urol. 1994; 152: 1970-2.
10. Moses TA, Kreder KJ, Thrasher JB: Compartment syndrome: an unusual complication of the lithotomy position. Urology. 1994; 43: 746-7.
11. Anema JG, Morey AF, McAninch JW, Mario LA, Wessells H: Complications related to the high lithotomy position during urethral reconstruction. J Urol. 2000; 164: 360-3.
12. Angermeier KW, Jordan GH: Complications of the exaggerated lithotomy position: a review of 177 cases. J Urol. 1994; 151: 866-8.
13. Audry G, Johanet S, Achrafi H, Lupold M, Gruner M: The risk of wound infection after inguinal incision in pediatric outpatient surgery. Eur J Pediatr Surg. 1994; 4: 87-9.
14. Jakse G, Manegold E, Reineke T, Borchers H, Brehmer B, Wolff JM, et al.: Expanded, radical perineal prostatectomy. Urologe A. 2000; 39: 455-62.
15. Krieger JN, Bailey RC, Opeya J, Ayieko B, Opiyo F, Agot K, et al.: Adult male circumcision: results of a standardized procedure in Kisumu District, Kenya. BJU Int. 2005; 96: 1109-13.
16. Barbagli G, Palminteri E, Lazzeri M, Guazzoni G, Turini D: Long-term outcome of urethroplasty after failed urethrotomy versus primary repair. J Urol. 2001; 165: 1918-9.
17. Wood DN, Andrich DE, Greenwell TJ, Mundy AR: Standing the test of time: the long-term results of urethroplasty. World J Urol. 2006; 24: 250-4.

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EDITORIAL COMMENT

The authors reported on intra and postoperative complications of reconstructive urethral surgery performed by a single surgeon. Data consisted of 153 procedures performed on 128 patients including a variety of techniques, as well as use of grafts and flaps. The authors included in the series one stage and two-stage repairs.

The authors stated that their "study was a retrospective review of all urethral reconstructions over a 6 year span and their goal was to provide descriptive data from a large single institution experience which stratifies complications after various reconstructive procedures and their impact on stricture recurrence". My contribution as a reviewer is to wonder about today's impact on knowledge of heterogeneous single-institution series like this. Notice for instance that only 4 of 9 clinical subgroups listed included more than 20 patients on it. If the authors had limited their evaluation to only those series of patients they could probably achieve more conclusive results even though still not statistically significant.

We accept the authors' comment that "in the arena of urethral reconstruction, single surgeon series of enough volume to draw statistical conclusion are very difficult to come by". On the other hand, only if patients with urethral stricture are classified according to clinical characteristics and type of surgery we can truly rely on results and use this data to counsel our patients before surgery.

In conclusion the authors deserve merit for their paper but we acknowledge the need of cooperative studies to better evaluate the role of different urethral surgeries in regards to overall success and complications.

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EDITORIAL COMMENT

The take-home message from the manuscript by Navai et al. is that urethroplasty can be accomplished with high success rates and few complications. The authors also ask several important questions that seek to better understand the factors associated with complications after urethroplasty. Yet, there are several issues that make these questions difficult to answer. First, many of the variables examined by the authors and others in similar manuscripts are correlated with one another. For instance, the etiology of stricture (e.g. history of hypospadias repair) can be linked with the location of stricture (e.g. penile urethra), the length of stricture, type of repair (e.g. two-stage repair with buccal graft), patient positioning and operative time. Hence, to really understand what factors predict complications, these covariates would be better examined in a multiple logistic regression model. Second, most urethroplasty series are small as the disease is not common and is frequently managed by other means. This combined with the fact that the outcome of interest, in this case complications, is also rare makes it difficult to then do subset analyses to understand the predictors of the outcome. As the authors suggest, we will be better prepared to explore these issues when we approach them through a multi-institutional collaborative database.

Still, the important lesson here remains that re-stenosis and complications are infrequent after urethroplasty. It remains the gold standard for the management of urethral stricture disease. The number of centers where patients can receive excellent definitive care for their urethral stricture continues to grow, as evidenced by Dr. Gonzales's experience.

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Surgical Technique

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Full-Thickness Abdominal Skin Graft for Long-Segment Urethral Stricture Reconstruction

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ABSTRACT

Multiple tissue sources have been used for urethral reconstruction in adults. Patients with lichen sclerosis (LS), long segment strictures, or prior oral graft use have less available tissue for urethroplasty. We describe a technique for the use of a full-thickness skin graft of hairless abdominal skin for long segment urethroplasty.

Key words: *skin grafting, urethroplasty*
Int Braz J Urol. 2008; 34: 602-8

INTRODUCTION

Reconstruction of long-segment adult urethral stricture disease as a result of lichen sclerosis (LS) or failed pediatric hypospadias repair remains a difficult urological problem mainly due to the deficiency of available extra-genital skin for grafting (1). Graft tissue has been utilized successfully for urethral reconstruction from various sites including buccal mucosa, genital skin and auricular tissue; however each tissue source has specific drawbacks (2). The ideal graft source would be extra-genital in origin, hairless, produce minimal postoperative morbidity at the harvest site, be inconspicuous postoperatively and abundant enough in length and width so as to avoid multiple urethral suture lines for men with long segment strictures. In an effort to develop an alternative to available graft sources for complex and long-segment strictures we describe harvest and application of a full-thickness abdominal skin graft for urethral reconstruction.

SURGICAL TECHNIQUE

The extent of the urethral stricture was evaluated preoperatively with cystoscopy and retrograde urethrogram. The area of abdominal wall to be harvested was demarcated and discussed with the patient preoperatively. Deep venous thrombosis precautions were taken, and all patients achieved a sterile urine culture prior to surgery.

For one or two-staged long segment urethral reconstructive procedures involving the mid or proximal bulbar urethra, the patient was placed in the low lithotomy position. Otherwise, those with stricture confined to the penile urethra and distal bulbar urethra were placed in the supine position. A ventral longitudinal shaft incision is made to expose the penile urethra to the level of the scrotum in men undergoing single-staged repair with a perineal counter-incision to access the bulbar urethra if needed. A bougie-à-boule sound is then used to identify the anatomically distal most aspect of the stricture. The

urethra is incised along its anterolateral edge throughout the length of the stricture with the edges of the urethrotomy calibrated to 24 F in the penile urethra and 26F for the bulbar urethra. The full extent of the urethrotomy is then measured in preparation for graft harvest. Alternatively, in men undergoing the first of a two-staged procedure for long segment stricture disease, a grooved director is placed within the urethra and a scalpel is used to open the urethra through the full thickness of the penile skin and urethra. The mucosa from the proximal urethrotomy site is then sutured to the overlying penile, scrotal, or perineal skin, depending on stricture length, with interrupted 5-0 vicryl sutures. All nonviable corpus spongiosum and urethral mucosa or tissue that is suspicious for lichen sclerosis is excised and sent for pathologic analysis in both single and two staged procedures.

Graft harvest of the abdominal wall involves excision of the skin of the right or left lower quadrant of the abdomen at the level of the anterior superior iliac crest (Figure-1). An area of hairless skin is identified and chosen in a location which is anatomically

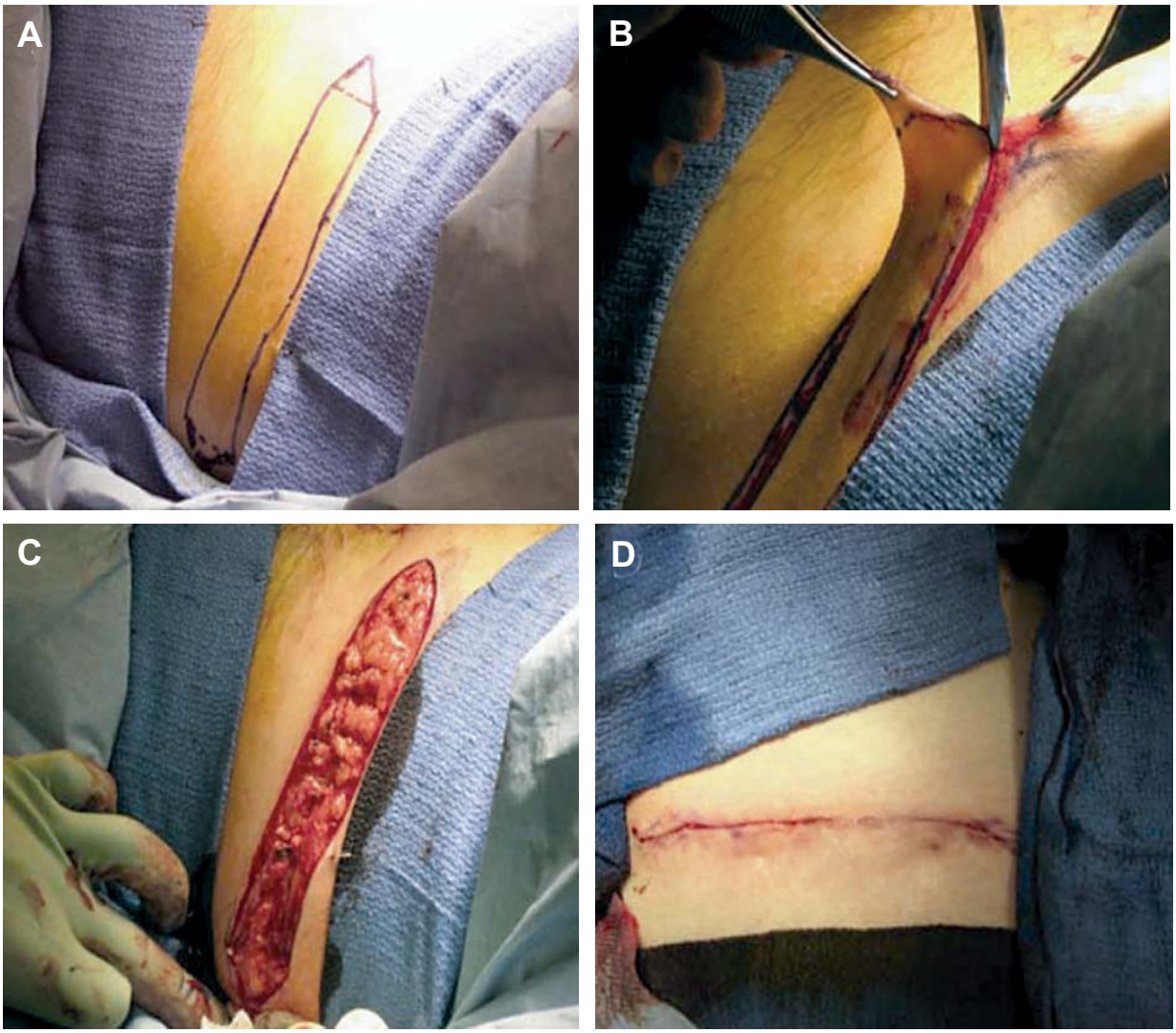

Figure 1 – *Harvest of a full-thickness abdominal skin. A)- Region of the abdominal skin is marked that is hairless on a region and is covered by the patient's belt. B) and C)- A full thickness skin graft is harvested. D)- The graft site is closed with deep dermal and subcutiticular sutures.*

positioned so that the patient's belt line will eventually conceal the wound (Figure-1A). A full thickness skin graft is harvested to the level of the subcutaneous tissue (Figure-1B and Figure-1C). Once the graft is sharply excised, the deep dermal tissue of the harvest site is closed with interrupted 3-0 vicryl sutures followed by a 4-0 vicryl subcuticular skin closure (Figure-1D). The graft is then prepared by sharp dissection over its dermal edge until transparent (Figure-2A).

For single-stage procedures, the epithelial side of the graft is sutured to the remaining mucosa of the urethral plate with 5-0 vicryl suture. In the first of a two-staged procedure, graft fixation to the dartos fascia is accomplished by suturing the graft to the urethral plate medially and the penile skin laterally (Figure-2B). Venting incisions or "pie crusting" is then completed through the graft, and quilting sutures are placed per square centimeter in order to fix the graft to the underlying dartos and corpora cavernosum to enhance inosculation and prevent sub-graft fluid collections (Figure-2B).

A 16F catheter is left in place for strictures limited to the penile urethra and an 18F catheter is placed for strictures extending into the bulbar urethra. All men undergoing the first of a two-staged procedure had a catheter placed for 5 days postoperatively in conjunction with a moisturized bolster dressing. All other patients undergoing a single procedure for repair had catheter drainage for three weeks postoperatively.

RESULTS

Abdominal skin was used in ten patients with long-segment urethral stricture disease (Table-

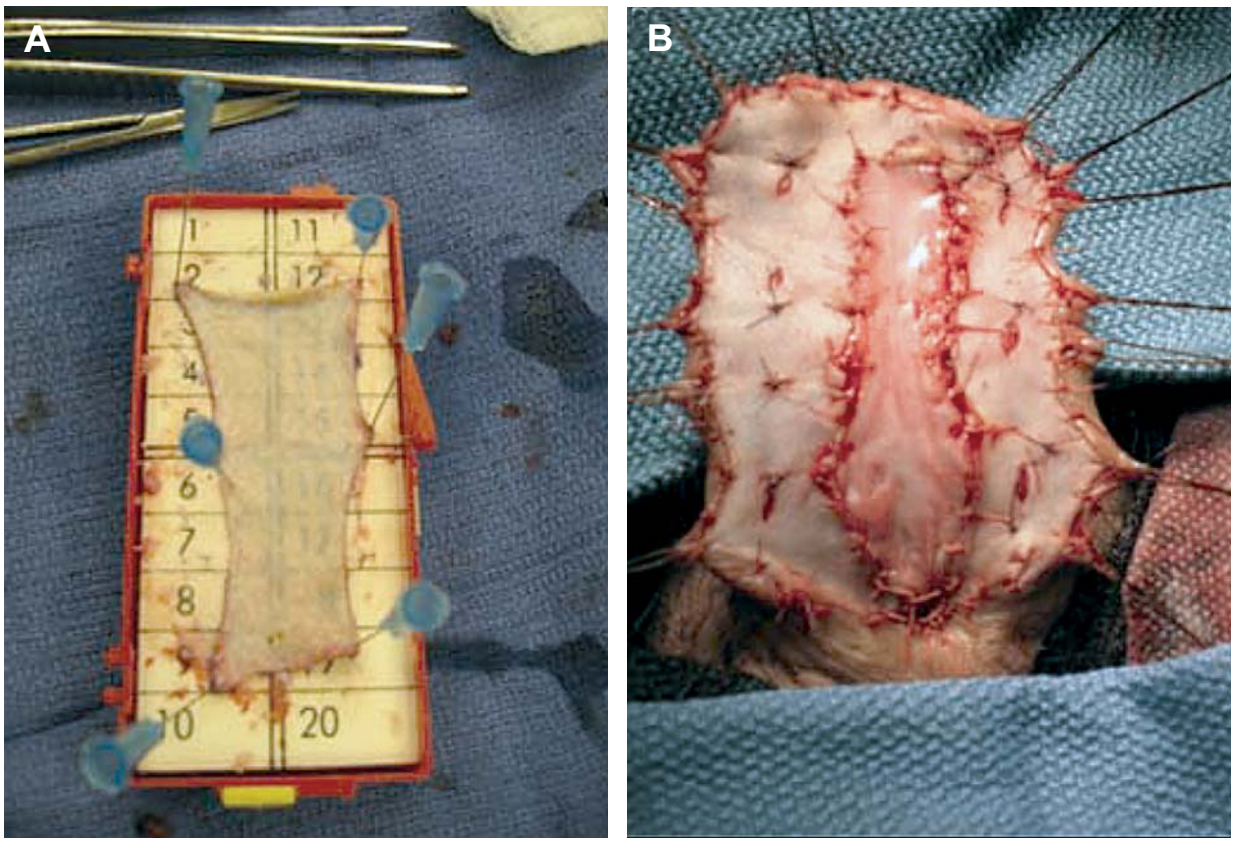

Figure 2 *– Processing and placement of full-thickness abdominal skin graft. A)- The harvested abdominal wall graft is thinned to transparency. B)- The graft is sewn into place around the urethral plate. The graft is then pie crusted and quilting sutures are placed.*

Table 1 – *Clinical demographics of patients undergoing abdominal wall skin graft.*

Patient	Age	Cause	Length (cm)	Graft Size (cm)	Graft Area (cm^2)	EBL (cc)	Type Repair	Recurrence	Comp
1	18	penoscrotal hypospadias	10	10x3	30	350	2-stage		
2	48	penoscrotal hypospadias	11	11x3.5	38.5	100	2-stage		UTI
3	54	LS	12	14x4	56	400	2-stage		
4	32	LS	8	8x3	24	300	2-stage		hair
5	77	LS	24	15x4	60	600	1-stage	11 months; 2 cm proximal bulbar urethra	
6		LS	22	20X4	80	800	1-stage		hair
7	55	unknown	19	19x2	38	450			
8	47	LS	10	10x4	40	750	2-stage		UTI
9	45	unknown	12	12x2	24	200	1-stage		
10	55	LS	21	14x3	32	600	1-stage	6 months; 2 cm distal bulbar urethra	

Comp. = complications; EBL = estimated blood loss; LS = lichen sclerosis; UTI = urinary tract infection.

1). Median patient age was 42 years (range 18-77 years). Mean stricture length was 12 cm (range 10-24 cm). The etiology of urethral stricture included failed hypospadias repair (2), LS (6) and unknown (2). Median follow-up was 17 months (range 3-25 months). Average graft area was 42.25 cm^2. Six of the ten patients underwent two-staged procedures with successful graft uptake in all men after the first stage and successful second stage closure in the two men completing both procedures (Figure-3A and Figure-3B). In the other four men, strictures were closed in one stage with a long segment graft. Mean estimated blood loss was 412 cc. Two patients with LS developed recurrent stricture formation at a mean time of 9 months from surgery. These were the first two patients in this series with prior urethroplasty utilizing buccal and auricular tissue and involved stricture lengths of 21 and 24 cm. Recurrent stricture length was 2 cm in each patient and was managed endoscopically.

All abdominal skin harvest sites healed well without complication. Two patients developed febrile urinary tract infections requiring oral antibiotics. Two patients grew hair from segments of the abdominal skin graft within six months of surgery, one after single stage urethroplasty and the other after the first of a two-staged procedure. These were the first two grafts harvested in this series when areas with hair were taken and the follicles removed. This method proved to be unsuccessful in its ability to prevent all future hair growth, and all subsequent grafts were harvested from hairless abdominal regions with no further occurrences of hair growth on the graft. All patients in this series were discharged on postoperative day one and reported minimal pain at the abdominal harvest site.

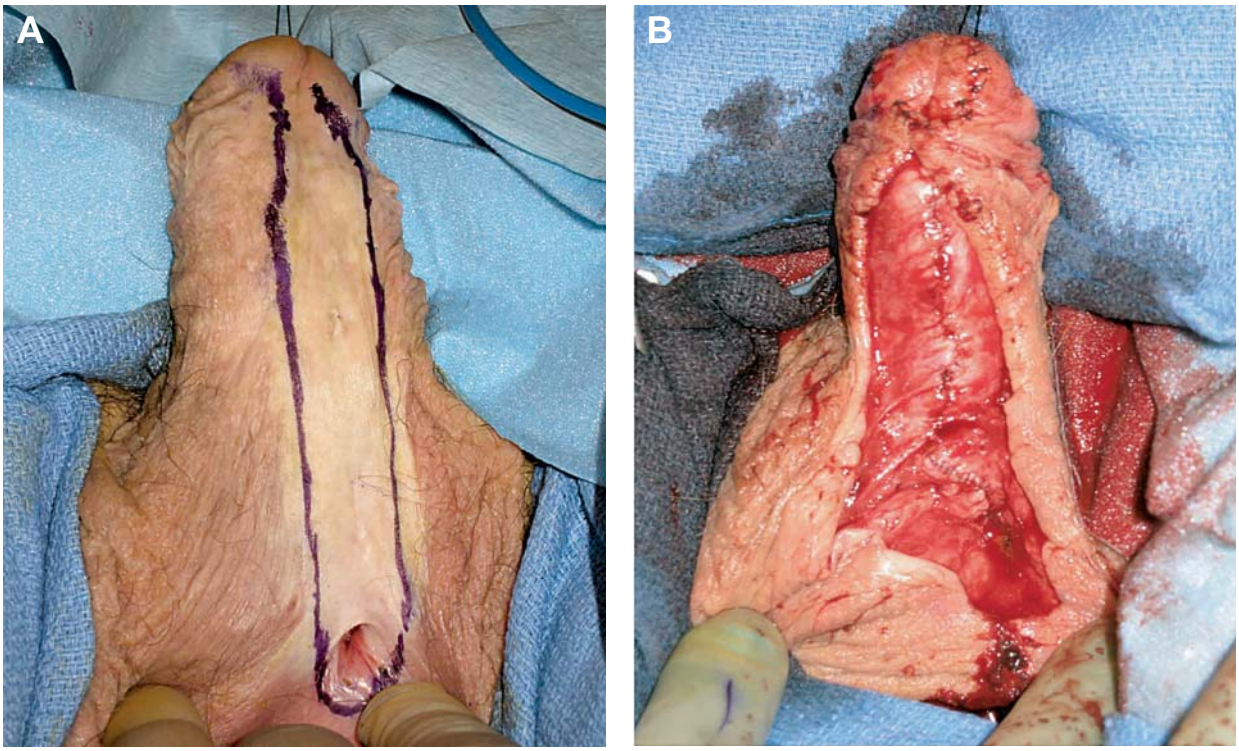

Figure 3 – *Second state urethroplasty. A) full-thickness abdominal skin graft six months after first stage urethroplasty, prior to second stage urethroplasty. B)- Rolled urethral tube after second stage urethroplasty.*

COMMENTS

Urethral reconstruction in patients with long segment stricture disease remains a complicated surgical problem especially in men with previous hypospadias surgery and those with LS as an etiology. The success rates of reconstruction in men with longer segment strictures of varied etiology has been reported to be 75% at five years with a median stricture length of 7cm (3). Urethral reconstruction for long segment stricture disease after previous hypospadias repair has a similar 75% success rate at nearly three years (4). Men with long-segment stricture disease secondary to LS appear to have a higher recurrence rate secondary to the progressive nature of this inflammatory disorder.

One of the critical events for urethral reconstruction of long-segment strictures involves obtaining the appropriate tissue for urethral defect substitution. Harvest of tissue from the surrounding penile skin is ideal, but this tissue is often deficient, scarred, or may be at risk for recurrence of LS. To repair long-segment defects, some authors have used composite repairs including genital fasciocutaneous flaps in conjunction with buccal or penile skin grafts. Berglund and Angermeir described the use of a combined penile or scrotal skin flap with buccal mucosa grafts in patients with strictures up to 24 cm in length with a success rate of 83% approaching 6 years of follow-up (5). While these authors were able to obtain good results from these techniques for long-segment strictures some of the potential drawbacks include the need to harvest graft tissue from multiple sites, the risk of suture line ischemia secondary to incorporation of multiple grafts into the anastomosis, the risk of hair growth on genital graft or flap tissue, and utilization of genital skin which may predispose to an LS related stricture recurrence.

Buccal mucosa alone has been demonstrated to be a good choice for extra-genital graft tissue with success rates reaching 90% in some series. However, a significant limitation of buccal mucosa for substitution in long segment stricture reconstruction involves the availability of this tissue. The cumulative length of

available oral mucosa is approximately 17 cm which requires harvest from both cheeks and potentially the lower lip. Complications reported with oral harvest from just one site include neurosensory deficits, changes of salivary flow, difficulty with mouth opening, and lip contracture (5,6). In one report, as many as 26% of men indicated negative or mixed feelings about the buccal mucosa graft harvest postoperatively with 16% reporting persistent numbness and 32% reporting oral tightness (2). Comparatively, we experienced no harvest site morbidity and limited patient complaints related to the abdominal wall harvest for long-segment strictures with a mean length of 12 cm.

The use of non-oral, extra-genital FTSG has previously been described in several smaller series for urethral reconstruction with reported success ranging from 25-50% (7). These outcomes may have been related, in part, to the widespread use of tube-grafts for reconstruction at this time, and the choice of single versus two-staged repair for complicated strictures. The use of full-thickness abdominal wall skin for long-segment stricture reconstruction has not been described previously. The advantages of this tissue are that it provides extra-genital tissue origin, the ability to harvest hairless segments up to 24 cm, and the limited graft site morbidity observed in this series. Furthermore, the abundant length and width of the abdominal skin graft allows for harvest of a single graft segment as compared to buccal mucosa or penile skin grafts which require multiple harvest sites and suture lines between grafts within an anastomosis for long-segment stricture defects. While abdominal skin tissue should not be the first choice for graft tissue until long-term outcomes are known, the availability of this tissue offers the reconstructive surgeon an additional option for substitution urethroplasty of long-segment strictures.

CONCLUSION

We describe a technique for full-thickness abdominal skin graft use in long-segment urethral stricture reconstruction. When harvested from hairless regions, these grafts have acceptable success rates with few complications at early follow-up. Selective use of abdominal skin grafts may be well suited for patients with long-segment urethral strictures in one or two stages when other graft sources are not available or feasible.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Xu YM, Qiao Y, Sa YL, Wu DL, Zhang XR, Zhang J, et al.: Substitution urethroplasty of complex and long-segment urethral strictures: a rationale for procedure selection. Eur Urol. 2007; 51: 1093-8; discussion 1098-9.
2. Dublin N, Stewart LH: Oral complications after buccal mucosal graft harvest for urethroplasty. BJU Int. 2004; 94: 867-9.
3. Moradi MR, Moradi A: Urethroplasty for Long Anterior Urethral Strictures: Report of Long-term Results. Urol J. 2006; 3: 160-4.
4. Barbagli G, De Angelis M, Palminteri E, Lazzeri M: Failed hypospadias repair presenting in adults. Eur Urol. 2006; 49: 887-94; discussion 895.
5. Berglund RK, Angermeier KW: Combined buccal mucosa graft and genital skin flap for reconstruction of extensive anterior urethral strictures. Urology. 2006; 68: 707-10; discussion 710.
6. Jang TL, Erickson B, Medendorp A, Gonzalez CM: Comparison of donor site intraoral morbidity after mucosal graft harvesting for urethral reconstruction. Urology. 2005; 66: 716-20.
7. Webster GD, Brown MW, Koefoot RB Jr, Sihelnick S: Suboptimal results in full thickness skin graft urethroplasty using an extrapenile skin donor site. J Urol. 1984; 131: 1082-3.

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EDITORIAL COMMENT

The authors reported on the use of full-thickness abdominal skin graft for urethral strictures as an "inlay" after extensive urethrotomy for long strictures. The paper was submitted as an operative technique description focusing mainly in the procedure itself with a limited number of patients treated (10) and only 6 completing the second-stage. Follow-up is also very short (17 months).

The paper has some merit but adds little to the present knowledge in urethroplasty. Since the popularization of mucosal grafts in urethral structure and hypospadias repair, there is a consensus that mucosal grafts are more appropriate and recently tunica vaginalis is also being studied as a valid option. Skin grafts have been extensively studied in the past with success and reported in the literature also with long term follow-up. Bracka has shown long-term clinical data in over 1000 patients with skin grafts and later buccal mucosa grafts including the second-stage urethroplasty. The argument of the authors that the suggested donor area is attractive should be based on clinical results in a larger series and not only on surgical technique descriptions.

In summary, I would like to encourage the authors to resubmit their experience later with more patients and a longer follow-up.

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REPLY BY THE AUTHORS

In this surgical technique manuscript, we describe the procedure to harvest, prepare and place a full-thickness skin graft for men with long segment urethral strictures. While long segment urethral reconstruction is relatively rare, the most difficult part of urethroplasty is finding an ideal tissue source for urethral reconstruction. Many have described the use of genital skin, non-genital skin and buccal mucosa as graft sources; these standard tissues sources are often deficient in men with prior urethroplasty or pediatric hypospadias repair, as several men in our study were. In our study, the mean stricture length was 12 cm with a range of 10 to 24 cm. In this population, the potential graft sources include composite grafts of multiple buccal grafts with the possible addition of skin grafts. Yet, almost 25% of men describe a complication after buccal harvest. The technique we describe is not meant to replace standard techniques of buccal or genital skin grafts, but is a supplemental technique to consider when approaching a complicated patient with few ideal graft sources. As the editor mentions, more data will be forthcoming.

The Authors

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Use of Tubularized Incised Plate Urethroplasty for Secondary Hypospadias Repair or Repair in Circumcised Patients

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ABSTRACT

Purpose: To retrospectively review our experience of the tubularized incised plate (TIP) urethroplasty in a series of re-operative hypospadias repairs or circumcised children.
Materials and Methods: Between September 2001 and September 2007, 17 children (mean 4.6 years, range 7 months to 15 years), were referred for hypospadias re-operation. Some of these patients had previously undergone circumcision and missed hypospadias. In all cases, the TIP urethroplasty was covered with an additional layer of subcutaneous tissue or dartos flap. The original location, associated complications and results were recorded.
Results: There were 4 (30.7%), incidences of complications of TIP re-operation, 2 meatal stenosis, one stenosis with small fistula and one dehiscence. Re-operation was necessary in only one patient of our series (7.6%) and the others were cured by dilatation. No complications occurred in the circumcised patents.
Conclusion: Using TIP urethroplasty as described by Snodgrass, is a suitable method for treating primary and re-operative cases. It can also be used successfully in patients, who do not have a healthy skin flap and in circumcised patients when there is a lack of foreskin.

Key words: *urethroplasty; hypospadias; urethral plate; circumcision*
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INTRODUCTION

Numerous methods for repair of hypospadias have been introduced. However, urethrocutaneous fistula or neourethral dehiscence was the most troublesome complication. These problems are the main difficulty in re-operations, because in these cases urethral reconstruction is required, but only a small amount of penile foreskin is available. On the other hand, the vasculature of previously operated tissues may be suboptimal, resulting in further complications. In 1994, Warren Snodgrass described a procedure using tubularized incised plate (TIP) urethroplasty with excellent results (1). The TIP urethroplasty has also been used successfully in re-operative and complex hypospadias repairs (2-4).

Although, tubularized incised plate urethroplasty is well described, there are few reported experiences pertaining to complicated hypospadias or circumcised patients that are re-operated by this technique. We report our results in using the TIP urethroplasty with a local flap in previous hypospadias failures and circumcised patients with intact urethral plate.

MATERIALS AND METHODS

Between September 2001 and September 2007, 134 children (mean age 4 years, range 7 months

to 15 years) were referred for hypospadias repair or re-operation. Four patients had fistula after circumcision due to the aggressive use of cautery and thus were excluded from this study. Seventeen [17] patients had a failed hypospadias repair or circumcised without reconstruction, while 113 had primary hypospadias.

This study included 17 patients (aged 18 months to 15 years, mean 4.6 years) who had previously undergone 1-to 3 failed hypospadias repair or circumcision. The previous techniques utilized Mathieu repair in two, Thiersh-Duplay in four, failed on lay flap in one and unknown in six (Table-1).Also, four [4] children were circumcised without hypospadias repair. Glanular hypospadias also were excluded from this study. The interval from the last surgery to TIP re-operation was 6 months to 11 years. Testosterone was administered in 3 patients prior to re-operation.

After the primary evaluation, tubularized incised plate urethroplasty was performed for correction of complications related to the previous hypospadias surgery. All of the re-operations were performed by the same surgeon.

After general anesthesia, a stay suture was placed through the glans for traction. Then the penis was degloved and any meatal stenosis or fistula opened widely, to prevent subsequent stricture formation. An artificial erection was carried out for ventral curvature, as a necessary step. Dorsal placation was performed on 3 patients. Parallel incisions separated the glans wings from the urethral plate and the plate was incised in the mid-line as described by Snodgrass (1). A 6F or 8F stent was passed into the bladder for post operative urinary diversion, then, urethroplasty was performed using subcuticular 6/0 vicryl interrupted sutures. The epithelium of the urethral plate was inverted toward the lumen to avoid fistula formation. Care was taken to avoid suturing the distal urethral plate too snugly, which may result in meatal stenosis. Usually only 1 or 2 sutures beyond the mid glans level of the plate were needed, leaving the neomeatus oval in configuration (3). In long neourethra, we used a ventral dartos pedicle to cover the repair, while the second layer was placed by adjacent dartos and peri-urethral tissues and in

Table 1 – *Summary of patients' characteristics and results.*

Age (years)	**N of Previous Operations**	**Location**	**Complication**
3	1 (T. Duplay)	D	Stenosis
15	3 (unknown)	D	None
9	3 (unknown)	SC	None
3	1 (Mathieu)	SC	None
2	2 (T. Duplay)	D	Stenosis/fistula
4	1 (onlay flap)	P	Glanuloplasty dehisced
4	1 (unknown)	SC	Stenosis
5	1 (unknown)	D	None
2	1 (T. Duplay)	SC	None
4	1 (unknown)	D	None
3	1 (T. Duplay)	SC	None
2	1 (unknown)	M	None
3	1 (Mathieu)	SC	None
5	1 (circumcision)	SC	None
10	1 (circumcision)	SC	None
3	1 (circumcision)	M	None
1.5	1 (circumcision)	SC	None

SC = sub coronal; D = distal shaft; M = mid shaft; P = proximal.

some patients with a satisfactory prepuce we used dorsal tissue.

In circumcised patients, the neourethra was covered with a mini pedicle of subcutaneous tissues dissected from the small remained dorsal skin. Because the urethral plate was intact in these patients, the urethroplasty was easier to perform.

The catheter within the urethra was secured distally to the glans with the traction suture. A compression dressing was applied. All patients were discharged from the hospital one day after surgery. Catheter and dressing were removed after four days. Patients were examined twice in the first month, with follow-up within a 6 month period. Patients who had an acceptable cosmetic appearance and voided from the end of the penis with no difficulty were considered as successful surgery.

RESULTS

The demographic characteristics of patients are presented in Table-1. The mean follow-up after surgery was 15 months (range 4-24 months). There were four complications; a four-year old boy that was referred after a failed repair by on-lay flap technique. It was our first experience and we placed a small Foley catheter at surgery instead of a stent. The day after surgery he developed severe bladder spasms. Subsequently, the patient's glanuloplasty dehisced which required re-operation. Two children developed meatal stenosis that responded to 2-3 times calibration. The fourth child developed a pin hole fistula and stenosis. After 6 weeks calibration (twice per week), both of them were cured. The remaining 13 patients including circumcised patients had excellent results, i.e. a strong and vertical urinary stream was observed and the slit-like meatus was constructed at the tip of the glans (Table-1). We had no complications in the four circumcised patients with hypospadias.

COMMENTS

In the correction of complicated hypospadias, it is preferable to use vascularized preputial or penile skin. When genital skin is unavailable or insufficient, it may be necessary to choose extragenital tissues such as skin, bladder mucosa and buccal mucosa, in order to complete a successful repair. Duckett et al.(5) comment that buccal mucosa grafts are the best urethral replacement for redo surgery and for stricture disease, and the meatus will be durable. In contrast, hypospadias repair with Snodgrass incised plate urethroplasty in primary cases, has gained widespread acceptance because it is versatile, and has the advantages of reliably creating a vertically oriented meatus, while having a lower complication rate than other techniques. These excellent results have been reported in literature as primary repair (1,3). Although the use of Snodgrass urethroplasty has been extended from primary to re-operative hypospadias (2,4,6,7), these reports do not appear to be very conclusive.

In the present series, we had 4 children in which the circumcision was performed by general physicians who overlooked their hypospadias. This was a new experience for us and despite the lack of prepuce, TIP technique had excellent results for these patients and without any complications (Table-1). Although the number of cases was , apparently limited, absence of the prepuce did not worsen the success rate of the procedure.

In another group of patients (n=13), our complications rate (30.7%) was related to four patients: i.e. two meatal stenoses, one stenosis with a small fistula and one dehiscence. Comparing these two small groups, it seems that the scar tissue on urethra is more important than lack of tissue for the flap and moreover influences the results. This study, and also the report of Yang et al. (8), demonstrated that the meatal stenosis is the most frequent form of complications in re-operative TIP urethroplasty especially in distal types. Although a wide neomeatus has been made, the meatal stenosis had the most complications. If we ignore circumcised patients (non re-operated hypospadias), results would be similar to Snodgrass and Lorenzo (3) who reported the usage of TIP urethroplasty to repair proximal hypospadias (33%). Although their cases were proximal, complications in re-operation (2) were 3 in 15 (20%), and is similar to those reported by Shanberg et al. (6), and Borer et al. (9) 24%, 15%,

respectively. It is very important to note that in only one patient of our series, re-operation was necessary while others were cured by dilatation; this indicates that the ultimate success rate without another operation was 92.4%. We had a patient with dehiscence glanuloplasty that underwent a successful second redo tubularized incised plate urethroplasty re-operation and responded satisfactorily.

Shanberg et al. (6) described the creation of a dartos flap from subcoronal shaft skin and reported only one fistula among their 13 patients. Çakan et al. (10) reported TIP urethroplasty, in 37 re-operative patients with a success rate of 78.4%. The satisfactory outcomes were higher in patients < 5 years. El-Sherbiny et al. (7) and others (11,12) also reported the complication rate for hypospadias in adults being higher than children, however, in our series, they were not different. In Elicevik et al. series, the overall complication rate was 26% and the ultimate success rate of tubularized incised plate urethroplasty reoperation after treatment of complications was 97% (13).

For prevention of fistula, when possible, the neo-urethra was covered with a blanket of tunica vaginalis or some other buffering vascularized layer as an alternative flap for multilayer coverage of the urethroplasty. Therefore, the incidence of fistula was only one case that could be due to meatal stricture. Meatal stenosis is the most reported form of complication and usually responds to dilatation. Although uroflowmetry was not performed, meatal stenosis was evaluated clinically. Based on the opinion of Duckett et al., flowmetry is a good objective measure of caliber, but observation of a good full stream is subsequently more revealing in follow-up. Ideally one should have both (5).

The limitation of our study was the degree of scarring of the plate, because the most of our cases had a small scar on urethral plate and none of our patients had previously undergone a TIP urethroplasty repair. The authors conclude that this technique is adequate for patients with a heavily scarred urethral plate.

In conclusion, using the TIP urethroplasty as described by Snodgrass et al., is a suitable method for treating the re-operative cases. It can also be used successfully in patients who do not have a healthy skin flap and for circumcised patients when there is a complete lack of foreskin.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Snodgrass W: Tubularized, incised plate urethroplasty for distal hypospadias. J Urol. 1994; 151: 464-5.
2. Snodgrass WT, Lorenzo A: Tubularized incised-plate urethroplasty for hypospadias reoperation. BJU Int. 2002; 89: 98-100.
3. Snodgrass W, Koyle M, Manzoni G, Hurwitz R, Caldamone A, Ehrlich R: Tubularized incised plate hypospadias repair for proximal hypospadias. J Urol. 1998; 159: 2129-31.
4. Hayashi Y, Kojima Y, Mizuno K, Nakane A, Tozawa K, Sasaki S, et al.: Tubularized incised-plate urethroplasty for secondary hypospadias surgery. Int J Urol. 2001; 8: 444-8.
5. Duckett JW, Coplen D, Ewalt D, Baskin LS: Buccal mucosal urethral replacement. J Urol. 1995; 153: 1660-3.
6. Shanberg AM, Sanderson K, Duel B: Re-operative hypospadias repair using the Snodgrass incised plate urethroplasty. BJU Int. 2001; 87: 544-7.
7. El-Sherbiny MT, Hafez AT, Dawaba MS, Shorrab AA, Bazeed MA: Comprehensive analysis of tubularized incised-plate urethroplasty in primary and re-operative hypospadias. BJU Int. 2004; 93: 1057-61.
8. Yang SS, Chen SC, Hsieh CH, Chen YT: Reoperative Snodgrass procedure. J Urol. 2001; 166: 2342-5.
9. Borer JG, Bauer SB, Peters CA, Diamond DA, Atala A, Cilento BG Jr, et al.: Tubularized incised plate urethroplasty: expanded use in primary and repeat surgery for hypospadias. J Urol. 2001; 165: 581-5.
10. Cakan M, Yalçinkaya F, Demirel F, Aldemir M, Altug U: The midterm success rates of tubularized incised plate urethroplasty in reoperative patients with distal or midpenile hypospadias. Pediatr Surg Int. 2005; 21: 973-6.
11. Senkul T, Karademir K, Iseri C, Erden D, Baykal K, Adayener C: Hypospadias in adults. Urology. 2002; 60: 1059-62.

12. Hensle TW, Tennenbaum SY, Reiley EA, Pollard J: Hypospadias repair in adults: adventures and misadventures. J Urol. 2001; 165: 77-9.

13. Eliçevik M, Tireli G, Demirali O, Unal M, Sander S: Tubularized incised plate urethroplasty for hypospadias reoperations in 100 patients. Int Urol Nephrol. 2007; 39: 823-7.

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EDITORIAL COMMENT

The authors report their experience with tabularized incised plate urethroplasty (TIPU) for hypospadias repair in 13 patients after previous failed attempts and in 4 after previous circumcision. Five patients experienced post-operative complications and 1 eventually required re-intervention. The authors conclude that the TIPU repair is a viable option even in such complex cases.

Although the conclusion is acceptable, patients with previous failed repairs and those with previous circumcision should be differentiated. In the latter, the issue is the lack of tissue for second-layer coverage of the urethroplasty, which may expose to an increased risk of fistula formation; in redo cases, instead, there might also be the issue of the presence of a scarred urethral plate unsuitable for the urethroplasty.

Indeed, in the absence of preputial tissue several alternatives exist for second-layer coverage of the urethroplasty accounting for the absence of increased morbidity in circumcised patients (1). For mid-shaft or distal hypospadias, as in the current series, the best choice is, in our opinion, the Y-to-I spongioplasty (2). This is performed rotating over the urethroplasty suture the residual spongiosum remnants, normally located underneath and laterally to the urethral plate. In order to achieve a double-layer coverage without overlapping sutures, a dartos flap based on the hypospadic meatus can be flipped over the re-approximated spongiosum. This is indeed the kind of coverage we also use in patients elected for preputial reconstruction.

Second-layer coverage can prove trickier, instead, in secondary repairs due to the paucity of good quality tissue available. Dartos flaps can often be mobilized laterally to the urethral plate and crossed above the neo-urethra in a "double breast" fashion. In a few cases, however, use of a tunica vaginalis flap can be the only option (3).

With regard to the degree of urethral plate scarring in redoes, if the plate appears healthy and supple, even despite previous hinging (4), a redo TIPU repair is worth attempting. This was indeed the case in all the patients in the present series where, however, it is of note that the vast majority of secondary repairs had a distal hypospadias, and had had only one

previous surgery. The scenario might be quite different in cases with more severe forms of hypospadias and multiple previous failed repairs. Under these circumstances, the urethral plate can be severely and grossly scarred. If so, urethral plate substitution is, in our opinion, advisable and a two-stage oral mucosa urethroplasty is the procedure of choice (5).

REFERENCES

1. Snodgrass WT, Khavari R: Prior circumcision does not complicate repair of hypospadias with an intact prepuce. J Urol. 2006; 176: 296-8.
2. Yerkes EB, Adams MC, Miller DA, Pope JC 4th, Rink RC, Brock JW 3rd: Y-to-I wrap: use of the distal spongiosum for hypospadias repair. J Urol. 2000; 163: 1536-8; discussion 1538-9.
3. Gürdal M, Karaman MI, Kanberoğlu H, Kireççi S: Tunica vaginalis reinforcement flap in reoperative Snodgrass procedure. Pediatr Surg Int. 2003; 19: 649-51.
4. Nguyen MT, Snodgrass WT: Tubularized incised plate hypospadias reoperation. J Urol. 2004; 171: 2404-6; discussion 2406.
5. Haxhirexha KN, Castagnetti M, Rigamonti W, Manzoni GA: Two-Stage repair in hypospadias. Indian J Urol 2008; 24: 226-232

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EDITORIAL COMMENT

The manuscript clearly reports the experience using tubularized incised plate (TIP) technique in 17 patients, 13 of them undergone previous hypospadias failure with different techniques (Mathieu in 2, Thiersh-Duplay in 4 and, failed on-lay flap in one and unknown in 6), the remaining 4 patients were circumcised patients with intact urethral plate. In patients with intact urethral plate no complications were described. Instead, complications were observed in patients who underwent failed urethroplasty that causes scarring of the urethral plate. Reading this study, TIP urethroplasty continues to be the first surgical choice in hypospadia repair.

Otherwise, in those cases with urethral plate too scarred and where urethral vascularization has been compromised by previous surgery, we believe that it would be interesting to use a modification of the tubularized incised plate technique by adding a dorsal free buccal or lingual mucosal graft in the attempt to avoid meatal stenosis.

Under these conditions, most authors have proposed a one stage procedure using the graft as a ventral onlay or tube, with a complication rate of 32% and 50%, respectively (1), Snodgrass and Elmore (2) reported on dorsal buccal mucosa grafts in a two stage operation with the overall success rate of 65%.

In 2008 Ye et al. expanded Hayes and Malone's one step technique even to complex re-do hypospadias with long urethral strictures with interesting results (3). The oral graft is placed dorsally on a good quality vascular bed of tunica albuginea, with tubularization of the composite urethra. The dorsal inlay buccal mucosal graft has the advantage of the TIP technique: a) enlarge diameter of the neo urethra; b) decrease recurrence of meatal stricture. Our unpublished experience with lingual mucosal graft in single stage dorsal inlay urethroplasty in previous failed hypospadias repair is very similar with that of Ye et al.

In conclusion we think that single stage dorsal inlay oral mucosa approach is a helpful option for complex re-do hypospadias when there is no virgin urethral plate.

REFERENCES

1. Hensle TW, Kearney MC, Bingham JB: Buccal mucosa grafts for hypospadias surgery: long-term results. J Urol. 2002; 168: 1734-6; discussion 1736-7.
2. Snodgrass W, Elmore J: Initial experience with staged buccal graft (Bracka) hypospadias reoperations. J Urol. 2004; 172: 1720-4; discussion 1724.
3. Ye WJ, Ping P, Liu YD, Li Z, Huang YR: Single stage dorsal inlay buccal mucosal graft with tubularized incised urethral plate technique for hypospadias reoperations. Asian J Androl. 2008; 10: 682-6.

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EDITORIAL COMMENT

In this article, authors retrospectively reviewed the outcome of tubularized incised plate urethroplasty (TIPU) for hypospadias reoperations and repairs in circumcised patients. In their experience, 4 of 17 cases had complications. While reoperation was required in 1 case, the other 3 cases whose complications were meatal stenosis in 2 and stenosis with small fistula in 1 were cured by dilation. The authors concluded that TIPU is a safe and efficacious procedure for hypospadias reoperations and repairs in circumcised patients.

Currently, TIPU is widely accepted for primary repair of distal hypospasias and hypospadias reoperations. One of the key points in this procedure in reoperative cases would be quality of urethral plate. Several studies reported in the literature have suggested that complication rate increases in reoperative cases if the urethral plate has been resected or is obviously scarred (1,2). Therefore, careful estimation of urethral plate is crucial if TIPU is planned for hypospadias reoperation.

The other key point is reinforcing layer of neourethra. Spongioplasty and neourethral coverage with dorsal dartos flap are commonly used in primary repair by TIPU to reinforce neourethra (3,4). However, urethral sponge tissue beside the urethral plate is usually unavailable in reoperative cases. Hence, neourethral coverage by dorsal dartos flap would have more important role to prevent complications. In circumcised cases as reported in this article, dorsal dartos flap may be inadequate to reinforce the neourethra though urethral sponge tissue neighboring the urethral plate is preserved for spongioplasty. In such cases, authors made efforts to cover the neourethra with pedicled subcutaneous tissue. Tunica vaginalis is also reported as an alternative tissue for neourethral coverage if subcutaneous tissue may be inadequate to reinforce the neourethra (5). These procedures for coverage are quite important and should be performed to prevent operative complications.

I agree with authors that TIPU is safe and effective for hypospadias reoperations. However, preoperative estimation of urethral plate as well as access to information of previous surgery should be done to decide the surgical procedure in reoperative cases. Also, during surgery, neourethral coverage with well vascularized tissue should be performed to avoid complications.

REFERENCES

1. Snodgrass WT, Lorenzo A: Tubularized incised-plate urethroplasty for hypospadias reoperation. BJU Int. 2002; 89: 98-100.
2. Eliçevik M, Tireli G, Demirali O, Unal M, Sander S: Tubularized incised plate urethroplasty for hypospadias reoperations in 100 patients. Int Urol Nephrol. 2007; 39: 823-7.
3. Yerkes EB, Adams MC, Miller DA, Pope JC 4th, Rink RC, Brock JW 3rd: Y-to-I wrap: use of the distal spongiosum for hypospadias repair. J Urol. 2000; 163: 1536-8; discussion 1538-9.
4. Djordjevic ML, Perovic SV, Vukadinovic VM: Dorsal dartos flap for preventing fistula in the Snodgrass hypospadias repair. BJU Int. 2005; 95: 1303-9.
5. Gürdal M, Karaman MI, Kanberoðlu H, Kireççi S: Tunica vaginalis reinforcement flap in reoperative Snodgrass procedure. Pediatr Surg Int. 2003; 19: 649-51.

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EDITORIAL COMMENT

The evaluated 17 cases represent a very inhomogeneous group. They even have been further split up into two groups: 4 after circumcision and 13 redo hypospadias. The age ranges from 7 month to 15 years, 3 of 17 were treated with testosterone, 4 different hypospadia localizations were included. Thus, the number of the subgroups becomes very small. Operative procedure includes TIP technique plus dorsal plication in 3, use of ventral dorsal pedicle, and the use of dorsal tissue or no flap.

Four out of 13 hypospadias repairs had complications, of whom 3 were treated by dilatation, which resulted in a success rate of 92.4% for both groups.

The discussion compares the study with numerous other studies achieving similar results. However, other operative techniques for redo hypospadias like buccal mucosa flaps are not mentioned.

Due to the very inhomogeneous group and the small number of cases no conclusion can be drawn. This study does show some aspects of the TIP procedure, however it does not prove at all that the TIP procedure is suitable for redo hypospadias in patients with or without foreskin.

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Extravaginal Testicular Torsion: A Clinical Entity with Unspecified Surgical Anatomy

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ABSTRACT

Purpose: To review and evaluate the anatomical definitions of perinatal extravaginal torsion (EVT) of the testis.
Materials and Methods: An extensive review of the literature was made to reveal the prevalent anatomical background predisposing to EVT. Gross appearance of twisted testes obtained during surgery for 14 cases of EVT was used to test the validity of the above theories.
Results: The most commonly accepted suggestions describe an EVT within dartos muscle that includes all layers of spermatic cord or an EVT outside parietal layer of tunica vaginalis within internal spermatic fascia. However, both of them were found inadequately documented, while a large volume of controversial data has been accumulated, that raises doubts regarding the validity of such definitions. The gross appearance of twisted testes failed to confirm both an EVT including all layers of the spermatic cord and also an EVT outside tunica vaginalis as possible mechanisms of torsion.
Conclusion: The anatomical basis of EVT remains unclear and further investigation is required.

Key words: *testis; spermatic cord; anomalous; torsion*
Int Braz J Urol. 2008; 34: 617-26

INTRODUCTION

Extravaginal torsion (EVT) of the testis is reported to be the predominant mechanism of torsion in the fetus and neonate. In this kind of torsion, twist of the spermatic cord is taking place outside the sack of tunica vaginalis in the scrotum. Accordingly, this entity is considered to have a different surgical anatomy, than the one reported in older children and adults who demonstrate the bell clapper deformity and torsion of the testis occurs intravaginally (1). This article reviews and evaluates the current theories on the anatomical basis of EVT given that the low incidence of perinatal torsion and the poorly documented anatomical findings at operation have left surgical anatomy of this clinical entity poorly defined.

MATERIALS AND METHODS

Photographic data from 14 cases of perinatal testicular torsion, operated by Professor Waldschmidt and Professor Charissis between 1973 and 2006, were examined retrospectively to define the gross appearance of EVT. Moreover, an extensive review of the literature was carried out to reveal the most commonly accepted definitions concerning the surgical anatomy predisposing to EVT. In particular, all related articles appearing in PubMed under the search terms "extravaginal", "perinatal", "testicular torsion" were examined for reference in anatomy of perinatal torsion in addition with referred pathological anatomy of perinatal torsion in text books on Urology and Pediatric Surgery. Finally, evaluation of the proposed

† *In memorian*

theories illustrated by our gross appearance photos of the twisted mass was performed.

RESULTS

Gross Appearance of Extravaginal Torsion

EVT is considered to be an antenatal event and probably because of the different time intervals between time of torsion and time of observation, gross appearance of twisted mass varies from case to case. However, there were some common characteristics found in all of our cases that can be drawn and described. Our photographic data demonstrated that EVT is usually constituted by a narrow, twisted pedicle that suspends a dark globular mass containing an infracted testis and epididymis, which appears immediately after opening the skin and dartos muscle (Figure-1). Moreover, as histologically evidenced by the most substantiated work on the subject by Herman et al., twisted tissues are surrounded by a smooth membrane layer sequestering an underlying hemorrhage (2) (Figure-2). Moreover, in contrast with intravaginal torsion where torsion occurs intravaginaly, in cases of EVT, twists of the spermatic cord are located outside the cavity created by the two layers of tunica vaginalis (Figure-1,2 and 3). Finally, although due to the usual chronic character of this antenatal event in EVT scrotal anatomy is found greatly altered, and identification of particular anatomical structures within the twisted mass becomes very difficult, testicular attachments with the parietal layer of tunica vaginalis were in fact present, an observation in accordance with most other anatomical references on the subject (Figure-3) (3-5). Each theory on surgical anatomy of EVT must be consistent with these gross characteristics.

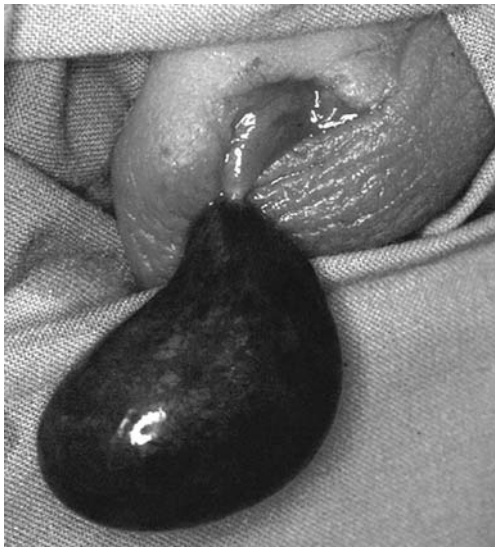

***Figure 1** – Gross appearance of perinatal torsion. Although appearance of extravaginal torsion varies from case to case, in general, after opening dartos muscle, intrascrotal contents appear as a dark mass containing the dying testis.*

Theories on the Anatomical Basis of Extravaginal Torsion

The literature review revealed 2 controversial anatomical definitions of EVT (6,7). These describe an extravaginal torsion within dartos muscle, including all layers of the spermatic cord and an extravaginal torsion within internal spermatic fascia, outside the parietal layer of tunica vaginalis (Figure-4). For discriminative reasons we will refer to them as EVT outside or inside the cremaster muscle.

Torsion Outside Cremaster Muscle

There is evidence that in perinatal period of life a lack of attachments of the entire scrotal contents with the scrotal wall is present, allowing testis and its tunics to demonstrate an unusual mobility. Cooper (1830) and Jerkings et al. (1983) first proposed this lack of attachment because of the ease with which the intrascrotal contents could be lifted out in newborns, without tearing any fascial attachments (5,6). More precisely, external spermatic fascia does not seem to be adherent to the dartos muscle. These attachments are suggested to be formed during the first 7 to 10 days of life anchoring the spermatic cord into the scrotum (7). Numerous authors use this fact to report that EVT is predisposed by this lack of attachments and accordingly, twists of the cord occur outside cremaster muscle and its fascia (external spermatic fascia), within dartos muscle, including all layers of spermatic cord (6-9) (Figure-4a). According to this point of view, EVT should become impossible after the first days of life, when connection of testicular tu-

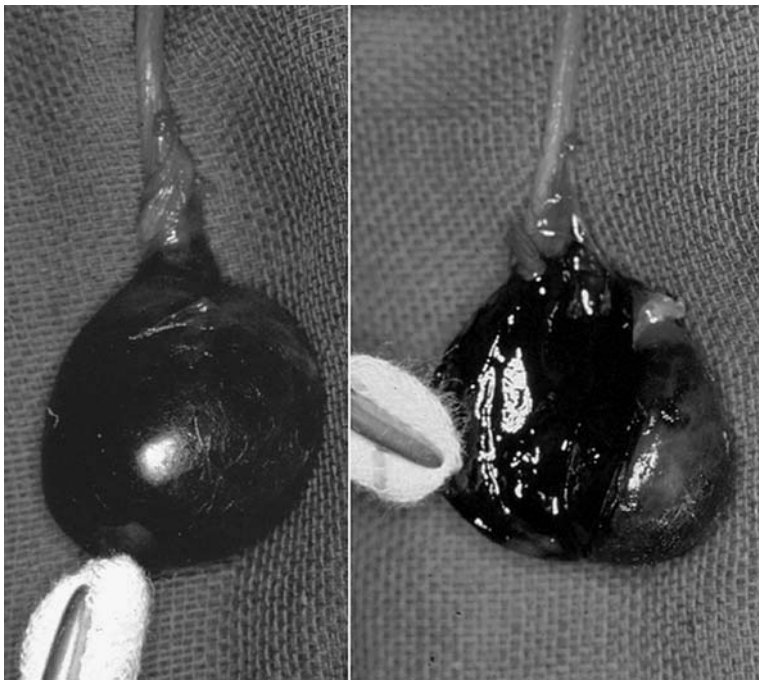

Figure 2 – *Hemorrhagic fluid from ischemic testis, restricted inside external spermatic fascia is a usual finding during surgery. The fact that the outer layer always sequesters the inner fluid indicates that this layer remains unaffected from the ischemic event. During dissection of twisted mass identification of particular structures is considered very difficult, due to the chronic character of this antenatal event.*

nics with the scrotum is established. Gross appearance of EVT reinforce the above mentioned theory, since the black necrotic twisted mass noted immediately on opening the dartos muscle clearly indicates a torsion involving all layers of spermatic cord (Figure-3).

However, this perinatal lack of attachments is a normal condition appearing in all newborns up to 7-10 days after birth. According to Noseworthy (2002) the above mentioned explanation of EVT poorly supports the relatively rare occurrence of this condition. If lack of fixation in all newborns was a predisposing factor for EVT, this should lead to a considerably higher incidence of EVT during the perinatal life (10). In addition, EVT has been reported in older patients at 12-14 years of age when such attachments are considered to be well established (11-13). In such cases, EVT in the presence of connection between dartos and external spermatic fascia remains unexplained by the examined theory, raising doubts on its validity.

As regards gross appearance, given that the outer membrane layers of the spermatic cord are very thin and transparent it is almost impossible by observation alone to distinguish the exact twisted layer of spermatic cord. In contrast, histological ischemic lessons outside tunica vaginalis observed in the removed specimens after orchidectomy has never, to our knowledge, been previously documented. Furthermore, the fact that hemorrhagic fluid is always confronted within an outer membrane layer, indicates that this layer (that is the external spermatic fascia and probably inner layers too) remains intact and is not included in the ischemic tissues (Figure-4).

Taking all the above factors into consideration, in cases of perinatal EVT doubts on whether or not external spermatic fascia is included in the twisted mass are reveled, while the mechanism that describes an EVT outside cremaster muscle including all layers of the spermatic cord remains to be defined.

Torsion Inside Cremaster Muscle

The second theory to explain EVT is that in the full-term infant, the spermatic cord and testis are free to rotate within the inguinal canal and scrotum,

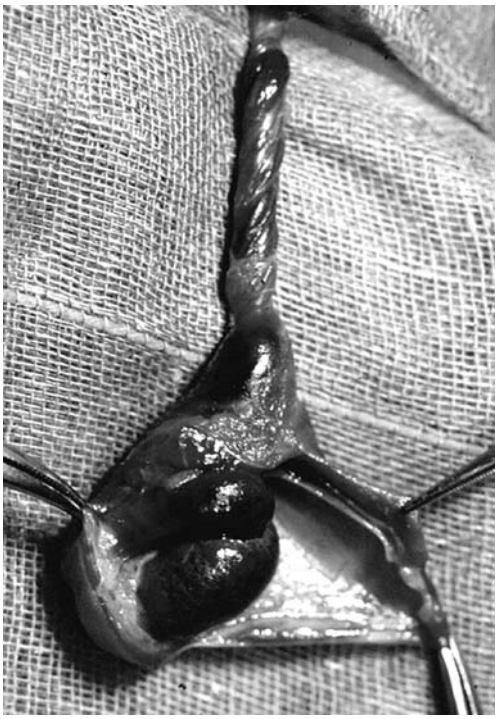

Figure 3 *– Twists of spermatic cord in case of extravaginal torsion (EVT) are located much more proximal compared with intravaginal testicular torsion. Moreover, in contrast with bell clapper deformity appearing in cases of intravaginal torsion, in EVT testicular attachments with tunica vaginalis appear to be present.*

due to lack of attachment between the testicular tunica vaginalis and the scrotum. Most authors refer to this theory (12,14-18) (Figure-4b). In matters of gross appearance, the smooth membrane layer usually covering the twisted mass, sequestering the underlying hemorrhagic fluid reinforce this theory, indicating that torsion occurs in an inner rather than an external spermatic layer. However, we have reasons to believe that this theory is based on a misinterpretation of the definition "lack of fixation of tunica vaginalis to the scrotum" as defined by Cooper (1830), which has been subsequently uncritically copied by most authors (5). It has usually been referred to as, "due to the recent descent of the gonad, there is an extreme mobility of tunica vaginalis within the scrotum before fixation of tunica vaginalis to the scrotal wall" (15,16), or "there is lack of firm attachment of parietal layer of tunica vaginalis with the scrotum" (2). However, literally, parietal layer of tunica vaginalis is never fixed to the scrotum, but its outer associated membranes (cremaster muscle and fascias) will. Therefore, inadequate fixation of tunica vaginalis to the scrotum is a term incorrectly used for the description of the normal lack of connections of the entire scrotal contents with

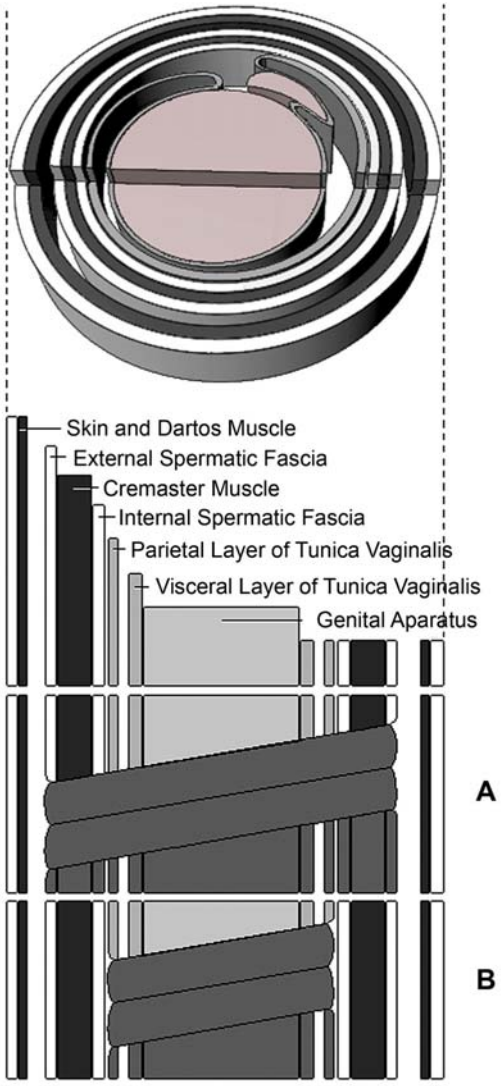

Figure 4 *– Diagrammatic illustration of scrotal membrane layers outside genital apparatus (testis, epididymis, spermatic cord and spermatic vessels) and proposed anatomical explanations of extravaginal torsion (EVT). Ischemic tissues under torsion are demonstrated by the same color. A)- EVT outside cremaster muscle. B)- EVT inside cremaster muscle.*

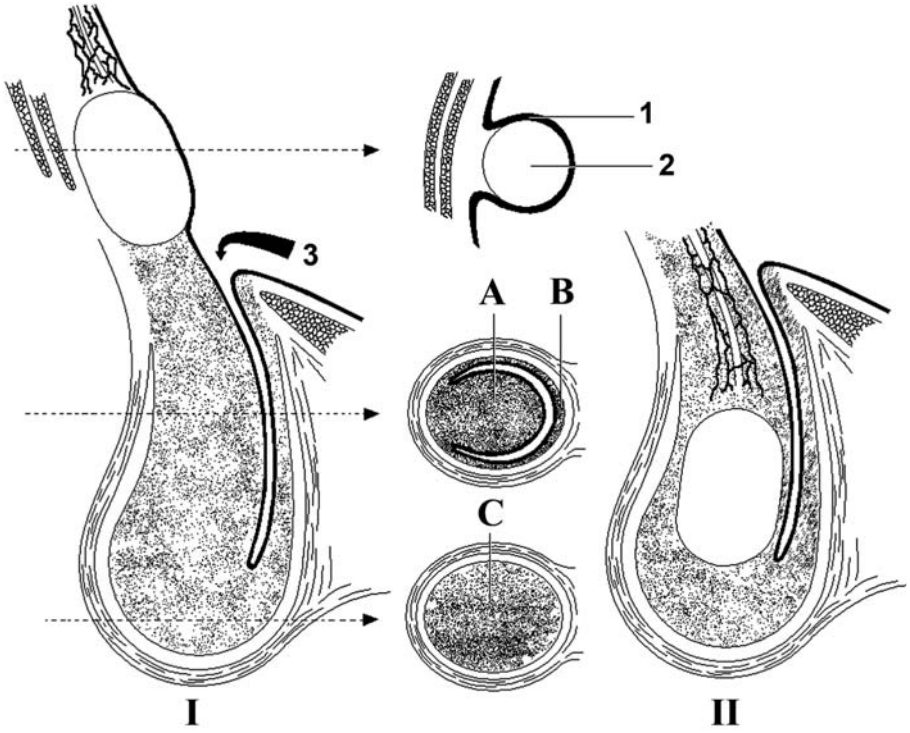

Figure 5 – *Schematic illustration of the anatomical associations between testis, gubernaculum and peritoneum before (I) and after (II) the descent of the testis. A = plica gubernaculi, B = Pars vaginalis gubernaculi, C = Pars infravaginalis gubernaculi, 1 = peritoneum, 2 = gonad, 3 = processus vaginalis.*

the scrotal wall in the first days of life, as described by Cooper (5).

Moreover, not only, perinatal lack of attachment between testicular tunica vaginalis and its outer associated membranes in the scrotum have never, in fact, been documented, but also there is no obvious etiological reason to explain why such a lack should be present in the first place. During embryogenesis, both the parietal layer of tunica vaginalis (derivative of the peritoneum forming the parietal layer of processus vaginalis) and the derived by the pars vaginalis gubernaculum outer associated membranes (internal spermatic fascia, cremaster muscle and external spermatic fascia) were never separate (19). This firm relationship negates the possibility of a perinatal absence of such attachments (Figure-5).

On the contrary, even assuming an absence of attachments between tunica vaginalis and internal spermatic fascia, torsion outside tunica vaginalis could not possibly occur. Given that in EVT testicular anatomy is considered to be normal (absence of bell clapper deformity) in scrotal and inguinal region the testis, epididymis, spermatic vessels and vas deference lie posteriorly connected with the internal spermatic fascia through a wide mesentery (mesogonadal - mesorcheon) and cannot move freely (20) (Figure-6).

These factors prove that, there is no embryological basis to support a perinatal lack of tunica vaginalis attachments with the internal spermatic fascia, while as in every scrotum with normal anatomy, in cases of EVT, rotation inside cremaster muscle cannot occur (21).

COMMENTS

The validity of the anatomical basis of EVT has been previously questioned. Mushat (1932) in his work on mechanism of testicular torsion raised

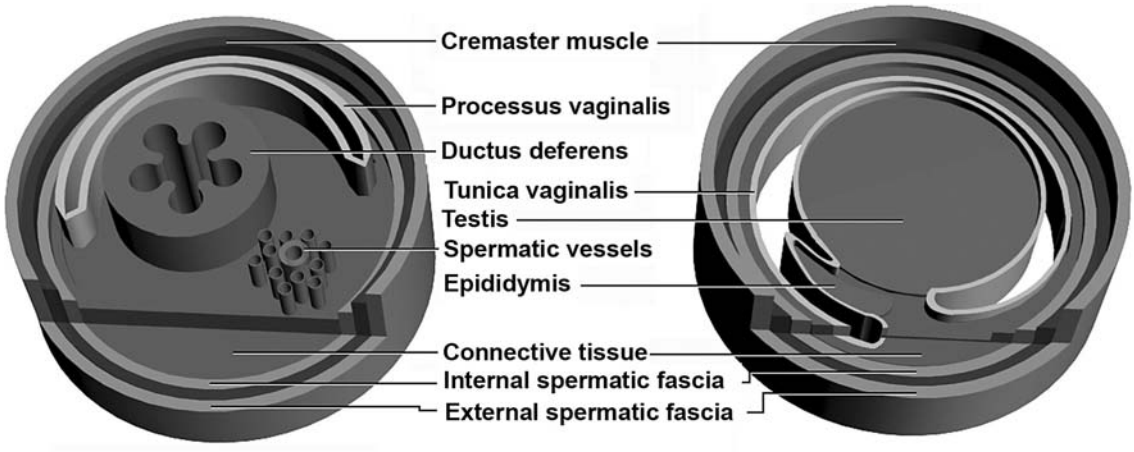

Figure 6 *– Diagrammatic illustration of normal anatomy in inguinal and scrotal region. Posterior, the extraperitoneal connective tissue anchors through testicular mesentery the functional elements to internal spermatic fascia. Skin and dartos muscle are not shown.*

doubts on whether EVT was actually possible (21). Additional doubts on whether current anatomical interpretation is correct are derived from data suggesting the possibility of the existence of a bell clapper deformity in case of perinatal torsion. As stated above and demonstrated by our photographic data EVT is considered to be characterized by connection of testis with tunica vaginalis, in contrast with intravaginal torsion where posterior attachment of testis with tunica vaginalis is absent and scrotal structures demonstrate the bell clapper deformity. Investigation of contralateral testes in cases of vanishing testis syndrome, a condition representing the final effect of antenatal torsion revealed the presence of a contralateral bell clapper deformity in the remarkable percentage of 86% of cases (15,22-25). Given that bell clapper deformity is usually bilateral, existence in the ipsilateral, where antenatal torsion has occurred, of a bell clapper deformity as well before the vanishing event is very possible. Therefore, the question whether presence of connection between testis and tunica vaginalis in case of EVT represents normal anatomy or fibrotic connections of an underlying bell clapper deformity due to the chronic character of this antenatal event remains to be defined. This fact would reinforce the majority of authors, who support an EVT within dartos muscle, though under a different hypothesis than the one proven to be incorrect by our study.

CONCLUSION

In summary, the two most commonly accepted anatomical definitions of perinatal testicular torsion namely an extravaginal torsion within dartos muscle, including all layers of spermatic cord and an extravaginal torsion outside parietal layer of tunica vaginalis within internal spermatic fascia remain questionable. In the first case, although there is evidence of perinatal lack of attachments between external spermatic fascia and dartos muscle, such torsion has not been proved with certainty. On the contrary, a large body of literature argues against this explanation. In the second case, doubts on whether there is lack of attachments between testicular tunica vaginalis and scrotum have been revealed. Yet, even if such a lack was actually present, testicular torsion inside internal spermatic fascia would still be impossible, since genital apparatus remains fixed by its wide mesorchium to external membrane layers of the scrotum. Finally, suspicions regarding the existence of a bell clapper deformity in all cases of EVT were raised, a fact confronting the current understanding of the condition. It is concluded that the prevalent anatomical definitions of EVT fail to explain adequately the phenomenon of perinatal torsion and to allow an evidence based documentation of the indicated treatment modality. EVT still remains a

condition of unknown etiology, pathophysiology and surgical anatomy and thus further investigation in the field is required.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Waldschmidt J: Hodentorsion. In: Waldschmidt J, Hamm B, Schier F (ed.), Das acute Skrotum. Stuttgard – Verlag, Hippokrates. 1990; pp. 27-48.
2. Herman A, Schvimer M, Tovbin J, Sandbank J, Bukovski I, Strauss S: Antenatal sonographic diagnosis of testicular torsion.Ultrasound Obstet Gynecol. 2002; 20: 522-4.
3. Whitaker RH: Diagnoses not to be missed. Torsion of the testis. Br J Hosp Med. 1982; 27: 66-9.
4. Mishriki SF, Winkle DC, Frank JD: Fixation of a single testis: always, sometimes or never. Br J Urol. 1992; 69: 311-3.
5. Cooper Sir Astley: Observations on the structure and disease of the testis. Longman, London, 1830.
6. Jerkins GR, Noe HN, Hollabaugh RS, Allen RG: Spermatic cord torsion in the neonate. J Urol. 1983; 129: 121-2.
7. Sheridan WG, Davies DG: Extravaginal testicular torsion. Br J Clin Pract. 1988; 42: 128-30.
8. Kay R, Strong DW, Tank ES: Bilateral spermatic cord torsion in the neonate. J Urol. 1980; 123: 293.
9. Junnila J, Lassen P: Testicular masses. Am Fam Physician. 1998; 57: 685-92.
10. Noseworthy J: Testicular torsion. In: Ashcraft K.W (ed.), Pediatric Surgery 3rd ed. WB Saunders, Philadelphia, 200; 674-80.
11. Das S, Singer A: Controversies of perinatal torsion of the spermatic cord: a review, survey and recommendations. J Urol. 1990; 143: 231-3.
12. Barker K, Rapeer FP: Torsion of the testis. Br J Urol. 1964; 36: 35-41.
13. Johnston JH: The testicles and the scrotum. In: DI Williams (ed.), Pediatric Urology. London, Q Butterworths. 1968; pp. 450-74.
14. Sorensen MD, Galansky SH, Striegl AM, Koyle MA: Prenatal bilateral extravaginal testicular torsion--a case presentation. Pediatr Surg Int. 2004; 20: 892-3.
15. Belman AB, Rushton HG: Is the vanished testis always a scrotal event? BJU Int. 2001; 87: 480-3.
16. Al-Salem AH: Intra-uterine testicular torsion: early diagnosis and treatment. BJU Int. 1999; 83: 1023-5.
17. Traubici J, Daneman A, Navarro O, Mohanta A, Garcia C: Original report. Testicular torsion in neonates and infants: sonographic features in 30 patients. AJR Am J Roentgenol. 2003; 180: 1143-5.
18. Arena F, Nicotina PA, Scalfari G, Visalli C, Arena S, Zuccarello B, et al.: A case of bilateral prenatal testicular torsion: Ultrasonographic features, histopathological findings and management. J Pediatr Urol. 2005; 1: 369-72.
19. Pham SB, Hong MK, Teague JA, Hutson JM: Is the testis intraperitoneal? Pediatr Surg Int. 2005; 21: 231-9.
20. Hollinshead WH: The perineum. In: Hollinshead WH (ed.), Anatomy for Surgeons Vol 2. 2nd ed. New York, Harper and Row. 1971; pp. 853-68.
21. Mushat M: The pathological anatomy of testicular torsion; explanation of its mechanism. Surgery, Gynecology and Obstetrics. 1932; 54: 758-63.
22. Gong M, Geary ES, Shortliffe LM: Testicular torsion with contralateral vanishing testis. Urology. 1996; 48: 306-7.
23. Belman AB, Rushton HG: Is an empty left hemiscrotum and hypertrophied right descended testis predictive of perinatal torsion? J Urol. 2003; 170: 1674-5; discussion 1675-6.
24. Bellinger MF: The blind-ending vas: the fate of the contralateral testis. J Urol. 1985; 133: 644-5.
25. Harris BH, Webb HW, Wilkinson AH Jr, Stevens PS: Protection of the solitary testis. J Pediatr Surg. 1982; 17: 950-2.

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EDITORIAL COMMENT

Most cases of fetal and neonatal testicular torsion are diagnosed at birth either by absence of the testis in the scrotum or inguinal region (vanishing testis), or by the presence of a hard testis fixed to the scrotal skin. These cases are thought to be caused by an extravaginal torsion of the spermatic cord (EVT), due to inadequate attachments between the layers of the spermatic cord, usually completed only after few weeks of life. Despite prompt surgical exploration of the ischemic testes in the neonatal period, their salvage rate is very low, and the real debate is if early contralateral testicular fixation is warranted. Cases of testicular torsion occurring later, in previously normal testes, are also caused by an intravaginal torsion of the spermatic cord, by the bell-clapper deformity, that usually is observed also in the contralateral testis (1). In these cases, since the salvage rate of the affected testis rises to almost 50%, emergency surgical exploration is always recommended, and must include the contralateral testicular fixation (2).

The work by Dr Kyriazis and associates evaluates the anatomical definitions of the perinatal EVT, based mainly on a thorough review of the literature. The bibliographical survey is well performed, and the authors elegantly discuss the two theories on the anatomical basis of the EVT, the one occurring inside, and the other outside the cremaster muscle. They also propose an evaluation of a photographic data from 14 previously operated cases. Unfortunately, although illustrative, this evaluation is superficial and presented without scientific methodology. Furthermore, they present no pathological data of their cases that could give support to any of the two mentioned theories.

Although this work does not address the issue of the management of EVT, I encourage the authors to review their material and include more significant information of their cases, including age of the patients, management of the contralateral testes and pathological data, that would surely enrich the scarce literature on the subject.

REFERENCES

1. Favorito LA, Cavalcante AG, Costa WS: Anatomic aspects of epididymis and tunica vaginalis in patients with testicular torsion. Int Braz J Urol. 2004; 30: 420-4.
2. Sorensen MD, Galansky SH, Striegl AM, Mevorach R, Koyle MA: Perinatal extravaginal torsion of the testis in the first month of life is a salvageable event. Urology. 2003; 62: 132-4.

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EDITORIAL COMMENT

Testicular torsion is divided into two types, intravaginal and extravaginal. Intrauterine testicular torsion (IUTT) is of the extravaginal type. IUTT was first described by Taylor in 1897 and when compared to intravaginal torsion, it is a very rare condition that is being recognized with increasing frequency (1). One reason for this is the adoption of routine thorough examination of all newborns prior to their discharge. We however recommend that this routine general examination be done in the immediate postpartum period as well as prior to discharge. This will obviate any delay in diagnosis and treatment of IUTT since the majority of them will manifest in the immediate postpartum period (2). IUTT is a very rare condition that may also be difficult to recognize when seen for the first time and so it may be missed or confused with other conditions. To obviate delay in diagnosis, physicians caring for these patients should be aware of this.

Since its first description, controversies continue to exist regarding: (1) its exact cause, (2) the need for urgent exploration and (3) the necessity for contra lateral orchidopexy.

The cause as well as the anatomical basis of IUTT is not known. In this issue, Kyriazis et al. in an extensive review attempted to evaluate the anatomical basis of intrauterine torsion. Although IUTT is usually a prenatal event, the exact timing and duration of torsion are not known and there are reports of prenatally diagnosed torsion. Tripp and Homsy reported a case of bilateral torsion diagnosed prenatally at 35 weeks gestation and Hubbard et al. reported a case of unilateral torsion diagnosed at 35.5 week gestation (3,4). On the other hand, and although most cases of IUTT are apparent at birth, there are reports of torsion occurring after delivery or within the first week after birth (5). It is believed that IUTT is the main cause of monorchidism, which is supported by the fact that a vas deference, epididymis, calcification or hemosiderine pigmentation is present in about 90% of the cases (6). In cases of IUTT, controversy still continues regarding the urgency for surgical exploration as well as the need for contra lateral orchidopexy. Some investigators advocate delayed operation, and consider this not an emergency (7). This is to obviate the anesthetic risk imposed on the neonate as well as the low salvage rate of these testes. If such a policy is adopted, then these patients should not be operated on at all as ultimately the affected testis will atrophy. On the contrary, these patients are healthy, of good birth weight and without any other associated anomalies that impose an anesthetic risk (2). Keeping this in mind as well as the hope of testicular preservation, we like others adopted a policy of early surgical intervention (2,8). Olguner et al. reported a patient at the postnatal 28th hour with right scrotal erythema and swelling. Emergency technetium Tc 99m pertechnetate scintingraphy showed hypo perfusion in both sides and because the patient underwent surgery immediately, the left testis was judged viable, treated by means of detorsion and saved while the right testis was necrotic (8). Early surgical exploration also establishes the diagnosis and excludes other rare causes such as benign and malignant tumors and traumatic hematocele.

Another controversial point is whether contra lateral orchidopexy is justified. Some investigators suggested that since predisposing factors are lacking in extravaginal torsion, there is no need for contra lateral orchidopexy (6). This however is difficult to establish. On the other hand, the increasing number of reported cases with bilateral intrauterine torsion supports a predisposing factor (3,8-10), and although asynchronous bilateral torsion is rare, it can however occur at any time and has been reported as early as 48 hours after torsion on the other side (10). To obviate the risk of anorchia, we like others advocate routine and simultaneous contra lateral exploration and orchidopexy. This is a simple procedure, has no or minimal morbidity and safeguards against contra lateral torsion.

REFERENCES

1. Taylor MR: A case of testicular strangulation at birth, castration, recovery. Br Med J. 1897; 1: 458.
2. Al-Salem AH: Intrauterine testicular torsion: a surgical emergency. J Pediatr Surg. 2007; 42: 1887-91.
3. Tripp BM, Homsy YL: Prenatal diagnosis of bilateral neonatal torsion: a case report. J Urol. 1995; 153: 1990-1.
4. Hubbard AE, Ayers AB, MacDonald LM, James CE: In utero torsion of the testis: antenatal and postnatal ultrasonic appearances. Br J Radiol. 1984; 57: 644-6.
5. Burge DM: Neonatal testicular torsion and infarction: aetiology and management. Br J Urol. 1987; 59: 70-3.
6. Lamesch AJ: Monorchidism or unilateral anorchidism. Langenbecks Arch Chir. 1994; 379: 105-8.
7. Cumming DC, Hyndman CW, Deacon JS: Intrauterine testicular torsion: not an emergency. Urology. 1979; 14: 603-4.
8. Olguner M, Akgür FM, Aktuð T, Derebek E: Bilateral asynchronous perinatal testicular torsion: a case report. J Pediatr Surg. 2000; 35: 1348-9.
9. Weingarten JL, Garofalo FA, Cromie WJ: Bilateral synchronous neonatal torsion of spermatic cord. Urology. 1990; 35: 135-6.
10. LaQuaglia MP, Bauer SB, Eraklis A, Feins N, Mandell J: Bilateral neonatal torsion. J Urol. 1987; 138: 1051-4.

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EDITORIAL COMMENT

The authors challenge established anatomical and pathological principles of "extravaginal" testicular torsion through a discussion on the clinical findings, a literature review and a focused anatomical discussion. The importance of this discussion lies within the implications for clinical management in this group. The debate within pediatric surgical literature between the active exploration of the perinatal torsion and its conservative management is firmly grounded in the surgical precepts that intra and extra vaginal torsions are separate anatomical and surgical anomalies.

The paper debunks the accepted theories of extravaginal torsion. The authors argue that the simple lack of perinatal attachments which is the clinical norm in the first seven to ten days does not equate to the relative infrequency of the condition. The absence of a clear definition of extravaginal torsion and the specter of presence of bell clapper deformity leads to a requirement for a much more aggressive surgical management of this condition.

Despite the relative infrequency of the asynchronous torsion in the literature as pediatric urologists we all seem to have one or more of these patients in our own units leading to real concerns of under reporting (1). A significant body of opinion argues against conservative management due to incidence of asynchronous events (2-4). Baglaj et al. identified 48 cases of bilateral perinatal torsions in the literature (5). Synchronous torsion occurred in 67% thus asynchronous torsion occurred in 33%. Urgent exploration of the torted testis and empiric exploration and orchidopexy for the contralateral testis is recommended in all cases of perinatal torsion. Parental counseling which explains the relatively low salvage rate and the high asynchronous torsion rate is warranted.

The challenge for pediatric surgeons is to examine all the excised perinatal testicles that in order to delineate the pathology. Further anatomical studies are required on the scrotal anatomy of neonates with fully descended testes who die in the perinatal period in order to define the normal anatomical attachments of the testes.

REFERENCES

1. Beasley SW, McBride CA. The risk of metachronus (asynchronous) contralateral torsion following perinatal torsion. N Z Med J. 2005; 118: U1575.
2. Cuervo JL, Grillo A, Vecchiarelli C, Osio C, Prudent L: Perinatal testicular torsion: a unique strategy. J Pediatr Surg. 2007; 42: 699-703.
3. Yerkes EB, Robertson FM, Gitlin J, Kaefer M, Cain MP, Rink RC: Management of perinatal torsion: today, tomorrow or never? J Urol. 2005; 174: 1579-82; discussion 1582-3.
4. Sorensen MD, Galansky SH, Striegl AM, Mevorach R, Koyle MA: Perinatal extravaginal torsion of the testis in the first month of life is a salvageable event. Urology. 2003; 62: 132-4.
5. Baglaj M, Carachi R: Neonatal bilateral testicular torsion: a plea for emergency exploration. J Urol. 2007; 177: 2296-9.

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Intravesical Protrusion of the Prostate as a Predictive Method of Bladder Outlet Obstruction

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ABSTRACT

Objective: Pressure-flow study is the gold standard for diagnosis of bladder outlet obstruction (BOO). A prospective study was carried out to compare urodynamic evaluation and measurement of intravesical protrusion of the prostate for diagnosing BOO.

Materials and Methods: Patients presenting with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia and suspected BOO were prospectively evaluated through conventional urodynamics and classified according to the bladder outlet obstruction index (BOOI). They also underwent abdominal ultrasound measurement of the intravesical prostatic protrusion (IPP) and prostatic volume. The IPP was classified into three stages: grade I under 5 mm; grade II, between 5 and 10 mm; and grade III over 10 mm.

Results: Forty-two patients, mean age 64.8 ± 8.5 years were enrolled. Transabdominal ultrasound determined a mean prostatic volume of 45 ± 3.2 mL. Achieved IPP's values were the following: grade I - 12 (28.5%), grade II - 5 - (12%) and grade III - 25 (59.5%). The results of prostate volume differed significantly between obstructed and non-obstructed men ($p = 0.033$) and for IPP among obstructed, inconclusive and non-obstructed men ($p = 0.016$). For IPP, the area under ROC curve was 0.758 (95% confidence interval - 0.601 to 0.876), and the cutoff point to indicate BOO was 5 mm with 95 % sensitivity (75.1 - 99.2) and 50 % specificity (28.2 - 71.8).

Conclusion: IPP and prostatic volume measured through abdominal ultrasound are noninvasive and accessible methods that significantly correlate to urinary BOO, and are useful in the diagnosis of male urinary obstructive problems.

Key words: *bladder outlet obstruction; prostate; volume; flowmetry; sensitivity and specificity*
Int Braz J Urol. 2008; 34: 627-37

INTRODUCTION

Bladder outlet obstruction (BOO) is characterized by increased detrusor pressure and reduced urinary flow rate. Pressure-flow studies are the gold standard for BOO determination. However, this method is an invasive and expensive procedure with limited availability.. Therefore, attempts have been made to diagnose BOO through noninvasive methods that can be divided into 2 categories: non-urodynamically based measurements and noninvasive urodynamics.

Non-urodynamically based measurements include symptoms, post-void residual urine (PVR), Prostate Specific Antigen (PSA) and ultrasound derived measurements, such as prostate volume, bladder wall thickness, bladder weight and intravesical prostatic protrusion (IPP). Noninvasive urodynamics include uroflowmetry, use of a penile cuff, the condom-method and Doppler urodynamics (1).

It is well known that the prostate's anatomic conformation together with intravesical prostatic protrusion (IPP) may affect normal voiding.

Earlier studies have previously demonstrated that the ultrasonographic measurement of IPP could identify BOO. A total of 200 patients were assessed with invasive urodynamics and transabdominal ultrasound. The relationship of IPP to BOO showed that as IPP grade increased in severity, BOO grade also increased. The sensitivity and specificity of diagnosing BOO were 76% and 92% for over 10 mm IPP, 17% and 53% for between 5 and 10 mm IPP and 7% and 56% for under 5 mm IPP, respectively. PVR more than 100 mL showed 75% sensitivity and 91% specificity for predicting BOO in the population studied (2).

The objective of this study was to define how the IPP and prostate volume, measured through abdominal ultrasound, might alter voiding and determine the accuracy of this measurement compared to conventional urodynamics in diagnosing BOO.

MATERIALS AND METHODS

A prospective study was carried out in Latin-American patients presenting with lower urinary tract symptoms (LUTS) and evaluated by urinalysis to exclude urinary tract infection.

Patients who had been previously submitted to urologic surgeries, or had urologic neoplasia, bladder calculus or presented any type of neurological abnormality or using alpha-blockers, anticholinergics, antiandrogens or another medications which may affected the voiding patterns were excluded from this study.

In the period ranging from June to August/2005, after Ethics Committee approval and written informed consent, these patients were evaluated using anamnesis, International Prostatic Symptoms Score (IPSS) and IPSS Quality of Life (IPSS-QoL) questionnaires, physical, neurological, digital rectal examination and conventional urodynamic evaluation (Dynapack, Dynamed, 2004) and classified according to BOOI.

Urodynamics were done according to the "good urodynamic practices" recommended by the International Continence Society (3). Bladder outlet obstruction index (BOOI), defined as the detrusor's pressure at the maximum urinary flow (pdet_qmax) minus two times the maximum flow (qmax): BOOI = pdet_qmax - 2 x qmax. Values below 20 were considered non-obstructed, between 20 and 40 inconclusive and higher than 40, obstructed (4). Postvoid residual urine volume was measured during urodynamic investigation, after free uroflowmetry (free flow).

After one week the patients underwent an ultrasound study performed by the same physician (J.B.) blinded to the urodynamic results performed by L.O.R. Abdominal ultrasound (Toshiba model Powervision 6000) was performed in the sagittal plane, using transductor frequencies between 3 and 6 MHz, and IPP along with the prostatic volume were measured. According to Yuen et al. (5), the bladder was filled with at least 100 mL of urine in order to consider the IPP determination; this was achieved through the ingestion of one liter of water in a two hour period after voiding. IPP was defined by the distance from the tip of the prostate's protrusion into the vesical lumen to the bladder neck measured in millimeters (Figure-1). Measurements were divided into three stages: grade I < 5 mm, grade II 5-10 mm, grade III > 10 mm (2). Prostate volumes were determined through software (Powervision 600) for automatic measurement and expressed in milliliters (mL).

The statistical analysis was performed through Kruskal-Wallis and Dunn's post test to multiple comparison, and area under ROC curve, using MedCalc version 5.00.019 and SAS System for Windows version 9.1.3.

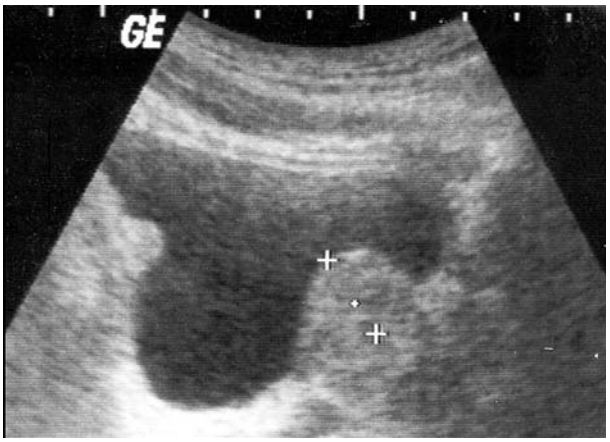

Figure 1 *– Sagittal views of bladder and prostate using transabdominal ultrasonography. Vertical distance from tip of protrusion to base of bladder is the intravesical prostatic protrusion measurement.*

Table 1 – *Clinical and demographic characteristics.*

Clinical and Demographics Characteristics	Rate
Age	64.9 (56 to 73) years
Latin-American Caucasians	100%
IPSS	13 (6 to 20)
Ultrasound transabdominal examination	45 (5.5 to 155) mL
Qmax	8.5 (5.5 to 13) mL/s
Pdet_Qmax	58.1 (35 to 126)
Post voiding residue	70 (0 to 250) mL

IPPS = International Prostate Symptom Score.

RESULTS

The clinical and demographic characteristics are shown in Table-1.

The pressure/flow study showed mean Qmax of 8.5 ± 4.3 mL/s, Pdet.qmax of 58.1 ± 26 cm H_2O, and postvoid residual urine volume after free flow of 70 ± 177 mL. Based on BOOI, 20 (47.6%) patients presented obstruction, 12 (28.5%) were inconclusive and 10 (23.9%) did not present obstruction. The mean BOOI was 28.6 (SD 13.4).

IPP's values obtained were as follows: grade I - 12 (28.5%), grade II - 5 - (12%) and grade III - 25 (59.5%).

Comparing prostatic volume and IPP with BOOI we found according to Kruskal-Wallis and Dunn's post test that the results of prostate volume differed significantly between obstructed and non-obstructed men (p = 0.033) and the results of IPP differed significantly among obstructed, inconclusive and nonobstructed men (p = 0.016), Table-2.

Table-3 demonstrates that IPP's grade III reached up to 80% sensitivity and 68 % specificity for diagnosing BOO. Positive predictive value was 70 % and the negative predictive value 79 %.

Considering the slight IPP superiority over prostate volume to detect obstruction, we calculated the IPP cutoff point to indicate obstruction as 5 mm with 95 % sensitivity (75.1 - 99.2) and 50 % specificity (28.2 - 71.8); likelihood ratio of positive test result 1.90 and likelihood ratio of negative test result 0.10.

The area under ROC curve was 0.758 (95 % confidence interval - 0.601 to 0.876) for IPP and 0.718 (95% confidence interval - 0.558 to 0.846) for prostate volume, Figure-2.

A flow diagram for IPP on diagnostic accuracy is showed in Figure-3.

Table 2 – *Prostate volume, IPP and BOOI (Kruskal–Wallis; Dunn's test).*

Prostate Volume (mL)				**IPP** (mm)			
BOOI	N	Mean	SD	BOOI	N	Mean	SD
Nonobstructed	10	29.8	19.4	Nonobstructed	10	7.6	8.5
Doubt	12	43.2	33.1	Doubt	12	8.5	7.0
Obstructed	20	53.6	32.9	Obstructed	20	15.4	6.6

p = 0.033 (prostate volume); p = 0.016 (IPP); IPP = intravesical prostatic protrusion.

Table 3 – *IPP grade III accuracy.*

Measurement	%	95% CI	N / Total
Sensitivity	80.0	55.7 ; 93.4	19/21
Specificity	68.2	45.1 ; 85.3	19/25
Positive predictive value	69.6	46.9 ; 85.9	13/19
Negative predictive value	78.9	53.9 ; 93.0	19/27
Accuracy	73.8	57.7 ; 85.6	32/46
LR +	2.51		
LR -	0.29		

CI = confidence interval; IPP = intravesical prostatic protrusion; LR = likelihood ratio; N = number of patients.

COMMENTS

LUTS are one of the most common complaints in the elderly men and benign prostate obstruction is one of the most frequent causes. Pressure flow study has been recommended before surgical treatment of prostate enlargement by many authors. Searching for new accurate methods that could substitute the gold standard pressure-flow study demonstrates the need for lowering costs, expanding accessibility and relieving patient discomfort .

Since transrectal methods can producegreat discomfort to the patient, abdominal ultrasound was demonstrated to be equivalent to rectal ultrasound for

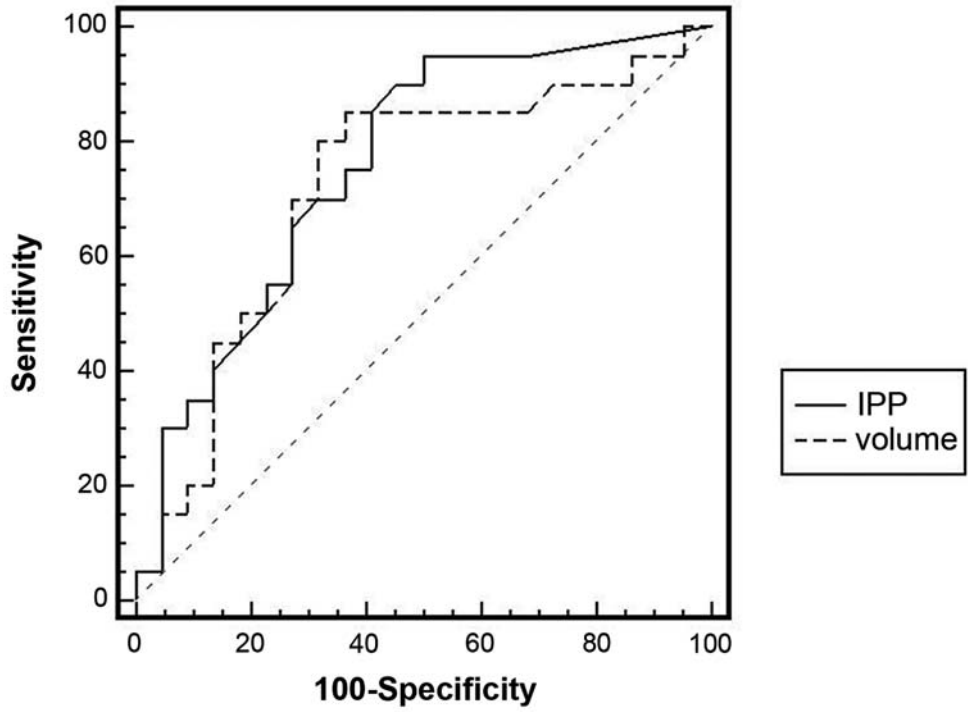

Figure 2 – *Receiver Operating Characteristic (ROC) curve for intravesical prostatic protrusion (IPP) and prostate volume.*

measuring the prostate when bladder volume is over 100 mL (5,6).

Clinical data such as IPSS, post voiding residue and flowmetry have been previously demonstrated to correlate mostly to lower urinary tract functional status rather than mechanical obstruction itself (7-9). Therefore, noninvasive measurements of the prostate intend to delineate a morpho-functional correlation in order to orient conduct towards LUTS secondary to benign prostate obstruction.

Almost all studies on IPP measurements come from Asia and it is unknown if the results in Asians are valid for Latin-Americans or Caucasians as well.

Chia et al. (2) demonstrated the possibility of using the IPP measurements for diagnosing BOO, which was also a predictor of the capacity for spontaneous voiding after acute urinary retention in Tan et al. study (10).

Other authors have suggested determining bladder weight, bladder wall width or prostate conformation through abdominal or rectal ultrasound (11-14).

Kojima et al. demonstrated, studying 104 patients, that the bladder weight more than 35 g performed thought transabdominal ultrasound is strongly associated with bladder outlet obstruction on pressure-flow studies (15).

A bladder wall thickness of 5 mm appeared to be the best cutoff point to diagnose bladder outlet obstruction, since 63.3% of patients with bladder wall thickness less than 5 mm were unobstructed while 87.5% of those with a bladder wall thickness 5 mm or greater were obstructed in a study including 174 patients of Manieri et al. at 150 mL bladder filling (16).

Hakenberg et al. (17) found that mean bladder wall thickness was 3.33 mm in healthy men and 3.67 mm in men with LUTS and BPE, measuring all patients at different bladder fillings. BOO was found in 95.5% of men with a detrusor wall thickness greater than or equal to 2 mm in Oelke et al. study, at 250 mL or more bladder filling (18).

Recently, Blatt et al. (19) who performed urodynamics evaluation and abdominal ultrasound among patients with different types bladder dysfunction, found that mean bladder wall thickness in patients with normal urodynamics, bladder outlet obstruction, detrusor overactivity and increased bladder sensation was 2.0, 2.1, 1.9 and 1.8 mm, respectively. No significant difference was found between the groups. In particular, there was no difference in bladder wall thickness between patients with normal urodynamics, and those with bladder outlet obstruction ($p = 0.31$) or detrusor overactivity ($p = 0.31$).

The inconsistency as regards the results obtained and the lack of technique standardization have limited their clinical use until now.

Intravesical protrusion seems to corroborate with urinary obstruction through a "valve ball" mechanism, in which the prostate's lateral and medium lobes interfere on the complete opening of the vesical neck while the patient urinates (10). According to this mechanism and based on the present study, it was demonstrated that the intravesical protrusion of the prostate relates not only to the urinary obstruction itself, but it also provides information concerning the severity of obstruction. It has been demonstrated that the greater the IPP, the higher BOOI (20). Still significant, but to a lesser extent, results of prostatic volume obtained through ultrasound and PSA also related to the degree of obstruction (21-24).

Utilizing receiver-operator characteristic curves, the area under the curve for IPP were 0.772, and 0.858 for Lim et al. (21) and Keqin et al. (20), respectively. The latter authors found 8.5 mm as the best cutoff value for IPP with 75.5 % of sensitivity and 82.6 of specificity.

Our findings, 0.758 for the area under the curve and 5 mm as the best cutoff value for IPP, are in agreement with these earlier investigations.

On the other hand, our study had a limited number of patients and presented great variability of results, which weakened its immediate clinical application. However, these early statistically significant results lead towards new tendencies and studies necessary to seek improved methods of diagnosing BOO as well as technique standardization.

CONCLUSION

IPP and prostatic volume measured through abdominal ultrasound are noninvasive and accessible methods that significantly correlate with urinary BOO,

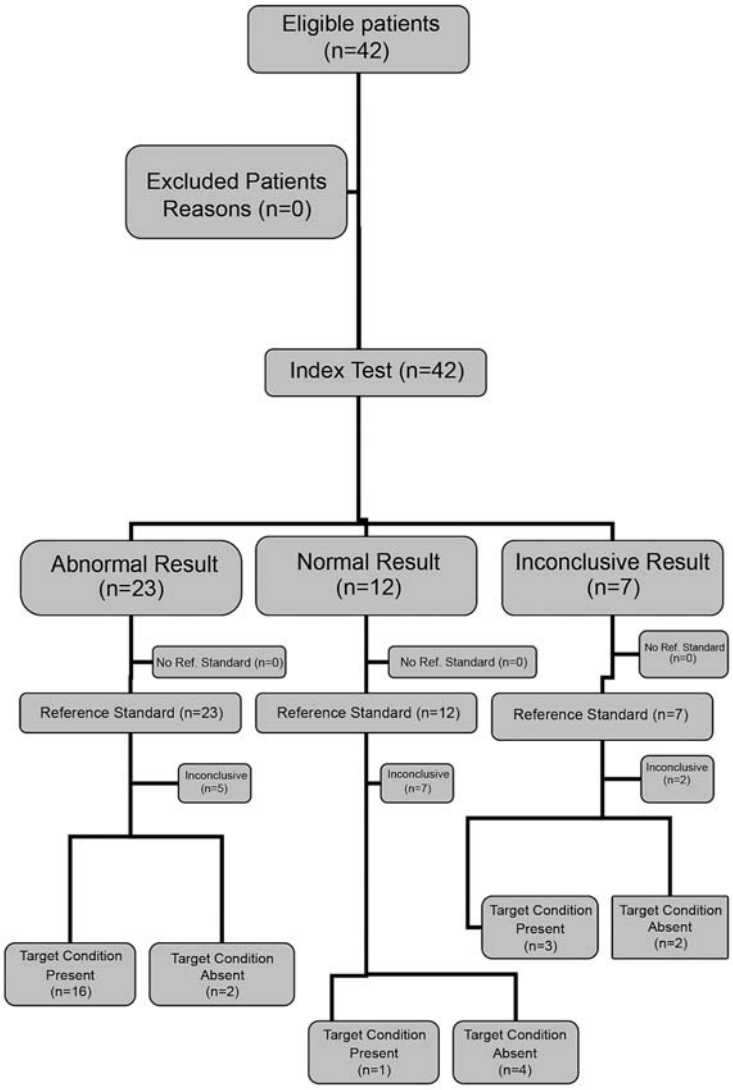

Figure 3 – *Flow diagram for intravesical prostatic protrusion on diagnostic accuracy.*

and diagnose male urinary obstructive problems. However, results are still variable and the small number of patients in this study renders further studies necessary for a final definite conclusion.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Belal M, Abrams P: Noninvasive methods of diagnosing bladder outlet obstruction in men. Part 1: Nonurodynamic approach. J Urol. 2006; 176: 22-8.
2. Chia SJ, Heng CT, Chan SP, Foo KT: Correlation of intravesical prostatic protrusion with bladder outlet obstruction. BJU Int. 2003; 91: 371-4.
3. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al.: Good urodynamic practices:

uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002; 21: 261-74.
4. Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int. 1999; 84: 14-5.
5. Yuen JS, Ngiap JT, Cheng CW, Foo KT: Effects of bladder volume on transabdominal ultrasound measurements of intravesical prostatic protrusion and volume. Int J Urol. 2002; 9: 225-9.
6. Ohnuki T, Kurokawa K, Katoh N, Fukabori Y, Shimizu K, Nakai K, et al.: Transrectal longitudinal ultrasonography of the prostate by electronic linear scanning. Hinyokika Kiyo. 1987; 33: 1385-8.
7. Netto Júnior NR, D'Ancona CA, de Lima ML: Correlation between the International Prostatic Symptom Score and a pressure-flow study in the evaluation of symptomatic benign prostatic hyperplasia. J Urol. 1996; 155: 200-2.
8. el Din KE, Kiemeney LA, de Wildt MJ, Rosier PF, Debruyne FM, de la Rosette JJ: The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol. 1996; 156: 1020-5.
9. Ezz el Din K, Kiemene LA, de Wildt MJ, Debruyne FM, de la Rosette JJ: Correlation between uroflowmetry, prostate volume, postvoid residue, and lower urinary tract symptoms as measured by the International Prostate Symptom Score. Urology. 1996; 48: 393-7.
10. Tan YH, Foo KT: Intravesical prostatic protrusion predicts the outcome of a trial without catheter following acute urine retention. J Urol. 2003; 170: 2339-41.
11. Ochiai A, Kojima M: Correlation of ultrasound-estimated bladder weight with ultrasound appearance of the prostate and postvoid residual urine in men with lower urinary tract symptoms. Urology. 1998; 51: 722-9.
12. Kuo HC: Clinical prostate score for diagnosis of bladder outlet obstruction by prostate measurements and uroflowmetry. Urology. 1999; 54: 90-6.
13. Ockrim JL, Laniado ME, Patel A, Tubaro A, St Clair Carter S: A probability based system for combining simple office parameters as a predictor of bladder outflow obstruction. J Urol. 2001; 166: 2221-5.
14. Kessler TM, Gerber R, Burkhard FC, Studer UE, Danuser H: Ultrasound assessment of detrusor thickness in men-can it predict bladder outlet obstruction and replace pressure flow study? J Urol. 2006; 175: 2170-3.
15. Kojima M, Inui E, Ochiai A, Naya Y, Ukimura O, Watanabe H: Ultrasonic estimation of bladder weight as a measure of bladder hypertrophy in men with infravesical obstruction: a preliminary report. Urology. 1996; 47: 942-7.
16. Manieri C, Carter SS, Romano G, Trucchi A, Valenti M, Tubaro A: The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. J Urol. 1998; 159: 761-5.
17. Hakenberg OW, Linne C, Manseck A, Wirth MP: Bladder wall thickness in normal adults and men with mild lower urinary tract symptoms and benign prostatic enlargement. Neurourol Urodyn. 2000; 19: 585-93.
18. Oelke M, Höfner K, Wiese B, Grünewald V, Jonas U: Increase in detrusor wall thickness indicates bladder outlet obstruction (BOO) in men. World J Urol. 2002; 19: 443-52.
19. Blatt AH, Titus J, Chan L: Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol. 2008; 179: 2275-8; discussion 2278-9.
20. Keqin Z, Zhishun X, Jing Z, Haixin W, Dongqing Z, Benkang S: Clinical significance of intravesical prostatic protrusion in patients with benign prostatic enlargement. Urology. 2007; 70: 1096-9.
21. Lim KB, Ho H, Foo KT, Wong MY, Fook-Chong S: Comparison of intravesical prostatic protrusion, prostate volume and serum prostatic-specific antigen in the evaluation of bladder outlet obstruction. Int J Urol. 2006; 13: 1509-13.
22. Dicuio M, Pomara G, Vesely S, Morelli G, Fabris FM, Ales V, et al.: The use of prostatic intravesical protrusion correlated with uroflowmetry: a new method to measure obstruction in patients with LUTS due to BOO without using P/F studies. Arch Ital Urol Androl. 2005; 77: 50-3.
23. Nose H, Foo KT, Lim KB, Yokoyama T, Ozawa H, Kumon H: Accuracy of two noninvasive methods of diagnosing bladder outlet obstruction using ultrasonography: intravesical prostatic protrusion and velocity-flow video urodynamics. Urology. 2005; 65: 493-7.
24. Oelke M, Höfner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H: Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol. 2007; 52: 827-34.

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EDITORIAL COMMENT

Benign prostatic hyperplasia (BPH) belongs to the most common benign diseases in the aging men. The prevalence of histological BPH increases with age and appears in approximately 40% of men aged 51-60 years and in approximately 90% of men aged 81-90 years (1). With increasing life expectancy worldwide more men will have these histological changes in their prostate and the probability of seeking professional help will increase as well. It is doubtful if health care systems can support the financial burden associated with the assessment and treatment of BPH-related symptoms and conditions in the future. Therefore, every approach to make the assessment and treatment easier, faster, and cheaper is highly welcome. The authors of the appending article report about their attempt and introduce a new non-invasive test to a broader public (2).

The BPH disease is characterized by benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), and lower urinary tract symptoms (LUTS). However, no clear correlations have been found between these three components and, therefore, each component has to be evaluated separately. Evaluation of BPE, by digito-rectal examination or transrectal ultrasound measurement, or LUTS, by history or questionnaires, is quick, cheap, easy, and without relevant morbidity. However, assessment of BOO has been more difficult until now. Only pressure-flow studies were able to detect and quantify bladder outflow resistance adequately. Urodynamic investigations are invasive, expensive, time-consuming, uncomfortable for the patients, widely unavailable, and necessitate a certain degree of education in terms of performance and interpretation of measurement results and artifacts. The morbidity of urodynamic measurements in men is in the range of 19% and includes dysuria, urinary tract infection, fever, bleeding, and acute urinary retention (3). There are even patients who died after urodynamic investigations because of urosepsis due to contaminated catheters (4). All of these factors are responsible that pressure-flow studies are only randomly performed. Therefore, there is a strong need to develop alternative techniques to measure BOO and to overcome the disadvantages of pressure-flow studies.

The article by Leonardo Reis and colleagues provides further evidence that ultrasound measurement of intravesical prostatic protrusion (IPP) is able to detect BOO in BPH patients quickly and non-invasively (2). Ultrasound machines belong to the standard armamentarium of urologists and are widely available. The IPP technique is easily applicable and the simple measurement of the distance between the bladder neck and the tip of the prostatic median lobe can qualify the patient as obstructed. IPP measurements were originally developed in Asia and results have also been limited to Asian patients (5). The authors of the current study investigated Latin-Americans with this new technique for the first time and could confirm that an IPP of 10 mm or more is a sensitive tool to detect BOO in patients from another part of the world (sensitivity 80%, positive predictive value 70%, likelihood ratio of positive test result 2.51). Therefore, no ethnical difference seems to exist and IPP measurements are of general value. The authors have to be congratulated to have presented a study, which was conducted according to all quality criteria of diagnostic accuracy tests.

Despite the achievements of the authors, the present study has to be classified as a pilot study to demonstrate the proof of principle. Only 42 patients were included in the trial which seems to be underpowered to draw general conclusions. The results are limited to BPH patients and other types of BOO cannot be studied with this technique (e.g. bladder neck stenosis, urethral strictures, or meatus stenosis). Furthermore, specificity of IPP measurements is low (68%) and, therefore, patients with an IPP distance of less than 10 mm cannot be safely classified as unobstructed. Until now, only ultrasound measurements of detrusor or bladder wall thickness have shown to have a high sensitivity (83%), specificity (95%), and likelihood ratio of a positive test result (17.6) which are superior to all other classic non-invasive tests for BOO evaluation (uroflowmetry, measurement of postvoid residual urine or prostate volume) (6). Future studies with adequate power, a multicenter and prospective evaluation approach, and the comparison of IPP with other non-invasive tests are necessary to judge the value of this emerging technique correctly.

REFERENCES

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol. 1984; 132: 474-9.
2. Reis LO, Barreiro GC, Baracat J, Prudente A, Levi D'Ancona CA: Intravesical protrusion of the prostate as a predictive method of bladder outlet obstruction. Int Braz J Urol 2008;
3. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP: Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. J Urol. 1998; 159: 191-4.
4. Cann KJ, Johnstone D, Skene AI: An outbreak of Serratia marcescens infection following urodynamic studies. J Hosp Infect. 1987; 9: 291-3.
5. Chia SJ, Heng CT, Chan SP, Foo KT: Correlation of intravesical prostatic protrusion with bladder outlet obstruction. BJU Int. 2003; 91: 371-4.
6. Oelke M, Höfner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H: Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol. 2007; 52: 827-34.

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EDITORIAL COMMENT

The concept of measuring intra-vesical protrusion of the prostate by ultrasound as a surrogate for bladder outflow obstruction is not a new one (1). The current paper provides further confirmation of the utility of this measurement and suggests that protrusion of 10 mm or greater correlates well with urodynamic obstruction (2). Along with other ultrasound-derived measurements such as post-void residual, bladder weight, bladder wall thickness, detrusor resistive index, prostatic weight, appearance, and velocity-flow video-urodynamics, this measurement was developed to prevent the need for, and the morbidity of, multi-channel pressure-flow studies (3). The plethora of different techniques suggests that none is perfect and in fact, in individual patients, cannot yet replace 'invasive' testing. Also, the true morbidity of these studies may not be all that significant (4).

On balance, while being suggestive of bladder outflow obstruction, measuring intra-vesical protrusion of the prostate by either abdominal or trans-rectal ultrasound is likely to remain an interesting but inconclusive finding!

REFERENCES

1. Ohnishi K, Watanabe H, Ohe H, Saitoh M. Development and clinical significance of protrusion of hypertrophic prostate into the bladder observed by transrectal ultrasonotomography. Nippon Hinyokika Gakkai Zasshi. 1985; 76: 1194-200.
2. Reis LO, Barreiro GC, Baracat J, Prudente A, Levi D'Ancona CA: Intravesical protrusion of the prostate as a predicting method of bladder outlet obstruction. Int Braz J Urol. 2008; in press.
3. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP: Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. J Urol. 1998; 159: 191-4.
4. Porru D, Madeddu G, Campus G, Montisci I, Scarpa RM, Usai E: Evaluation of morbidity of multi-channel pressure-flow studies. Neurourol Urodyn. 1999; 18: 647-52.

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EDITORIAL COMMENT

Benign prostatic hyperplasia (BPH) is one of the most common diseases in elderly men. Bladder outlet obstruction (BOO) should be well discriminated from BPH to better understand the pathology-physiology of this disease. BPH may lead to benign prostatic enlargement (BPE), BOO and lower urinary tract symptoms (LUTS). BOO might be or not be present in patients with BPH. On the other hand BOO may cause secondary bladder dysfunction and furthermore upper urinary tract damage. For these reasons, patients with BPH must be evaluated not only for LUTS but also for BOO.

Up to now, urodynamic evaluations have been accepted as the only objective method of assessing BOO. There is a lot to say about the disadvantages of pressure flow studies (PFS) which has been well described in the literature. It is invasive, uncomfortable, time-consuming and expensive. Moreover, there is a need for urethral catheterization, which causes partial obstruction during micturition and confers the undesirable consequences of possibly introducing infection and discomfort that may alter the micturition reflex. Hematuria, urinary tract infection and difficulty in urination are the side effects of this procedure (1). To avoid these disadvantages, in the last decade, the development of non-invasive evaluations for BOO has been the subject of numerous publications. Uroflowmetry, post-void residual urine, prostate volume (PV), bladder wall thickness and finally measurement of intravesical protrusion of the prostate (IPP) are used to estimate BOO in men with BPH. The rise of the idea that IPP might be a predictor of BOO can be explained by few words. IPP is caused by the enlarging lateral lobes and the median lobe, and may lead to dyskinetic movement of the bladder during voiding. This would cause more obstruction than if there were no protrusion and just bilateral lateral lobes, as the strong bladder contraction could force open a channel between the lobes.

A few investigators have considered IPP to be a useful predictor for evaluating BOO and bladder function. Chia et al. have suggested that IPP significantly correlates with BOO and is a better parameter than the other non-invasive parameters (2). Lim et al. have confirmed this study by comparing PV, prostate specific antigen (PSA) and IPP in the evaluation of BOO and IPP was the strongest predictor in this prospective study (3). In another study, it has been suggested that IPP degree is negatively correlated with Qmax and of patients with higher IPP degree, there is a higher presence of bladder overactivity and low bladder compliance.

Reis et al. provide a prospective data aiming to demonstrate whether the IPP of the prostate might replace the urodynamic evaluation, which is accepted to be an invasive and uncomfortable procedure (4). Despite the small number of patients, the results are in favor of detecting IPP might be enough to demonstrate the BOO without the need to urodynamic evaluation and comparable with the earlier investigations. These statistically significant results may lead to further investigations and force the urologists to replace measuring IPP instead of performing pressure flow studies in selected patients.

REFERENCES

1. Klingler HC, Madersbacher S, Djavan B, Schatzl G, Marberger M, Schmidbauer CP: Morbidity of the evaluation of the lower urinary tract with transurethral multichannel pressure-flow studies. J Urol. 1998; 159: 191-4.
2. Chia SJ, Heng CT, Chan SP, Foo KT: Correlation of intravesical prostatic protrusion with bladder outlet obstruction. BJU Int. 2003; 91: 371-4.
3. Lim KB, Ho H, Foo KT, Wong MY, Fook-Chong S: Comparison of intravesical prostatic protrusion, prostate volume and serum prostatic-specific antigen in the evaluation of bladder outlet obstruction. Int J Urol. 2006; 13: 1509-13.
4. Reis LO, Barreiro GC, Baracat J, Prudente A, D'Ancona CA: Intravesical protrusion of the prostate as a predictive method of bladder outlet obstruction. Int Braz J Urol. 2008; in press.

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REPLY BY THE AUTHORS

Although the current and others up-to-the-minute papers provide further confirmation of the utility of intravesical prostatic protusion (IPP) measurements and suggests that protrusion of 10 mm or greater correlates well with urodynamic obstruction, it is a limited method to accurately define obstruction (1). There are patients obstructed without IPP and unobstructed ones presenting with more than 10 mm IPP. By the other side, IPP measurements are still a science under development, and perhaps IPP measurements are more precise in determining the best patients for surgical treatment, once they were proved obstructed.

Intravesical protrusion seems to corroborate with urinary obstruction thought a "valve ball" mechanism in which the prostate's lateral and medium lobes interfere on the complete opening of the vesical neck during voiding. This way, the pharmacological response to alpha-blockers could be predicted by the IPP method (2). Men with an intravesical prostatic protrusion of 10 mm or less, compared to those with a larger intravesical prostatic protrusion, were 6 times more likely to have a successful trial without catheter after acute urinary retention (3).

Most patients in our present study presenting IPP of 10 mm or greater showed no response to alpha blockers and were submitted to surgical treatment in contrast to that presenting IPP of less than 10 mm. We are now conducting new prospective studies to prove the accuracy of this method to predict pharmacological treatment outcomes and surgical treatment suggestions.

Another minimal invasive method utilizes ultrasound measurements of detrusor or bladder wall thickness or weight. This method is inconsistent in technical standardization and there is no consensus among authors about its value (4). Bladder parameter to define obstruction is possibly not the best one, because it denotes the obstruction repercussion and imbalance in the detrusor function, which is much more than obstruction and probably occurs latter in the bladder neck obstruction process.

REFERENCES

1. Yu HF, He YH, Yu KY, Wang Q, Huang PT, Yang Y, et al.: Transabdominal ultrasound measurement of intravesical prostatic protrusion helps diagnosis of benign prostatic obstruction. Zhonghua Nan Ke Xue. 2008; 14: 628-30.
2. Tan YH, Foo KT: Intravesical prostatic protrusion predicts the outcome of a trial without catheter following acute urine retention. J Urol. 2003; 170: 2339-41.
3. Mariappan P, Brown DJ, McNeill AS: Intravesical prostatic protrusion is better than prostate volume in predicting the outcome of trial without catheter in white men presenting with acute urinary retention: a prospective clinical study. J Urol. 2007; 178: 573-7; discussion 577.
4. Blatt AH, Titus J, Chan L: Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol. 2008; 179: 2275-79.

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Relaxation of Rabbit Corpus Cavernosum Smooth Muscle and Aortic Vascular Endothelium Induced by New Nitric Oxide Donor Substances of the Nitrosyl-Ruthenium Complex

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ABSTRACT

Introduction: Endothelial dysfunction characterized by endogenous nitric oxide (NO) deficiency made 56% of patients affected with erectile dysfunction decline treatment with PDE-5 inhibitors. New forms of treatment are currently being developed for this group of patients.

Materials and Methods: The study compared the effect of sodium nitroprusside (SNP) and two substances of the nitrosyl-ruthenium complex, cis-[Ru(bpy)2(SO_3)(NO)]PF-6-9 ("FONO1") and trans-[Ru(NH_3)4(caffeine)(NO)]C13 ("LLNO1") on relaxation of rabbit corpus cavernosum smooth muscle and aortic vascular endothelium. The samples were immersed in isolated baths and precontracted with 0.1 μM phenylephrine (PE) and the corresponding relaxation concentration/response curves were plotted. In order to investigate the relaxation mechanisms involved, 100 μM ODQ (a soluble guanylate cyclase-specific inhibitor), 3 μM or 10 μM oxyhemoglobin (an extracellular NO scavenger) or 1 mM L-cysteine (a nitrosyl anion-specific scavenger) was added to the samples.

Results: All the NO donors tested produced a significant level of relaxation in the vascular endothelium. In corpus cavernosum samples, FONO1 produced no significant effect, but LLNO1 and SNP induced dose-dependent relaxation with comparable potency (pEC_{50} = 6.14 ± 0.08 and 6.4 ± 0.14, respectively) and maximum effect (Emax = 82% vs. 100%, respectively). All NO donors were found to activate soluble guanylate cyclase, since the addition of the corresponding inhibitor (100 μM ODQ) completely neutralized the relaxation effect observed. The addition of oxyhemoglobin reduced the relaxation effect, but did not inhibit it completely. In aortic vascular endothelium 3 μM oxyhemoglobin decreased the relaxation effect by 26% on the average, while 10 μM oxyhemoglobin reduced it by over 52%. The addition of 100 μM L-cysteine produced no significant inhibiting effect.

Conclusions: These results suggest that LLNO1 and FONO1 are potent vasodilators. LLNO1 was shown to induce a significant level of relaxation in rabbit corpus cavernosum. The substances tested were shown to activate soluble guanylate cyclase and release intracellular NO.

Key words: *nitric oxide; vascular endothelium; corpus cavernosum; nitrosil-ruthenium complex*
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INTRODUCTION

The vascular smooth muscles of the human corpus cavernosum are contracted tonically by adrenergic stimulation to maintain the penis flaccid (1). Conversely, penile erection occurs when the corpus cavernosum smooth musculature is relaxed by the activation of inhibitory nerve endings and the decrease in adrenergic stimulation.

Nitric oxide was shown to be the neurotransmitter released from the "non-adrenergic-non-cholinergic" nervous fibers that elicited corpora cavernosa relaxation and penile erection (2). Nitric oxide (NO) is the main inhibitory neurotransmitter in animal and human corpus cavernosum mediating penile erection (1). It was primarily the work of Palmer and Moncada that led to the discovery of NO as an endothelium-derived relaxing factor (3). NO activates soluble guanylate cyclase, which in turn induces cyclic guanosine monophosphate (cGMP) production from guanosine triphosphate. cGMP acts on intracellular effectors, such as protein kinase G, which reduce intracellular calcium levels and dissociate actin and myosin fibers, leading to smooth muscle relaxation (4).

NO donors are substances releasing NO in vivo or in vitro. The NO donor sodium nitroprusside (SNP) is a powerful vasodilator used clinically to treat acute hypertension. However, the substance is very unstable and may induce drug tolerance and release not only NO but also cyanide, which is toxic for the vascular endothelium (5).

Several more stable and less toxic NO donors have been tested over the past years. Some of these, S-nitrosoglutathione (GSNO) and S-nitroso-N-acetylcysteina-ethylester, have been used in studies with human corpus cavernosum strips mounted in isolated tissue baths with a promising potential for tissue relaxation (6).

Likewise, NO donors with ruthenium metal center have recently been the object of attention. These substances, which were initially used on rat hippocampus in vitro, have a potentializing effect shown to be reversible by pretreating tissues with oxyhemoglobin, an extracellular NO scavenger (7). Because the ruthenium metal center controls the levels of circulating NO by modulating the reduction potential of the latter, it can reduce the side effects of NO donors such as SNP in the clinical setting (8). In experiments using rat aortic vascular endothelium in vitro, substances of the nitrosyl-ruthenium complex produced a relaxation effect similar to that of SNP (9).

The objective of the present study was to compare the effect of SNP and of two substances of the nitrosyl-ruthenium complex, cis-[Ru(bpy)2(SO_3)(NO)]PF-6-9 (henceforth termed FONO1) and trans-[Ru(NH_3)4(caffeine)(NO)]C13 (henceforth termed LLNO1) upon the relaxation of rabbit corpus cavernosum smooth muscle and aortic vascular endothelium.

MATERIALS AND METHODS

The study was approved by the Ethics Committee for Animal Research of the Federal University of Ceara. Tissue samples were obtained from adult male New Zealand rabbits weighing 2-3 Kg. After anesthetizing the animal, the penis was excised and immediately immersed in Krebs-Henseleit solution. Following sternotomy and excision of the heart, the thoracic aorta was dissected, removed and sectioned into circular fragments, which were immediately immersed in Krebs-Henseleit solution.

The corpus cavernosum tissue was dissected following removal of the connective tissues of the tunica albuginea, with each penis providing two segments of corpus cavernosum (1 cm x 0.3 cm x 0.2 cm). The samples were mounted in isolated tissue baths containing 10 mL Krebs-Henseleit solution (37°C; pH 7.4) bubbled with carbogen (95:5 O_2/CO_2). The samples were mounted in the bath between two L-shaped electrodes, one of which was connected to an isometric force transducer and the other to a mobile rack for resting tension adjustment. All samples were subjected to 1g tension.

The samples were monitored for 60 minutes with resting tension adjustment and solution change at 15-minute intervals. Variations in tension were measured with isometric transducers and registered with a polygraph (Gemini 7070, Ugo-Basile, Varese, Italy).

Following the 60-minute resting period, the tissues were precontracted with 0.1 μM phenylephrine (PE) and relaxation concentration/response curves were plotted.

Methodology

Experiment 1: Following precontraction with 1 μM PE, graded concentrations (10^{-12} to 10^{-3} M) of SNP, FONO1 or LLNO1 were added to the baths and relaxation concentration/response curves were plotted.

Experiment 2: 10 μM oxyhemoglobin was added to the baths 30 minutes before precontraction with 1 μM PE to evaluate the associated NO release rates. Relaxation concentration/response curves were plotted as in the previous experiment.

Experiment 3: To determine whether the substances tested released the NO^- scavenger nitrosyl during relaxation, 100 μM L-cysteine (L-cyst) was added to the baths 30 minutes before precontraction with 1 μM PE. Relaxation concentration/response curves were plotted as in the previous experiment.

Experiment 4: To evaluate cGMP production induced by the test substances, 100 μM soluble guanylate cyclase-specific inhibitor was added to the baths 30 minutes before precontraction with 1 μM PE. Relaxation concentration/response curves were plotted as in the previous experiment.

Statistical Analysis

The relaxation effect corresponded to the plateau of phenylephrine contraction and was expressed as a percentage reversal. The maximum effect (Emax) was considered as the maximum amplitude response observed in the concentration-effect curve for each agent. The concentration required to produce half the maximum relaxation amplitude (EC_{50}) was determined after log transformation of the normalized concentration-response curves and expressed as negative logarithms (pEC_{50}) of the mean values for each tissue (n = 9). The statistical analyses were performed with the software GraphPad Prism 3.0 (Graph Pad Software Corporation, San Diego, CA.). Findings were expressed as average ± standard error (SE). In each group of experiments n indicates the number of samples analyzed. The statistical significance of differences between average values was determined with one-way variance analysis (ANOVA), followed by the Tukey-Kramer test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Evaluation of Relaxation Induced by Test Substances

Precontraction with 1 μM PE produced a 100% increase in basal tension (1g-2g) in rabbit corpus cavernosum (RbCC). The maximum relaxation (Emax) and maximum potency (pEC_{50}) produced by SNP was 109.7% ($p < 0.05$) and 6.4 ± 0.14, respectively. FONO1 induced little relaxation in RbCC samples (Emax: 31.2%). LLNO1 induced relaxation with potency and maximum effect similar to SNP (Emax: 81%; pEC_{50}: 6.14 ± 0.08) ($p < 0.05$) (Figure-1).

In aortic rings SNP yielded an Emax value of 112.4% and a pEC_{50} value of 7.8 ± 0.10 ($p < 0.05$). The corresponding values were 149.8% and 7.5 ± 0.38 for FONO1 and 112.8% and 7.02 ± 0.10 for LLNO1 ($p < 0.05$) (Figure-2).

Effect of Soluble Guanylate Cyclase-Specific Inhibitor on Tissue Relaxation Induced By Test Substances

Incubation of tissues with 100 μM soluble guanylate cyclase-specific inhibitor (ODQ) completely neutralized the tissue relaxation effect of the three substances tested (data not shown).

Effect of L-Cysteine on Relaxation Induced by Test Substances

Incubation with 100 μM of the NO^- scavenger L-cysteine produced no significant change in the tissue relaxation effect of the three substances tested. Emax and pEC_{50} remained unchanged for both corpus cavernosum strips and aortic rings (Figure-3).

Effect of Oxyhemoglobin on Tissue Relaxation Induced by LLNO1 and FONO1

Incubation with 3 μM of the extracellular NO scavenger oxyhemoglobin reduced, though not significantly, the relaxation power of the substances tested. Emax and pEC_{50} values were greater in aortic rings than in RbCC treated with LLNO1. However, when adding 10 μM oxyhemoglobin, LLNO1 and FONO1-induced tissue relaxation decreased significantly with regard to both Emax and pEC_{50}.

In samples treated with LLNO1, with the addition of 3 μM oxyhemoglobin Emax and pEC_{50} values decreased less for RbCC than for aortic vascular endothelium. The maximum effect of LLNO1 in RbCC decreased from 80% to 63.98% (Figure-4).

In samples of aortic rings treated with LLNO1, 3 μM oxyhemoglobin reduced maximum tissue relaxation from 112% to 48%. At 10 μM oxy-

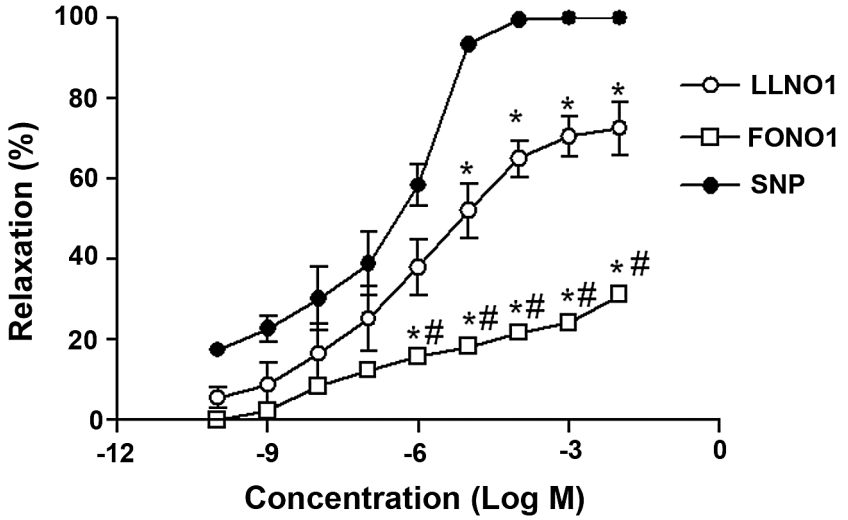

Figure 1 *– Effect of LLNO1, FONO1 and sodium nitroprusside (SNP) upon rabbit corpus cavernosum (RbCC) strips. The RbCC strips were precontracted with 1 μM phenylephrine and relaxation concentration/response curves (concentrations graded from 10^{-12} to 10^{-3} M) were plotted. Findings are expressed as average ± standard error, based on six experiments. * p < 0.05 vs. SNP (ANOVA followed by the Tukey-Kramer test). # p < 0.05 vs. LLNO1 (ANOVA followed by the Tukey-Kramer test).*

hemoglobin, the pEC_{50} value changed from 7.02 ± 0.10 to 6.9 ± 0.23 and the Emax value was further reduced to 38% ($p < 0.05$) (Figure-5).

In samples of aortic rings treated with FONO1, 3 μM oxyhemoglobin significantly reduced Emax and pEC_{50} values in relation to control samples (42.74% vs. 150% and 6.9 ± 0.23 vs. 7.5 ± 0.38, respectively; $p < 0.05$) (Figure-5). At 10 μM oxyhemoglobin, the Emax value was further reduced from 42.74% to 26% ($p < 0.05$) (Figure-5).

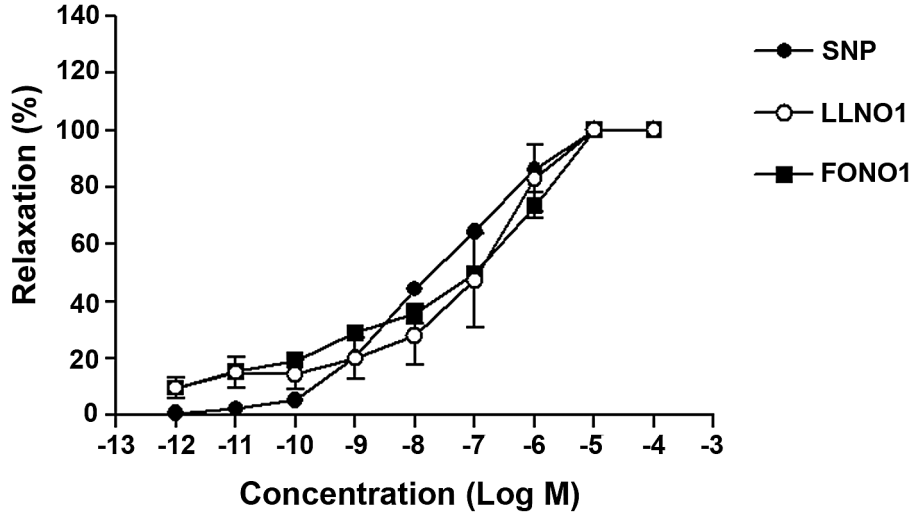

Figure 2 *– Effect of LLNO1 upon aortic vascular endothelium rings. The rings were precontracted with 1 μM phenylephrine and relaxation concentration/response curves (concentrations graded from 10^{-12} to 10^{-3} M) were plotted for LLNO1 and compared with sodium nitroprusside curves. Findings are expressed as average ± standard error, based on six experiments.*

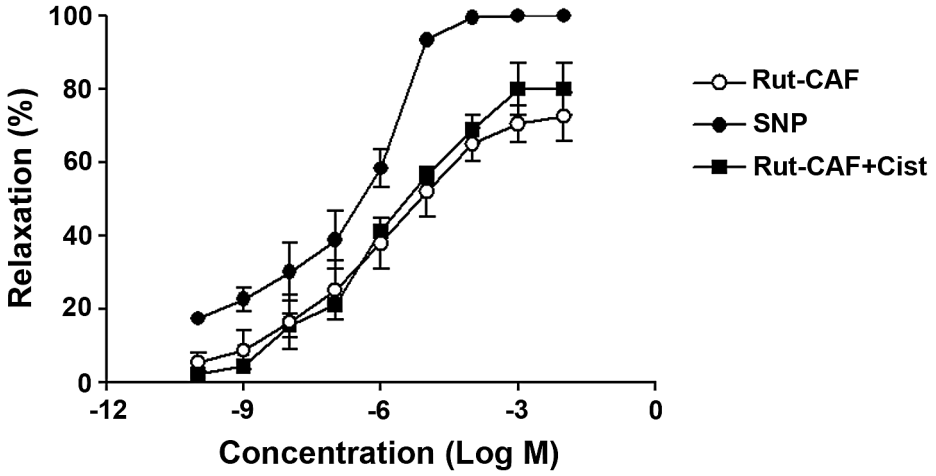

Figure 3 *– Effect of LLNO1 alone and in combination with L-Cysteine (L-Cyst) upon rabbit aortic rings. The rings were precontracted with 1 μM phenylephrine and relaxation concentration/response curves (concentrations graded from 10^{-12} to 10^{-3} M) were plotted for LLNO1 alone and in combination with 100 μM L-Cyst. Findings are expressed as average ± standard error, based on six experiments. p > 0.05 vs. LLNO1 + L-cyst, SNP, LLNO1 (ANOVA followed by the Tukey-Kramer test).*

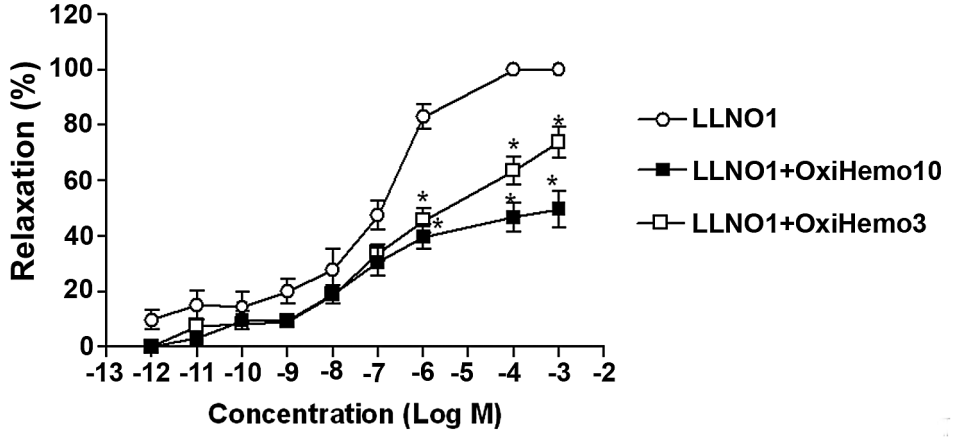

Figure 4 *– Effect of LLNO1 alone and in combination with oxyhemoglobin upon rabbit corpus cavernosum strips. The RbCC strips were precontracted with 1 μM phenylephrine and relaxation concentration/response curves (concentrations graded from 10^{-12} to 10^{-3} M) were plotted for LLNO1 alone and in combination with 3 μM or 10 μM oxyhemoglobin. Findings are expressed as average ± standard error, based on six experiments. * p < 0.05 vs. LLNO1 + oxyhemoglobin (ANOVA followed by the Tukey-Kramer test).*

COMMENT

Endothelial dysfunction is observed in many patients with erectile dysfunction or comorbidities such as arterial hypertension and diabetes (10). The syndrome is characterized by a deficiency in the endogenous production of nitric oxide (11). Since approximately 56% of subjects affected with erectile dysfunction decline treatment with the commercially available PDE-5 inhibitors (11), new drugs capable of increasing the availability of endogenous NO are being tested. The present study tested the ability of two

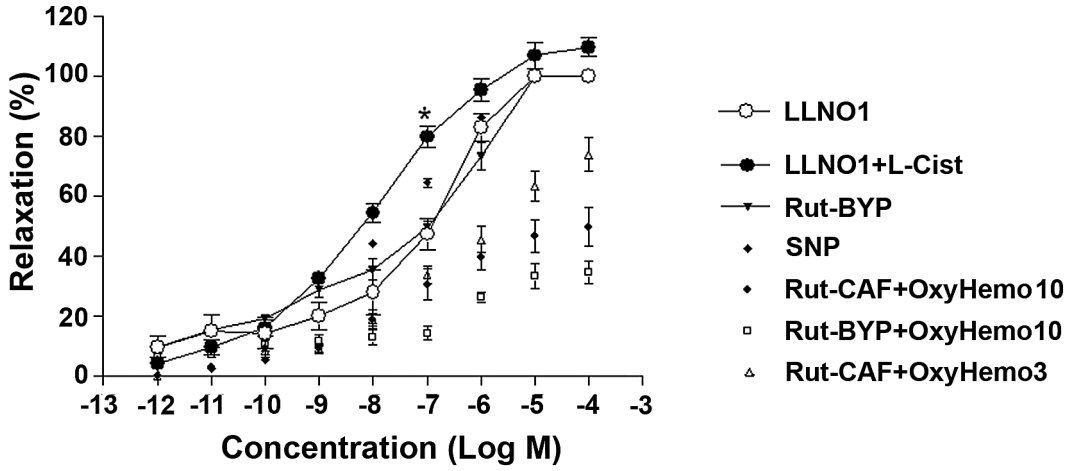

Figure 5 *– Effect of LLNO1 and FONO1 alone and in combination with oxyhemoglobin or L-cysteine upon aortic vascular endothelium rings. The rings were precontracted with 1 μM phenylephrine and relaxation concentration/response curves (concentrations graded from 10^{-12} to 10^{-3} M) were plotted for LLNO1 and FONO1 alone and in combination with 100 μM L-Cyst or 3 μM or 10 μM oxyhemoglobin. Findings are expressed as average ± standard error, based on six experiments. * $p < 0.05$ vs. LLNO1 + 3 μM or 10 μM oxyhemoglobin. FONO1 + 10 μM oxyhemoglobin (ANOVA followed by the Tukey-Kramer test).*

new substances of the nitrosyl-ruthenium complex to promote relaxation in rabbit corpus cavernosum smooth musculature and aortic vascular endothelium.

The fact that FONO1 and LLNO1 produced a larger maximum relaxation effect (Emax) in aortic vascular rings than SNP, with potencies (pEC_{50}) similar to SNP, shows that substances of this group are associated with greater endogenous NO availability than SNP. Similar results were published by Bonaventura and colleagues (9) in a study evaluating substances of the nitrosyl-ruthenium complex. In that study, one of the substances tested achieved a maximum effect of 102% and a pEC_{50} of 6.61 ± 0.09, thus supporting the present findings that substances of the nitrosyl-ruthenium complex can be potent vasodilators.

In this study, FONO1 failed to induce significant levels of relaxation in corpus cavernosum samples. The performance of LLNO1 was similar to that of SNP, though Emax values were lower than for vascular endothelium samples. This may be explained by the different mechanisms displayed by NO donors in vessels of different sizes. As demonstrated by Sathishkumar et al. (12), while NO donors of the thiol group, such as S-nitroso-N-acetylpenicillamine (SNAP), act on small vessels or peripheral vascular beds primarily through the activation of guanylate cyclase, they act on larger vessels by activating potassium ion channels leading to cell hyperpolarization. Our findings may also be explained by the fact that the inhibition of phosphodiesterase by caffeine in the LLNO1 structure increases the relaxation effect of NO donors. This would also account for the smaller effect of LLNO1 on large vessels, in comparison to FONO1, where caffeine is known to be vasoconstrictive. The study did not investigate alternative mechanisms, such as ion channel blockers, involved in tissue relaxation.

It has been demonstrated that oxyhemoglobin reduces the effect of substances of the nitrosyl-ruthenium complex upon rat hippocampus (7). The present study shows that the presence of oxyhemoglobin does not neutralize but reduces the relaxation effect dose-dependently. In other words, even in the presence of an extracellular scavenger, LLNO1 and FONO1 are still capable of inducing vasodilation by releasing intracellular NO.

Similar findings were reported by Figueredo et al. (13) in a study demonstrating that oxyhemoglobin reduces but does not completely neutralize the relaxation effect of SNP upon the vascular endothelium. This is supported by the findings of Bonaventura, et al.

who showed that oxyhemoglobin reduces the potency but not the maximum effect of substances of the nitrosyl-ruthenium complex upon rat aortic rings (9).

Studies by McDonald and Murad show that NO acts by activating soluble guanylate cyclase and thereby increasing the synthesis and availability of intracellular cGMP (14). When the authors incubated tissues with high doses of soluble guanylate cyclase-specific inhibitor (ODQ; 100 μM), the relaxation response induced by LLNO1 or FONO1 was completely neutralized, thus evidencing the participation of those substances in the NO/cGMP intracellular signaling mechanism. One of the flaws of our study was to have used doses of ODQ high enough to interfere with NO donation, as demonstrated by Feelisch and colleagues (15).

Bonaventura, et al. have shown that compounds of the nitrosyl-ruthenium complex act by donating free nitric oxide (NO) and nitrosyl anions (NO^-). However, the addition of the nitrosyl anion-specific scavenger L-cysteine did not reduce the relaxation effect produced by those compounds. It may thus be concluded that LLNO1 and FONO1, although they both pertain to the nitrosyl-ruthenium complex, do not trigger the release of nitrosyl anions when inducing relaxation. On-going studies are expected to identify which NO derivative is involved in LLNO1 and FONO1-induced relaxation.

Our results allow us to conclude that LLNO1 and FONO1 are potent vasodilators acting through different mechanisms capable of releasing intracellular NO and activating guanylate cyclase. Further studies are being carried out in order to evaluate the action of LLNO1 and FONO1 upon ATP-dependent potassium ion channels and calcium-activated medium and high-conductivity potassium ion channels and to quantify cAMP and cGMP dosages.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Andersson KE: Pharmacology of penile erection. Pharmacol Rev. 2001; 53: 417-50.
2. Bush PA, Aronson WJ, Buga GM, Rajfer J, Ignarro LJ: Nitric oxide is a potent relaxant of human and rabbit corpus cavernosum. J Urol. 1992; 147: 1650-5.
3. Palmer RM, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987; 327: 524-6.
4. Lohse MJ, Förstermann U, Schmidt HH: Pharmacology of NO:cGMP signal transduction. Naunyn Schmiedebergs Arch Pharmacol. 1998; 358: 111-2.
5. Bates JN, Baker MT, Guerra R Jr, Harrison DG: Nitric oxide generation from nitroprusside by vascular tissue. Evidence that reduction of the nitroprusside anion and cyanide loss are required. Biochem Pharmacol. 1991; (42 Suppl): S157-65.
6. Seidler M, Uckert S, Waldkirch E, Stief CG, Oelke M, Tsikas D, et al.: In vitro effects of a novel class of nitric oxide (NO) donating compounds on isolated human erectile tissue. Eur Urol. 2002; 42: 523-8.
7. Wieraszko A, Clarke MJ, Lang DR, Lopes LG, Franco DW: The influence of NO-containing ruthenium complexes on mouse hippocampal evoked potentials in vitro. Life Sci. 2001; 68: 1535-44.
8. Lopes GF, Wieraszko A, El-Sherif Y, Clarke MJ: Trans-Labilization of Nitric Oxide in RuII complexes by C-bound imidazoles. Inorg-Chim Acta. 2001; 312: 15-22.
9. Bonaventura D, de Lima RG, Vercesi JA, da Silva RS, Bendhack LM: Comparison of the mechanisms underlying the relaxation induced by two nitric oxide donors: sodium nitroprusside and a new ruthenium complex. Vascul Pharmacol. 2007; 46: 215-22.
10. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994; 151: 54-61.
11. Rendell MS, Rajfer J, Wicker PA, Smith MD: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999; 281: 421-6.
12. Sathishkumar K, Ross RG, Bawankule DU, Sardar KK, Prakash VR, Mishra SK: Segmental heterogeneity in the mechanism of sodium nitroprusside-induced relaxation in ovine pulmonary artery. J Cardiovasc Pharmacol. 2005; 45: 491-8.
13. de Figueiredo LF, Nelson SH, Mathru M, e Silva MR, Kramer GC: Effects of hemoglobin-based blood substitutes on vasoactivity of rat aortic rings. Artif Organs. 2001; 25: 928-33.
14. McDonald LJ, Murad F: Nitric oxide and cGMP signaling. Adv Pharmacol. 1995; 34: 263-75.

15. Feelisch M, Kotsonis P, Siebe J, Clement B, Schmidt HH: The soluble guanylyl cyclase inhibitor 1H-[1,2,4]oxadiazolo[4,3,-a] quinoxalin-1-one is a nonselective heme protein inhibitor of nitric oxide synthase and other cytochrome P-450 enzymes involved in nitric oxide donor bioactivation. Mol Pharmacol. 1999; 56: 243-53.

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EDITORIAL COMMENT

Worldwide only 50% of Viagra prescriptions are repeated. On the same hand, the drop-out rate of self-injection therapy varies from 40% to 70%. It means that we just do not have a therapy for erectile dysfunction that is totally accepted by most patients.

Despite already very well studied the NO donors continue to be a important topic of erectile dysfunction. The current study is very important as a practice of research and a resource of knowledge. Furthermore, a new NO donor molecule that produces erection may also mean a new way of releasing nitric oxide. Otherwise, NO donors have been exhaustively studied in the last three decades without any practical results. In this way, maybe one should pay much attention on the research of new molecules but NO donors that could produce erection and play a clinical role in its therapy.

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EDITORIAL COMMENT

In clinical practice when treating patients with erectile dysfunction (ED) it seems that the use of phosphodiesterase type 5 inhibitors (PDE-5-i) have an efficacy of less than 70%. This is lower than what was proposed by and expected from the phase III studies of the different PDE-5-I compounds. This is probably due to severe deficiency of endogenous nitric oxide (NO) in the endothelium, which appears in many patients with ED, but also with metabolic syndrome and related co-morbidities

such as long term diabetes and arterial hypertension.

Since the publications about NO in Nature in 1987 and the description in the New England Journal of Medicine in 1992 that NO is a mediator of relaxation of the corpus cavernosum in response to neurotransmission, intensive experimental work was done to explore the mechanism of action of NO and the clinical applications.

Finding a drug which will be capable of increasing the availability of NO could be an alternative therapeutic approach in the case of treatment failure with the available PDE-5-inhibitors.

NO donors are substances which release or lead to the release of NO. They are possible relaxants of corpus cavernosum and cause vasodilatation. Sodium nitroprusside (SNP) is a NO donor with a strong vasodilatation property, but it can not be used for treatment of ED due to its instable properties and some times the release of toxic components like cyanide.

In this study the authors aim to test in vitro the effect of two NO donor's substances (FONO1 and LLNO1) of the Ruthenium complex on the relaxation of smooth muscle of the corpora and vascular endothelium. In the medical literature there are only 41 studies concerning the use of Nitrosyl Ruthenium complex. Only one of the studies deals with the effect of the complex on the endothelium. This study is the first to test these two substances effect on the corpus cavernosum smooth muscle as previous studies were only performed using the vessels endothelium . The authors also try to evaluate the relaxation mechanism involved. A comparison was made with SNP.

The study presents a clear description of the experiments done but the action mechanism of the substances FONO1 and LLNO1 should be studied in vivo and in vitro in the near future. Both substances are associated with great endogenous NO availability and LLNO1 induced significant level of relaxation in the corpus cavernosum sample. I expect that in the near future these studies will contribute to the development of a new therapeutic approach on ED.

REFERENCES

1. Palmer RM, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987; 327: 524-6.
2. Bush PA, Aronson WJ, Buga GM, Rajfer J, Ignarro LJ: Nitric oxide is a potent relaxant of human and rabbit corpus cavernosum. J Urol. 1992; 147: 1650-5.
3. Masuda H, Tsujii T, Okuno T, Kihara K, Goto M, Azuma H: Accumulated endogenous NOS inhibitors, decreased NOS activity, and impaired cavernosal relaxation with ischemia. Am J Physiol Regul Integr Comp Physiol. 2002; 282: R1730-8.
4. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med. 1992; 326: 90-4.
5. Gur S, Kadowitz PJ, Trost L, Hellstrom WJ: Optimizing nitric oxide production by time dependent L-arginine administration in isolated human corpus cavernosum. J Urol. 2007; 178: 1543-8.

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UROLOGICAL SURVEY

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STONE DISEASE

Impact of body mass index on cost and clinical outcomes after percutaneous nephrostolithotomy

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Urology. 2008; 72: 756-60

Objectives: To evaluate the impact of body mass index (BMI) on clinical outcomes and costs associated with percutaneous nephrostolithotomy (PCNL).
Methods: We reviewed charts of 200 consecutive patients who underwent PCNL between September 2005 and May 2007. We recorded patient and stone characteristics and perioperative outcomes. BMI was available for 150 patients (75%), who comprised our study group. We obtained direct and subcomponent costs (room and board, laboratory, pharmacy, radiology, operating room, surgical supplies, anesthesia, and recovery room). We divided patients into four BMI categories: normal weight (BMI < 25), overweight (25 </= BMI < 30), obese (30 </= BMI < 40), and morbidly obese (BMI >/= 40). We compared groups with regard to baseline characteristics, intraoperative parameters, stone-free and complication rates, and hospital length of stay.
Results: Mean stone size and proportion of patients with staghorn, multiple, and bilateral calculi were similar among groups. The normal weight cohort had proportionately fewer recurrent stone formers and patients with a history of stone surgery, compared with the other groups (P = .005 and P = .03, respectively). We found no significant differences among groups with regard to stone-free and complication rates, operative time, length of stay, or need for multiple accesses. Median direct cost was marginally, but not significantly, higher in normal weight ($8124) compared with overweight ($6746), obese ($6740), and morbidly obese ($6719) patients (P = .75).
Conclusions: Body mass index had no impact on efficacy or complication rates of PCNL. Despite greater perceived difficulty in performing these procedures in overweight and obese patients, it was not more costly.

Editorial Comment

The authors present a compelling argument that BMI should not impact the decision to consider percutaneous nephrolithotomy as safety, efficacy and cost are not affected. The authors note that these conclusions are based on the experience of a single expert-endourologist at a high-volume tertiary referral center.
The authors noted a higher median length of stay (3 vs. 2 days) and higher cost for room and board for the normal weight patients. This could be a reflection of patient expectations. Patients who are experienced (ex. recurrent stone formers, history of stone disease) would have realistic expectations for post-operative recovery that might help drive them down a clinical treatment pathway to earlier discharge - the normal weight patients in this study were less experienced.

Selection bias may impact the results of retrospective studies. There was a strong trend (p=0.06) to the morbidly obese patients being younger (45 years) than the rest of the study cohort (55 years). It is possibly that older morbidly obese patients are directed to ureteroscopy or other modalities. Similarly, the authors note that the ASA class severity was similar across BMI, suggesting that the normal weight patients may have had higher than expected comorbid conditions that may have lead to referral to their tertiary center. This would inflate the costs and length of stay in the otherwise “healthy control” weight category.

One primary challenge in the morbidly obese is the initial percutaneous access. It would be interesting to evaluate the fluoroscopy time, radiation dose, and time to access for this cohort.

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Stone attenuation and skin-to-stone distance on computed tomography predicts for stone fragmentation by shock wave lithotripsy

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Urology. 2008; 72: 765–769

Objectives: To determine whether stone attenuation and the skin-to-stone distance (SSD) can predict for stone fragmentation by SWL independently. Identifying the factors predictive of shock wave lithotripsy (SWL) outcome would help streamline the care of patients with stones.
Methods: A retrospective review was performed of 111 patients undergoing initial SWL for a solitary, 5-20 mm, renal calculus. Stone size, location, attenuation value, and SSD were determined on pretreatment noncontrast computed tomography. The outcome was categorized as stone free, complete fragmentation <5 mm, and incomplete fragmentation >/=5 mm or unchanged at 2 weeks on kidney/ureter/bladder radiography.
Results: After SWL, 44 (40%) were stone free, 27 (24%) had complete fragmentation, and 40 (36%) of 111 patients had incomplete fragmentation. The stone attenuation of the successfully treated patients (stone free and complete fragmentation groups) was 837 +/- 277 Hounsfield units (HU) vs 1092 +/- 254 HU for those with treatment failure (incomplete fragmentation; P < .01). The mean SSD also differed: 9.6 cm +/- 2.0 vs 11.1 cm +/- 2.5 for the successful treatment group vs the treatment failure group, respectively (P = .01). On multivariate analysis, the factors that independently predicted the outcome were stone attenuation, SSD, and stone composition. When patients were stratified into 4 risk groups (stone <900 HU and SSD <9.0 cm, stone <900 HU and SSD >/=9.0 cm, stone >/=900 HU and SSD <9.0 cm, and stone >/=900 HU and SSD >/=9.0 cm), the SWL success rate was 91%, 79%, 58%, and 41%, respectively (odds ratio 7.1, 95% confidence interval 1.6-32 for <900 HU and SSD <9.0 cm group vs other 3 risk groups; P = .01).
Conclusions: The results of our study have shown that a stone attenuation of <900 HU, SSD of <9 cm, and stone composition predict for SWL success, independent of stone size, location, and body mass index. These factors will be considered important in the prospective design of a SWL treatment nomogram at our center.

Editorial Comment

This study helps establish parameters to guide the counseling of patients undergoing SWL. It is important to consider that the predictive stone attenuation and skin-to-stone distance will be dependent on the peak pressures at F2 and focal area of the lithotripter respectively. As such, this may require the establishment of criteria for each individual lithotripter.

Outcomes were defined by KUB at two weeks - one would expect that the sensitivity of KUB (at best 70%) would be higher for stones with higher stone attenuation and for thinner patients (smaller skin-to-stone distances). As such, the primary conclusions of the study may be skewed by the outcome measure selected - CT scan imaging would have provided a more critical evaluation for this study.

The authors note that collimation widths > 3 mm can impact stone attenuation measurements, smaller stones will have lower stone attenuation levels due to volume averaging with surrounding soft tissue, and indeed in this study stone size correlated with stone attenuation. However, concerns regarding radiation exposure warrant the continued use of 5-mm collimation widths.

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ENDOUROLOGY & LAPAROSCOPY

Laparoscopic management of intraperitoneal bladder rupture secondary to blunt abdominal trauma using intracorporeal single layer suturing technique

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J Trauma. 2008; 65: 234-6.

Background: Since Parra reported the first case of laparoscopic repair of bladder rupture caused by nonlaparoscopic injury to the bladder in 1994, several case reports have demonstrated the feasibility of this reconstructive surgical technique. We report the series of six patients that underwent laparoscopic repair of intraperitoneal bladder rupture (LRIB) because of blunt trauma using a single layer suturing technique. To our knowledge, this is the first series of LRIB reported secondary to blunt abdominal trauma.
Methods: From January of 2002 through June of 2006, a total of 139 patients were identified in our trauma registry with bladder ruptures secondary to abdominal blunt trauma. Among them 111 (79.8%) patients had associated pelvic injury. Seventy-one patients underwent surgical exploration and open bladder repair. Six cases were managed with laparoscopic technique. Patients were positioned in supine position and a three port-technique (5 mm, 10 mm, and 12 mm) was performed using the intracorporeal single layer suturing with a 3.0 Vycril (UR-6 needle). A close system Jackson-Pratt drain was placed in the retropubic space to monitor possible urine extravasation.
Results: The mean age of the patients was 47.3 years old (18-74 years). There were three female and three male patients. The average operation time was 43 minutes (31-75 minutes), mean length of bladder tear was 6.37 cm (5.3-7.7 cm), mean estimated blood loss was 16.6 cc (10-35 cc) and mean follow-up was 25.5 months (20-28 months). Two patients underwent combined orthopedic procedures. Computerized Tomography (CT) cystogram was performed between 5 days and 7 days after surgery with no signs of leakage in all patients.
Conclusion: LRIB perforation because of blunt abdominal trauma using single layer intracorporeal suturing technique is a minimally invasive alternative to open surgery in well selected patients with no other intrabdominal injuries or intracranial pressure issues, offering faster recovery and better cosmetic results.

Editorial Comment

This retrospective study demonstrated the development of minimally invasive laparoscopic surgery in trauma, especially for the bladder. This manuscript brings new concepts and changes in old "dogmas" such as, bladder repair in 2 layers, use of supra-pubic urine diversion, and use of minimally invasive approach to trauma. At Denver Health Medical Center, a level 1 trauma center, pioneering studies such as gastro-intestinal anastomosis performed in 1 layer demonstrated efficacious repair and gave birth to the similar concept of repair for the bladder. As stated in this study, the large number of trauma patients allowed the development of new minimally invasive techniques, i.e.; among the 111 patients with pelvic injuries during a period of less than 5 years, only 6 patients were able to benefit from this minimally invasive approach to repair the bladder. The authors emphasize the specific indications and selection of patients and contra-indications, such as, associated head trauma that may not allow the insufflation pressures or the "light" Trendelenburg position.

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Hand assisted retroperitoneoscopic nephroureterectomy with the patient spread-eagled: an approach through a completely supine position

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Purpose: We evaluated the feasibility of hand assisted retroperitoneoscopic nephroureterectomy for transitional cell carcinoma of the upper urinary tract with the patient completely supine (spread-eagled).
Materials and Methods: From October 2006 to January 2008 hand assisted retroperitoneoscopic nephroureterectomy with open bladder cuff excision was performed in 32 patients with upper tract transitional cell carcinoma. The patient was placed supine with the legs extended and abducted at 45 to 60 degrees, and the arms stretched out to the sides in the spread-eagle position. The patient was secured to the operation table with 3-inch tapes to permit lateral table tilt. The operation was completed via a 7 or 8 cm Gibson incision plus 2 laparoscopic ports.
Results: All procedures were successful. The mean time needed for hand assisted retroperitoneoscopic Nephroureterectomy and bladder cuff resection was 137.6 minutes. Mean estimated blood loss was 200 ml. Simultaneous transurethral endoscopic procedures were performed in 8 patients. Time to oral intake was 2.1 days and time to ambulation was 2.0 days. No specific complication was related to the position. All patients recovered to normal daily activity uneventfully.
Conclusions: Hand assisted retroperitoneoscopic nephroureterectomy with the patient completely supine is feasible and safe. The completely supine position has several advantages, including ease of patient positioning and the ability to perform simultaneous endoscopic procedures. It not only decreases the time and cost of changing position, but also avoids potential risks associated with the lateral decubitus position. Bowel interference with the visual field and mechanical bowel injury are not a concern using this approach.

Editorial Comment

The laparoscopic radical nephroureterectomy (LRNU) still remains a controversial subject, from the position of the patient to the optimal techniques to manage the distal ureter and the bladder cuff. The authors of this study propose an interesting patient positioning and surgical technique to perform the LRNU. It is extremely curious that a hand port is used in an already "tight" retroperitoneal space, creating difficult surgical maneuvers due to the lack of surgical field/space. Another interesting point is the preference of the authors for the 0-degrees laparoscope that can be easy to operate but may not offer the full range of visualization that a 30-degree or a flexible laparoscope may extend the view. The authors focused on the positioning of the patient and the lack of neurological or muscular complications that may occur during these laparoscopic procedures, fortunately very rare currently, since the "big" international learning curve has improved and better laparoscopic instrumentation, as well as, the knowledge of "laparoscopic anatomy" has been familiarized to the rest of the world through meetings, publications, etc. The oncological results appear similar to the other centers with high volume but the focus of the study seemed skewed towards the possible complications and advantage of not changing the patients positioning during this complex procedure. The authors should be congratulated for the attempt of optimizing the surgical technique of a known intricate procedure.

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IMAGING

Pelvic floor dysfunction: assessment with combined analysis of static and dynamic MR imaging findings

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Radiology. 2008; 248: 518-30

Purpose: To prospectively analyze static and dynamic magnetic resonance (MR) images simultaneously to determine whether stress urinary incontinence (SUI), pelvic organ prolapse (POP), and anal incontinence are associated with specific pelvic floor abnormalities.
Materials and Methods: This study had institutional review board approval, and informed consent was obtained from all participants. There were 59 women: 15 nulliparous study control women (mean age, 25.6 years) and 44 patients (mean age, 43.4 years), who were divided into four groups according to chief symptom. Static T2-weighted turbo spin-echo images were used in evaluating structural derangements; functional dynamic (cine) balanced fast-field echo images were used in detecting functional abnormalities and recording five measurements of supporting structures. Findings on both types of MR images were analyzed together to determine the predominant defect. Analysis of variance and the Bonferroni t test were used to compare groups.
Results: In the four patient groups, POP was associated with levator muscle weakness in 16 (47%) of 34 patients, with level I and II fascial defects in seven (21%) of 34 patients, and with both defects in 11 (32%) of 34 patients. SUI was associated with defects of the urethral supporting structures in 25 (86%) of 29 patients but was not associated with bladder neck descent. Levator muscle weakness may lead to anal incontinence in the absence of anal sphincter defects. Measurements of supporting structures were significant ($P < 0.05$) in the identification of pelvic floor laxity.
Conclusion: Combined analysis of static and dynamic MR images of patients with pelvic floor dysfunction allowed identification of certain structural abnormalities with specific dysfunctions.

Editorial Comment

Multifactorial dysfunction contributes to the etiology of pelvic organ prolapse: a) weakness, thinning and /or tearing of levator ani musculature; b) laxity and/or tearing of the endopelvic fascia and c) laxity and /or tearing of apical supporting ligaments of the vagina. Both static and dynamic magnetic resonance imaging studies have been shown to be useful for the evaluation of female pelvic floor dysfunction an entity that usually encompasses stress urinary incontinence, pelvic organ prolapse and anal incontinence. Although these techniques have been used more frequently in recent years, determination of precise anatomic causes of these clinical abnormalities are still not clear. The authors present the results of a prospective study performed in 59 women (15 volunteer nulliparous women-control group and in 44 women with a parity range of 0 to 7, and pelvic floor dysfunction). Combined analysis of static and dynamic MR images of the pelvic floor reveals that it is possible to differentiate whether prolapse is due to defects in the endopelvic fascia, to levator muscle weakness, or to abnormalities in both fascia and muscles. Another important conclusion: a) stress urinary incontinence is associated with structural defects in the urethral supporting structures rather than with bladder neck descent and b) in the absence of an anal sphincter defect, anal incontinence is associated with marked levator muscle weakness.

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Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity

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Objective: Most studies of contrast-induced nephropathy lack controls to distinguish it from nephropathy from other causes. We assessed the frequency and magnitude of serum creatinine changes in patients not receiving iodinated contrast material to compare with creatinine changes in publications regarding contrast nephropathy.
Materials and Methods: From the electronic medical records of an academic medical center, adults with creatinine determinations on five consecutive days who had not received contrast material during the previous 10 days were identified. The first creatinine level was compared with those on subsequent days. We calculated the frequency with which these levels exceeded thresholds used to identify contrast nephropathy in previous publications.
Results: Among 32,161 patients, more than half showed a change of at least 25% and more than two fifths, a change of at least 0.4 mg/dL. Among patients with baseline creatinine levels of 0.6-1.2 mg/dL, increases of at least 25%, 33%, and 50% occurred in 27%, 19%, and 11% of patients, respectively. Increases of 0.4, 0.6, and 1.0 mg/dL occurred in 13%, 7%, and 3% of patients. Among patients with baseline creatinine levels greater than 2.0 mg/dL, increases of at least 25%, 33%, and 50% occurred in 16%, 12%, and 7%. Increases of 0.4, 0.6, and 1.0 mg/dL occurred in 33%, 26%, and 18%. These increases were not different from the incidences of contrast nephropathy previously published.
Conclusion: The creatinine level increases in patients who are not receiving contrast material as often as it does in published series of patients who are receiving contrast material. The role of contrast material in nephropathy may have been overestimated.

Editorial Comment

Contrast agent-induced nephropathy (CIN) is the occurrence of renal failure, characterized by an increase in serum creatinine level or a fall in creatinine clearance, after the administration of an iodinated contrast agent. This entity occurs only in patients who have abnormal renal function before contrast agent injection. Unfortunately, the parameters used clinically (creatinine levels) for the estimative of the risk of CIN are imprecise. For this reason, one should calculate the creatinine clearance. Although contrast agents have been considered as one of the most frequent causes of in-hospital renal failure, many other concomitant risk factors exists such as dehydration, diabetes, previous extensive surgery and the use of nephrotoxic medications (e.g., gentamycin, nonsteroidal anti-inflammatory drugs, and certain chemotherapeutic drugs). Adequate hydration and the use N-acetyl cysteine or both can prevent CIN.

This report raises several questions, and the most important are: what if there is no such entity as CIN?, b) what if there is no real increase in serum creatinine level in the general population that can be attributed to the intravascular administration of contrast media? (1). It is obvious that until more rigorous studies including an appropriate control group address the issue of CIN, our understanding of the actual risk of CIN when administering IV contrast media is limited. We should also considerer that most studies have been shown that N-acetyl cysteine is useful for intra-arterial / intracardiac contrast but we do not know if the patient that receives intravenous contrast injection has the same risk of these patients. For this reason, we should not avoid doing a necessary iodinated contrast-enhanced radiological examination in a patient at risk of CIN. Obviously, the risk-benefit should be always balanced but in such situation, hyper-hydration should be immediately initiated and N-acetyl cysteine and non-ionic contrast material should be used.

Reference

1. Baumgarten DA, Ellis JH: Contrast-induced nephropathy: contrast material not required? AJR Am J Roentgenol. 2008; 191: 383-6.

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UROGENITAL TRAUMA

Long-term functional and morphological effects of transcatheter arterial embolization of traumatic renal vascular injury

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Objective: To assess the long-term morphological and functional outcome of superselective transarterial embolization (TAE) for treating traumatic renal vascular injury.
Patients and Methods: The surgical records of 124 patients with traumatic renal vascular injury managed by TAE between 1990 and 2004 were reviewed, of whom 81 completed a long- term follow-up and were included in the final analysis. Patients were followed using serum creatinine levels, grey-scale ultrasonography, intravenous urography (IVU) and radioisotopic renography using (99m)Tc-mercapto-acetyl triglycine (MAG3) and (99m)Tc-dimercaptosuccinic acid (DMSA).
Results: Embolization resulted in the cessation of haematuria in all patients but two (97.5%). At 3 months, serum creatinine levels increased in four of nine patients with a solitary kidney, but only one of them required haemodialysis. After a mean follow-up of 4.6 years, IVU showed a normal calyceal configuration in 70% of renal units, pyelonephritic changes in 26% and no dye excretion in 4%. DMSA scans showed no evidence of photopenic areas in 17 renal units (21%). The mean (sd) percentage of DMSA uptake by the corresponding kidney improved from 24 (9)% at the 3-month scans to 32 (10)% at the last follow-up scan ($P < 0.001$). Using MAG3, the mean (sd) glomerular filtration rate improved significantly from 26 (11) mL/min at the 3-month scan to 32 (9) mL/min at the last follow-up ($P < 0.05$).
Conclusions: Superselective TAE is safe and effective for traumatic renal vascular injury. The short-term deleterious effects were more pronounced in patients with a solitary kidney. The long-term follow-up showed functional and morphological improvements in the embolized renal units.

Minimally invasive endovascular techniques to treat acute renal hemorrhage

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J Urol. 2008; 179: 2248-52; discussion 2253

Purpose: We evaluated the effectiveness of endovascular therapy for severe renal hemorrhage.
Materials and Methods: We retrospectively reviewed cases compiled from the trauma database, billing records and interventional radiology logs at our institution from 1990 to 2007. Technical success was defined as the cessation of bleeding after angiographic embolization. Clinical success was defined as the absence of recurrent hematuria without the need for additional embolization.
Results: A total of 26 patients underwent angiography and endovascular treatment for renal hemorrhage. Mean patient age was 42 years (median 37, range 7 to 70). There were 20 males and 6 females. Mean clinical followup was 11.7 months. The mechanisms of injury were iatrogenic in 6 cases (renal biopsy in 5 and post-percutaneous nephrostomy placement in 1), trauma in 16 (blunt in 10 and penetrating in 6) and spontaneous rupture of a renal mass in 4. At presentation 16 patients (62%) were hemodynamically stable, while 10 (38%) were in shock. A total of 11 patients (42%) presented with gross hematuria, 7 (27%) had microscopic hematuria and 8 (31%) had no evidence of hematuria. A total of 16 patients (62%) had kidney injuries alone, while 10 (38%) also had significant concurrent injuries. Treatment failed in all 5 grade 5 acute renal injuries (100%) caused by external trauma. Technical and clinical success was achieved in 22 (85%) and 17 patients (65%), respectively.
Conclusions: Superselective embolization therapy for renal trauma provides an effective and minimally invasive means to stop bleeding. Overall our complication rate was minimal. Most renal traumas, including most grade 4 injuries, were effectively managed by conservative therapy. Embolization proved effective for grade 4 renal trauma for which conservative therapy failed. In our series embolization failed when applied to grade 5 injuries.

Editorial Comment

There has been a growing body of literature lately in support of managing the injured kidney with early angiography and embolization. Embolization therapy for the blunt splenic injury has been highly effective and successful. Once the decision has been made to manage the kidney injury nonoperatively, it appears that relative inclusion criteria for the use of selective embolization is symptomatic gross hematuria after penetrating renal trauma, contrast blush on CT scan (intravascular contrast extravasation), need for > 3 u RBC transfusion in a 24 hour period, or a symptomatic delayed renal bleed. Delayed renal bleeding typically occurs in 1-2 weeks after injury, when the clot lysis and there is hematoma liquefaction. In general, significant delayed bleed with observed AAST G3 or G4 renal injuries is very rare with blunt trauma 1%, but can occur in up to 24% with isolated penetrating injuries. As to effectiveness, kidney embolization is about 85% technically successful (the vessel can be embolized and subsequent show no flow on angiography) and about 65% clinically successful (35% will re bleed despite a technically and well performed embolization). Complications of post segmental infarction are rare, with pyrexia and fevers in about 10%, and persistent hypertension in less than 1%.

Renal bleeding from the kidney is usually due to a pseudoaneurysm or AV fistula. Embolizations of such vascular injuries are typically performed with permanent coils made from platinum. In our institution, we prefer the Tornado coils by Cook Urological. The Tornado coils come in 0.018", 0.035" and 0.038" wire size and once deployed are conical in shape 2 – 3 mm diameter. Platinum coils are highly radio-opaque and are of a softer metal so that they can achieve a tighter pack and have less vessel wall injury. To promote thrombogenicity attached to the coil walls are multiple Dacron side fibers.

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PATHOLOGY

False positive labeling of prostate cancer with high molecular weight cytokeratin: p63 a more specific immunomarker for basal cells

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Occasional nonspecific staining of prostate cancer cells with high molecular weight cytokeratin (HMWCK) can lead to false-negative diagnoses. We compared p63 and HMWCK immunostaining to check their specificity for basal cell identification. Out of 6887 prostate cancer cases sent in consultation to one of the authors over 1.5 years, we identified 22 (0.3%) cases with HMWCK labeling of cancer cells, including 20 needle biopsies and 2 transurethral resections of prostate (TURP). Cases were sent in consultation because of the confusing immunostaining pattern, where prostate cancer cells labeled with HMWCK at the outside institutions. In 6 cases, p63 immunostains were also received from the outside institution, whereas in the remaining 16 cases p63 immunohistochemistry was performed at our institution. In 14 cases, we used either an extra destained hematoxylin and eosin slide or a negative control slide for immunohistochemistry with antibodies to p63, and in the 2 remaining cases submitted unstained slides were used. The Gleason scores were 3+3=6 in 20 cases and 4+4=8 in 2 cases. The size of the tumor on needle biopsy ranged from 0.5 to 6.0 mm (mean 1 mm) and on the 2 TURP cases consisted of 44 and 68 cancer glands, respectively. The number of tumor cells positive for HMWCK in each of the needle biopsy cases ranged from 3 to 48 (mean 13 cells), whereas on the 2 TURP cases 26 and 10 cells were labeled with HMWCK. Corresponding stains for p63 on the same cases were negative in 18 cases. In 3 of 4 cases, p63 labeled 1, 1, and 2 tumor cells, respectively. The fourth case had 5 positive cells on p63 staining with 4 positive for HMWCK. To assess whether overstaining was a factor, we evaluated the intensity of HMWCK staining in the basal cells of the benign glands, which was moderate in 6 and strong in 16 cases. The cytoplasm of benign secretory cells showed focal weak (n = 3), diffuse weak (n = 1), and focal moderate (n = 2) staining for HMWCK. HMWCK labeling of prostate cancer cells is uncommon and does not seem to be solely attributable to overstaining. p63 is a more specific marker for basal cells than HMWCK, with less labeling of tumor cells. Recognition of this phenomenon and performing stains for p63 when it occurs can help prevent underdiagnosing prostatic carcinoma.

Editorial Comment

On a previous published study from the same Institution, it was shown that prostate adenocarcinoma cells may show aberrant expression for p63 immunostaining (1). In this study they describe another rare occurrence of aberrant expression: positivity for high-molecular weight cytokeratin (HMWCK). Both p63 and HMWCK are markers for basal cells which are absent in neoplastic acini.

Both are important reports of a pitfall for the pathologist while diagnosing prostate cancer. It is important for the urologist to know that immunohistochemistry is used only in some selected cases with difficult differential diagnosis and not routinely in all cases showing adenocarcinoma. More importantly, the urologist must know that even using immunohistochemistry the diagnosis may not be definitive, that is, it may be yet "suspicious but not diagnostic of adenocarcinoma".

Why this happens? There are several benign conditions mimicking adenocarcinoma that show absence of basal cells in some of the acini: partial atrophy (2), adenosis, small branches of normal acini, and atypical PIN (PINATYP) (3). In small lesions using immunohistochemistry, these conditions may show absent basal cells in all of the acini, and in absence of other criteria for the diagnosis of cancer the pathology report is still "suspicious but not diagnostic of adenocarcinoma".

References

1. Osunkoya AO, Hansel DE, Sun X, Netto GJ, Epstein JI: Aberrant diffuse expression of p63 in adenocarcinoma of the prostate on needle biopsy and radical prostatectomy: report of 21 cases. Am J Surg Pathol. 2008; 32: 461-7.
2. Wang W, Sun X, Epstein JI: Partial atrophy on prostate needle biopsy cores: a morphologic and immunohistochemical study. Am J Surg Pathol. 2008; 32: 851-7.
3. Kronz JD, Shaikh AA, Epstein JI: High-grade prostatic intraepithelial neoplasia with adjacent small atypical glands on prostate biopsy. Hum Pathol. 2001; 32: 389-95.

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Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology

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The distinction between cribriform Gleason pattern 3 and 4 prostate cancer is controversial. Out of 3590 prostate cancers sent to one of the authors over 7 months, 30 needle biopsy cases were selected that possibly represented cribriform Gleason pattern 3 cancer. Thirty-six digital images were taken and sent to 10 experts in prostate pathology. Consensus was defined when at least 7/10 experts agreed on the grade. Sixty-seven percent (n = 24) of images reached consensus (23 pattern 4; 1 pattern 3). Of the 12 nonconsensus images, 7 were favor pattern 4 (6/10 experts agreed), 1 was favor pattern 3 (6/10 experts agreed), and 4 were equivocal (< 6 experts agreed). The most common criteria used to call pattern 4 in the 23 consensus pattern 4 images were in frequency: irregular contour, irregular distribution of lumens, slit-like lumens, large glands, number of glands, and small lumens. In the only consensus pattern 3 image, criteria used were regular contour, small glands, regular distribution of lumens, and uniform round lumens. Discrepancy between experts was qualified as primarily objective (different criteria present) in 38%, subjective (different interpretation of the same criteria) in 12%, and mixed (both objective and subjective) in 50%. The most frequent situation with different interpretations of the same criteria were regular versus irregular contour and small versus large glands, with the former more common. Even in this highly selected set of images thought to be the best candidates for cribriform pattern 3 from a busy consult service, most experts interpreted the cribriform patterns as pattern 4. Moreover, most of the cribriform foci investigated (73%) were associated with more definitive pattern 4 elsewhere on the needle biopsy specimen. In conclusion, most of the small cribriform cancer foci seen on needle biopsy should be interpreted as Gleason pattern 4 and not pattern 3.

Editorial Comment

The cribriform pattern (glands in glands) is a very peculiar arrangement frequently seen in adenocarcinoma of the prostate. In metastases of unknown origin, this pattern seen in older men is almost always adenocarcinoma from the prostate. Obviously this pattern is not exclusively seen in prostate cancer. It may also be seen in carcinoma of the breast, gastrointestinal tract and other organs.

In the standard Gleason grading, cribriform pattern could correspond to patterns 2, 3, or 4. In the revised Gleason grading published in 2005 (1), cribriform pattern should never correspond to pattern 2, and very rarely to pattern 3. Most of the times it corresponds to grade 4. Cribriform pattern 3 is only diagnosed for well circumscribed glands of the same size as normal glands.

Reference

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.

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INVESTIGATIVE UROLOGY

Localization and expression of inducible nitric oxide synthase in biopsies from patients with interstitial cystitis

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Purpose: Interstitial cystitis is a chronic inflammatory disease of the bladder and luminal nitric oxide has been shown to be increased in the bladder in patients with interstitial cystitis. We analyzed endogenous nitric oxide formation and inducible nitric oxide synthase gene expression in the bladder of patients with interstitial cystitis to obtain further knowledge of the localization of inducible nitric oxide synthase in the bladder mucosa.
Materials and Methods: Six patients with interstitial cystitis and 8 controls were studied. In these 2 groups endogenous nitric oxide formation was measured and inducible nitric oxide synthase expression in bladder biopsies was analyzed at the transcriptional and protein levels by real-time polymerase chain reaction and Western blot, respectively. Immunohistochemistry for inducible nitric oxide synthase was also performed.
Results: Patients with interstitial cystitis had higher inducible nitric oxide synthase mRNA expression and nitric oxide formation than controls ($p < 0.01$ and < 0.001, respectively). Inducible nitric oxide synthase protein expression was up-regulated in the interstitial cystitis group. Immunohistochemistry showed that inducible nitric oxide synthase was predominantly localized to the urothelium in patients with interstitial cystitis but inducible nitric oxide synthase-like immunoreactivity was also found in macrophages in the bladder mucosa.
Conclusions: The increased levels of endogenously formed nitric oxide in patients with interstitial cystitis correspond to increased inducible nitric oxide synthase mRNA expression and protein levels in these patients. Furthermore, inducible nitric oxide synthase was found to be localized to the urothelium but it was also found in macrophages in the bladder mucosa. Whether high levels of endogenously formed nitric oxide are a part of the pathogenesis in interstitial cystitis and whether it has a protective or damaging role remain to be elucidated.

Editorial Comment

Analyzing patients with interstitial cystitis (IC) and controls, the authors evaluated whether high levels of endogenous nitric oxide (NO) in the bladder in patients with IC also correspond to increased levels of iNOS at a transcriptional and protein level. Also, the authors studied the location of iNOS in the bladder mucosa.

It was found that the bladder luminal NO concentration was significantly increased in patients with IC when compared to controls. At the transcriptional level iNOS expression was detectable in biopsies from patients with IC as well as in controls. However, iNOS mRNA expression was significantly higher in biopsies from patients with IC when compared to controls. In addition, iNOS protein expression was found in the biopsies of patients with IC but not in the biopsies of controls.

This important study opens new avenue for understanding the pathophysiology of IC and also for additional diagnostic tools of this until now under understanding disease.

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Effect of cyanoacrylic glue on penile fracture: an experimental study

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Purpose: We investigated the effect of Glubran(R)2 cyanoacrylic glue on rat cavernous tissue after forming penile fractures experimentally as well as the histopathological effect. We also investigated its clinical use.
Materials and Methods: Experimental penile fracture was formed by incising from the proximal dorsal side of the penis in 32 Wistar Albino rats. The rats were randomly assigned to 4 main groups of 8 each. In the control group the incision was not repaired and it was left to secondary healing. In the glue group cyanoacrylic glue was only applied to the incision region. In the primary repair group the incision was primarily repaired and in the final group cyanoacrylic glue was applied to the incision region following primary repair. Three weeks later penectomy materials were examined histopathologically.
Results: When the control group was compared with the other groups, the differences in cavernous tissue healing with fibrosis and hyperemia-bleeding were statistically significant ($p = 0.043$ and 0.003, respectively). In the glue group fibrosis was observed in 2 rats. This group was the best according to cavernous healing. Although there was no significant difference between the control group and the other groups according to inflammation ($p = 0.057$), the glue group was better than the primary repair group ($p = 0.026$). No significant inflammation or hyperemia-bleeding was observed in the glue group. When the experimental groups were evaluated for histopathological parameters, it was observed that the best results were obtained in the glue group.
Conclusions: Cyanoacrylic glue can be used in cavernous surgery due to its hemostatic, adhesive and anti-inflammatory properties.

Editorial Comment

The authors investigated the effect of Glubran2 for penile fracture repair. They studied 4 groups of 8 rats each, after creating experimental penile fracture by incising the proximal dorsal side of the penis with

a number 15 lancet. In group C the incision was not repaired but was left to secondary healing. In group G cyanoacrylic glue was only applied on the incision region and the tissue was compressed to become adhered for 2 to 3 minutes. In group P the incision was primarily repaired with 6-zero polydioxanone. In group PG cyanoacrylic glue was applied on the incision region following primary repair.

The authors found that there was no inflammation and hyperemia-bleeding in only group G. In group PG only 1 rat had these histopathological features. Total healing was observed in all rats in the 2 groups. Slight fibrosis developed in the cavernous tissue in groups G and PG, similar to that in rats in group P, and the authors stated that this finding showed that cyanoacrylic glue has no effect on preventing fibrosis. The authors concluded that Glubran2 can be used in cavernous surgery due to its hemostatic, adhesive and anti-inflammatory properties, and that application of this material on the ruptured region of corpus cavernosum without suturing seems to be beneficial according to the primary repair method.

The authors are to be commended for that elegant study and for providing a new option that would be used in the future for cavernous repair. Nevertheless, it is important to point out that "penile fracture" is defined as "a rupture of the corpus cavernosum due to a blunt trauma in an erect penis. Lesions on a flaccid penis or lesions in the suspensor ligament of the penis are not included in this definition". So, the mechanism of injury used in this experimental work is far different from a fracture. It would be better to name it as a "cavernous lesion". A lesion caused by a scalpel in the albuginea is much less traumatic than a lesion caused by a blunt trauma to an erect penis with a thin albuginea submitted to a high intracavernosal pressure. A typical penile fracture is followed by swelling, hematoma and penile deformity, which would cause greater inflammatory reaction.

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RECONSTRUCTIVE UROLOGY

Surgical techniques in substitution urethroplasty using buccal mucosa for the treatment of anterior urethral strictures

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Eur Urol. 2008; 53: 1162-71

Objectives: Since the resurgence in the use of buccal mucosa (BM) in substitution urethroplasty in the late 1980s and early 1990s, there has been controversy as to which surgical technique is the most appropriate for its application.
Methods: The authors performed an updated literature review. Several centres have published widely on this topic, and the points considered include the use BM in dorsal onlay grafts, ventral onlay grafts, and tubularised grafts and the role of two-stage procedures.
Results: In experienced hands, the outcomes of both dorsal onlay grafts and ventral onlay grafts in bulbar ure-

throplasty are similar. The dorsal onlay technique is, however, possibly less dependent on surgical expertise and therefore more suitable for surgeons new to the practice of urethroplasty. The complications associated with ventral onlay techniques can be minimised by meticulous surgical technique, but in series with longer follow-up, complications still tend to be more prevalent. In penile urethroplasty, two-stage dorsal onlay of BM (after complete excision of the scarred urethra) still provides the best results, although in certain circumstances a one-stage dorsal onlay procedure is possible. In general, ventral onlay of BM and tube graft procedures in the management of penile strictures are associated with much higher rates of recurrence and should therefore be avoided.

Conclusions: In experienced hands the results of the ventral and dorsal onlay of BM for bulbar urethroplasty are equivalent. Two-stage procedures are preferable in the penile urethra, except under certain circumstances when a one-stage dorsal onlay is feasible.

Editorial Comment

Since the initial reported use of buccal mucosa for urethral reconstruction in 1894, the properties of the tissue itself have not substantially changed despite improvements in suturing materials, instruments and reconstructive surgical techniques (1).

Patterson and Chapple compared the most frequently used published techniques of urethroplasty. They concluded that the technique does not seem to be as critical for the success of the transplant as the high surgical skills required reconstructive surgery (2). This takes into an account the use of 5/0 or even 6/0 sutures under magnification reducing host tissue and buccal mucosa traumatization (3). The substantial knowledge is that buccal mucosa has good elasticity, supports neo-vascularization because of its lamina propria, boosts the local immune status with its increased amount of IgA, provides similarity to cytoceratin and ensures a low risk of inflammation or scar development.

Thus, buccal mucosa with its satisfying long-term outcome is still the golden standard against which we have to validate any new material or approach (4).

References

1. Sievert KD, Seibold J, Schultheiss D, Feil G, Sperling H, Fisch M, et al: [Reconstructive urology in the change, from it's beginning to the close future] Urologe A. 2006;45 (Suppl 4): 52-58. Article in Germany.
2. Patterson JM, Chapple CR: Surgical techniques in substitution urethroplasty using buccal mucosa for the treatment of anterior urethral strictures. Eur Urol. 2008; 53: 1162-71.
3. Andrich DE, Mundy AR: What is the best technique for urethroplasty? Eur Urol. 2008, Aug 19. [Epub ahead of print]
4. Sievert KD, Amend B, Stenzl A: Tissue engineering for the lower urinary tract: a review of a state of the art approach. Eur Urol. 2007; 52: 1580-9.

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Lichen sclerosus of the male genitalia and urethra: surgical options and results in a multicenter international experience with 215 patients

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Eur Urol. 2008 Jul 30. [Epub ahead of print]

Background: Surgical options in male patients with genital lichen sclerosus (LS) involving the anterior urethra still represent a challenging issue.
Objective: To review the outcome of surgical treatment in patients with genital and urethral LS.
Design, Setting, and Participants: Multicenter, international, retrospective, observational descriptive study performed in two specialized centers. Two hundred fifteen male patients underwent surgery for histologically proven genital LS involving the foreskin and/or the anterior urethra.
Intervention: Circumcision (34 cases), meatotomy (15 cases), circumcision and meatotomy (8 cases), one-stage penile oral mucosal graft urethroplasty (8 cases), two-stage penile oral mucosal graft urethroplasty (15 cases), one-stage bulbar oral mucosal graft urethroplasty (88 cases), and definitive perineal urethrostomy (47 cases). Measurements: Primary outcome was considered a failure when any postoperative instrumentation was needed, including dilation, or when recurrence was diagnosed. Results and Limitations: The average follow-up was 56 mo (range: 12-170 mo). Circumcision showed 100% success rate with no recurrence of the disease; meatotomy, 80% success rate; circumcision and meatotomy, 100% success rate; one-stage penile oral mucosal graft urethroplasty, 100% success rate; two-stage penile oral mucosal graft urethroplasty, 73% success rate; one-stage bulbar oral mucosal graft urethroplasty, 91% success rate; and definitive perineal urethrostomy, 72% success rate. Limitations include short follow-up for recording neoplastic degeneration and no instrument to investigate quality of life.
Conclusions: Patients with LS disease restricted to the foreskin and/or external urinary meatus showed a high surgery success rate. In patients with penile urethral strictures or panurethral strictures, the use of one-stage oral graft urethroplasty showed greater success than the staged procedures.

Editorial Comment

Although the cause of lichen sclerosus (LS) is still unknown, its clinical course has been well described in recent years, and in particular, in a current review of Kulkarni et al. (1). It is still astonishing that histological evaluation is not or incorrectly performed, according to the data by Jasaitiene et al. Thorough histological evaluation revealed that LS occurs almost equal in boy and men (2).

With the systematic retrospective work-up of Kulkarni et al., it became obvious that early diagnosis and correct treatment leads to a long-term satisfying outcome (3). Therefore, it should be requested that any resected tissue of the foreskin, glans or urethra has to be examined by a pathologist with the exclusion of LS.

Even for the most extensive reconstruction, the authors suggest the use of buccal mucosa in a one-stage urethroplasty, which is opposite to Patterson and Chapple who suggest the two stage approach, to have a higher success rate (4). This contribution makes it once again obvious how important it might be to exclude LS both for the course of the disease as well as the result of a possible reconstructive surgery.

References

1. Pugliese JM, Morey AF, Peterson AC: Lichen sclerosus: review of the literature and current recommendations for management. J Urol. 2007; 178: 2268-76.
2. Jasaitiene D, Valiukeviciene S, Vaitkiene D, Jievaltas M, Barauskas V, Gudinaviciene I, et al.: Lichen sclerosus et atrophicus in pediatric and adult male patients with congenital and acquired phimosis. Medicina (Kaunas). 2008; 44: 460-6.

3. Kulkarni S, Barbagli G, Kirpekar D, Mirri F, Lazzeri M: Lichen sclerosus of the male genitalia and urethra: surgical options and results in a multicenter international experience with 215 patients. Eur Urol. 2008; Jul 30. [Epub ahead of print]
4. Patterson JM, Chapple CR. Surgical techniques in substitution urethroplasty using buccal mucosa for the treatment of anterior urethral strictures. Eur Urol. 2008; 53: 1162-71.

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UROLOGICAL ONCOLOGY

Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma

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Objective: To provide a systematic review of the side effects associated with sorafenib, sunitinib, and temsirolimus and to provide an outline of possible preventive or therapeutic measures.
Methods: We performed a PubMed-based systematic review of side effects associated with the three agents and relied on product monographs and prescribing information to provide an outline of treatments aimed at reducing these toxicities.
Results: Side effects range from < 1% to 72%. Grade 3/4 side effects are less common and range from < 1% to 13% for sorafenib, < 1% to 16% for sunitinib, and 1% to 20% for temsirolimus. Overall, sunitinib causes the most grade 3/4 side effects and sorafenib causes the fewest grade 3/4 side effects, although head-to-head trials are required to compare safety profiles of all three kinase inhibitors. Virtually all side effects can be managed effectively.
Conclusion: Prevention, recognition, and prompt management of side effects are of key importance and avoid unnecessary dose reductions, which may undermine treatment efficacy.

Editorial Comment

Three targeted medical therapies against metastatic renal cancer have recently been approved and are more and more widely used. Either as a therapist himself or in counseling his/her patients in further medical therapy the urologist faces a new generation of drugs with unfamiliar side-effects. The article focuses on the side effects of sunitib, sorafenib and temsirolimus as reported in the literature from all phase I, II and III studies. This article is worthwhile reading, profound and detailed and is recommended for every urologist dealing with this tumor entity.

The authors not only describe the side-effects of treatment but also give detailed advice on the management of hematologic, systemic or endocrinologic, cardiac, gastrointestinal, cutaneous and laboratory adverse events. Moreover, dose-modifications are suggested. Finally, a helpful questionnaire to monitor the patents course and standardized prescriptions are given.

Again, strongly advised reading for everyone dealing with medical therapy against renal cancer.

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Prepubic urethrectomy during radical cystoprostatectomy

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Eur Urol. 2007; 51: 915-21

Objectives: In muscle-invasive bladder cancer, the risk of developing a urethral recurrence after cystectomy varies between 4% and 18%, especially when an ileal conduit is performed. For this reason, some authors advocate a urethrectomy in these indications. At our center, we developed the technique of prepubic urethrectomy. We assessed the feasibility and implications of this technique over 20 yr of use.
Patients and Methods: We retrospectively analyzed the medical files of 180 consecutive male patients who underwent a urethrectomy simultaneously with cystectomy for invasive bladder cancer between 1985 and 2005. We describe our technique step-by-step, and present possible technical difficulties and complications of urethrectomy.
Results: The mean increase in operative time with the prepubic urethrectomy over cystoprostatectomy alone was 17 min (range: 15-25). Postoperative complications occurred in 10 (5.5%) patients. A subcutaneous penile haematoma was noted in four (2.2%) patients, two of whom needed a circumcision later on. A scrotal haematoma was seen in five (2.7%) patients; two needed a surgical drainage and three were treated conservatively. A prepubic collection was noted in one patient who was also treated conservatively. No thromboembolic or neurologic complications were encountered. Conclusions: When a urethrectomy is indicated, it can best be performed by using the prepubic approach, because it is easier and less time-consuming than the perineal approach, and has very limited and easily manageable complications.

Editorial Comment

Urologic surgeons familiar with radical cystectomy are confronted with the risk of urethral recurrences. Indications for this procedure vary between different authors, but in cases with multifocal carcinoma in situ or clear infiltration of the prostate simultaneous urethrectomy mostly is recommended.

These authors describe an elegant and time-saving procedure to perform prepubic urethrectomy and report their 20 years of experience.

Remarkably, in 180 cases of en-bloc urethrectomy together with radical cystectomy the authors experienced only 10 patients with complications.

From my own experience in many such cases I can only recommend this operative procedure and would advice anyone with experience in operative urology to thorough reading of this article.

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NEUROUROLOGY & FEMALE UROLOGY

Postoperative urinary incontinence after total abdominal hysterectomy or supracervical hysterectomy: a metaanalysis

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Objective: A metaanalysis of randomized trials was conducted to evaluate if the type of hysterectomy, total abdominal hysterectomy or supracervical hysterectomy, has an impact on the development of urinary incontinence.
Study Design: We searched MEDLINE, EMBASE, CINAHL, Biological Abstract, and the Cochrane Library up to February 2007; abstracts at major meetings and bibliographies of retrieved articles were scanned. A fixed effect model was used to calculate summary relative risk estimates and 95% confidence intervals (CIs).
Results: Analysis showed no statistical difference in the risk of developing stress or urge urinary incontinence in women who underwent supracervical hysterectomy compared with women who underwent total abdominal hysterectomy (relative risk, 1.3; 95% CI, 0.94-1.78; P = 0.16 and relative risk, 1.37; 95% CI, 0.77-2.46; P = 0.25).
Conclusion: There is no statistical evidence of a different risk for developing either stress or urge urinary incontinence after a supracervical hysterectomy or a total hysterectomy.

Editorial Comment

The authors noted a current trend towards supracervical hysterectomy as opposed to a total hysterectomy in an effort to diminish surgical impact on underlying patient anatomic structures that involve continence. The authors performed a meta-analysis to gather their data: this spanned relevant articles between 1996 and 2007, ongoing clinical trials, and abstracts performed on the topic. They specifically reviewed comparison of total abdominal hysterectomy and supracervical hysterectomy with regards the development of stress or urinary urge incontinence.

The authors noted that there was no difference between supracervical hysterectomy and total hysterectomy with regards to voiding dysfunction (stress urinary incontinence, urinary urge incontinence or symptoms of overactive bladder). In fact, they noted that there was a non-significant trend towards increased risk for voiding dysfunction with a supracervical hysterectomy as opposed to total abdominal hysterectomy.

This study highlights the difference between anecdotal and observational notations versus scientific analysis. Their findings of a non-statistical increase in supracervical approach associated voiding dysfunction as opposed to total abdominal hysterectomy may temper the enthusiasm for the completion of this operation sheerly based on the perception of preventing future voiding dysfunction. As pointed out by the authors, the difficulty in comparing the efficacy of observational studies versus scientific studies is that the former may be performed as an accumulation of experience over a career while the latter may involve a follow-up of significantly less time.

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Outcomes following sling surgery: importance of definition of success

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Purpose: The assessment of incontinence therapies is complicated by the diverse outcomes instruments and definitions of success used by investigators. We defined this effect by using varied definitions of success to perform outcomes analysis following sling placement.
Materials and Methods: A retrospective review of patients undergoing SPARC (314) and autologous rectus pubovaginal sling (127) placement was performed, with 204 patients with the SPARC and 67 with pubovaginal sling completing questionnaire surveillance with the minimum 12-month follow-up. Outcomes were assessed using a questionnaire comprising validated incontinence questionnaires (Urogenital Distress Inventory and Incontinence Impact Questionnaire) and additional items addressing satisfaction. Success rates were compared using alternate definitions of success across all outcomes measures (eg dry rate, pad rate, percent improvement, degree of satisfaction).
Results: Wide variations in outcomes were seen depending on the definition used for success (SPARC success range 33% to 87%, pubovaginal sling 40% to 79%). Total absence of leakage was the strictest definition of success while continued use of 1 to 3 liners was associated with the highest success rates. In addition, 74% of patients with SPARC placement and 66% with the pubovaginal sling reported willingness to undergo sling surgery again despite the treatment failing to meet the criteria for success under multiple definitions. Finally, the individual sling type (SPARC vs. pubovaginal) associated with the superior success rate varied with the definition of success. However, these differences failed to achieve statistical significance.
Conclusions: Our data suggest that success rates following sling placement are significantly affected by the definition of success. Investigation to define standardized outcomes measures following incontinence surgery is of great importance to the urological community.

Editorial Comment

The authors delve into the complicated world of gauging success after sling surgery. Their study pool for analysis was 271 patients of which 204 received the SPARC™ suburethral sling while 67 underwent a pubovaginal sling using autologous fascia. The authors found that if the strictest definition of success was utilized, that is, “dry is dry”, patients had a markedly lower success rate than when light pads was used as the definition of success. In addition, they noted that if the patient was improved by greater than 50% they were more prone to recommending the surgery or repeating the surgery as opposed to those not reaching 50%. These authors also compared the two techniques in a sliding scale of metrics of success noting the potential significant difference in the reported success rate. The two operations did have some disparity in that the SPARC™ operation had a higher pad free rate reported while the pubovaginal sling had more patients stating that they were dry.

One should strongly consider reading this excellent article in its entirety prior to judging the efficacy of reported sling operations. The authors make several excellent points in their discussion section including the call for completely dry to be used only in the strictest sense of the word. Of note is that the paper did not expand into postoperative complications including voiding dysfunction and its affect on sling success and outcomes.

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PEDIATRIC UROLOGY

Nerve sparing robotic extravesical ureteral reimplantation

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J Urol. 2008; 179: 1987-9; discussion 1990

Purpose: Laparoscopic transvesical ureteral reimplantation with or without robot assisted surgical devices is being developed as an alternative to open surgery. We sought to review our experience with an extravesical robotic technique, to determine whether postoperative voiding dysfunction might be avoided with pelvic plexus visualization and to evaluate the overall feasibility of this approach to ureteral surgery.
Materials and Methods: A total of 41 patients underwent robotic extravesical reimplantation for bilateral vesicoureteral reflux. The patients were divided into groups based on bladder capacity as measured by voiding cystourethrogram. The operation was performed via a transperitoneal approach with robotic assistance using the da Vinci Surgical System.
Results: Operative success rates were 97.6%. There were no complications. There were no episodes of urinary retention documented by bladder scanning.
Conclusions: Robotic extravesical reimplantation is in its infancy, and visualization of the pelvic plexus appears to be paramount in avoiding postoperative voiding complications. This approach appears to be a feasible and reasonable option for vesicoureteral reflux correction.

Editorial Comment

Forty-one patients underwent retrospective chart review after robotic extravesical reimplantation for vesicoureteral reflux grades III-V regardless of duplication anomalies. Indication for surgery was breakthrough pyelonephritis despite prophylactic antibiotics. Voiding diaries, uroflow, post-void residual measurements and constipation issues were addressed pre-operatively. All patients underwent cystoscopy with ureteral catheters placed in the aid of the dissection. One camera port and two other robotic ports were used. The authors were careful to do a nerve-sparing technique and felt that the robot with its better visualization allowed the nerves to be easily spared. All patients had an overnight catheter. The average operating time was 2.33 hours with an average length of stay of 26.1 hours. Post-void residual urines were checked by bladder scan and all patients voided after the catheter was removed and there was a mean residual of 13 mL of urine in the bladder. One patient had reflux on a three month VCUG and no patients had hydronephrosis on the ultrasound at 3 and 6 months postoperatively.

The authors should be congratulated on a study well done with good and careful follow up of the pre- and post-op bowel and bladder management. This shows that extravesical nerve-sparing robotic reimplantations can be done safely with excellent results. Always the question for endoscopic procedures in children: "is it an improvement over the open surgical techniques and does it offer patient benefit?" I believe those answers will in time become clear but as yet it remains to be seen.

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Unilateral vesicoureteral reflux: does endoscopic injection based on the cystoscopic appearance of the ureteral orifice decrease the incidence of de-novo contralateral reflux?

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Objective: In patients with unilateral vesicoureteral reflux (VUR), it has been suggested that injection of a non-refluxing but cystoscopically abnormal contralateral ureteral orifice (UO) with dextranomer/hyaluronic acid (Dx/HA) should be performed to prevent the development of de-novo contralateral VUR. We evaluate the effectiveness of this practice.
Patients and Methods: Patients with primary unilateral VUR undergoing injection of Dx/HA from 2002 to 2005 at two institutions were eligible. Patients with unilateral VUR with cystoscopically abnormal contralateral UOs were injected with Dx/HA, while patients with normal appearing UOs received no treatment. Multivariate logistic regression models were used to estimate the impact of prophylactic injection on the development of de-novo contralateral VUR.
Results: In total, 101 patients with unilateral VUR and an abnormal appearing contralateral UO underwent prophylactic injection of Dx/HA while 45 patients with a normal appearing contralateral UO were untreated. In patients receiving prophylactic Dx/HA, 9% (9/101) of the previously non-refluxing ureters developed de-novo VUR. Similarly, 13% (6/45) of patients with a normal appearing UO treated by observation alone developed de-novo VUR (P=0.55). The overall incidence of 10% (15/146) de-novo contralateral VUR matches published results where this protocol was not followed.
Conclusions: Our findings suggest that cystoscopic assessment and prophylactic treatment of an abnormal appearing, non-refluxing contralateral UO with Dx/HA is of little clinical benefit and should be abandoned.

Editorial Comment

This research was done at both the Mayo Clinic and the Division of Urology in Minneapolis, Minnesota. It was noted that 7-20% of patients undergoing unilateral endoscopic injection therapy or ureteroneocystostomy will develop de-novo contralateral vesicoureteral reflux. The authors cystoscopically evaluated 146 patients on the contralateral side during a 3½ year period with unilateral reflux before the refluxing side underwent Deflux® therapy. If the ureteral orifice was deemed abnormal by the pediatric urologists, either from orifice appearance or from hydrodistention appearance, the contralateral ureter was treated with Deflux® also. The average age was approximately six years with 91% of the patients being female. 69% were judged to have an abnormal appearing ureteral orifice and were injected with Deflux®; while 31% of the patients were judged to have a normal orifice and were not injected. Cyclical voiding cystourethrograms or nuclear cystograms were performed at three months and de-novo vesicoureteral reflux developed in 9% when the orifice was prophylactically treated with Deflux® and in 13% when the orifice was judged normal and no Deflux® was treated. This was not statistically significant. The author's conclude that prophylactic treatment of abnormal ureteral orifices should not be performed since it showed no benefit over no treatment at all.

Decades ago, urologists spent significant time cystoscopically judging ureteral orifice and position and eventually studies showed that the results correlated very well with radiographic vesicoureteral reflux grading and the practice was generally abandoned. With new information about hydrodistention of the ureter, this concept has been revisited and this manuscript suggests that there is no benefit in this evaluation or in the prophylactic treatment of these ureters and yet again this practice can be laid aside.

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