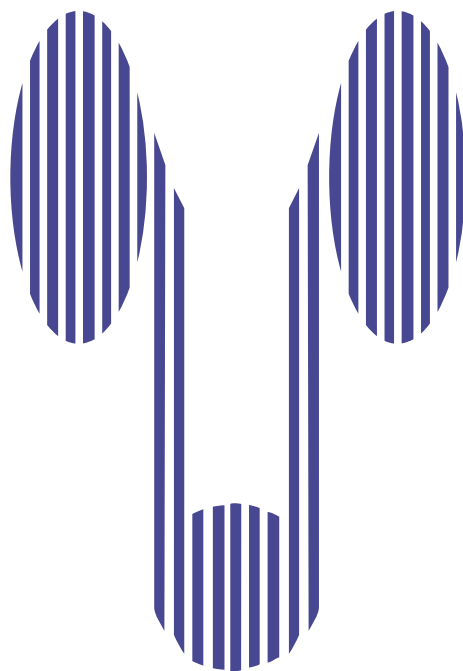


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EDITOR'S COMMENT

The July - August 2005 issue of the *International Braz J Urol* presents important contributions from different countries, and as usual the Editor's Comment highlights some important papers.

Doctor Rocha and co-workers, from Pellegrin University Hospital Center, Bordeaux, France, analyzed on page 299 the changes in serum catecholamine concentrations in response to surgical stress in patients with pheochromocytoma who undergone videolaparoscopic adrenalectomy. After studying 12 cases, the authors found that pneumoperitoneum significantly increases serum noradrenaline concentrations, manipulation of the adrenal gland significantly increases the serum concentrations of noradrenaline and adrenaline, and the pheochromocytoma ablation significantly decreases serum noradrenaline concentrations.

Doctors Al-Qudah & Santucci, from Detroit Receiving Hospital and Wayne State University School of Medicine; Michigan, USA, presented on page 315 an extensive study of complications following urethroplasty after analyzing 62 urethroplasties (24 anterior anastomotic, 19 buccal mucosal and 10 fasciocutaneous, 9 posterior anastomotic) with mean follow-up of 29 months. The authors found that serious complications after urethroplasty (3% early and 18% late) appear similar to those reported elsewhere, but minor bothersome complications appear to occur in much higher numbers than previously published (39% early and 40% late). Doctors Allen F. Morey, from Brooke Army Medical Center, Texas, USA and Massimo Lazzeri from Casa di Cura Santa Chiara Firenze, Florence, Italy, world recognized experts in urethroplasties, provided excellent editorial comments on this paper.

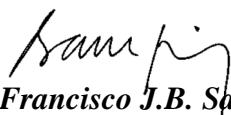
Doctor Abreu and colleagues, from Urological Hospital of Brasília, Federal District, Brazil, presented on page 362 a technique to perform laparoscopic radical cystoprostatectomy followed by constructing a Y-shaped reservoir extra-corporeally with titanium staples through a 5-cm muscle-splitting Pfannenstiel incision. The authors operated on 2 male patients diagnosed with muscle invasive transitional cell carcinoma of the bladder. Doctors Benjamin R. Lee, from Long Island Jewish Medical Center, New York, USA, and Stephen Y. Nakada, from University of Wisconsin Hospital and Clinics, Madison, Wisconsin, USA, well-known skillful laparoscopic urologists provided our readers with important editorial comments on this advanced laparoscopic procedure.

Doctor Tucci Jr. and co-workers, from University of Sao Paulo, Ribeirao Preto, Brazil, investigated on page 384 the action of verapamil on the mitochondrial function of kidneys submitted to ischemia without blood reperfusion. The authors aim to study isolated early and late ischemic effects. They concluded that administration of verapamil before warm ischemia provides partial and

short-lasting functional protection of the mitochondrial function in kidneys perfused with sodium rich saline. With Euro-Collins solution, verapamil did not show any additional beneficial effect. This fact led the authors to conclude that protective action is effective only under conditions that facilitate increased sodium uptake and/or potassium loss.

Doctor Antunes and colleagues, from Federal University of Sao Paulo, Brazil, presented on page 331 a study on the influence of age in determining the pathological features of biopsies from patients diagnosed with prostate cancer. The authors evaluated the histological grade, presence of perineural invasion and estimate of tumor volume through measurement of the maximum percentage of tissue with cancer in one fragment and total percentage of tissue with cancer in the sample, in a cohort of 547 patients. Interestingly, the authors found that age did not represent a determining factor for pathological findings concerning Gleason score and estimate of tumor volume by the variables in use.

Finally, it is again my pleasure to verify that the *International Braz J Urol* is continuing growing in acceptance and circulation. During the last two months, we received more than 60,000 on-line visits from 118 different countries, and these figures include the *International Braz J Urol* among the most read urological journals.


Dr. Francisco J.B. Sampaio
Editor-in-Chief

ASSESSMENT OF SERUM CATECHOLAMINE CONCENTRATIONS IN PATIENTS WITH PHEOCHROMOCYTOMA UNDERGOING VIDEOLAPAROSCOPIC ADRENALECTOMY

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ABSTRACT

Introduction: We analyzed the changes in serum catecholamine concentrations, i.e. adrenaline and noradrenaline, in response to surgical stress in patients with pheochromocytoma who undergone videolaparoscopic adrenalectomy.

Materials and Methods: Between January 1998 and March 2002, 11 patients underwent 12 videolaparoscopic adrenalectomies. In one case, the adrenalectomy was bilateral. Serum catecholamines were measured at 6 surgical times: T0: control before induction; T1: following the induction, laryngoscopy and intubation sequence; T2: after installing the pneumoperitoneum; T3: during manipulation-exeresis of the pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient was extubated and was hemodynamically stable.

Results: Mean concentrations of serum noradrenaline were significantly different when the T0 and T2 surgical times were compared (T0: 3161 pg/mL; T2: 40440 pg/mL; $p < 0.01$), T0 and T3 (T0: 3161 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T1 and T3 (T1: 5531 pg/mL; T3: 46021 pg/mL; $p < 0.01$), T2 and T4 (T2: 40440 pg/mL; T4: 10773 pg/mL; $p < 0.01$) and T3 and T5 (T3: 46021 pg/mL; T5: 2549 pg/mL; $p < 0.001$). Mean concentrations of serum adrenaline were significantly different when the T0 and T3 surgical times were compared (T0: 738 pg/mL; T3: 27561 pg/mL; $p < 0.01$).

Conclusion: The pneumoperitoneum significantly increases serum noradrenaline concentrations, manipulation of the adrenal gland significantly increases the serum concentrations of noradrenaline and adrenaline, and the pheochromocytoma ablation significantly decreases serum noradrenaline concentrations.

Key words: pheochromocytoma; laparoscopy; catecholamines

Int Braz J Urol. 2005; 31: 299-308

INTRODUCTION

Pheochromocytoma is an uncommon and important neoplasia because, despite its rarity, it is associated with catecholamine-induced hypertension, which can be resolved by neoplasia excision. The definitive treatment for pheochromocytoma is surgical ablation of the adrenal gland and/or paragangliomas.

Before the 1950s, the peroperative mortality was between 20 and 25% of cases with a preoperative diagnosis of pheochromocytoma and around 50% of cases without a preoperative diagnosis of pheochromocytoma. The lack of proper control for hypertensive crises and cardiac arrhythmias during manipulation and ablation of the pheochromocytoma was responsible for this high mortality. The advances in peroperative

control and the preoperative introduction of alpha 1-adrenergic blockade have significantly reduced mortality rates (1).

The first laparoscopic adrenalectomies were described by Gagner et al. and Higashihara et al. in 1992 (2,3). Studies have shown that videolaparoscopic adrenalectomy offers lower morbidity than open surgery (4,5). The videolaparoscopic technique has become the preferred option for treating adrenal tumors (6), however some doubts remain about the use of videolaparoscopy for management of pheochromocytomas due to cardiovascular risks that are potentially higher when compared to open surgery. Such risks are related to catecholamine release. Factors such as the use of carbon dioxide, the increase in abdominal tension and manipulation of the adrenal gland have been implied in catecholamine release (7).

Thus, in order to validate the videolaparoscopic technique in the management of pheochromocytomas, it is important to determine potential changes in serum catecholamine concentrations, as well as the relationship between such changes and higher cardiovascular risk.

This study aimed to assess changes in serum catecholamine concentrations, i.e. adrenaline and noradrenaline, in response to surgical stress in patients with pheochromocytoma undergoing videolaparoscopic adrenalectomy.

MATERIALS AND METHODS

The study was performed between January 1998 and March 2002 in 11 patients undergoing 12 videolaparoscopic adrenalectomies. The study included patients diagnosed with pheochromocytoma, which was confirmed through dosing of serum and urinary catecholamines. Abdominal and pelvic computerized tomography was performed in 8 patients, magnetic resonance imaging in 10 patients and scintigraphy with ^{131}I -metaiodobenzylguanidine in 10 patients.

Blood collections for dosing catecholamines, adrenaline and noradrenaline, by high-pressure liquid chromatography (HPLC) were performed at the following times: T0: control before induction; T1: following the induction, laryngoscopy and intubation

sequence; T2: during the creation of pneumoperitoneum; T3: during manipulation-extraction of the pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following the intervention when the patient was extubated and hemodynamically stable.

All patients underwent preoperative cardiovascular assessments, including Doppler echocardiography and 24-hour Holter. Preparation started 15 days before the intervention by associating a alpha 1 blocker (prazosin: *alpress*® LP 5 mg/day) and a beta 1 blocker (bisoprolol: *détensil*® 10 to 20 mg/day). Three days before the intervention, an intravenous alpha 1 blocker, urapidil® (250 mg/day in continuous perfusion and hourly control of blood pressure), was started as a replacement to oral therapy and maintained until the end of the intervention. Oral pre-anesthetic medication consisted of 5 mg midazolam (short-acting benzodiazepine) associated with 0.5 mg atropine (muscarinic receptor blocker).

General anesthesia was standardized as follows: induction with propofol ($2\text{-}2.5\text{ mg/Kg}^{-1}$) and sufentanil ($0.8\text{-}1\text{ }\mu\text{g/Kg}^{-1}$) IV for control of blood pressure (BP), orotracheal intubation facilitated by cisatracurium 0.15 mg.Kg^{-1} ; maintenance with continuous perfusion of sufentanil and cisatracurium and administration of sevoflurane or isoflurane with pure oxygen. Following induction, BP was continuously monitored using an arterial catheter connected to a blood pressure meter (Baxtertm). Hydration was started with crystalloids $10\text{-}15\text{ mL/Kg}^{-1}\text{h}^{-1}$ (isotonic saline solution, Ringer solution). Ventilation was adapted in order to maintain the PCO_2 between 35 and 45 mmHg. Urapidil was maintained in a continuous infusion of 10 mg/h^{-1} until ligation of the adrenal vein. Tension peaks were defined as systolic blood pressure (SBP) over 160 mmHg, and were treated through administering nicardipine (2-4 mg) aiming to maintain SBP between 120-160 mmHg. Episodes of sinus tachycardia, as defined by a heart rate (HR) over $100\text{-}120\text{ b/min}^{-1}$, were treated by the administration of esmolol 100 mg in order to maintain the HR under 100 b/min^{-1} . Cardiovascular shock, as defined by SBP lower than 80 mmHg, was treated by administering ephedrine 3-6 mg IV.

The adrenalectomies were performed as described by Rocha et al., 2003 (8). Patients were positioned in lateral decubitus opposite the lesion. Four trocars were used - 3 10-mm and one 5-mm. The first trocar (10 mm) was introduced by "open" laparoscopy to the lateral margin of the rectus muscle of the abdomen approximately 4 cm cranial to the umbilical scar. The second trocar (10 mm) was placed on the epigastric midline. The third trocar (10 mm) was placed lateral to the first trocar, between the lateral margin of the rectus muscle of the abdomen and the anterior axillary line. The fourth trocar (5 mm) was placed lateral to the third trocar, between the anterior axillary line and the middle axillary line. The pneumoperitoneum was maintained at 12 mmHg. When the left adrenal gland was operated on, the intra-abdominal procedure started with an incision in the parietocolic gutter and dissection of two thirds of the descending colon. The spleen was withdrawn to expose the upper region of the renal cavity. The left renal vein was dissected and the adrenal vein was then identified, dissected and sectioned with metallic clips. Following this, the adrenal gland was dissected on the cleavage plane between the adrenal gland and the kidney. Arteries and occasional small accessory veins were sectioned with clips or after bipolar coagulation around the gland. The adrenalectomy specimen was removed inside an endosac (Endocath 10®) through a trocar orifice that was enlarged by 1 cm on each side. The trocar orifices were closed in 2 planes. When the right adrenal gland was operated on, the right liver lobe was withdrawn after sectioning of the triangular ligament. The renal cavity was exposed above the right colic angle. The cava vein was dissected up to the adrenal vein, which was then sectioned with clips. The following surgical times were similar to the left adrenalectomy.

The ligation of the adrenal vein was performed early, with minimal previous dissection of the adrenal gland.

To statistically analyze the results, Graphpad Prism software was employed, using non-parametric methods: Kruskal-Wallis test and Dunn's multiple comparisons test.

The statistical significance value was established at 95 % ($p < 0.05$).

RESULTS

No surgical conversion was required. The mean length of intervention was 127 min (75 to 195 min). Blood loss was between 0 and 1000 mL with a mean value of 105 mL.

The mean serum noradrenaline concentrations were significantly different ($p < 0.05$) when comparing T0 and T2 surgical times (T0: 3161 pg/mL; T2: 40440 pg/mL; $p < 0.01$), T0 and T3 (T0: 3161 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T1 and T3 (T1: 5531 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T2 and T4 (T2: 40440 pg/mL; T4: 10773; $p < 0.01$) and T3 and T5 (T3: 46021 pg/mL; T5: 2549 pg/mL; $p < 0.001$). There was no statistical difference ($p > 0.05$) when the other surgical times were compared (Figure-1).

Mean serum adrenaline concentrations were significantly different when comparing the T0 and T3 surgical times (T0: 738 pg/mL; T3: 27561 pg/mL; $p < 0.01$). There was no statistical difference ($p > 0.05$) when the other surgical times were compared (Figure-2).

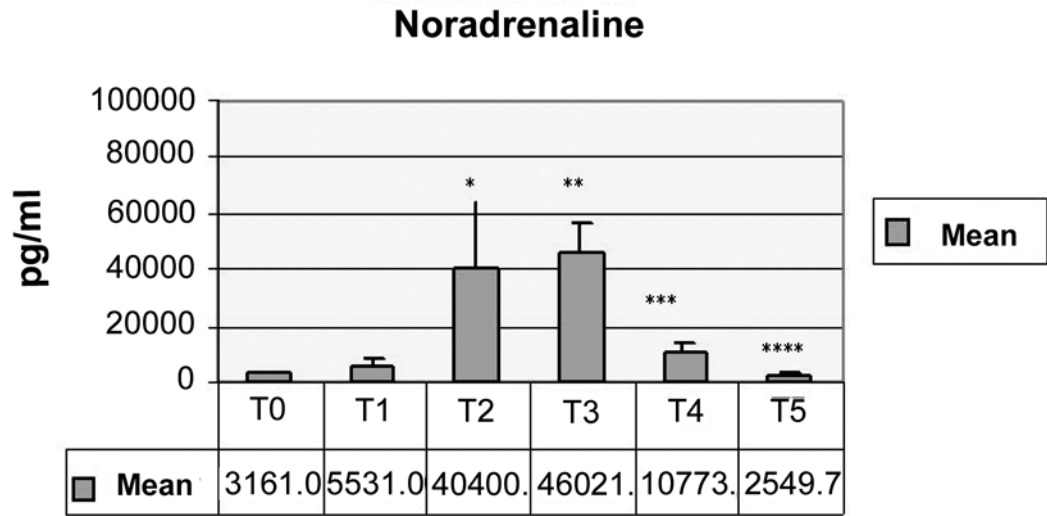
During the creation of the pneumoperitoneum (T2), 6 hypertension peaks were observed, which were associated with sinus tachycardia in 3 cases. Manipulation or exeresis of the adrenal gland (T3) caused 8 hypertension peaks associated with sinus tachycardia in 2 cases.

Patient 5 presented atrial and ventricular extrasystoles during these 2 surgical times (T2 and T3) and was treated with intravenous (IV) esmolol.

The therapeutic outcome was reached in all cases, with SBP decreasing from 178 +/- 12 to 129 +/- 11 mmHg ($p < 0.001$) and diastolic blood pressure (DBP) from 99 +/- 13 to 73 +/- 11 mmHg ($p < 0.001$).

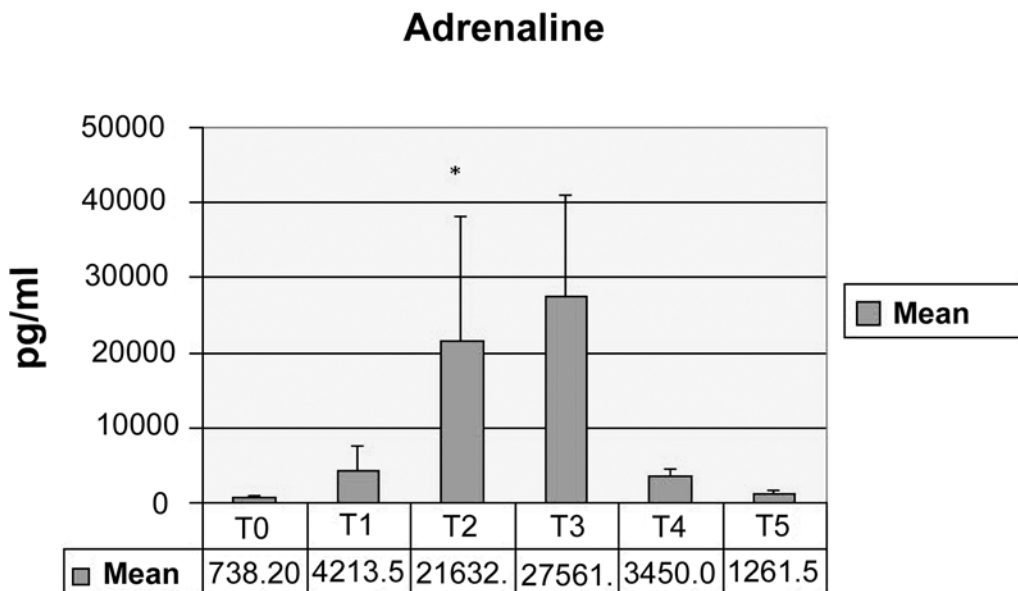
Following tumor ablation (T4), 5 hypertensive episodes were observed (Table-1).

Return to oral diet occurred between the first (D1) and the third (D3), with a mean of 1.9 days. Removal of the drain occurred between D2 and D3. Deambulation was authorized between D1 and D3 with a mean of 2.18 days. Discharge from hospital occurred between D3 and D6 with a mean hospital stay of 3.8 days. There was one damage to the adrenal vein, which was treated during surgery with no



* $p < 0.01$ comparing T2 to T0, ** $p < 0.001$ comparing T3 to T0 and T1, *** $p < 0.01$ comparing T4 to T2, **** $p < 0.0001$ comparing T5 to T3. T0: control before induction; T1: following the sequence induction-laryngoscopy-intubation; T2: during creation of pneumoperitoneum; T3: during manipulation-exeresis of pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient is extubated and hemodynamically stable.

Figure 1 – Mean serum noradrenaline concentrations at different surgical times.



* $p < 0.01$ comparing T2 to T0. T0: control before induction; T1: following the sequence induction-laryngoscopy-intubation; T2: during creation of pneumoperitoneum; T3: during manipulation-exeresis of pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient is extubated and hemodynamically stable.

Figure 2 – Mean serum adrenaline concentration at different surgical times

Table 1 – Changes in blood pressure (BP) and heart rate (HR) during creation of pneumoperitoneum (T2), manipulation-exeresis (T3), ablation of pheochromocytoma (T4) and employed measurements.

Parameters	1	2	3	4	5	6 (Right Side)	6 (Left Side)	7	8	9	10	11
BP (mmHg)	165/95	167/90	165/85	197/112	200/116	-	-	-	-	200/113	-	-
HR (b.min ⁻¹)	-	110	-	140	-	-	-	-	-	118	-	-
Bolus nicardipine (mg)	6	6	4	4	4	-	-	-	-	6	-	-
Bolus esmolol (mg)	-	100	-	100	-	-	-	-	-	-	-	-
Bolus urapidil (mg)	-	-	-	50	-	-	-	-	-	-	-	-
BP (mmHg)	180/110	165/90	177/95	166/70	180/100	-	177/112	189/107	188/106	-	-	-
HR (b.min ⁻¹)	120	110	-	-	-	-	-	-	-	-	-	-
Bolus nicardipine (mg)	4	4	6	4	4	-	-	3	2	-	-	-
Bolus esmolol (mg)	100	100	-	-	-	-	-	-	-	-	-	-
Bolus urapidil (mg)	-	-	-	-	-	-	25	-	-	-	-	-
Total dose of urapidil (mg)	70	60	40	100	60	125	-	40	40	60	50	40
BP (mmHg)	-	70/50	-	62/47	80/40	-	76/53	-	-	72/44	-	-
Bolus ephedrine (mg)	-	6	-	6	3	-	6	-	-	6	-	-

need for conversion to open surgery. This patient received transfusion of 2 units of red blood cells concentrate.

All patients were reassessed 6 months after intervention and presented normalized BP with no requirement for treatment.

COMMENTS

Laparoscopy effectively offers advantages for open surgery, that is less severe postoperative pain, early deambulation, reduced hospital stay and prompt return to daily activities (9,5). However, the surgery for management of pheochromocytoma differs from the approach used for other adrenal tumors due to the increased cardiovascular risks during the surgical intervention related to catecholamine release (2,10).

This study confirms that creation of pneumoperitoneum and tumor manipulation during videolaparoscopic ablation of pheochromocytoma are accompanied by a significant release of serum catecholamines. This release is probably responsible for hemodynamic disorders such as hypertensive peaks and sinus tachycardia.

Insufflation of pneumoperitoneum is associated with an increase in serum catecholamines, either by stimulus to mechanical compression or a change in tumor vascularization (11,12). Additionally, carbon dioxide used to insufflate the pneumoperitoneum can lead to hypercapnia, which would increase sympathetic tonus, thus changing tension levels (13).

In the cases evaluated in this study, the creation of the pneumoperitoneum produced an important release of noradrenaline into the blood stream, thus increasing its concentration when compared with preoperative values ($p < 0.01$). This release was variable and unpredictable between one patient and the other. In this series, pneumoperitoneum increased mean serum noradrenaline concentrations 12.7 times the baseline value and mean serum adrenaline concentrations increased 29.3 times the baseline value. These results are in agreement with the study by Joris et al. (7), who observed an increase in plasma catecholamine concentrations by 7 to 16 times the

baseline value following the creation of pneumoperitoneum in patients with pheochromocytoma undergoing videolaparoscopic surgery.

Manipulation and ablation of the pheochromocytoma during laparoscopy equally produce an exaggerated release of serum catecholamines (14). In the series described in this study, manipulation and exeresis of pheochromocytoma (T3) evolved with high concentrations of serum noradrenaline and adrenaline. When assessing the mean concentrations of serum noradrenaline ($p < 0.001$) and adrenaline ($p < 0.01$), statistical differences were observed between T3 and pre-induction control (T0). In this series, despite early ligation of the adrenal vein, we observed an elevation in catecholamine concentrations during dissection of the adrenal gland.

According to some authors, tension variations are less important or equivalent during laparoscopy when compared to laparotomy (11). Joris et al. (15), studied hemodynamic changes relative to pneumoperitoneum with carbon dioxide in 20 healthy patients undergoing elective laparoscopic cholecystectomy. They also assessed the changes in several neurohumoral mediators, which can contribute to hemodynamic changes, such as plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins. Peritoneal insufflation resulted in significant reduction in cardiac output, as well as an increase in blood pressure and systemic and pulmonary vascular resistance. Laparoscopy resulted in a progressive and significant increase in plasma concentrations of cortisol, adrenaline, noradrenaline, renin and vasopressin. Prostaglandins and endothelins showed no significant change. The authors concluded that vasopressin and catecholamines probably measured the increase in systemic vascular resistance during insufflation of pneumoperitoneum with carbon dioxide.

Fernandez-Cruz et al. (10), reported that, in the case of pheochromocytomas, videolaparoscopic adrenalectomy is associated with a lesser increase in catecholamine levels in peripheral circulation when compared with laparotomy, and that hypertensive peaks are related to direct manipulation of the adrenal gland. The authors compared 23 videolaparoscopic adrenalectomies (non-functioning adenomas, aldosterone-

producing adenoma, Cushing's adenoma and Cushing's disease) using insufflation of pneumoperitoneum with carbon dioxide, with 8 videolaparoscopic adrenalectomies for pheochromocytoma using insufflation of pneumoperitoneum with helium, and with eight 8 adrenalectomies performed by the conventional open approach. They studied the serum changes in catecholamine levels and correlated them with intraoperative cardiovascular disorders in patients with pheochromocytoma. There was no significant difference between videolaparoscopic adrenalectomies due to pheochromocytoma compared to videolaparoscopic adrenalectomies due to other lesions, as regards surgical time, blood loss, hospital stay and return to usual activities. Results for these parameters were unfavorable to the open adrenalectomies group. A major increase in plasma catecholamine levels occurred in patients with pheochromocytoma during tumor manipulation in the videolaparoscopy group (17.4 times for adrenaline and 8.6 times for epinephrine) and in the open surgery group (34.2 times for adrenaline and 13.7 for noradrenaline). Cardiovascular instability was associated with open surgery only.

Among the studied cases, in 6 out of 12 adrenalectomies (50%), hypertensive peaks occurred during the creation of pneumoperitoneum (T2) and in 8 out of 12 adrenalectomies (66.6%), hypertensive peaks occurred during manipulation and exeresis of the gland. These hemodynamic changes occurred simultaneously with an increase in catecholamine levels during the creation of pneumoperitoneum and manipulation / exeresis of the gland.

Two independent predictive factors for perioperative morbidity are the secreting characteristic of the tumor, and its size (16). An excessive and unpredictable peroperative catecholamine release can lead to a serious clinic condition associated with malignant hypertension, mydriasis, pulmonary edema (17) and even acute heart failure (18).

Despite the association between the creation of pneumoperitoneum (T2) and manipulation (T3) of the adrenal gland with an increase in serum rates of noradrenaline and adrenaline, the adrenalectomies were performed with low morbidity. A laparoscopic exeresis of pheochromocytoma can be performed, but it requires proper preoperative preparation and careful

perioperative anesthetic surveillance of blood pressure and occasional cardiac arrhythmias. The preoperative preparation is intended to decrease cardiovascular morbidity and includes alpha adrenergic blockade and, if required, beta adrenergic blockade. Hypertensive peaks in pheochromocytoma are related to the stimulation of alpha 1 receptors (19). In the series under study, preoperative control was achieved by previous blockade of alpha 1 receptors by prazosin and urapidil. Beta adrenergic blockade is not systematic and depends on the presence of associated tachycardia (19).

Two problems occur during pheochromocytoma surgery, and they require opposite solutions: 1) the catecholamine release during tumor manipulation leads to a risk of paroxysmal hypertension and episodes of sinus tachycardia, which can be effectively treated by associating nicardipine (calcium channel antagonist) and esmolol (selective beta blocker); 2) the significant decrease in catecholamine levels following tumor ablation can, contrarily, cause severe hypotension, which can be worsened by the persistent effects of alpha 1-antagonist drugs that have been introduced during preoperative preparation (19). Thus, the use of alpha 1-antagonists (Urapidil®) available for injection with short half-live and short action can be used during the preoperative period, offering a potential solution to both problems (20).

In a series with 8 patients, Joris et al. (7) used alpha 1-adrenergic blockers for preoperative preparation. During the intervention, they used an infusion of nicardipine (calcium channel blocker) for treating and preventing increases in blood pressure. Six of the 8 patients (75%) showed increased blood pressure higher than 25% of the baseline value during the creation of pneumoperitoneum. The authors reported that hemodynamic changes were easily treated through a continuous infusion of nicardipine associated with a beta blocker. The authors stated that no episode of acute hypotension (blood pressure lower than 60 mmHg) was observed in the 8 patients, probably because they had received vasodilators and/or were normotensive before surgery.

In the present series, during 12 adrenalectomies, 5 of the patients (41.6%) had hypotensive episodes and systolic blood pressure lower than 80 mmHg, and were treated by administering bolus ephed-

drine and volume reposition with crystalloids. However, no patient in this series presented pressure levels under 60 mmHg. Episodes of hypotension were related to the decrease in serum catecholamine concentrations observed after ablation of the gland. Serum noradrenaline concentrations, following adrenal ablation (T4), significantly decreased ($p < 0.01$) when compared with serum noradrenaline levels during creation of pneumoperitoneum (T2). When compared at T4 and T2, the decrease in serum adrenaline concentrations was not significant, probably due to the reduced number of study cases and the large variation in serum adrenaline concentration among the patients.

This study is in agreement with data from the literature, showing that videolaparoscopic adrenalectomy is feasible for management of pheochromocytomas and presents a low morbidity rate. The creation of pneumoperitoneum and the manipulation of the adrenal gland are related to an increase in serum catecholamines concentrations, and the ablation of the pheochromocytoma is related to a decrease in noradrenaline concentrations. In some cases, the changes in serum catecholamine concentrations correlate with hemodynamic disturbances, which, however, were easily treated.

CONCLUSION

The barotrauma promoted by installing the pneumoperitoneum with a pressure of 12 mmHg in patients with pheochromocytoma induced a significant increase in serum noradrenaline concentrations. In patients with pheochromocytoma undergoing videolaparoscopic adrenalectomy, surgical stress during manipulation of the adrenal gland promoted significant increases in serum concentrations of noradrenaline and adrenaline. The serum noradrenaline concentrations significantly decreased following ablation of the pheochromocytoma when compared with serum concentrations during creation of pneumoperitoneum and manipulation of adrenal gland.

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EDITORIAL COMMENT

The authors are to be congratulated for their excellent paper on laparoscopic surgery for pheochromocytoma but, in fact, the authors' overall conclusions were already expected.

Many papers concur that during adrenal manipulation (either laparoscopic or open), an increase in serum catecholamine usually occurs, with the possibility of hemodynamic events (1-5). As well, other papers have already shown the effects of pneumoperitoneum on the intra-abdominal vasculature - namely an increase in vascular resistance, a decrease in venous drainage and consequently, transient renal

and liver dysfunction, intestinal congestion and increased serum catecholamine release. After desufflation, all parameters return to normal levels (6-10).

Unfortunately, there was no open adrenalectomy control group in order to compare the results.

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LAPAROSCOPIC SURGERY FOR TREATMENT OF INCISIONAL LUMBAR HERNIA

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ABSTRACT

Objective: To present results obtained with laparoscopic correction of incisional lumbar hernia in patients with minimum follow-up of 1 year.

Materials and Methods: We prospectively studied 7 patients diagnosed with incisional lumbar hernia after physical examination and computerized tomography. We used laparoscopic transperitoneal access through 3 ports. One polypropylene mesh was introduced in the abdominal cavity and fixed by titanium clamps to the margins of the hernia ring following release of the peritoneum.

Results: All cases were successfully completed with no conversion required. Mean surgical time was 120 minutes and discharge from hospital occurred between the 1st and the 2nd postoperative days. There were no intraoperative complications or hernia recurrence in any case. Postoperatively, we had 2 minor complications: one case of seroma that resolved spontaneously after 60 days and one patient presenting lumbar pain that persisted until the 3rd postoperative month. The return to usual activities occurred on average 3 weeks following intervention. Of the 7 patients, 6 were satisfied with the esthetical and functional effect produced by the procedure.

Conclusions: The surgical correction of incisional lumbar hernia by laparoscopic access is an excellent option for a minimally invasive treatment, with adequate long-term results.

Key words: lumbar region; hernia; surgical procedures, operative; laparoscopy

Int Braz J Urol. 2005; 31: 309-14

INTRODUCTION

Lumbar hernias are not common, with 2 weak sites existing in the region: the superior (Grynfeltt-Lesshaft) and inferior (Petit) lumbar triangle. All others are known as diffuse lumbar hernias, which are usually associated with conventional extraperitoneal lumbar access (1).

Some surgical repair procedures have been described; the most frequently used being either the open technique with primary closure or the use of prosthetic material. Open surgery requires a large incision and extensive exposure and dissection of the herniated area. Additionally, the margins of the her-

nia ring are poorly defined and often require a peritoneal opening for establishing its limits (2,3).

Despite the wide use of the laparoscopic techniques for treating ventral abdominal hernias, a few services have reported sporadic cases using the laparoscopic approach for correction of lumbar defects. Preliminary results suggest that this technique shows advantages concerning patient recovery, especially in shorter hospital stays and prompt returns to normal activities (3-6).

This study aims to present and discuss the long-term results of the laparoscopic repair for incisional lumbar hernias.

MATERIALS AND METHODS

Patient Selection and Follow-up

From January 2002 to January 2004, we prospectively studied 7 patients with incisional lumbar hernias who had undergone previous lumbotomies. Diagnosis was obtained by physical examination, including palpation of the ring's margins, and documented through computerized tomography (Figure-1). Patients with any formal contraindication for laparoscopic surgery, coagulation disorders or connective tissue disease were excluded from the study.

Variables pertaining to patients were described and analyzed, such as age, gender, body mass index (BMI), cause of previous lumbar incision such as data relative to the procedure and patient's outcome, such as surgical time, blood loss, analgesic requirements, complications, conversion rate, hospital stay, recovery time until returning to normal activities, and functional and esthetic features.

All included patients were followed up by our outpatient service 7, 30, 90, 180 days and finally 1 year following surgery, when a patient satisfaction questionnaire was applied and a control computerized tomography was performed to objectively document the results. The minimal follow-up time for including the results in this study was 1 year.

Surgical Time

Laparoscopic repair with transperitoneal access was used in all cases. Antibiotic prophylaxis was performed with cefalotin. Patients were placed in right or left lateral decubitus according to the side of herniation and the table was inclined 60 degrees. The first 10-mm Hasson trocar was inserted through the umbilical incision under direct viewing (Figure-2). The cavity was then insufflated through the access trocar with CO₂, until a tension of 15 mm Hg was reached. Immediately afterwards, the 0 degree optics was introduced and the cavity was inspected to check for the presence of the hernia ring. The herniation area was transilluminated through the peritoneal cavity in order to plan the proper size of the polypropylene mesh (Figure-3).

The second 5-mm port was placed under direct viewing at the mid-clavicular line 2 cm below

the umbilical scar, and the third 12-mm port (suited for the stapler) was placed at the midline between the navel and the xiphoid process (Figure-2).

The peritoneum was released while medially withdrawing the colon that is typically included in the defect in order to expose the entire hernia ring (Figure-4). External palpation of the wall can help to accurately delimitate the defect. The surgical table must allow the patient to be arranged in many different positions for complete dissection of the defect.



Figure 1 – Computerized tomography showing the abdominal wall defect in the lumbar region.

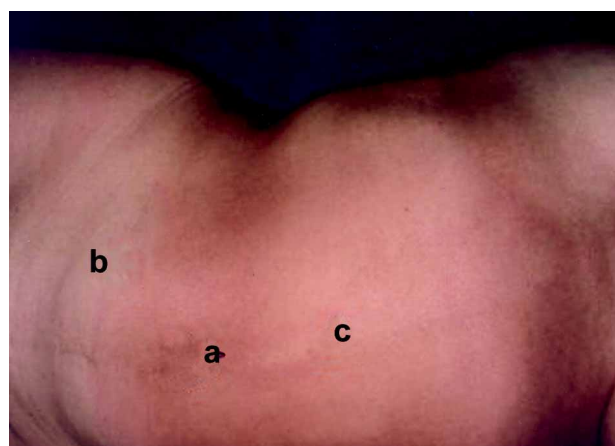


Figure 2 – Position of the ports in the abdominal region for repair of incisional lumbar hernia: a = 10-mm trocar at the umbilicus; b = 5-mm trocar at mid-clavicular line, 2 cm below the umbilicus; c = 12-mm trocar at midline between umbilicus and xiphoid process.

Subsequently, the mesh was inserted into the cavity through the 12-mm trocar and fixed on the wall by an articulate hernia “stapler” using titanium clamps at the margins of the defect (Figure-4). Fixation limits are paravertebral musculature posteriorly, the costal arch superiorly, the iliac spine inferiorly and the abdominal wall musculature anteriorly. During this procedure, CO₂ tension was reduced to 7-10 mm Hg in order to make the fixation of the mesh easier. Next, the entire mesh was covered by the previously dissected peritoneum and clamped to the wall to prevent it contacting the intestinal loops. Finally, the

cavity was reviewed, the ports were removed and the incisions were closed. No drain was left close to the mesh.

RESULTS

Mean age was 52 years (40 - 65), with BMI from 20-25 (5 cases) and 26-30 (2 cases).

The wall defects ranged in size from 6 x 8 cm to 10 x 15 cm (mean 8 x 12 cm).

Three patients were male and 4 were female, with 4 cases occurring on the left side and 3 cases

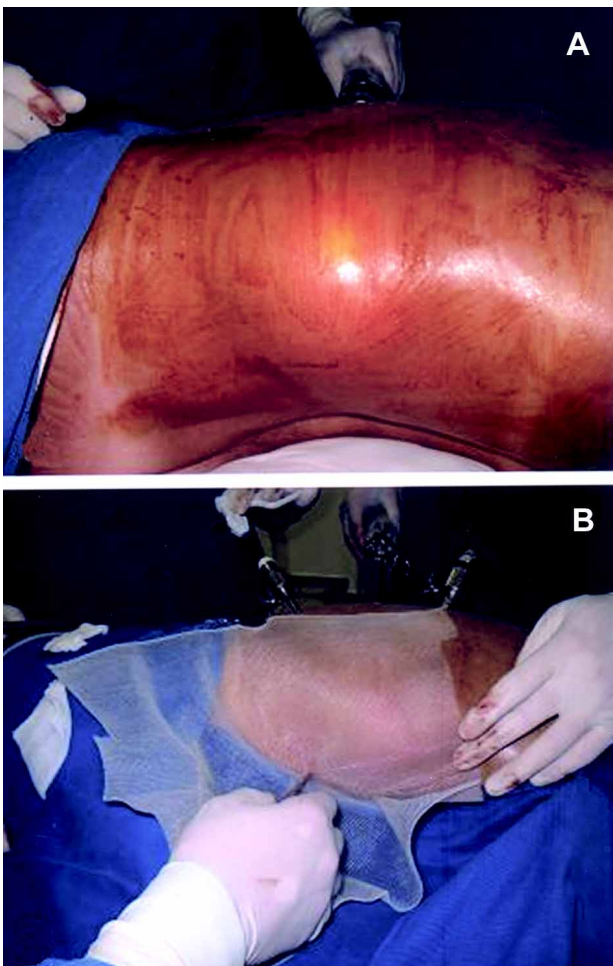


Figure 3 – A) Transillumination of herniation area through the peritoneal cavity. B) Planning of polypropylene mesh size.

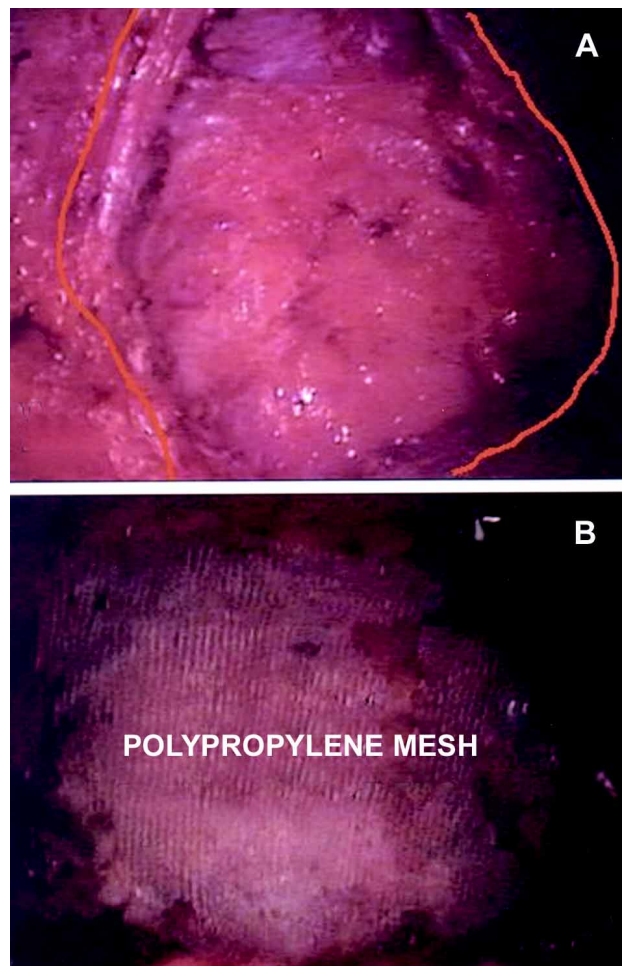


Figure 4 – A) Dissected hernia ring. B) Mesh fixed to the wall with titanium clamps on the defect's margins.

on the right side. In relation to the surgery that caused the previous lumbar incision, there were 3 cases of nephrectomy for kidney donation, 2 cases of nephrectomy due to renal tumor, 1 case of nephrectomy due to hydronephrosis and 1 case of pyelolithotomy.

All procedures were successfully completed by laparoscopic access. During laparoscopic inspection it was possible to distinctively assess the size of the hernia ring and anatomical structures involved in the hernial defect in all patients. The polypropylene mesh was easily inserted into the cavity and fixed by titanium clamps to the ring margins through the 12-mm port.

Surgical time ranged from 90 to 150 minutes (mean 120). There were no intraoperative complications and mean blood loss was 70 mL (50 - 80). Analgesia was obtained using only dipyron on the first postoperative day in 6 cases. Discharge from hospital occurred on average 12 to 36 hours (mean 24) following surgery. Patients returned to their usual activities 2 to 5 weeks after surgery (mean 3).

As far as postoperative complications were concerned, we found 2 minor complications, specifically one case of seroma that resolved spontaneously after 60 days and one female patient presented lumbar pain that lasted until the 3rd postoperative month. This case, which was interpreted as neuropathic pain, required treatment with major analgesics, tricyclic anti-depressants and corticoids for symptom improvement. Probably, a clamp used for fixating the mesh was applied to some nervous bundle at the posterior abdominal wall.

We did not observe a recurrence of hernia in any of the patients during a mean follow-up of 12 months.

The control tomography performed 1 year after surgery revealed good positioning of the mesh that had been fixed by clamps and repair of the defect in all patients (Figure-5). The esthetic and functional aspect of the defect as reported by the patient was very adequate in 6 out of 7 cases when compared with the preoperative aspect. One patient who presented muscular atonia at the incision's anterior portion before surgery was partly satisfied with the esthetic result.

COMMENTS

Lumbar hernias are relatively rare, with a little more than 300 cases found in the literature (1,2,7). They can be classified into congenital (10 - 20%) or acquired (80 - 90%) hernias. Acquired hernias are divided into 2 types – spontaneous and traumatic (incisional) (1,2,4).

The present study included patients with acquired traumatic lumbar hernias secondary to lumbar incision for conventional renal surgery. Though the classical lumbotomy is still largely used in our country, the increasing use of laparoscopic and percutaneous surgery for treating surgical conditions of the kidneys and adrenal glands will certainly reduce the occurrence of such complications.

In general, lumbar hernias are diagnosed using clinical criteria (6). The main complaint of patient is the perception of a reducible tumor with solid consistency in the incision area, which can be accompanied by lumbar discomfort. Recent publications describe the importance of computerized tomography to identify the hernia, demonstrating in detail the anatomy and differential diagnosis with other pathologies (1,6,8). The computerized tomography was an important diagnostic method for identifying, confirming and objectively documenting the hernia in this study.

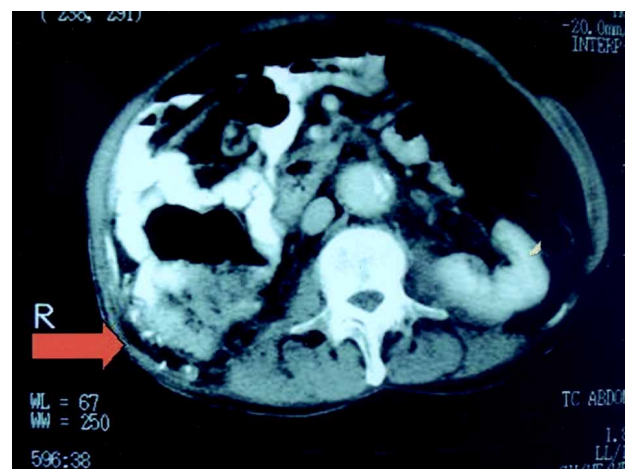


Figure 5 – Control tomography performed 1 year after surgery evidenced good positioning of the clamp-fixed mesh and repair of hernial defect.

When untreated, lumbar hernia can reach gigantic proportions, thus increasing the risk of incarceration (25%) and strangulation (8%) (6). The hernial content can include the epiploon, small or large bowel, spleen and the kidney itself (1).

If permitted by the patient's general condition, the lumbar hernia always has surgical indication with several techniques being described in the literature. Due to its rarity, there is no standardized technique. The difficulty in delimiting the margins of the fascial defect, the weakness of the involved structures, the participation of a bone element, and the surgeon's expertise are all elements taken into account during surgical planning (1,6).

The open technique for reconstruction of lumbar hernias requires a large incision, which is often associated with more severe pain, a longer convalescence period and increased morbidity (1,4). For the conventional repair of such hernias, natural structures from the region itself or synthetic materials (made of polypropylene or polytetrafluoroethylene) can be used. Results described for surgery without mesh have been poor, probably due to the low tensile quality of the local tissues, which is why the repair with synthetic material has been preferred (1,4,5).

With the intention of reducing the morbidity observed with the conventional technique while maintaining the results from open surgery with mesh, the laparoscopic access has been recently described.

Using the expertise in repair of ventral hernias that has been accumulated in many centers, the same principles could be applied to lumbar hernias as well. Initial experiences have shown significant advantages of the laparoscopic approach over conventional surgery. The majority of studies describing this technique has reported low morbidity, less significant pain and earlier returns to normal activities (2,4,6). Other studies have confirmed that this access promotes optimal visualization of the ring's limits, is safe and simple, and is considered a minimally invasive procedure (2,3,9).

The repair of lumbar hernia by laparoscopic approach was first published in 1997 by Heniford et al. (7). The following year, Arca et al. (4) published the first results from experience with 7 patients with lumbar hernias treated by the laparoscopic approach.

The authors concluded that there was improved visualization of the anatomical defects, reduced hospital stay, and no recurrence in this sample during a 15-month period.

In the present study, we observed an excellent exposure of structures and achieved perfect anatomical visualization of the hernia ring. There was little postoperative pain, reduced mean hospital stay, and the return to usual activities occurred promptly. During the 12-month follow-up period, no recurrence of herniation was evidenced. In one case, the posterior hernial defect was repaired, but patient satisfaction was not completely achieved due to atonia of the abdominal wall secondary to a nervous lesion occurring after the lumbotomy.

Among the small number of published studies on laparoscopic repair of lumbar hernias, none of them has described significant complications (2-7). Comparative studies between the open and laparoscopic approach reported in the literature refer only to the surgical treatment of ventral incisional hernias. There are no such studies involving lumbar herniation, which, in a certain way, does not allow us to definitely conclude which access is best (10,11). Our impression, however, is that the laparoscopic repair seems to have advantages concerning the visualization of the hernial defect and the postoperative recovery.

CONCLUSIONS

The laparoscopic repair of incisional lumbar hernia is a minimally invasive procedure with moderate complexity, which promotes adequate functional and esthetic results. It provides excellent exposure and definition of the wall defect limits, mild postoperative pain, short hospital stay and early return to normal activities. If comparative studies confirm the superiority of the laparoscopic approach in relation to the open technique, the laparoscopic procedure could become the method of choice for repair of lumbar hernias.

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EXTENDED COMPLICATIONS OF URETHROPLASTY

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ABSTRACT

Introduction: An extensive study of complications following urethroplasty has never been published. We present 60 urethroplasty patients who were specifically questioned to determine every possible early and late complication.

Materials and Methods: Retrospective chart review of urethroplasty patients between August 2000 and March 2004. An "open format" questioning style allowed maximal patient reporting of all complications, no matter how minor.

Results: 60 patients underwent 62 urethroplasties (24 anterior anastomotic, 19 buccal mucosal and 10 fasciocutaneous, 9 posterior anastomotic) with mean follow-up of 29 months. Early complications occurred in 40%, but only 3% were major (rectal injury and urosepsis). Early minor complications included scrotal swelling, scrotal ecchymosis and urinary urgency. Late complications occurred in 48%, but only 18% were significant (erectile dysfunction, chordee and fistula). Late minor complications included a feeling of wound tightness, scrotal numbness and urine spraying. Fasciocutaneous urethroplasty caused the most significant complications, and buccal mucus urethroplasty the least, while also resulting in the lowest recurrence rate (0%).

Conclusions: Serious complications after urethroplasty (3% early and 18% late) appear similar to those reported elsewhere, but minor bothersome complications appear to occur in much higher numbers than previously published (39% early and 40% late). While all the early complications were resolved and most (97%) were minor, less than half of the late complications were resolved, although most (82%) were minor. These complication rates should be considered when counseling urethroplasty patients, and generally tend to support the use of buccal mucosal onlay urethroplasty as it had the lowest rate of serious side effects.

Key words: urethra; urethral stricture; surgery; complications

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INTRODUCTION

Urethroplasty has excellent success rates against urethral stricture (1-5), that far exceed that seen with direct visual internal urethrotomy (DVIU) and dilation (6,7). The total impact of urethroplasty on the patient is unknown as an extensive study of complications after urethroplasty has not yet been published. We present our experience with 60 ure-

throplasty patients especially questioned so as to determine every possible early and late complication.

MATERIALS AND METHODS

A retrospective chart review of 60 consecutive patient who underwent 62 urethroplasty operations between August 2000 and March 2004, including 24 anterior anastomotic, 19 ventral onlay buccal

mucosal graft, 10 fasciocutaneous onlay flap, and 9 posterior anastomotic urethroplasties. In 2 patients, multiple simultaneous procedures were performed: 1 patient had a proximal buccal graft plus distal fasciocutaneous flap, another had a proximal anastomotic plus distal fasciocutaneous flap. The patient mean age was 46 years (18 to 78 years) with a mean follow-up of 29 months (10 to 53 months).

Patients' records were reviewed regarding stricture cause, stricture length determined by retrograde urethrogram (RUG), location, type of urethroplasty, early complications, results of postoperative urethrogram, postoperative flow rates, late complications and stricture recurrence. Strictures ranged from 0.5 to 11 cm in length (mean 2.8 cm) and etiology, location, and treatments varied (Table-1). All spontaneous complaints were meticulously recorded. Further "open format" questioning allowed maximum

patient reporting of all complications, no matter how minor. Each patient was asked, "Is there anything at all bothering you after surgery?" Later, they were prompted with "Is there anything else you can think of?" Finally, they were specifically prompted for complaints concerning voiding, sexual function, wound problems, and mouth problems (after buccal graft harvest).

All patients were operated on by the same surgeon (RAS). All patients received perioperative antibiotics and were free of urinary tract infection on the day of surgery. Standard techniques for urethroplasty were followed, including meticulous tissue handling, watertight closure, loop magnification and careful high lithotomy positioning.

RESULTS

Overall, early complications occurred after 40% of operations and late complications occurred after 48%. Early complications were major in only 3% of cases (rectal injury and urosepsis). The majority of early complications were minor (scrotal swelling ,scrotal ecchymosis and urinary urgency) and all resolved.

Not including stricture recurrence, late complications were major in 18% of cases (erectile dysfunction - ED, chordee and fistula). Only 9/25 (36%) of the patients with minor late complications (feeling of wound tightness, scrotal numbness and urine spraying) resolved spontaneously or with medication. Stricture recurrence occurred after 10% of operations.

Among patients with anterior anastomotic urethroplasty, 25% and 54% had early and late complications respectively (Table-2). None of the patients had early major complications and 5/24 (20%) of them had late major complications. For patients with posterior urethroplasty, 56% (early) and 44% (late) had complications, and 2/9 (22%) patients had late major complications (Table-3). For buccal mucosal onlay patients, 37% had early and late complications. 1/19 (5%) of the early and 0/19 (0%) of the late patients had serious complications (Table-4). Fasciocutaneous urethroplasty patients had 60% early and late complications. 1/10 (10%) and 4/10 (40%) of the patients had serious early and late complications respectively (Table-5).

Table 1 – Etiology of urethral strictures, location and type of urethroplasty, overall early and late complications in 60 patients with 62 urethral strictures.

Etiology of Stricture	N	(%)
Balanitis xerotica obliterans	1	(2)
Congenital	1	(2)
GU instrumentation	10	(17)
Inflammatory	11	(18)
Trauma	16	(27)
Unknown	21	(35)
Total	60	(100)
Location of Stricture	N	(%)
Prostato-membranous	1	(2)
Membrano-bulbar	8	(13)
Penile	12	(19)
Bulbar	41	(66)
Total	62	(100)
Type of Urethroplasty	N	(%)
Anastomotic	24	(39)
Buccal mucosal onlay	19	(31)
Fasciocutaneous	10	(16)
Posterior	9	(15)
Total	62	(100)

EXTENDED COMPLICATIONS OF URETHROPLASTY

Table 2 – Anterior anastomotic urethroplasty complications, n = 24.

Early Complications	N (%)	Late Complications	N (%)
Minor Complications		Minor Complications	
Failure to void	1 (4)	Perineal hypoesthesia	1 (4)
Retrograde urethrography leak	1 (4)	Post void leak	4 (17)
Mild scrotal tenderness	1 (4)	UTI	1 (4)
Foley fall out	1 (4)	Penile pain	1 (4)
Scrotal ecchymosis	1 (4)	Scrotal pain	1 (4)
Urgency (self limiting)	1 (4)	Scrotal scar	1 (4)
All	6 (25)	Wound discomfort	1 (4)
None	18 (75)	Irritative LUTS	1 (4)
		Stream spraying	1 (4)
		Ejaculatory dysfunction	1 (4)
		All	10 (42)
Major Complications		Major Complications	
None	24 (100)	Chordee	1 (4)
		Erectile dysfunction (Viagra responsive)	4 (17)
		All *	5 (21)
		Recurrence	2 (8)

* 2 patients had both minor and major complications

Table 3 – Posterior anastomotic urethroplasty complications, n = 9.

Early Complications	N (%)	Late Complications	N (%)
Minor Complications		Minor Complications	
Failure to void	1 (11)	Scrotal pain	1 (11)
Retrograde urethrography leak	1 (11)	Post void leak	1 (11)
Scrotal swelling	1 (11)	All	2 (22)
Scrotal ecchymosis	2 (22)		
Epididymitis	1 (11)		
Urgency	1 (11)		
All	5 (56)		
None	4 (44)		
Major Complications		Major Complications	
None	9 (100)	Chordee	1 (11)
		Erectile dysfunction	1 (11)
		All	2 (22)
		Recurrence	0 (0)

EXTENDED COMPLICATIONS OF URETHROPLASTY

Table 4 – Buccal mucosal onlay urethroplasty complications, n = 19.

Early complications	N (%)	Late Complications	N (%)
Minor Complications		Minor Complications	
Hematuria	1 (5)	Hand numbness	1 (5)
Retrograde urethrography leak	3 (16)	Perineal hypoesthesia	1 (5)
Scrotal hematoma	1 (5)	Post void leak	2 (5)
Small wound dehiscence	1 (5)	Scrotal hyperesthesia	1 (5)
Wound tightness	1 (5)	Stensen's duct squirting	
All	7 (37)	Saliva out of mouth when eating	1 (5)
		UTI	1 (5)
		All	7 (37)
Major Complications		Major Complications	
Urosepsis	1 (5)	None	19 (100)
		Recurrence	0 (0)

COMMENTS

Early and late effects of urethroplasty, including complications, have not been extensively reported in the literature. They are usually discussed as part of

broader reports of operative outcomes that generally concentrate on rates of surgical success, and only discuss the most easily recognized complications such as erectile dysfunction and incontinence. Compared to these other studies, our data indicate a high degree

Table 5 – Fasciocutaneous urethroplasty complications, n = 10.

Early Complications	N (%)	Late Complications	N (%)
Minor Complications		Minor Complications	
Epididymitis	1 (10)	Penile pain	1 (10)
Foley fall out (replaced)	1 (10)	Penile shortening	1 (10)
Penile ecchymosis	1 (10)	Post void leak	5 (50)
Penile swelling	1 (10)	Stress incontinence	1 (10)
Penile skin necrosis	1 (10)	Urine spraying	1 (10)
UTI	1 (10)	All	6 (60)
Retrograde urethrography leak	2 (20)		
All	6 (60)		
Major Complications		Major Complications	
Rectal injury	1 (10)	Chordee	2 (20)
All	1 (10)	Temporary fistula	2 (20)
		All *	4 (40)
		Recurrence	4 (40)

* 4 patients had recurrence and late complications

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Table 6 – Comparing complications after anterior anastomotic urethroplasty in this study to 168 patients reported at the University of California San Francisco, Santucci et al. (ref. 2).

Complication	Santucci et al. (%)	Present Study (%)
Thigh numbness	2	0
Small wound dehiscence	1	0
Scrotal hematoma	< 1	0
Erectile dysfunction	< 1	17
Catheter dislodgment	< 1	9
Wound infection	< 1	0

of patient complaints, likely because our method of inquiry encouraged the voicing of all possible concerns, and, in this method, some minor issues that would not be considered true “complications” are reported. When other centers determined complication rates by direct inquiry, the reported rates of complications also increased. In a report of ED after anterior anastomotic urethroplasty from a single center determined first by chart review, (2) then later by patient questionnaire, (8) ED rates rose from < 1% to 27%.

Overall, 40% of our patients had early complications and 48 % had late complications. The complication rate differed by urethroplasty type, as has been previously reported (9,10). For example, in our series the rate of serious complications after anterior anastomotic urethroplasty was 21%, while that for fasciocutaneous onlay urethroplasty was 40%. This corresponds to results already published. Andrich et al. (11) reported a significantly higher rate of complications after fasciocutaneous urethroplasty (33%) compared to anastomotic urethroplasty (7%).

Table 7 – Comparing complications after fasciocutaneous urethroplasty in this study to 84 patients reported at the Institute of Urology in London, Andrich et al. (ref. 11).

Complication	Andrich et al. (%)	Present Study (%)
Erectile dysfunction	2	0
Post-void dribbling	28	50
Diverticulum	12	0
UTI	5	0
Fistula	3	20
Chordee	3	20
Recurrence	21 (at 5 years)	40

Table 8 – Reported complications after anterior anastomotic urethroplasty.

Reference	N	Mean Follow-up (months)	Early Complications (%)	Late Complications (%)	Recurrence Rate (%)	All Complications (%)
Lindell et al. (1993), ref. 14	49	48	-	10	4	-
Schlossberg (2000), ref. 15	130	45	-	-	2	8
Santucci et al. (2002), ref. 2	168	70	6	-	5	-
Current study	24	26	25	54	8	-

EXTENDED COMPLICATIONS OF URETHROPLASTY

Table 9 – Reported complications after posterior urethroplasty (for posterior urethral distraction defects).

Reference	N	Approach	Mean Follow-up (Months)	Early Complications (%)	Late Complications (%)	Recurrence Rate (%)
Mundy (1996), ref. 16	82	Perineal*	60	Urgency 66 Stress Incontinence 37 Impotence 26	Impotence 7 **	12
Morey & McAninch (1997), ref. 17	52	Perineal and transpubic	> 12 months	-	-	11
Flynn (2003), ref. 1	109	Perineal *	64	-	-	5
Current study	9	Perineal	26	56	44	0

* Procedures including inferior pubectomy and supra-corporal re-routing of urethra. ** Permanent erectile dysfunction.

Table 10 – Reported complications after buccal mucosal onlay urethroplasty.

Reference	N	Approach	Mean Follow-up (Months)	Early Complications (%)	Late Complications (%)	Recurrence Rate (%)
Kellner et al. (2004), ref. 18	23	Ventral	50	9		13
Kane et al. (2002), ref. 19	53	Ventral	25	6		6
Pansadoro et al. (2003), ref. 4	65	Ventral and dorsal	41	6	8	3
Elliott et al. (2003), ref. 3	60	Ventral	47	0		10
Andrich et al. (2001), ref. 5	29	Ventral	60		21	14
Andrich et al. (2001), ref. 5	42	Dorsal	60		17	5
Fichtner et al. (2004), ref. 20	32	Ventral	> 60		13	13
Present study	19	Ventral	19	42	37	0

Only 2 series report complications with enough detail to compare directly to our data. Complications after anastomotic urethroplasty were published from University of California-San Francisco (UCSF) (2) (Table-6) and detailed complications of 84 fasciocutaneous urethroplasty were published from the Institute of Urology in London (Table-7) (11). The UCSF series showed a comparable degree of nuisance complications but they differed in their makeup (Table-6) and showed a much lower rate of ED than seen in our series. This may be due to incomplete questioning of the patients, as this rate climbed sharply when this group later specifically queried the patients about erectile dysfunction (8). The London series also showed some of the same complications we have seen (such as post void dribbling), while in their series urinary tract infection (UTI) and urethral diverticula were seen there, but not in our data. In general, we

report a significantly higher overall rate of complications than that reported elsewhere, even when minor complications are not counted (Tables-8, 9, 10, 11).

Minimal urinary leakage after voiding was common and may be an expected result of decreased urethral elasticity as a result of stricture disease or its treatments. It is so common that likely all patients should be warned before urethroplasty surgery, as surgery seems to cause or unmask it clinically in a certain percentage.

Complications of Positioning

We had positional complications in only one patient (2%) who had temporary hand numbness. None of our patients reported thigh numbness. Previous reports have generally shown a higher percentage of positional complications than seen in our series, ranging between 10-20% (12,13). We attribute

Table 11 – Reported complication post fasciocutaneous urethroplasty.

Reference	N	Type of Urethroplasty	Mean Follow-up (months)	Early Complications (%)	Late Complications (%)	Recurrence Rate (%)	All Complications (%)
Andrich et al. (2003), ref. 11	84	fasciocutaneous	120			31	33
Andrich et al. (2003), ref. 11	84	fasciocutaneous	60			21	
McAninch & Morey (1998), ref. 21	54	fasciocutaneous	41			13	
El-Kasaby et al. (1996), ref. 22	29	fasciocutaneous (for stricture and complex hypospadias)	19				17
Morey et al. (2000), ref. 23	15	fasciocutaneous (Q flap)	43 (in 13)			13	33
Lindell et al. (1993), ref. 14	18	Quartey	48			6	67
Present study	10	fasciocutaneous	26	60	60	40	60

our low rates to surgery times that were kept as short as possible and the evolution of meticulous positioning protocols over time using multiple aids including a gel-padded bean bag, sequential compression devices, compression stockings, and arm padding, all which have been previously described (2).

Success Rates

Success rates varied by urethroplasty type (Tables-2, 3, 4, 5, 12). Ventral buccal mucosal onlay had the highest success rate (100%), even when used against reasonably long strictures (mean stricture length was 3.4 cm). Posterior anastomotic urethroplasties also had a 100% success rate over the observation period. The next most successful was anterior anastomotic urethroplasty (92%) for mean stricture length of 1.6 cm. Fasciocutaneous urethroplasty had the lowest success rate (60%) and was of course used only against the longest strictures (mean 5.7 cm).

Limitations

This study has 2 limitations. The first is that some groups have small numbers (9 patients in the posterior anastomotic group) but overall we believe it gives a good overview of the expected sequellae of a wide range of urethroplasty surgery operations. The second is that it is retrospective in nature, and while we understand the theoretical advantage of prospective versus retrospective studies, it is not certain that a prospective study would give any more accurate results than we have obtained here.

CONCLUSION

Meticulous follow up of post urethroplasty surgery patients shows a high percentage of early and late complications, although many of these are minor in scope. Serious complications (3% early and 18% late) appear similar to those reported elsewhere, but minor bothersome complications appear to occur in much higher numbers than previously published (39% early and 40% late). All early complications were resolved and most (97%) were minor, but less than half of the late complications were resolved and a lower percentage (82%) was minor. A full reckoning of the

Table 12 – Urethral stricture recurrence in urethroplasty patients and its management.

Success Rate and Postoperative Recurrence Management	N (%)
Anterior Anastomotic Urethroplasty	24 (100)
No recurrence	22 (92)
Recurrence treated with single DVIU	1 (4)
Recurrence treated with two DVIU	1 (4)
Buccal Mucosal Onlay Urethroplasty	19 (100)
No recurrence	19 (100)
Fasciocutaneous Urethroplasty	10 (100)
No recurrence	6 (60)
Recurrence awaiting treatment	1 (10)
Recurrence treated with two DVIU	1 (10)
Recurrence treated with three DVIU	1 (10)
Recurrence treated with perineal urethrostomy	1 (10)
Posterior Anastomotic Urethroplasty	
No recurrence	9 (100)

DVIU = direct visual internal urethrotomy

impact of urethroplasty surgery, including these minor complaints that nonetheless bother the patient will help the patient and surgeon understand the full implications of planned urethroplasty surgery.

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EDITORIAL COMMENT

This is an interesting retrospective analysis of extensive early and late complications after urethroplasties performed by the same experienced surgeon (RAS). Although the manuscript tried to add new information to the literature of complications after urethral surgery, several concerns and issues have to be considered.

Unfortunately, the 60 consecutive patients enrolled in the analysis cannot be considered a homogeneous group. The authors included patients with anterior and posterior urethral strictures, with different etiologies, with a wide range in length, and, furthermore, they used different techniques. No surgery was performed for repairing strictures in patients with hypospadias failure and no dorsal onlay buccal mucosa grafts were done in this series. Ruling out these 2 conditions could represent a significant limitation to reporting complications. I suggest that the main criteria for studying early and late complications are a homogeneous group of patients chosen according to selective criteria.

Other points of interest include the relatively small sample size, which the authors correctly mention in the discussion, and the short-term follow-up. The mean follow-up was reported to be 29 months with a range between 10-53 months. Long-term follow-up (5 years) is important in estimating the rates of recurrence (late complications). The longer and more you follow patients after surgery, the less you will be satisfied with your results, although these results are considered quite good after 2 years.

To the reader, the method of studying the complications appears vague, excessively subjective and imprecise. The authors investigated only the local perineal and urethral complications, forgetting the oral complications after buccal mucosa graft (BMG), which they performed on 19 patients. BMG has emerged as safe and reliable material for urethral reconstruction but the morbidity associated with harvesting BMG is still an open problem (1). Recently, Barbagli investigated the early and late complications after BMG harvest from a cheek in a homogeneous series of 90 patients (2). He used a closed questionnaire administered by telephone by a neutral person

not on the staff of the hospital, which included 6 questions designed to investigate the early (first 10 post-operative days) complications and 14 questions to investigate the late ones. The early complications were bleeding (4%), pain (21%) and swelling (42%). The main late complication was perioral numbness for 1 month (34%), while no significant discomfort due to the scar, difficulty with mouth opening, difficulty in smiling or changes in the face physiognomy were reported.

In conclusion, the choices that are available to reconstruct the urethra are continuously developing and focused attention is required to old and new concepts. The successful management of urethral strictures, which in other words means an increase of long-term positive outcome and a low rate of complications, is demanding for reconstructive surgeons and it depends on different factors, including surgical skill as well as the right criteria for patient and surgery selection. Certainly, the use of a fasciocutaneous flap or graft should not compromise penile length, should not cause chordee and should not affect penile appearance. Oral morbidity should be considered after BMG in order to avoid permanent late sequel in mouth function. Finally, sexual function can be placed at risk by any urethral surgery and any dissection, especially for posterior urethral reconstruction, should avoid interference with the neurovascular bundles to the penis.

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EDITORIAL COMMENT

Limiting Complications from Urethroplasty

Complications from urethral reconstruction may occur either in relation to the local, technical nature of the repair (re-stenosis, dribbling, spraying, scrotal numbness, skin necrosis) or to high lithotomy positioning (lower extremity compartment syndrome, neuropraxia, rhabdomyolysis). There is no question that expertise in urethral reconstruction reduces the incidence of both conditions and that longer strictures are more problematic than short.

The most important thing we have done to reduce position-related complications has been to avoid prolonged leg elevation at all costs. Our comprehensive literature review on this subject published in 2000 (reference 12 in the article) indicated clearly that high lithotomy-related complications occur predominantly during procedures lasting 5 hours or longer. We have since adopted a “5-hour rule” for high lithotomy positioning that has completely eliminated this problem in our practice. For complex cases, we proceed in a distal-to-proximal manner with the patient supine, elevating the legs only when necessary to reach the perineum. In panurethral reconstructions, we often re-prep and re-drape at the halfway point after repositioning.

Grafts are better than penile skin flaps for bulbar urethral reconstructions because they are equally efficacious and much more efficient technically. By harvesting the buccal grafts at the beginning of the case with the patient in the supine position, the legs may be elevated, again, only when exposing the perineum.

To reduce stricture recurrence from anastomotic and posterior urethroplasty, the key is to adequately excise all periurethral fibrotic tissue. I like to use multiple traction sutures in the scar to “lift” it out (as taught by Dr. McAninch) in a way that a 28F bougie passes easily. Tension-free anastomosis is accomplished by extensively mobilizing the distal urethral segment from its scrotal attachments, especially on its ventral aspect where no blood supply exists.

To reduce stricture recurrence from graft and flap procedures, the question that must be asked is, “What am I patching on to?” I suspect many failures occur due to an inadequate urethral plate and often try to “salvage” a deficient plate by mobilizing, excising, and/or grafting until the plate is approximately 1 cm wide.

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PATHOLOGICAL EXTENSION OF PROSTATE CANCER AS DEFINED BY GLEASON SCORE ON BIOPSY

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ABSTRACT

Introduction: Based on the importance of the Gleason score on the behavior of prostate adenocarcinoma, this study attempts to predict the extension of prostate adenocarcinoma pre-operatively, as defined by the Gleason score on biopsy, in individuals who will undergo radical prostatectomy.

Materials and Methods: We selected 899 individuals who underwent retropubic radical prostatectomy from 1988 to 2004. Clinical and pathological data obtained in the preoperative period were retrospectively analyzed through digital rectal examinations of the prostate, initial serum PSA levels and pathological data provided by biopsy. The Gleason score on biopsy was assessed and divided into 3 groups: 2 to 6, 7, and 8 to 10, and correlated with the possibility of the disease being confined to the prostate.

Results: From the 899 selected patients, 654 (74%) showed Gleason scores of 2 to 6, 165 (18%) had a score of 7 and 80 (9%) had scores of 8 to 10 on biopsy. The likelihood of confined diseases, extraprostatic extensions, invasion of seminal vesicles and lymph nodal involvement were respectively: 74%, 18%, 8% and 0.8% for a Gleason score of 2 to 6, 47%, 30%, 19% and 4% for a Gleason score of 7, and 49%, 29%, 18% and 4% for a Gleason score of 8 to 10.

Conclusion: In patients who will undergo radical prostatectomy due to prostate adenocarcinoma, a Gleason score of 7 on biopsy shows the same behavior as a Gleason score of 8 to 10 in relation to extension of disease.

Key words: prostatic neoplasms; neoplasm staging; biopsy; needle; pathology
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INTRODUCTION

The risk for progression of prostate cancer following radical prostatectomy (RP) is predicted by Gleason score, and pathological and surgical margins (1). The histological grade is regarded as a highly relevant prognostic factor (2,3), and in tumors with high Gleason score, the disease is often associated with aggressive biological behavior and risk of occult disease

(4,5). Attempting to determine the extension of the disease preoperatively is fundamental, since even tumors with a high Gleason score, but in a confined disease, present a disease-free outcome in 60% to 71% of cases (6). It is known that the recurrence of prostate cancer is higher in individuals with Gleason scores of 8 to 10 than with a score of 7, as defined by the surgical specimen. In such cases, the disease is confined in 43.1% and 9.2% for Gleason 7 and 8-10 respectively (7).

Preoperative prediction of the extension of the disease, which is determined by simply discriminating the Gleason score in the histopathology of biopsy fragments, will allow us to anticipate the possibility of extraprostatic disease in patients who will undergo RP.

Since there are no accurate data establishing if the Gleason score on biopsy could predict the location of prostate cancer (confined versus extraprostatic), this study aimed to compare prostate tumors with Gleason scores of 2 to 6, 7 and 8 to 10 as defined by biopsy, and to verify the presence of extraprostatic disease following radical prostatectomy through the pathological parameters of the surgical specimen.

MATERIALS AND METHODS

We retrospectively studied 961 patients undergoing retropubic radical prostatectomy with bilateral selective iliac lymphadenectomy due to prostate adenocarcinoma, in the period from September 1988 to December 2002. The patient age range was from 40 to 83 years, with a mean age of 62.9 ± 7.4 years.

The study included patients whose medical records indicated the total number of fragments removed on biopsy, the number of fragments with cancer, Gleason score, PSA and pathological study of the surgical specimen. Fifty-four patients who received neoadjuvant treatment were excluded, as were another 8 who were diagnosed through endoscopic resection of the prostate or transvesical prostatectomy, thus totaling 899 patients. The mean PSA was 10.1 ± 7.7 ng/mL (ranging from 0.3 to 72 ng/mL). In relation to clinical stage, 432 (48%) patients were classified as T1c, 219 (24%) as T2a, 173 (19.3%) as T2b, 68 (7.6%) as T2c and 7 (0.8%) as T3a. The mean percentage of affected fragments was $41\% \pm 24\%$ (ranging from 5% to 100%). The mean Gleason score on biopsy was 5.8 ± 1.3 .

Pathological Assessment

All surgical specimens, consisting of prostate, seminal vesicles and obturator lymph nodes, were assessed by the same pathologist. Specimens were fixed in 10% formalin for 6 hours in average and un-

derwent a routine of measuring and weighing the gland on a digital balance with 2 decimal places of precision. Thin transversal sections were performed in the surgical margins relative to the bladder neck and the prostate apex. Using the urethra as a reference, the remaining gland had its margins stained with India ink, and was then sequentially sliced each 0.3 millimeters. Eight to 10 sections from each lobe were included for histological study. Seminal vesicles were sectioned at their base, and longitudinal sections were subsequently made for histological examination. Obturator lymph nodes were dissected and sliced for inclusion in the study.

The material underwent the usual processing in preparation for microscopic examination, with dehydration in alcohol, clearing in xylol and embedding in paraffin. Fragments were stained with hematoxylin and eosin and then analyzed under a binocular light microscope. The assessed parameters were:

Histological grade and Gleason score – The Gleason histological classification was used for assessing tumor differentiation, considering exclusively the acinar pattern.

Surgical margins – Positive margins were defined as the presence of a tumor in the surgical transection margins, as defined by the presence of India ink.

Infiltration of periprostatic tissue – Invasion of fat tissue and periprostatic neurovascular plexus was considered as non-confined disease.

Infiltration of seminal vesicles – Involvement of seminal vesicles was considered only when the tumor invaded their parenchyma, and not the adventitial area.

Lymph nodal metastases – Obturator lymph nodes containing tumor are considered as positive metastases.

Statistical analysis was performed with the qui-square test with values of $p < 0.05$ being defined as significant.

RESULTS

Table-1 summarizes the pathological data for the Gleason score on biopsy and the location of prostate adenocarcinoma. Of the 899 selected patients,

Table 1 – Gleason score on biopsy and location of prostate cancer in the surgical specimen.

Gleason Score on Biopsy	Patients	Organ-confined	Extraprostatic	Positive Seminal Vesicle	Positive Lymph Nodes
2 to 6	654 (73%)	484 (74%)	118 (18%)	50 (8%)	2 (< 1 %)
7	165 (18%)	78 (47%)	50 (30%)	31 (19%)	6 (4%)
8 to 10	80 (9%)	39 (49%)	23 (29%)	15 (19%)	3 (3%)
Total	899 (100%)	601 (67%)	191 (21%)	96 (11%)	11 (1%)

2 to 6 vs. 7 or 8 to 10 ($p < 0.05$); 7 vs. 8 to 10 ($p > 0.05$)

we observed that 654 (73%) had a Gleason score of 2 to 6. Another 165 (18%) presented a Gleason score of 7, and 80 (9%) had a Gleason score of 8 to 10, as identified by biopsy. Among the patients with a Gleason score of 7, 78 (47%) had organ-confined location, 50 (30%) presented extraprostatic invasion, 31 (19%) had involvement of seminal vesicle and 6 (4%) showed lymph nodal involvement. Those tumors with a Gleason score of 8 to 10 presented prostate-confined disease in 39 (49%) of patients, 23 of them (29%) had extraprostatic disease and 3 (3%) showed lymph nodes affected by the disease.

There was a significant difference only when comparing Gleason scores of 2 to 6 with a 7 or an 8 to 10, with no significant difference observed between the latter 2 groups.

COMMENTS

Our study showed that in individuals undergoing prostate biopsy, the presence of Gleason pattern 4 or 5 determines a risk of 51 to 53% for extraprostatic disease in the surgical specimen.

Merely dividing the Gleason score into ranges of 2 to 6 and 7 to 10 seems reasonable for predicting the extension of disease, since in univariate analysis the behavior of a Gleason score 7 was statistically identical to the behavior of patients with Gleason scores of 8 to 10. In our opinion, the similarity in findings of extraprostatic disease between 7 and 8 to 10 can be explained by the presence of a pattern of 4 or 5 (8), which is invariably present. Patients with up to 10% of pattern 4 or 5 in the surgical specimen have more than a 70% probability of becoming disease-free, while individuals with more than 50% of pat-

tern 4 or 5 present progressive disease in 82% of cases (9).

The percentage of positive fragments on biopsy correlates to tumor volume. Additionally, the presence of a 4 or 5 pattern in the surgical specimen also determines a worse prognosis concerning outcome (10), however, as we have demonstrated, the chance of identifying confined disease is the same for 7 and for 8 to 10. Moreover, we could observe that patients with a Gleason score lower than 7 present a recurrence of the disease in 13% of cases, and this rate approaches 60% with a Gleason score between 7 and 10 (11). In our sample, we showed that 49% of individuals with a Gleason score between 8 and 10 had confined disease, 19% had neoplastic involvement of the seminal vesicles, and in only 8% of patients with a score lower than or equal to 6 were the seminal vesicles affected by the tumor. There is some controversy as whether a Gleason score of 7 has a different outcome from a score of 8 to 10 in relation to confined disease and recurrence (5). As we know, the Gleason score is composed of the 2 volumetrically prevalent patterns in the specimen, thus a Gleason score of 7 can be 3 + 4 or 4 + 3. Since the percentage of pattern 4 influences whether the disease is confined or not (10), studies comparing Gleason scores of 7, 4 + 3 and 3 + 4 have been published. Chan et al. (12) observed 34.7% of confined disease in patients undergoing radical prostatectomy with a Gleason score of 7 in the surgical specimen. However, the risk of progression was 20% higher with scores of 4 + 3 than in the 3 + 4 group after a 10-year follow-up. However, in order to obtain the results, many of these studies derived from the surgical specimen and not from the biopsy (5), which may not be

equal if we calculate the difference between Gleason scores of 3 + 4 and 4 + 3 from the biopsy fragments. A study conducted by Grober et al. (13) demonstrated that there was no difference between the 2 groups (3 + 4 and 4 + 3) of Gleason score 7 on biopsy in terms of the disease being confined or not, having extraprostatic extension or showing involvement of the seminal vesicles, which agrees with our data. In fact, a score 7 on biopsy should take into account not only the first score pattern, but PSA levels and the number of positive fragments on biopsy as well (14); if we have 4 + 3 with 2 or less fragments affected by tumor in 68.7% of patients, the disease will be confined. On the other hand, if the score is 3 + 4 with more than 2 affected fragments, this number will drop to 41.1%. These data have been confirmed by Peller et al. (15) who, when comparing patients with Gleason scores of 7 and 100% positive fragments on biopsy with a Gleason score of 8 and the same number of positive fragments, were able to show agreement in 97% of cases for predicting confined disease.

When comparing our results with Tefilli et al. (7), we verified that when the Gleason score is between 2 and 6, 74% of the patients have confined disease versus 69% with non-confined disease. On the other hand, with a score of 7, we see 47% versus 43%; that is, quite similar values. However, when comparing patients with a Gleason score between 8 and 10, we found 48.8% of patients with confined disease versus only 9.2% with non-confined disease. This difference can be explained by the fact that the mean PSA in patients with a score of 7 was 12 ng/mL versus 25 ng/mL in patients with a Gleason score between 8 to 10 (7). Epstein et al. (1) found a rate of confined disease of 30% in men with a Gleason score of 7, and, of them, approximately 70% were disease-free after 10 years.

In relation to a Gleason score ≥ 8 , we found 9.5% to 31% of patients with confined disease (7). It is relevant that these patients had localized disease, because 82% of these individuals are not likely to have recurrent disease during a 5-year follow-up, despite the high Gleason score (16). Egan & Bostwick (17) demonstrated that individuals with a Gleason score of 7 had confined disease in 48% of cases versus 53% in men with a Gleason score of 8. In our

study, we found 48.8% of confined disease with a score between 8 and 10. As shown previously, there is a wide variation in results when we attempt to use isolated parameters for predicting confined disease, and this is due to several factors that are involved in prostate adenocarcinoma. Since the construction of the first nomogram for predicting confined disease using PSA, clinical stage and Gleason score, more than one parameter is used in order to reduce the probability of error (3).

CONCLUSION

It is important to consider the presence of Gleason grade 4 or 5 on prostate biopsy for planning the management of prostate cancer. In these cases, the disease is organ-confined in the pathological examination of the surgical specimen in only half the cases.

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performed the statistical analysis.*

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PROSTATE BIOPSY: IS AGE IMPORTANT FOR DETERMINING THE PATHOLOGICAL FEATURES IN PROSTATE CANCER?

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ABSTRACT

Introduction: The influence of age on the aggressiveness of prostate cancer (PCa) is controversial. This study aims to assess the influence of age in determining the pathological features of biopsies from patients diagnosed with PCa.

Patients and Methods: We selected 1422 patients with clinical suspicion of PCa; among them, 547 (38.5%) had received a diagnosis of adenocarcinoma. Patients were categorized into the following age groups: up to 50 years old, 51 to 60 years, 61 to 70 years, 71 to 80 years, and over 80 years. The evaluated variables were histological grade, presence of perineural invasion and estimate of tumor volume through measurement of the maximum percentage of tissue with cancer in one fragment and total percentage of tissue with cancer in the sample.

Results: The mean age of patients was 66.4 years, with age range from 32 to 94 years. The estimate of tumor volume by maximum percentage of tissue with cancer in one fragment ($p = 0.064$), total percentage of tissue with cancer in the sample ($p = 0.443$), and Gleason score ($p = 0.485$) were not statistically different in relation to the age groups under study. The presence of perineural invasion occurred more frequently among the 50 years and 81 years age groups when compared with patients aged from 51 to 60 and from 61 to 80 years ($p = 0.005$).

Conclusions: Age did not represent a determining factor for pathological findings concerning Gleason score and estimate of tumor volume by the variables in use.

Key words: prostatic neoplasms; age groups; biopsy; needle; neoplasm staging; pathology

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INTRODUCTION

Currently, prostate cancer (PCa) is the most frequent tumor in males and the second cause of death due to cancer (1). Following the advent of prostate-specific antigen (PSA), the diagnosis of PCa began to involve individuals from increasingly younger age groups. Thus, while only approximately 0.8 to 1.1% of cases of PCa were diagnosed in men under 50 years old during the '70s and '80s, this rate today reaches 4% of cases (2,3).

Determining the aggressiveness of PCa is fundamental for selecting the proper management, and studies assessing the influence of age on tumor aggressiveness have showed controversial results. Though most studies have historically demonstrated that younger men have more aggressive and lethal tumors (4,5), more recently other authors have pointed to a relationship between advanced age and high-grade, more voluminous lesions (6,7).

However, the majority of recent studies assessing the influence of age on pathological features

of PCa involve only patients that are candidates to curative treatments such as radical prostatectomy (RP) or radiotherapy. Such studies have shown conflicting results, since while some authors report that younger patients are more likely to have favorable pathological findings and higher chances of cure when treated by RP (2,3,6,8,9), other have demonstrated that they present similar results, or even a higher likelihood of biochemical recurrence among the oldest individuals when treated by RP or radiotherapy (10,11).

Pathological data from the biopsy, such as Gleason score, tumor volume and the presence of perineural invasion, are factors admittedly associated with the prognosis of patients diagnosed with PCa (12-17). Thus, since more and more patients from younger age groups are being diagnosed with PCa, the knowledge of different features of tumors in this group of patients gains enormous importance.

This study aims to assess the influence of age in determining the pathological features of biopsy in patients diagnosed with PCa.

MATERIALS AND METHODS

During the period from January 2001 and December 2003, we analyzed samples of prostate biopsies from 1422 patients with clinical suspicion of PCa due to an increase in serum PSA or a noticeable change during digital rectal examinations. Of these, 547 (38.5%) were diagnosed with adenocarcinoma. Among patients with this diagnosis, 245 (45%) received the definitive diagnosis of adenocarcinoma only after the slide was re-viewed, and whose initial analysis showed findings such as prostate intra-epithelial neoplasia (PIN), atypical small acinar proliferation (ASAP) or presence of adenocarcinoma in less than 5% of the entire sample. After excluding 1 patient whose Gleason score was not available, we totaled 546 patients.

For pathological analysis, fragments of prostate biopsy were placed in special cassettes and dispatched in 10% formalin. Next, they were identified in relation to biopsy location, numbered, processed for inclusion in paraffin and divided into 5- μ m sections. The same pathologist evaluated all slides and tumors were graded according to Gleason score.

Patients were categorized into the following age groups: up to 50 years of age, 51 to 60 years of age, 61 to 70 years of age, 71 to 80 years of age and over 80 years of age. Variables in use were: histological grade; presence of perineural invasion; and estimate of tumor volume by measuring the maximum percentage of tissue with cancer in one fragment, and the total percentage of tissue with cancer in the sample.

The statistical assessment was performed using the Pearson qui-square and Kruskal-Wallis tests. P values < 0.05 were considered statistically significant.

RESULTS

The mean age of patients was 66.4 years, with an age range of from 32 to 94 years. Table-1 shows the distribution of patients diagnosed with prostate adenocarcinoma in relation to the age groups. Only 5% of the patients were aged 50 years or less. The mean number of biopsied fragments was 11.3, with a range of from 1 to 31 fragments.

In relation to estimate of tumor volume, information regarding the maximum percentage of tissue with cancer in one sample fragment was available for 543 patients. The median for this occurrence was 70%, with a range of from 1 to 100%. The total percentage of tissue with cancer in the sample was available for 377 patients; the median was 12%, with a range of from 0.4% to 100%. An assessment of Gleason score was available for all patients. The median score was 7, with a range of from 4 to 10. Table-2 shows the distribution of patients according

Table 1 – Patient distribution according to age group in years.

Age Group	N Patients (%)
≤ 50	30 (5)
51 - 60	116 (21)
61 - 70	205 (37)
71 - 80	168 (31)
≥ 81	27 (5)
Total	546 (100)

Table 2 – Distribution of Gleason scores in categories of well differentiated, moderately differentiated and poorly differentiated tumors.

Gleason Score	N Patients (%)
2 a 6	214 (39)
7	156 (29)
8 a 10	176 (32)
Total	546 (100)

to scores from 2 to 6, 7 and from 8 to 10. Information concerning perineural invasion was available for 539 patients, and it was present in 137 (25%).

When assessing the relationship between age groups and the aforementioned features, we observed that, in relation to the maximum percentage of cancer in one fragment, the ≤ 50 year and ≥ 81 year age groups seem to present, on average, the same maximum percentage of cancer in one fragment, and it

appears to be higher than the percentage observed in the 51 to 80 year age group. We also observed that the 61 to 70 year age group showed the highest variability. Through the Kruskal-Wallis test, the observed differences have shown to be only marginally significant ($p = 0.064$) (Table-3).

According to the total percentage of cancer in the sample, we observed that the ≤ 50 year and ≥ 81 year age groups presented, on average, higher values than other age groups. We also observed higher variability in these 2 age groups when compared with values from other age groups. Through the Kruskal-Wallis test, no statistically significant difference was observed in the total percentage of cancer in the sample between the age groups under assessment ($p = 0.443$) (Table-4).

In relation to Gleason scores, despite 47% of patients aged up to 50 years presenting Gleason scores 2 and 6, and 48% of patients over 80 years presenting

Table 3 – Descriptive measures of maximum % of cancer in one fragment according to age group (Kruskal-Wallis, $p = 0.064$).

	Age Group (Years)				
	≤ 50	51 - 60	61 - 70	71 - 80	≥ 81
Mean	75.5%	64.6%	63.2%	65.8%	76.5%
Standard Deviation	29.5%	28.3%	32.4%	28.6%	28.1%
Median	90%	60%	70%	70%	90%
Minimum	1%	1%	1%	5%	10%
Maximum	100%	100%	100%	100%	100%
N. Observations	29	116	204	168	26

Table 4 – Descriptive measures of total % of cancer in the sample according to age group (Kruskal-Wallis, $p = 0.443$).

	Age Group (Years)				
	≤ 50	51 - 60	61 - 70	71 - 80	≥ 81
Mean	23.9%	19.7%	17.4%	18.0%	24.2%
Standard Deviation	25.3%	18.9%	18.6%	19.2%	28.9%
Median	16.5%	14.0%	10.0%	12.0%	16.0%
Minimum	1%	0.8%	0.4%	0.6%	1.3%
Maximum	100%	90%	100%	100%	100%
N. Observations	24	92	137	109	15

scores between 8 and 10, these findings were not statistically significant ($p = 0.485$), (Table-5).

In relation to the presence of perineural invasion, Table-6 shows that there was association concerning age group ($p = 0.005$). In order to assess where this association occurs, we performed the chi-square test, which demonstrated that the ≤ 50 year and ≥ 81 year age groups showed the same percentage of perineural invasion ($p = 0.621$). The 61 to 70 year and from 71 to 80 year age groups showed the same distribution of perineural invasion ($p = 0.479$). Thus, according to these results, we could say that, on average, the percentage of perineural invasion was 41% for the ≤ 50 year and ≥ 81 year age groups, 15% for the from 51 to 60 year group, and this percentage can be estimated at 26% for the 61 to 80 year group ($p = 0.001$).

COMMENTS

In the present study, the authors have demonstrated that the data from the biopsy, such as estimate of tumor volume by maximum percentage of tissue with cancer in one fragment and total percentage of tissue with cancer in the sample as well as Gleason score, were not statistically different in relation to the age groups under study. On the other hand, the presence of perineural invasion occurred more frequently among the ≤ 50 year and ≥ 81 year age groups when compared with patients aged between 51 and 60 and between 61 and 80.

Tumor volume, the presence of perineural invasion, and Gleason score are known to be associated with prognosis in patients diagnosed with PCa (12-17). There is no agreement concerning the best

Table 5 – Patient distribution according to age group and Gleason scores (chi-square, $p = 0.485$).

Age Group (Years)	Gleason			Total
	2 a 6	7	8 a 10	
≤ 50	14 (47%)	7 (23%)	9 (30%)	30 (100%)
51 a 60	52 (45%)	35 (30%)	29 (25%)	116 (100%)
61 a 70	78 (38%)	59 (29%)	68 (33%)	205(100%)
71 a 80	63 (37%)	48 (29%)	57 (34%)	168 (100%)
≥ 81	7 (26%)	7 (26%)	13 (48%)	27 (100%)
Total	214 (39%)	156 (29%)	176 (32%)	546 (100%)

Table 6 – Patient distribution according to age group and presence or absence of perineural invasion (chi-square, $p = 0.005$).

Age Group (years)	Perineural Invasion		Total
	Present	Absent	
≤ 50	11 (38%)	18 (62%)	29 (100%)
51 - 60	17 (15%)	98 (85%)	115 (100%)
61 - 70	50 (25%)	151 (75%)	201 (100%)
71 - 80	47 (28%)	120 (72%)	167 (100%)
≥ 81	12 (44%)	15 (56%)	27 (100%)
Total	137 (25%)	402 (75%)	539 (100%)

method for measuring tumor volume (18). One study analyzing 190 biopsies in men with PCa undergoing RP showed that the percentage of tissue with cancer on biopsy was the main predictive factor for post-operative biochemical recurrence, surpassing even serum PSA and Gleason score. Similarly, the percentage of tissue with cancer is an independent variable of risk for involvement of seminal vesicles and extraprostatic disease (19).

The presence of perineural invasion in the prostate biopsy specimen from patients diagnosed with PCa represents an independent variable of risk for biochemical recurrence in patients regarded as high and low risk and treated by RP or radiotherapy (16,17). One study of 381 patients with localized PCa undergoing radiotherapy has demonstrated that 5-year disease-free survival rates were 50% versus 80% in low-risk patients and 29% versus 53% in high-risk patients with and without perineural invasion respectively (16). Our study has revealed that the percentage of perineural invasion was 41% in the ≤ 50 year and ≥ 81 year age groups, 15% for the between 51 to 60 year group, and this percentage was estimated at 26% for the between 61 and 80 year group ($p = 0.001$).

Histological grade as defined by the Gleason score, together with serum PSA, is regarded as the main prognostic factor for post-operative tumor progression by many authors (12). Recently, one study of 3478 patients undergoing RP has demonstrated that 10-year disease-free survival was estimated in 77%, 64%, 50% and 32% of patients with Gleason score of from 2 to 6, 7 (3 + 4), 7 (4 + 3) and from 8 to 10 respectively (20). In our study, there was a balance between age groups and Gleason scores.

Analyses of the relationship between age and PCa aggressiveness have shown controversial results in the literature. Studies performed before the PSA era point to a relationship between younger patients and more aggressive tumors (4,5). Other authors have found no differences in recurrence rates of the disease among younger patients. One study comparing 46 patients younger than 60 years of age and 193 patients aged between 65 and 74 years of age showed that both groups had similar behavior when compared for cellular differentiation, presence of metastases and survival (10). Other authors have demonstrated that

patients younger than 50 years with PCa presented symptoms, histological grades and stages that were similar to the older population with PCa (11).

More recent studies, however, have shown that younger patients with PCa present a higher number of organ-confined tumors and better response to treatment. One study assessing the influence of age on pathological stage of 444 men with localized PCa undergoing RP has revealed that there were no age-related differences for clinical stages A1, A2 and B2; however, when patients classified as B1 (disease confined to less than 1 lobe) were assessed in relation to age, we observed a statistically significant trend towards a progressive increase in pathological stage with increasing age. A trend towards higher Gleason scores was observed in older patients as well. Mean Gleason score was 5, 6 and 7 for patients aged from 34 to 49 years, 50 to 59 years and 60 to 75 years respectively (7).

Herold et al. (21) studied the correlation between patient's age and occurrence of distant metastases in 567 patients receiving radiotherapy as definitive treatment for PCa. They split the population into a group aged up to 65 years, and another aged over 65 years. Patient's age was an independent predictive factor for metastasis on univariate and multivariate analyses, with patients older than 65 years presenting a higher number of distant metastases. Carter et al. (6) divided a population of 492 patients with T1c stages undergoing RP into groups of from 40 to 50 years (69 patients), 51 to 60 years (227 patients) and 61 to 73 years (196 patients). We observed that there was a percentage increase in a Gleason score of 7 with increasing age and similarly, higher probability of detecting disease in a potentially curable stage among younger patients. Subsequently, Khan et al. (2) analyzed 2897 patients with PCa undergoing RP and compared the under 50 years of age cases (341 patients) with 50 years or older cases (2556 patients). Younger patients showed a lower incidence of extraprostatic extension (25% versus 31%), involvement of seminal vesicles (2% versus 6%), positive surgical margins (3% versus 9%) and a trend towards higher disease-free survival rates.

The exact mechanisms explaining the characteristic differences of PCa among age groups are

not quite understood yet. Recent studies point to lower Gleason scores among younger patients, suggesting that the elderly have biologically more aggressive tumors (8). Some studies stress the difficulties for accurately staging the PCa in the elderly, since these patients have a higher frequency of benign prostate hyperplasia (BPH), and thus, younger men have more easily palpable tumors than older ones, where the lesions can be masked by BPH (7).

Biopsy studies have shown that PCa starts between the 4th and 5th decades of life and, with increasing age, the frequency of high-grade and more voluminous tumors increases as well, which are variables with prognostic significance as previously shown (22). In the present study, the fact that younger patients present tumor features similar to older patients can suggest that, in its natural history, the PCa has a more aggressive behavior from the start, contrarily to the theory that more aggressive tumors result from an evolving process of initially well-differentiated tumors over the years.

One advantage of the present study is that, contrary to recent studies assessing the influence of age on PCa, it included patients undergoing prostate biopsy with low, intermediate and high-grade tumors who subsequently received several kinds of treatment. The fact that the remaining studies involve patients that are candidates for curative treatment for cancer means that many patients with poorly differentiated tumors and some elderly patients with insignificant tumors could have been excluded from such analyses, thus restricting their interpretation.

Finally, we have concluded that age does not represent a determining factor for pathological findings relative to Gleason score and estimate of tumor volume by the variables in use, and that the presence of perineural invasion seems to occur less frequently among patients younger than 50 or older than 80 years. However, due to non-inclusion of serum PSA analysis and the small number of patients younger than 50 and older than 80 years, these results should be carefully interpreted. New studies assessing biopsies from patients with uniform distribution between the age groups should be performed in order to determine the real influence of age on PCa differentiation.

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TESTICULAR HISTOPATHOLOGICAL DIAGNOSIS AS A PREDICTIVE FACTOR FOR RETRIEVING SPERMATOZOA FOR ICSI IN NON-OBSTRUCTIVE AZOOSPERMIC PATIENTS

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ABSTRACT

Objective: Histological testicular pattern has a predictive role in the possibility of finding spermatozoa for ICSI in cases of non-obstructive azoospermia because some individuals could show residual spermatogenic sites in the testis. The aim of this study was to evaluate the sperm retrieval rate in each of the histopathological groups (hypospermatogenesis-Hypo, spermatogenic maturation arrest-MA, Sertoli cell only-SCO and testicular hyalinization) in patients assisted in our clinic.

Materials and Methods: Retrospective study from March 1997 to October 2002. We analyzed 14 patients with mean age of 34.3 ± 0.7 , with non-obstructive azoospermia. All patients were submitted to previous diagnostic biopsy (Bx) elsewhere and came to our institution for treatment. After an average of 12 months (8 - 20), they were submitted to a new Bx procedure to retrieve sperm.

Results: Previous diagnostic Bx showed the following histopathological results: 5 patients with MA, 4 with Hypo and 5 SCO. In the following Bx (for sperm retrieval) spermatozoa was found in 33% of the procedures in patients with MA, 50% in patients with Hypo and 40% of the procedures in patients with SCO.

Conclusion: Previous diagnostic Bx can help in patient counseling concerning the result of sperm retrieval.

Key words: azoospermia; testis; biopsy; histopathology; sperm injections, intracytoplasmic
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INTRODUCTION

The advent of intracytoplasmic sperm injection (ICSI) has represented a major breakthrough in the treatment of infertile men. Men with non-obstructive azoospermia could be biological fathers due to the possibility of testicular sperm extraction (1,2). High rates of sperm retrieval in ICSI procedures performed with sperm retrieved by testicular biopsy have been described (3).

Finding sperm in the testis in cases of non-obstructive azoospermia vary according to the histopathological pattern of the testis (4). The

most frequent histopathological patterns are: hypospermatogenesis (Hypo), spermatogenic maturation arrest (MA), Sertoli cell only (SCO) and testicular hyalinization (5).

The possibility of finding sperm in SCO cases is around 20%, in Hypo patients it is 80% and in MA it is around 50% (5). The aim of this work was to evaluate the retrieval sperm frequency in each of the histopathological groups in our institution.

MATERIALS AND METHODS

This was a retrospective study performed between March 1997 and October 2002. We analyzed

14 patients with mean age of 34.3 ± 0.7 years with non-obstructive azoospermia who had undergone diagnostic testicular biopsies in other centers. 12 months after the first biopsy a new procedure was performed to retrieve spermatozoa and in 12 cases the ICSI was performed simultaneously. The groups were classified according to the biopsy diagnosis: spermatogenic maturation arrest (MA), hypospermatogenesis (Hypo) and Sertoli Cell Only (SCO). Two patients underwent ICSI – one from the hypo group and one from the MA group. We performed 2 ICSI cycles and 2 biopsies each, resulting in 16 procedures for sperm retrieval.

Sperm Collection by Testicular Biopsy (TESE)

The testicular biopsy was performed after the spermatic cord was blocked using local anesthesia, specifically 2% Xylocaine without epinephrine or under endovenous sedation. Using a number 11 cold scalpel, a longitudinal incision was performed in the scrotum order to expose the testicles. Testicular compression was conducted, leading to glandular tissue herniation that was excised. The tunica albuginea was closed with monofilament nylon 5-0 sutures. Three fragments of glandular tissue were retrieved when the testicular volume was smaller than 15 cc, and 6 fragments were removed in the other cases (Figure-1). When no sperm was found in the first biopsied testicle, the procedure was performed on the other. All fragments were weighed in an OHAUS analytical standard electronic balance (USA).

The material collected was carefully dissected in a Petri dish containing human tubal fluid modified medium (HTFmod-Irvine Scientific, USA) with 2 cold scalpels (number 22). Then the material was analyzed to identify the presence of spermatozoa under optical microscope (x400). The material was kept in a sterile Eppendorf at 37°C for 3-4 hours to allow the sperm to migrate to the medium surface.

RESULTS

The average time between the previous diagnostic biopsy and the sperm retrieval for ICSI was 12 months (8-20 months). The average weight of testicular tissue excised for sperm retrieval was 0.0659 g (0.0044 to 0.1761). Sperm finding at retrieval biopsies according to the histopathological diagnosis are shown in Table-1. One patient who underwent two biopsies (sperm retrieval) for 2 different ICSI cycles had a previous biopsy with histopathological diagnosis of hypospermatogenesis and in both biopsies sperm were found. The other patient (MA group) showed one biopsy with the presence of sperm and another one with no sperm found. The average break time between those biopsy procedures was 12 months (8 to 20). After all ICSI procedures, there were 3 pregnancies (1 in the MA group and 2 in the Hypo). The sperm retrieval biopsy results are shown in Table-1 according to the histopathological diagnosis.

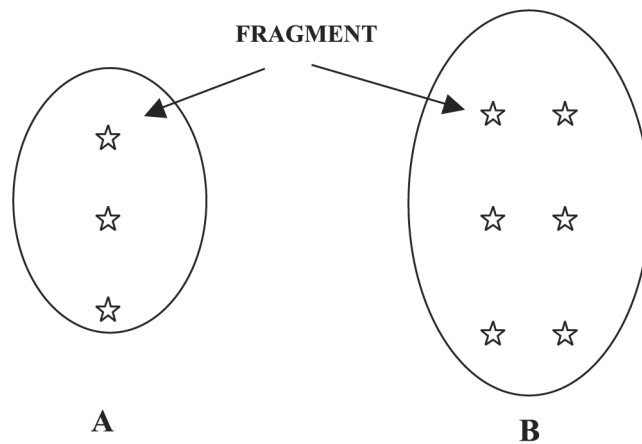


Figure 1 – Diagram of fragments retrieval according to testicle size. A) Testis volume < 15 cc; B) Testis volume > 15 cc.

Table 1 – Sperm retrieval biopsy results according to histopathological diagnosis.

	MA	Hypo	SCO	Total
Total patients	5	4	5	14
Total procedures	6	5	5	16
Presence of Spz	2	3	2	7

Spz = spermatozoa, MA = spermatogenic maturation arrest, Hypo = hypospermatogenesis, SCO = Sertoli cell only.

COMMENTS

Residual spermatogenesis sites in the testis can be found in patients with non-obstructive azoospermia; however there are as yet no defined prognostic parameters for this finding (6). Data such as testicular volume, FSH serum concentration and presence of associated male pathologies cannot be used as predictive factors of success (4). Previous data showed that age and serum FSH levels failed in foresee the presence or absence of spermatozoa in the testicular biopsy (7,8). However, techniques such as molecular markers and RT-PCR are useful in predicting the presence of testicular sperm (9-11).

Brugo-Olmedo et al. (12) showed that the B-inhibin plasma levels, as a Sertoli Cell activity measurement, could be related to the chance of retrieval spermatozoa in patients with non-obstructive azoospermia. Patients with biopsies where sperm was found presented significantly high levels. However other studies failed to correlate B-inhibin levels and the chances of sperm retrieval in the testis (13,14). According to Schoor et al. (2), a diagnostic testicular biopsy is one parameter for determining the testicular histopathology pattern and apparently it is the strongest indicator to foresee the possibility of finding sperm in the testis in the sperm retrieval procedure (7,8). Several studies have suggested that the presence of one focus of elongated spermatides or spermatozoa in a diagnostic biopsy is related to high sperm retrieval rates for ICSI (4,15).

Controversial results have been shown in non-obstructive azoospermia patients as to what is the best technique for sperm retrieval. According to Schoor et al. (2), a testis biopsy could promote scars that make

the following biopsy procedures more difficult. Sousa et al. (4) consider testicular biopsy the best method for sperm retrieval in non-obstructive azoospermic patients, considering that in testicular atrophy cases percutaneous sperm aspiration was not able to provide enough material for ICSI. Considering that spermatogenesis recovery after a biopsy procedure is slow, it is essential to avoid unnecessary biopsies (16). A maximum of 3 procedures must be performed and, whenever possible, they should be associated with cryopreservation techniques (4,2). This care reduces the risk of complications without impairing fertilization and pregnancy rates (16). In our patients showing normal testicular volume, 6 tissue fragments were retrieved from different sites and 3 fragments showed reduced testicle volume. Schlegel (17) states that the micro-dissection technique was the one that presented the best retrieval results when compared with multiple biopsy techniques, however this is not a consensus yet.

There is a discrepancy between our results and the literature on the likelihood of obtaining sperm in non-obstructive azoospermic patients; the percentage of our patients with positive sperm retrieval according to histological testicular pattern was 50% in patients with hypospermatogenesis, 33% in patients with spermatogenic arrest and 40% in patients with SCO against 80%, 50% and 20%, respectively in the literature (5). Probably the main reason for that was the small size of our sample.

Although histopathological testicular pattern plays a role in the probability of finding sperm in subsequent sperm retrieval procedures, we do not recommend it without simultaneous cryopreservation. Although this sample size was limited, it is still

important that other authors publish their data in order to allow a definition about what is the real chance of sperm retrieval in each histopathological pattern.

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EFFICACY, SAFETY AND TOLERABILITY OF SILDENAFIL IN BRAZILIAN HYPERTENSIVE PATIENTS ON MULTIPLE ANTIHYPERTENSIVE DRUGS

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ABSTRACT

Objective: To evaluate the efficacy, safety and tolerability of sildenafil among Brazilian patients with hypertension treated with combinations of anti-hypertensive drugs.

Materials and Methods: One hundred twenty hypertensive men aged 30 to 81 years old under treatment with 2 or more anti-hypertensive drugs and with erectile dysfunction (ED) lasting for at least 6 months were enrolled at 7 research centers in Brazil. Patients were randomized to receive treatment with either sildenafil or placebo taken 1 hour before sexual intercourse (initial dose of 50 mg, adjusted to 25 mg or 100 mg according to efficacy and toxicity). During the following 8 weeks, patients were evaluated regarding vital signs, adverse events, therapeutic efficacy, satisfaction with treatment and use of concurrent medications.

Results: The primary evaluation of efficacy, which was based on responses to questions 3 and 4 of the International Index of Erectile Function, showed significant differences regarding treatment with sildenafil ($p = 0.0002$ and $p < 0.0001$, respectively). In the assessment of global efficacy, 87% of the patients treated with sildenafil reported improved erections, as compared with 37% of patients given placebos ($p < 0.0001$). The other secondary evaluations supported the results favoring sildenafil. The most frequent adverse events among patients treated with sildenafil were headaches (11.4%), vasodilation (11.4%) and dyspepsia (6.5%). There were no significant changes in blood pressure measurements in both groups.

Conclusion: Sildenafil is efficacious and safe for the treatment of hypertensive patients with ED who receive concurrent combinations of anti-hypertensive drugs.

Key words: erectile dysfunction; sildenafil; hypertension; anti-hypertensive drugs

Int Braz J Urol. 2005; 31: 342-55

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for sexual intercourse (1). ED is multi-

factorial and associated with several risk factors, such as hypertension, diabetes mellitus, peripheral vascular and coronary artery disease, neurological diseases, alcohol abuse, smoking, depression and others. The prevalence of ED varies according to age and the pres-

ence of co-morbidities. In addition, the proportion of men that report ED varies from country to country (2). According to a recent survey, approximately 46% of Brazilian men report some degree of ED, which may lead to an impaired quality of life in many cases (3).

Hypertension is a public health problem of global proportions. Although national estimates are scarce and may not represent the overall population, regional surveys have shown that the prevalence of hypertension in Brazil varies from 22% to 44% (4). Hypertension is frequently accompanied by other medical problems, including dyslipidemias, diabetes mellitus, heart disease and smoking, which may also cause or aggravate ED. It has recently been estimated that 42% of American men with ED are also hypertensive (5). Men with hypertension have an up to four-fold increase in the risk of developing ED, especially with the use of drugs such as beta-blockers and thiazides, which may have ED as side effects (6,7). Among patients with hypertension, ED may decrease the quality of life, self-esteem and the relationship with a partner. Although the exact pathogenesis of ED in men with hypertension has not been fully elucidated, in many cases psychogenic factors accompany the organic abnormalities that are secondary to hypertension, thus contributing to the aggravation of ED.

Several clinical trials have demonstrated the efficacy of sildenafil in the treatment of ED with various causes (8-10). Most adverse events reported in the clinical studies of sildenafil, including headaches, flushing and nasal congestion are thought to be related to the vasodilating properties of the drug. The incidence of these adverse events increases with higher doses of sildenafil. The possibility of potentiating the effect of anti-hypertensive medications has been a major concern regarding the use of sildenafil for the treatment of hypertensive men with ED. Preliminary clinical trials have not shown clinically significant changes in blood pressure levels among patients who were treated with sildenafil and concurrent anti-hypertensive medications. There is, however, little information in the literature regarding the use of regimens of multiple anti-hypertensive drugs (11).

The objective of the present study is to investigate the efficacy, safety and tolerability of sildenafil in outpatients with hypertension and who were on treatment with combinations of anti-hypertensive drugs.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Eligible patients were men aged 18 years or older who had had a stable sexual relationship for the previous 6 months, with a clinical diagnosis of ED of at least 6 months' duration, and with hypertension that was being treated with at least 2 drugs from any of the following classes: diuretics, alpha-blockers, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium-channel blockers. To be eligible for the study, patients also had to have a score ≤ 25 in the erectile function domain of the International Index of Erectile Function (IIEF) (12). Exclusion criteria were any of the following: concurrent treatment with nitrates, the presence of any genital deformity or sexual disturbance that precluded sexual intercourse, the use of any form of treatment for ED within the 4 weeks preceding enrollment, alcohol or drug abuse, the presence of retinitis pigmentosa, degenerative retinopathy or any major medical condition, and the inability to fill in the event log or comply with the study. The protocol was reviewed and approved by the Institutional Review Boards of all participating centers, and all patients enrolled in the study provided written informed consent.

Study Design

Candidate patients were initially evaluated through a complete history, including sexual function, and a complete physical examination, including the determination of blood pressure (BP) and heart rate in sitting and in supine position. On the initial visit, patients also underwent laboratory exams (complete blood count, sodium, potassium, creatinine, glucose, transaminases, cholesterol, triglycerides, prolactin, testosterone and urinalysis) and electrocardiogram. Four weeks later, eligible patients were randomized to receive treatment with sildenafil or placebo. Randomization was achieved through computer-

generated blocks of random numbers. Sildenafil and placebo tablets had the same appearance and were dispensed in identical containers. Patients were instructed to take the study drug 1 hour before intended sexual intercourse and not more than once daily. Based on previous studies, the initial dose of sildenafil was 50 mg. In subsequent visits, this dose could be increased to 100 mg or decreased to 25 mg depending on efficacy and tolerability. Patients were evaluated 2, 4 and 8 weeks after randomization. Vital signs, the use of concurrent medications, compliance and the results obtained with the study treatment were assessed at each visit. Treatment could last for a maximum of 8 weeks.

Assessment of Efficacy, Safety and Tolerability

Patients were instructed to record in the event log the amount of medication taken and the results achieved with treatment. The intent-to-treat (ITT) population was defined as those patients who took at least one dose of a study drug and recorded at least one efficacy measurement during treatment. In addition, the sample of patients who could be evaluated was comprised of those with complete follow up and responses to the IIEF questions during the study. The assessment of efficacy was done in these patients. The primary efficacy parameter was the difference in pre-treatment and post-treatment scores for questions 3 and 4 of the IIEF. Secondary measures of treatment efficacy were the difference in pre-treatment and post-treatment scores for other questions and for the domains of the IIEF, patients' responses to the Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire (EDITS) (13) and the assessment of global efficacy, and the proportion of successful attempts at sexual intercourse. Patients were instructed to register all symptoms experienced during the study, and also to report promptly in the event of a serious adverse effect. All cases of treatment interruption were recorded, regardless of the cause leading to discontinuation.

Statistical Analysis

Based on the assumption that the minimum clinically relevant treatment difference between sildenafil (combined dose groups) and placebo with

regards to IIEF scores (questions 3 and 4) is 0.75 and that the common variance is 2.3, sample sizes of at least 65 subjects per treatment group (sildenafil and placebo) were required to detect the specified difference between the two treatment groups, with a power of 80% and a type I error rate of 5%. The comparisons between groups regarding the change from baseline in IIEF questions were assessed with unpaired Student's t test. Mann-Whitney tests were applied to compare the two groups regarding each question of the EDITS questionnaire. Comparisons between sildenafil and placebo groups regarding the behavior of BP during the study, were done using analysis of variance for repeated measurements. Multiple comparisons were based on Wald's statistics. The differences between proportions of satisfactory responses in the assessment of global efficacy were compared using the Pearson's Chi-square test. The proportion of successful attempts at intercourse was compared between the two groups using a generalized estimation equation model assuming a uniform structure for the correlation. All hypothesis testing considered a p value ≤ 0.05 as statistically significant.

RESULTS

Patient Characteristics

One hundred and fifty-three patients were recruited from seven research centers in Brazil. One hundred and twenty patients took at least one dose of the study drug; 87 of them completed the 8 weeks of treatment and could be evaluated. Table-1 shows the main demographic and clinical characteristics of the ITT sample at baseline. There were no statistically significant differences in any of these characteristics between groups. The age of the patients varied between 30 and 81 years, the time since the start of ED varied from 0.6 and 30 years, and the time since hypertension was diagnosed varied from 2 to 52 months. The etiology of erectile dysfunction, which was determined on clinical grounds, was similar between both groups, and approximately two-thirds of patients had ED of mixed etiology.

The anti-hypertensive medication most frequently utilized by the patients in both groups was a

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Table 1 – Patient characteristics at baseline (intent-to-treat sample, N = 120)

Variable	Sildenafil, N = 61 (%)	Placebo, N = 59 (%)
Age, years		
Mean	59.4	60.6
Range	35 to 79	30 to 81
Smoking	13 (21.3)	15 (25.4)
Alcohol use	30 (49.2)	30 (50.2)
Duration of erectile dysfunction, years		
Median	2.0	2.3
Range	0.6 to 24	0.6 to 30
Etiology of erectile dysfunction		
Organic	11 (18)	11 (18.6)
Psychogenic	9 (14.8)	7 (11.9)
Mixed	41 (67.2)	41 (69.5)
Duration of hypertension, months		
Mean ± standard deviation	11.7 ± 9.0	11.2 ± 9.6
Range	2 to 43	2 to 52

diuretic, followed by ACE inhibitors, calcium-channel blockers, beta-blockers and alpha-blockers (Figure-1). Patients remained on the same anti-hypertensive regimen for the whole study period. Eighty-seven

patients (44 in the sildenafil group and 43 in the placebo group) took 2 anti-hypertensive drugs, 27 patients (15 in the sildenafil group and 12 in the placebo group) took 3 anti-hypertensive drugs, and 6 (2

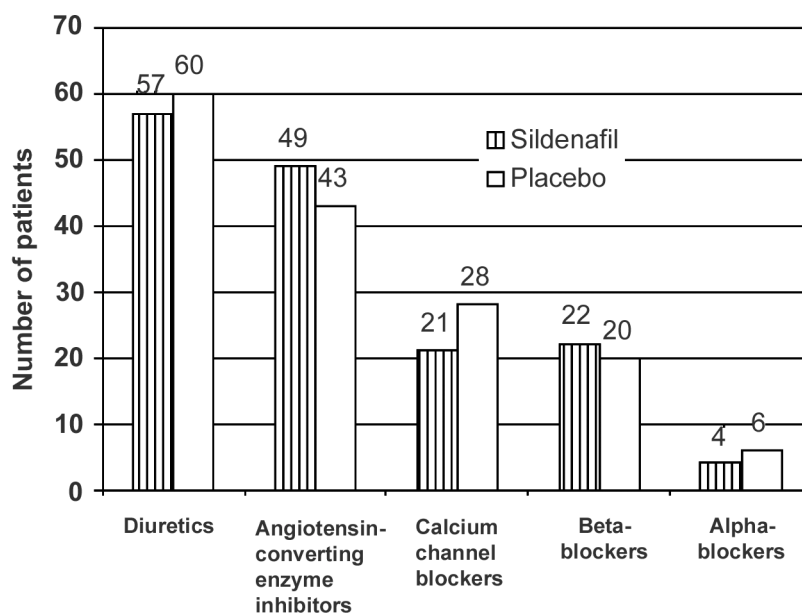


Figure 1 – Anti-hypertensive drugs in both groups.

in the sildenafil group and 4 in the placebo group) took 4 or more anti-hypertensive drugs. The most frequent co-morbidities were dyslipidemias, diabetes mellitus and ischemic heart disease. The baseline electrocardiogram was considered normal in 43% of the patients; the most frequent abnormalities in the remaining cases were arrhythmias, aberrant electric conduction and ventricular hypertrophy. There were no significant changes in the electrocardiograph readings between both groups.

Therapeutic Efficacy

At the conclusion of the study, 33 patients (54.1%) were taking 50 mg of sildenafil, 24 (39.3%) were taking 100 mg, and 4 patients (6.6%) were taking 25 mg. For patients taking the placebo, the proportions were 20.3%, 74.6% and 5.1% respectively. Compared with patients that took the placebo, patients treated with sildenafil had more ability to achieve an erection sufficient for sexual intercourse ($p = 0.0002$), and also to maintain erections during the sexual intercourse period ($p < 0.0001$) (Table-2). Similarly, the differences between the scores for other IIEF questions before and after treatment, favored the group treated with sildenafil. As shown in Table-3, with the exception of questions 6, 9 and 11 of the IIEF (frequency of intercourse, ejaculation and desire), all other differences achieved statistical significance. When the questions were grouped and the differences were analyzed according to the IIEF domain, there

was a significant difference favoring sildenafil in four of the five IIEF domains; the only domain for which no such difference was evident was the sexual desire domain (Figure-2).

The secondary efficacy analyses confirmed the superiority of sildenafil over placebo for the treatment of ED in patients who are on multiple anti-hypertensive drugs. There were significant differences favoring sildenafil in all 11 questions of the EDITS questionnaire, and all statistical comparisons between the two groups yielded p values of < 0.007 . The assessment of global efficacy showed that 87% of the patients treated with sildenafil reported improvement in their erections; this same proportion was 37% among patients that took the placebo ($p < 0.0001$). The analysis of event logs demonstrated statistically significant differences between the two groups in the proportions of successful attempts at sexual intercourse. Among patients treated with sildenafil, successful attempts were reported in 54%, 61% and 73% of the times after 2, 4 and 8 weeks of treatment. Among patients that took the placebo, these same proportions were 13%, 20% and 29% ($p < 0.0001$ for the comparison between groups at each time point).

Safety and Tolerability

Adverse Events

The analysis of safety and tolerability was based on the ITT sample of 120 patients. Twenty-

Table 2 – Mean \pm standard deviation scores on questions 3 and 4 of International Index of Erectile Function (IIFE). Evaluable sample, $N = 87$.

IIFE Questions	Sildenafil (N = 46)			Placebo (N = 41)			P
	Pre-treatment	Post-treatment	Difference	Pre-treatment	Post-treatment	Difference	
3) Penetration Ability	2.15 \pm 1.37	4.04 \pm 1.33	1.89 \pm 1.49	2.05 \pm 1.60	2.61 \pm 1.63	0.56 \pm 1.75	0.0002
4) Maintenance Frequency	2.04 \pm 1.41	3.96 \pm 1.40	1.91 \pm 1.71	1.95 \pm 1.56	2.24 \pm 1.59	0.29 \pm 1.90	< 0.0001

P values refer to comparisons between differences. IIFE, International Index of Erectile Function.

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Table 3 – Mean \pm standard deviation scores on questions 1, 2 and 5 to 15 of International Index of Erectile Function (IIFE). Evaluable sample, N = 87.

IIFE Questions	Sildenafil (N = 46)			Placebo (N = 41)			P
	Pre-treatment	Post-treatment	Difference	Pre-treatment	Post-treatment	Difference	
1) Erection Frequency	2.26 \pm 1.44	4.22 \pm 1.25	1.96 \pm 1.33	2.00 \pm 1.58	2.59 \pm 1.50	0.59 \pm 1.28	< 0.0001
2) Erection Firmness	1.98 \pm 1.34	4.09 \pm 1.26	2.11 \pm 1.39	1.80 \pm 1.36	2.27 \pm 1.50	0.46 \pm 1.43	< 0.0001
5) Maintenance Ability	2.09 \pm 1.26	4.20 \pm 1.19	2.11 \pm 1.37	2.22 \pm 1.26	2.63 \pm 1.51	0.41 \pm 1.86	< 0.0001
6) Intercourse Frequency	2.35 \pm 1.39	4.15 \pm 1.28	1.80 \pm 1.51	2.05 \pm 1.38	3.44 \pm 1.38	1.39 \pm 2.10	= 0.2902
7) Intercourse Satisfaction	2.09 \pm 1.36	4.15 \pm 1.23	2.07 \pm 1.50	1.76 \pm 1.30	2.34 \pm 1.42	0.59 \pm 1.84	< 0.0001
8) Intercourse Enjoyment	2.04 \pm 1.09	3.80 \pm 1.00	1.76 \pm 1.21	1.78 \pm 1.27	2.37 \pm 1.26	0.59 \pm 1.60	< 0.0001
9) Ejaculation Frequency	3.20 \pm 1.85	4.24 \pm 1.21	1.04 \pm 1.76	2.39 \pm 1.84	2.93 \pm 1.60	0.54 \pm 1.89	= 0.3206
10) Orgasm Frequency	2.89 \pm 1.66	4.28 \pm 1.17	1.39 \pm 1.74	2.51 \pm 1.78	2.95 \pm 1.63	0.44 \pm 2.03	= 0.0129
11) Desire Frequency	3.41 \pm 1.13	4.04 \pm 0.97	0.63 \pm 1.39	3.39 \pm 1.45	3.83 \pm 1.14	0.44 \pm 1.34	= 0.2966
12) Desire Level	2.98 \pm 0.72	3.52 \pm 0.91	0.51 \pm 0.92	3.07 \pm 1.03	3.17 \pm 0.83	0.10 \pm 1.09	= 0.0085
13) Overall Satisfaction	2.11 \pm 1.18	4.15 \pm 1.23	2.04 \pm 1.50	2.15 \pm 1.06	2.32 \pm 1.31	0.17 \pm 1.26	< 0.0001
14) Relationship Satisfaction	2.52 \pm 1.26	4.09 \pm 1.09	1.57 \pm 1.44	2.22 \pm 1.11	2.71 \pm 1.44	0.49 \pm 1.36	= 0.0006
15) Erection Confidence	2.41 \pm 0.91	3.63 \pm 1.04	1.22 \pm 0.99	2.24 \pm 1.02	2.41 \pm 1.09	0.17 \pm 1.20	< 0.0001

P values refer to comparisons between differences.

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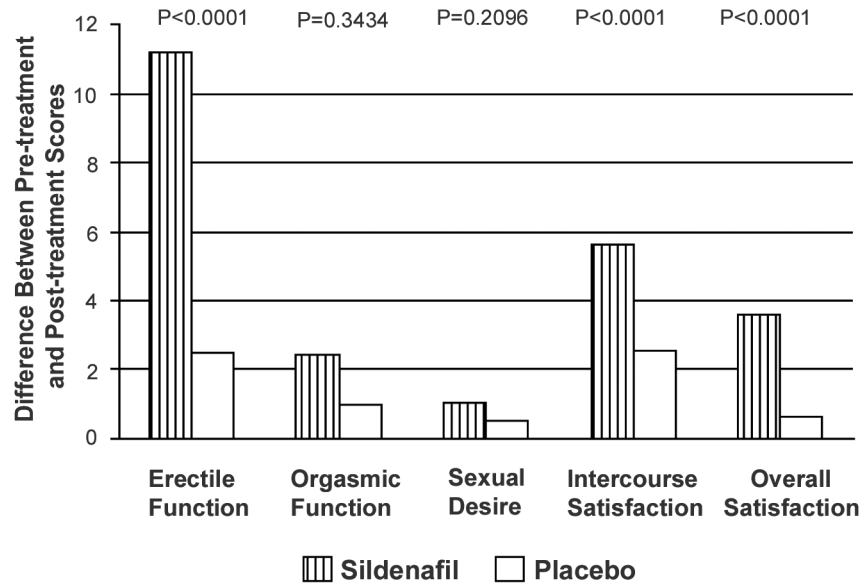


Figure 2 – Comparison between the efficacy of sildenafil and placebo, assessed by domains of the International Index of Erectile Function (evaluable sample, N=87). P values refer to the difference between sildenafil and placebo in pretreatment and post-treatment scores for each domain.

two patients had their treatment with the study drug discontinued. Only 3 patients (1 treated with sildenafil and 2 with placebo) had their treatments interrupted due to adverse events. In all other cases, discontinuation of treatment was due to insufficient clinical response (1 case in the sildenafil group and 7 in the placebo group) or other reasons (7 cases in the sildenafil group and 4 in the placebo group). Adverse events were registered in 82% of the patients treated with sildenafil and in 40% of the patients that took placebo. Of all these events, only 4 in each group were graded as severe. Table-4 shows the most frequent adverse events that were considered related to study drugs. Among patients treated with sildenafil, the most common adverse events were headache (11.4% of the patients), vasodilation (11.4%) and dyspepsia (6.5%). Four patients had serious adverse events according to protocol definitions (cerebrovascular accident, pulmonary edema/heart failure, atrial fibrillation/arrhythmia and polytrauma); the former 3 events occurred in patients treated with sildenafil, and the latter occurred in a patient that was taking placebo. None of these events were deemed to be re-

lated to the study drugs. The case of poly-trauma was secondary to a car accident, and this patient died during the study.

Table 4 – Adverse events occurring in 2% or more of patients (intent-to-treat sample, N = 120).

Adverse Event	N Patients (%)	
	Sildenafil (N = 61)	Placebo (N = 59)
Vasodilation or facial flushing	8 (13.1%)	2 (3.4%)
Headache	7 (11.4%)	2 (3.4%)
Rhinitis	6 (9.8%)	1 (1.7%)
Dyspepsia	4 (6.5%)	0 (0%)
Dizziness	2 (3.2%)	1 (1.7%)
Abdominal pain	2 (3.2%)	1 (1.7%)
Paresthesia	2 (3.2%)	0 (0%)
Hypertension	1 (1.6%)	3 (5.1%)
Chest pain	1 (1.6%)	2 (3.4%)
Flu-like syndrome	1 (1.6%)	2 (3.4%)
Diarrhea	1 (1.6%)	2 (3.4%)
Total	35 (57.3%)	16 (27.1%)

Behavior of the Blood Pressure (BP)

Figures-3 to 6 show patients' BP behavior during the 4 weeks of eligibility assessment and the 8 weeks of treatment, both in the supine (Figures-3 and 4) and seating (Figures-5 and 6) positions. There were no significant changes between the BP measurements when patients treated with sildenafil or placebo were compared. In both groups, there were progressive decreases in both systolic and diastolic BP readings during the study.

COMMENTS

Several organic and psychological factors interact to maintain a normal erectile function (1,14). Penile erection is a hemodynamic event that depends

on the relaxation of the smooth muscle cells of the trabeculae and arterioles of the corpora cavernosa. In response to sexual stimulation, non-adrenergic non-cholinergic nerve fibers and arteriolar endothelial cells of the penis release nitric oxide (NO), a potent vasodilator that stimulates the activity of guanylate cyclase and leads to an increase in cyclic guanosine-3',5'-monophosphate (cGMP). The ultimate effect is calcium depletion from the cytosolic space and cavernous smooth muscle relaxation. Phosphodiesterase 5 (PDE5), an enzyme that is present in the corpora cavernosa, inactivates cGMP, thus terminating NO-cGMP-mediated smooth muscle relaxation. Inhibition of PDE5 enhances penile erection by preventing cGMP degradation (15). Sildenafil is a potent and selective inhibitor of PDE5 (16).

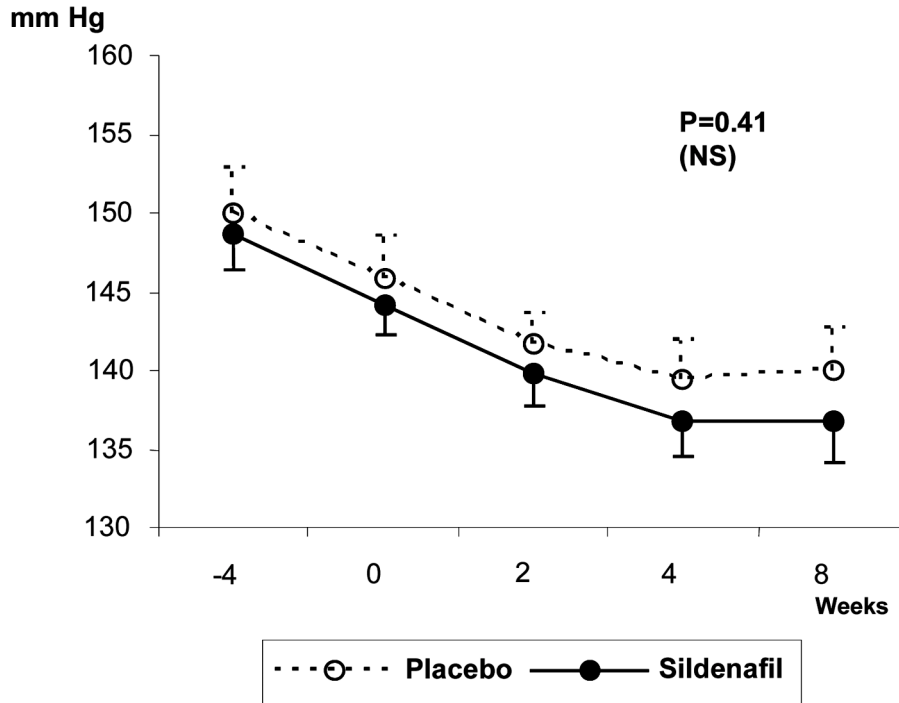


Figure 3 – Blood pressure (BP) behavior during the study. Systolic BP in the supine position. P values refer to the comparisons between sildenafil and placebo. NS = not significant.

USE OF SILDENAFIL IN HYPERTENSIVE PATIENTS

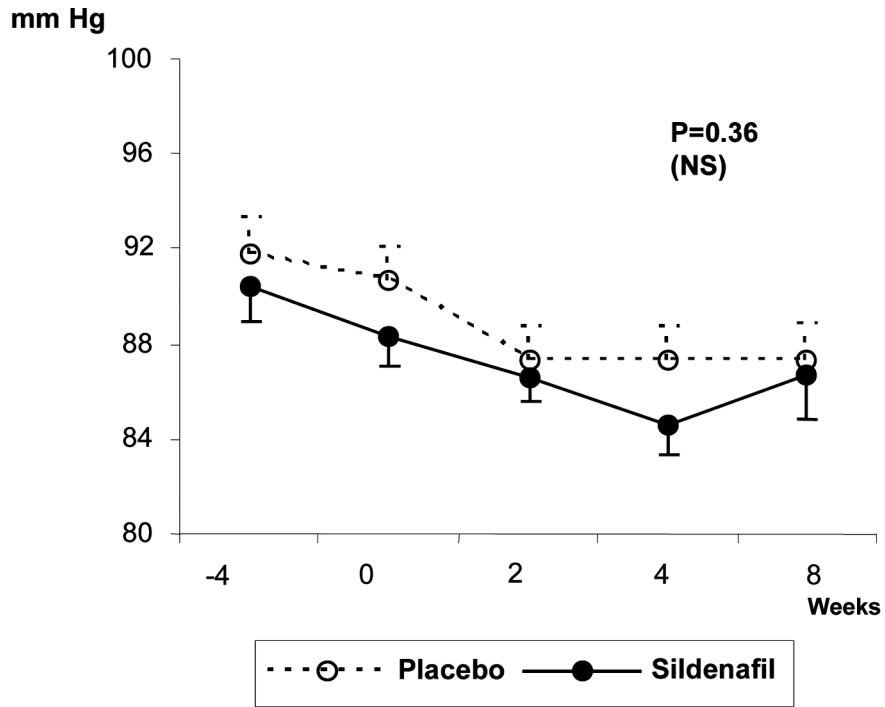


Figure 4 – Blood pressure (BP) behavior during the study. Diastolic BP in the supine position. P values refer to the comparisons between sildenafil and placebo. NS = not significant.

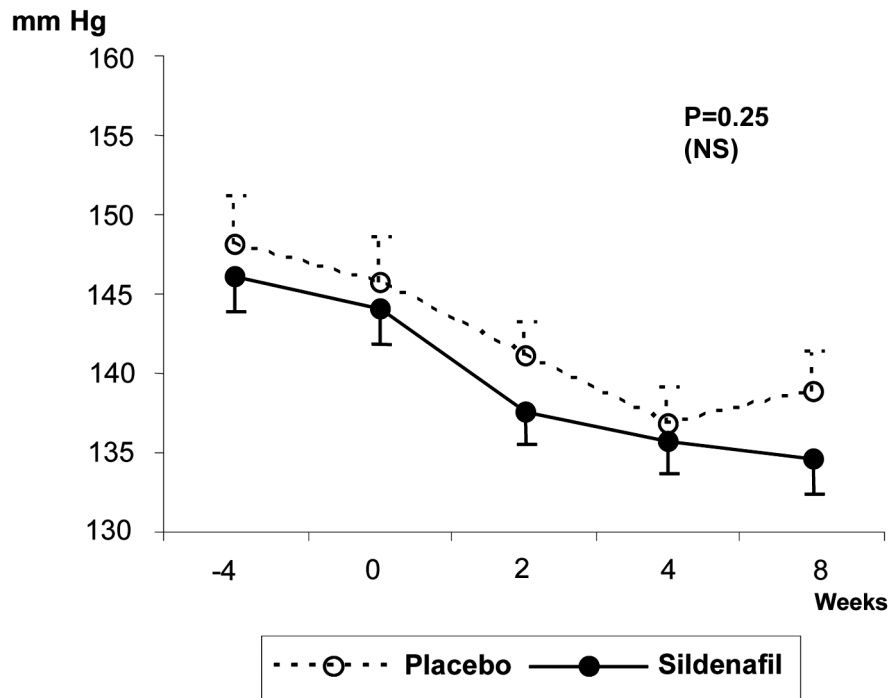


Figure 5 – Blood pressure (BP) behavior during the study. Systolic BP in sitting position. P values refer to the comparisons between sildenafil and placebo. NS = not significant.

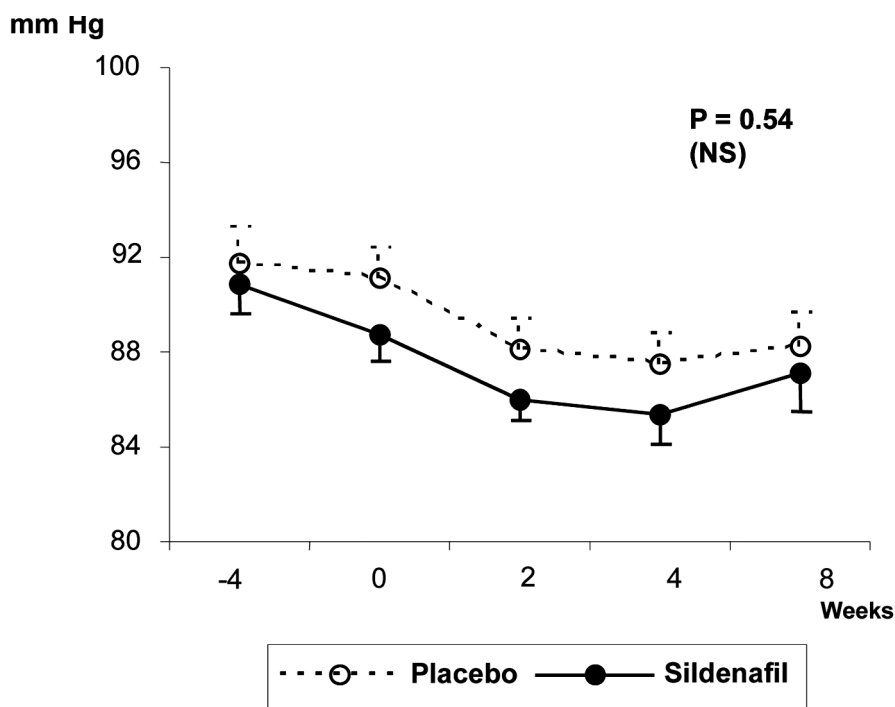


Figure 6 – Blood pressure (BP) behavior during the study. Diastolic BP in sitting position. P values refer to the comparisons between sildenafil and placebo. NS = not significant.

There is abundant evidence pointing to the relationship between ED and atherosclerosis and its risk factors. Abnormalities in blood flow to the penis, which are frequent in patients with atherosclerosis and diabetes mellitus, are a common factor underlying organic ED. Approximately 40% of patients with ED who are older than 50 years have associated atherosclerosis. It is also estimated that ED occurs in approximately 50% of patients with diabetes, regardless of the type; in these patients, the incidence of ED seems to correlate with age and the severity of diabetes (17,18). Patients with conventional risk factors for atherosclerotic coronary artery disease, such as smoking, low levels of high-density lipoprotein cholesterol and diabetes, are at increased risk for developing ED (19).

Most adverse events reported in the clinical studies of sildenafil have been dose-dependent and secondary to vasodilation; among such events, headache, flushing and nasal congestion are the most fre-

quent. The effects of sildenafil on BP have been well characterized (20-23). In physiological conditions, sildenafil may lead to a mild to moderate decrease in BP. In normotensive men, doses of 100 mg of sildenafil may decrease systolic BP by up to 8-10 mm Hg, and diastolic BP by up to 3-6 mm Hg (21). The hypotensive effect of sildenafil may also be seen among patients with hypertension, although its magnitude may not be clinically significant in comparison to pretreatment BP levels (22,23). The peak hypotensive effect of sildenafil typically occurs approximately one hour after ingestion, and coincides with peak plasma levels. In healthy men, the BP decreases induced by sildenafil return to pretreatment levels within 4 to 8 hours; these decreases are usually asymptomatic (20).

Some authors have attempted to investigate the safety of the concurrent administration of sildenafil and anti-hypertensive drugs. Most of the studies reported to date have looked at one anti-hy-

pertensive agent used in isolation. Studies with diuretics, alpha-blockers, beta-blockers, ACE inhibitors, angiotensin II receptor antagonists, and calcium-channel blockers have shown that these agents may usually be given concurrently with sildenafil with no clinically significant hypotensive effect (22). Mild (2 to 4 mm Hg) decreases in systolic and diastolic BP have been seen among patients with hypertension who were on treatment with single anti-hypertensive drugs and who took sildenafil (24). In addition, the type and frequency of adverse events seen in such patients have not differed from those that are seen among patients who are not in treatment for hypertension (24,25). Sildenafil does not seem to have pharmacodynamic interactions with anti-hypertensive drugs that act through NO-independent mechanisms (23,25,26).

There is relatively little information in the literature regarding the use of sildenafil in patients with hypertension who are being treated with combinations of anti-hypertensive drugs (11). Kloner et al. have found no difference in the frequency of adverse events in patients taking sildenafil who were on treatment with one, two or three anti-hypertensive drugs. In that study, the concurrent use of sildenafil and multiple anti-hypertensive agents led to no apparent increase in the frequency or severity of angina, myocardial infarction or other serious cardiac events (27).

In the present study, the use of sildenafil significantly improved the erectile function of Brazilian men with hypertension who were under treatment with multiple anti-hypertensive drugs. As compared with patients who took a placebo, patients treated with sildenafil had significant improvements in their ability to achieve and maintain an erection. Secondary assessments confirmed the superiority of sildenafil that led to global improvements in 87% of the patients. This proportion of improvement is similar to that seen in other studies of sildenafil, including those in patients without hypertension. The present study also confirms that sildenafil produces no significant effect on sexual desire. Importantly, our study demonstrates the safety and tolerability of sildenafil in patients with hypertension who are under treatment with combinations of anti-hypertensive drugs. Treatment with sildenafil was well tolerated, and dose adjustments during the study possibly contributed to a

reduction in the frequency of adverse events. As in other studies, headache, vasodilation and dyspepsia, typically of mild intensity, were the most frequent treatment-related adverse events. Interestingly, the effects of sildenafil on BP were not different from those produced by placebo.

CONCLUSION

In conclusion, our results indicate that sildenafil is efficacious, safe and well tolerated in the treatment of ED in patients with hypertension who are being treated with combinations of anti-hypertensive drugs.

Drs. Ari Timerman, João C. F. Braga and Marcus Malachias collaborated on the study.

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DISCLAIMER

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EDITORIAL COMMENT

Many researchers have suggested that erectile dysfunction (ED) co-exists with other diseases because they share common risk factors. Based on published studies, ED has been found in patients with hypertension, hyperlipidemia, diabetes mellitus, depression, ischemic heart disease, coronary heart disease, peripheral vascular disease etc. However, published information on the prevalence of these concurrent diseases in men with ED has been limited in terms of the number or sample size of the studies.

ED is common among men taking anti-hypertensive drugs to control blood pressure. Actually, ED could be caused either by hypertension itself, by the anti-hypertensive drugs or by the combination of both.

The impact of ED on the patient's quality of life is much more important than the impact of hypertension itself. Because of this, any well conducted study to evaluate the efficacy and safety of the 5 PDE inhibitors is very welcome.

Although this is a sponsored study, it was well designed and it is important for to emphasize that even patients receiving multiple anti-hypertensive drugs can be treated with 5 PDE inhibitors. The results found

in the present study are quite promising. Otherwise, perhaps a more reasonable success rate in such patients (presenting cardiovascular diseases) would be around 70% (1).

Furthermore, despite the knowledge that these drugs are safe even in critical patients and in doses as high as 400 mg 4 times a day (2), the expected side effects in this population seems to reach 40% (1).

In any event, the message of the study is that 5 PDE inhibitors are safe and present a high success rate even in critical patients with hypertension who are being treated with multiple anti-hypertensive drugs.

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EDITORIAL COMMENT

This well-designed study and clearly written paper is another important Brazilian contribution to the international urological literature. Previously, there was scant information on the effects of sildenafil in hypertensive patients who are taking multiple antihypertensive agents. This report demonstrates that

sildenafil is efficacious and safe for the treatment of erectile dysfunction (ED) in men taking various combinations of antihypertensive drugs. The report also demonstrates that despite its vasodilatory action, sildenafil does not complicate treatment or interfere with control of hypertension in these men.

This is important information because it might have been predicted that men with hypertension severe enough to require multiple antihypertensive agents would have more advanced ED, which is more difficult to treat successfully. In fact, analyzing the data presented in the tables, the pre-treatment scores on the erectile function domain (questions 1-5 and 15) of the International Index of Erectile Function (IIEF) were 12.26 and 12.93 in the placebo and sildenafil groups. These pre-treatment scores are slightly lower than the pre-treatment scores seen in most other sildenafil clinical trials, suggesting that the men in this study might have had slightly more severe ED than men in other

studies. The post-treatment score on the erectile function domain in the placebo group in this study rose only to 14.75, demonstrating a mild placebo effect, while the post-treatment score in the sildenafil group rose to 24.14, clearly demonstrating the efficacy of sildenafil. The score of 24.14 is somewhat higher than has been reported in most other sildenafil clinical trials, showing that sildenafil is as effective in men using multiple antihypertensive agent combinations as in many other groups of men with ED.

The authors are to be congratulated for completing an excellent study that fills one of the gaps in the international literature on sexual medicine.

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LAPAROSCOPIC TREATMENT OF REFLUXING SEGMENTAL MEGAURETER

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ABSTRACT

We discuss the case of a 13-year old boy with urinary infection who was preoperatively diagnosed with left vesicoureteral reflux associated with paraurethral saccule. Laparoscopic Lich-Gregoir anti-reflux surgery was then proposed. Intraoperatively, we observed segmental megaureter that was successfully treated by the proposed technique without ureteral modeling, contrary to the rule that respects the 3-5 times ratio between the submucous path and the ureteral diameter.

Key words: ureter; congenital abnormalities; replantation; laparoscopy
Int Braz J Urol. 2005; 31: 356-8

INTRODUCTION

The diagnosis of segmental megaureter in children is uncommon and, when treatment is required, there is no therapeutic standardization. We describe one case of primary refluxing segmental megaureter with episodes of acute pyelonephritis that was treated by laparoscopy. There was no available published work on the laparoscopic treatment of megaureter.

CASE REPORT

A 13-year-old male patient was investigated due to an episode of acute left pyelonephritis. An ultrasound of the urinary tract showed signs suggestive of scar in the left renal parenchyma and dilation of the juxtavesical ureter on the same side. Voiding cystourethrography demonstrated a low grade left vesicoureteral reflux and an image compatible with left paraureteral saccule (Figure-1).

The proposed management was by Lich-Gregoir anti-reflux surgery through transperitoneal laparoscopic approach. We performed 4 punctures

with 2 trocars measuring 10 mm and 2 trocars measuring 5 mm. During the procedure, we observed refluxing segmental megaureter instead of the paraureteral saccule as previously diagnosed.

Following ureteral dissection, we performed a long incision on the detrusor muscle and a wide lateral dissection of the bladder mucosa, and the entire dilated ureteral segment was placed in the submucous tunnel. Variable bladder fillings with saline solution made this dissection easier. The peritoneal cavity was drained by a Penrose drain for 24 hours and the vesical catheter was maintained for 48 hours. Surgical time was 180 minutes.

The patient remained asymptomatic and the control tests after 7 months demonstrated absence of vesicoureteral reflux and absence of dilation in the left kidney respectively on voiding cystourethrography and ultrasound (Figures-2 and 3).

COMMENTS

In children, megaureter can be defined as an ureter whose diameter is larger than 7 mm. Currently,

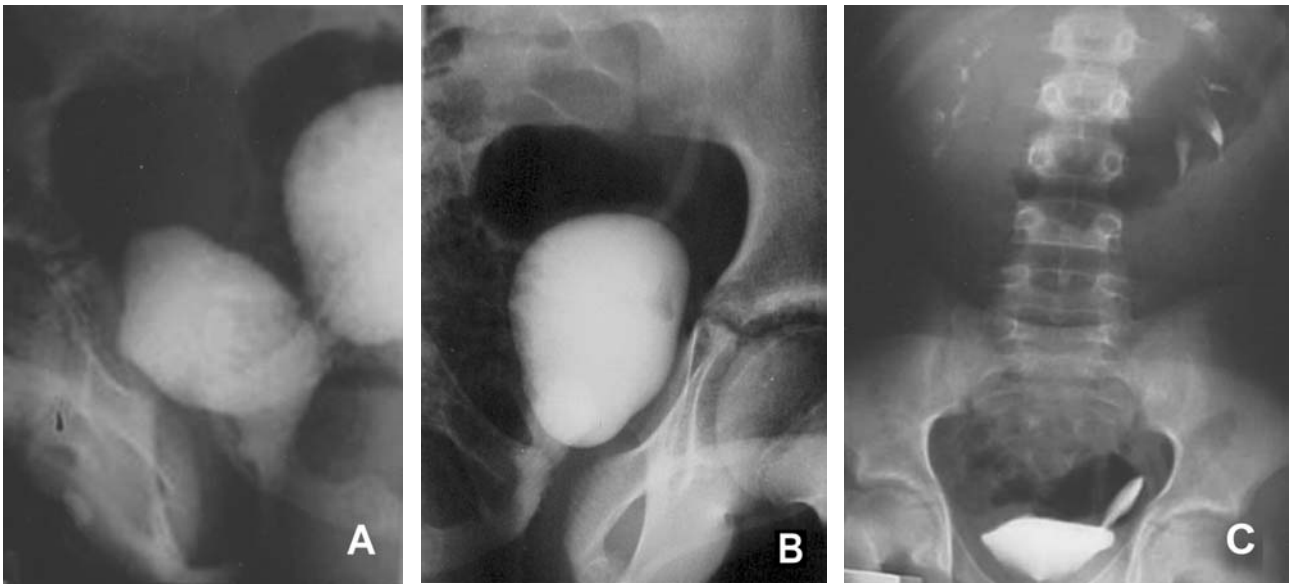


Figure 1 – A) and B) Voiding cystourethrography showing diverticular image and left vesicoureteral reflux; C) Excretory urography revealing kidneys with good function and left distal ureter with slight dilation.

megaureter is thought to be related to 20% of urological anomalies diagnosed during the prenatal period (1).

The diagnosis of refluxing megaureter is usually established by ultrasound of the urinary tract that shows ureteral dilation and is complemented by void-

ing cystourethrography. In this case, the patient also underwent an excretory urography that showed dilation in the distal ureteral segment that was milder than the voiding cystourethrography had shown.

For a successful ureterovesical replantation of refluxing megaureter, ureteral modeling is required

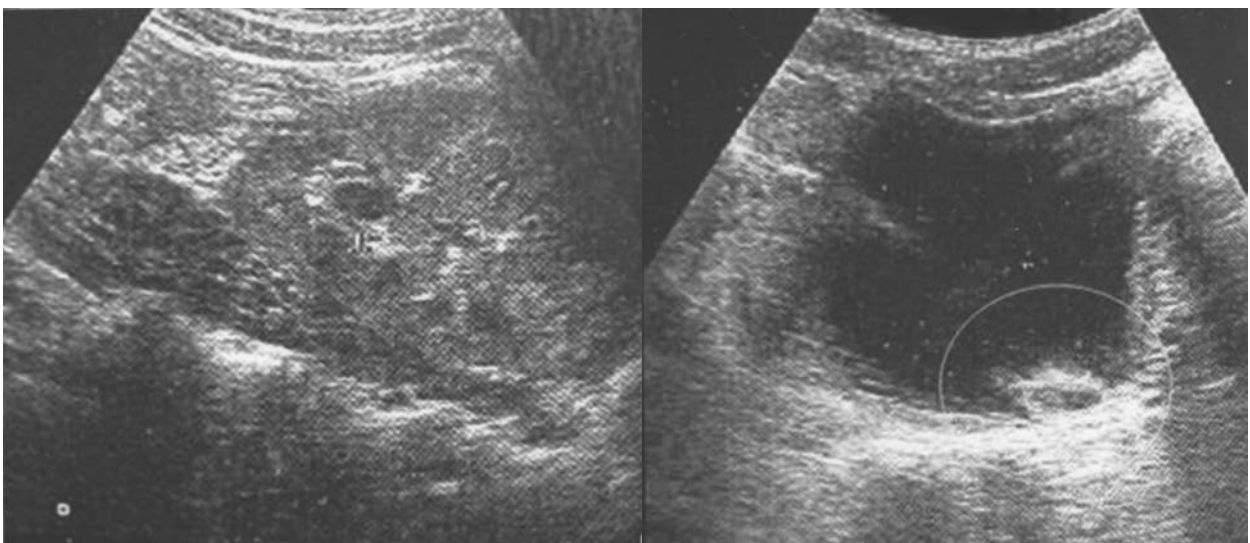


Figure 2 – Postoperative ultrasonography showing absence of dilation in left kidney and collapsed intravesical ureter.



Figure 3 – Postoperative cystourethrography showing absence of vesicoureteral reflux.

in order to maintain the proper 3-5 ratio between the length of the submucous path and the ureteral diameter. Several authors had good results with the extravesical Lich-Gregoir technique for treating vesicoureteral reflux, with the well-established advantages of laparoscopy (2,3).

The intraoperative finding of segmental megaureter prompted the decision to implant the di-

lated ureteral segment in the submucous path. We have no knowledge of any other report of laparoscopic treatment for segmental megaureter that was performed as we did. Surprisingly, though the relationship between the ureteral diameter and the length of the submucous path was not maintained, the vesicoureteral reflux disappeared and the walls of the submucous ureter remained in contact, giving the impression on ultrasound of an empty ureterocele (Figure-2). Perhaps the elasticity in the dilated ureteral segment could explain the favorable result. It remains unknown if this method of minimally invasive treatment would be effective in cases of non-segmental megaureter. Other studies are required in order to question the validity of the diameter/length of submucous path ratio in anti-vesicoureteral reflux technique.

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PRE-PUBERTAL TESTICULAR DERMOID CYST TREATED WITH CONSERVATIVE SURGERY

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ABSTRACT

We present a case of testicular dermoid cyst that was treated with transinguinal excision of the testicular cyst with preservation of the healthy testicular parenchyma. We have reviewed the literature for clinical features and therapeutic approach in benign cystic tumors in the pre-pubertal testis.

Key words: testis; benign neoplasms; dermoid cyst; infant
Int Braz J Urol. 2005; 31: 359-61

INTRODUCTION

The most common testicular tumors in children are teratomas with a predominance of benign lesions. Simple cysts and dermoid cysts are rare but uniformly benign, thus enabling surgery with gonadic preservation. It is important to recognize their clinical and radiological features so that the selected therapy implies minimal sequelae. We present one case of testicular dermoid tumor in an infant, which was surgically treated and with preservation of the healthy ipsilateral testicular parenchyma.

MATERIALS AND METHODS

A 5-month old patient was brought to our service for evaluating an increase in scrotal volume that had been perceived some months earlier. He presented normal male genitalia with increased volume of the left gland, which was painless and regular with no transillumination. Ultrasound revealed a left testicular cyst measuring 23 mm at its maximal diameter and a well-defined and regular wall with no calcification, suggesting it was benign (Figure-1). The patient returned when he was 10 months old, maintaining the same clinical picture, with no increase in

the lesion. A new ultrasound demonstrated a left testicular cyst measuring 17 mm at its maximal diameter that was causing parenchymal compression and atrophy. The affected testis was then explored by inguinal access. We verified an increased volume of the gland resulting from an ovoid cystic lesion, which was entirely intratesticular (Figure-2). The lesion was regular and featured thickened walls and smooth internal and external contours, and it measured 20 mm at its maximal diameter, and was enucleated through compression of the spermatic cord using a longitudinal anterior testicular incision with preservation of the surrounding testicular parenchyma (Figure-2). The histological examination described a cystic structure

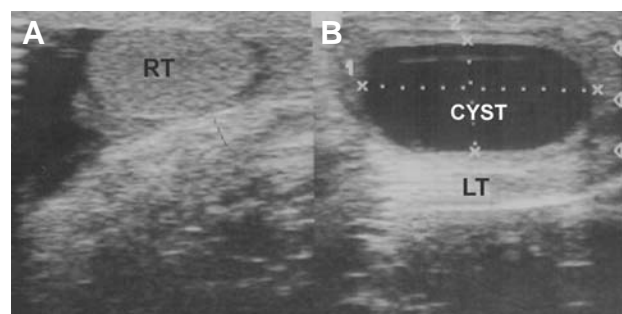


Figure 1 – Preoperative ultrasound assessment. A) Normal right testis (RT). B) Cyst and compressed left testis (LT).

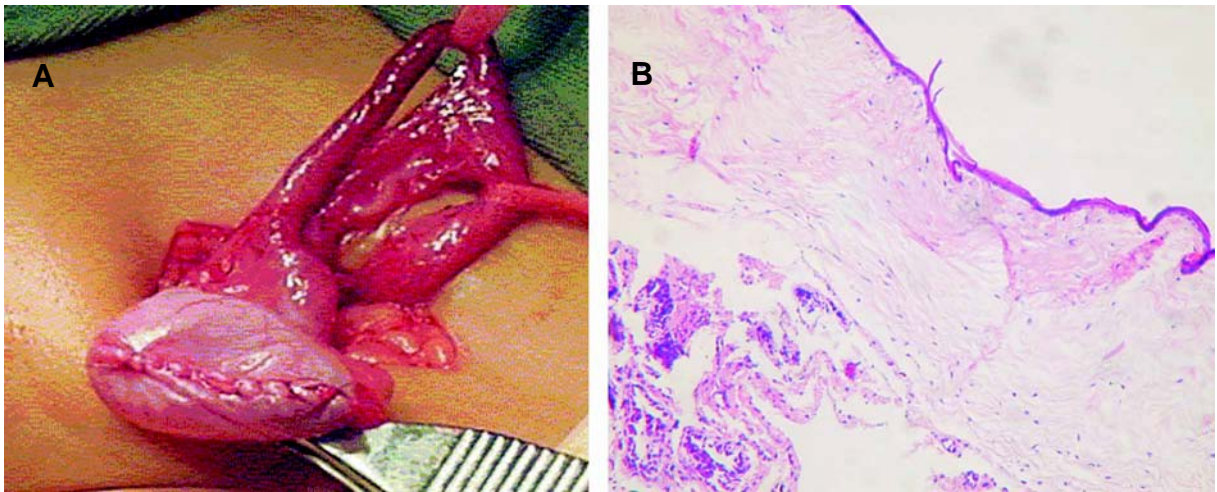


Figure 2 – A) Aspect of gonad following reconstruction. B) Histological examination showing epithelium and support connective tissue of the cyst amidst the testicular parenchyma, compatible with dermoid cyst.

with typical squamous epithelium and fibrous connective external wall amidst normal testicular parenchyma, compatible with a dermoid cyst (Figure-2). After an 18-month follow-up, the patient remains asymptomatic, the operated testis is topical and normal on palpation, with similar size to the contralateral testis and normal parenchyma on ultrasound (maximum diameter: 16 mm in right testis and 20 mm in left testis).

COMMENTS

Testicular tumors are uncommon in pediatrics (1 case in 100,000 individuals per year), with incidence peaks in infants and teenagers, and less than 1% of cases are benign cysts (1). In infants, teratomas predominate. The literature mentions approximately 300 cases of testicular dermoid cysts occurring mostly in young adults (only 23 cases in children) (2). Recently, Metcalfe et al. (3) have questioned these data, presenting 10% dermoid cysts among testicular tumors in children aged up to 16 years in an institutional sample of 51 lesions over 18 years.

Simple and dermoid testicular tumors clinically manifest as an increase in scrotal volume and painless scrotal mass. Ultrasound treatments of testicular dermoid cysts reveal typical properties, such as regular cystic lesions whose content has variable

sonographic features. The lesion shows echogenic thickened walls, which can be viewed as internal echoes with no acoustic enhancement, or as “onion-skin” patterns caused by the accumulation of multiple layers of keratin debris, which are avascular on Doppler image. Possibly the presentation is less typical in younger patients due to the shorter progression time, with less marked internal tumoral desquamation which, as seen in this case, makes differential diagnosis with simple cysts difficult since the latter are characterized by thin walls and anechoic regular content. Teratomas, which are typically solid-cystic, can be exclusively cystic, and complex lesions with multiple septations strongly suggest teratoma. Surgery is indicated in cases where there is diagnostic uncertainty involving malignant tumors and for resolving or preventing atrophy due to secondary compression by the cyst.

The traditional surgery for testicular tumors is transinguinal orchiectomy. However, since the ‘90s, the predominance of benign features among cystic testicular tumors in children and among pre-pubertal testicular teratomas, as well as the demonstration of cases with successful gonadic preservation and absence of malignancy in peritumor biopsies from testicular dermoid cysts, have led several authors to indicate simple inguinal enucleation of the tumor with compression of the spermatic cord until its benign

features have been confirmed (3). Histopathological criteria include entirely intraparenchymal lesion with keratin debris, fibrous external wall with squamous epithelial cells on the inside, no evidence of mesodermal or endodermal tissue, and no abnormalities in the remaining testicular parenchyma. The albuginea layer is sutured and the gonad is returned to the scrotum. Some authors suggest that biopsies should be made on adjacent parenchymal areas in order to exclude teratomatous elements or "in situ" testicular carcinoma. When considering the uniformly favorable results of simple enucleation, the use of the inguinal access has been questioned since it is esthetically inferior, and transscrotal surgery has been preferred. The limited experience, the possibility of diagnostic error and the difficulty of analyzing the alpha-fetoprotein values in children during the first semester of life have, for safety and legal reasons, maintained the transinguinal access as the rule so far.

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LAPAROSCOPIC ASSISTED RADICAL CYSTOPROSTATECTOMY WITH Y-SHAPED ORTHOTOPIC ILEAL NEOBLADDER CONSTRUCTED WITH NON-ABSORBABLE TITANIUM STAPLES THROUGH A 5 CM PFANNENSTIEL INCISION

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ABSTRACT

Introduction: We performed a laparoscopic radical cystoprostatectomy followed by constructing a Y-shaped reservoir extra-corporeally with titanium staples through a 5-cm muscle-splitting Pfannenstiel incision.

Surgical technique: Upon completion of the extirpative part of the operation, the surgical specimen was entrapped and removed intact through a 5-cm Pfannenstiel incision. Through the extraction incision, the distal ileum was identified and a 40 cm segment isolated. With the aid of the laparoscope, the ureters were brought outside the abdominal cavity and freshened and spatulated for approximately 1.5-cm. Bilateral double J ureteral stents were then inserted up to the renal pelvis and the ureters were directly anastomosed to the open ends of the limbs of the neobladder. Following this, the isolated intestinal segment was arranged in a Y shape with two central segments of 14 cm and two limbs of 6 cm. The two central segments were brought together and detubularized, with two sequential firings of 80 x 3.5 mm and 60 x 3.5 mm non-absorbable mechanical stapler (Multifire GIA - US Surgical) inserted through an opening made at the lowest point of the neobladder on its anti-mesenteric border. The neobladder was reinserted inside the abdominal cavity and anastomosed to the urethra with intracorporeal laparoscopic free-hand suturing.

Conclusion: Although this procedure is feasible and the preliminary results encouraging, continued surveillance is necessary to determine the lithiasis-inducing potential of these titanium staples within the urinary tract.

Key words: bladder neoplasms; laparoscopy; cystectomy; urinary reservoirs; neobladder, surgical stapling

Int Braz J Urol. 2005; 31: 362-9

INTRODUCTION

Initially restricted to a few centers of excellence, the worldwide experience with laparoscopic radical cystectomy is clearly on the increase (1). Nowadays, the extirpative portion of the procedure

does not represent a limiting factor and pure laparoscopic techniques are employed to expeditiously perform radical cystectomy and pelvic lymphadenectomy (2,3). Nonetheless, there is a trend to perform the reconstructive procedures necessary to create the urinary diversion extracorporeally, using

conventional open surgical technique in an attempt to reduce the overall surgical time (1). Recently, the Italian group from Piedmont has described an “easy, fast and reliable” technique to create an orthotopic Y-shaped ileal neobladder open surgically using non-absorbable titanium staples (4). Based on these promising results, we sought to perform a laparoscopic radical cystoprostatectomy followed by the construction of a Y-shaped reservoir extracorporeally through a 5 cm muscle-splitting Pfannenstiel incision. Therefore maximizing the benefits of a minimally invasive approach including, decreased postoperative pain, shorter hospital stay, quicker recovery, better cosmesis without a significant increase in the operative time.

Herein, we describe the surgical technique and present our preliminary results with laparoscopic assisted radical cystoprostatectomy with Y-shaped orthotopic ileal neobladder using non-absorbable titanium staples.

SURGICAL TECHNIQUE

Laparoscopic radical cystoprostatectomy was performed using a 5-port transperitoneal approach, which has been described in detail elsewhere (1-3). Upon completion of this extirpative part of the operation, the surgical specimen was entrapped in a Lapsac and removed intact through a 5-cm muscle-splitting Pfannenstiel incision (Figure-1). Through the extraction incision, the distal ileum was identified and brought outside the abdominal cavity. Using conventional open

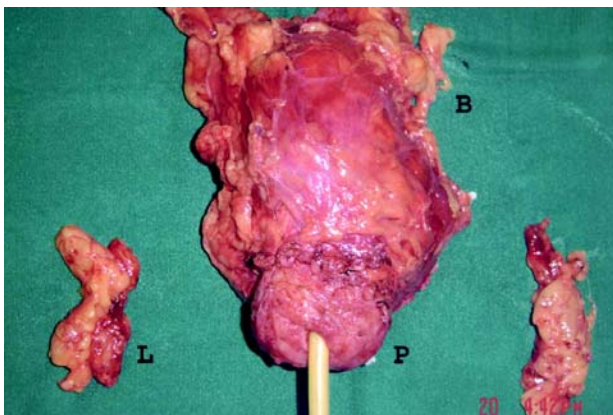


Figure 1 – Photograph showing intact surgical specimen: bladder (B), prostate (P) and lymph nodes (L).

surgical techniques, a 40 cm ileal segment was isolated 15 to 20 cm proximal to the ileocecal valve and a side-to-side entero-entero anastomosis was performed to re-establish bowel continuity. Through the laparoscope, the ureters, which were previously anchored to the anterior abdominal wall with a stay stitch, were identified and also brought outside the abdominal cavity. Laparoscopic viewing was used to ensure the ureters were not twisted or rotated. Subsequently, the ureters were freshened and spatulated for approximately 1.5-cm. Bilateral, 6F double J ureteral stents were then inserted up to the renal pelvis and the ureters were directly anastomosed to the open ends of the limbs of the neobladder using running sutures of 4-0 PDS (Figure-2). Following this, the isolated intestinal segment was arranged in a Y shape with 2 central segments of 14 cm and two limbs of 6 cm. The 2 central segments

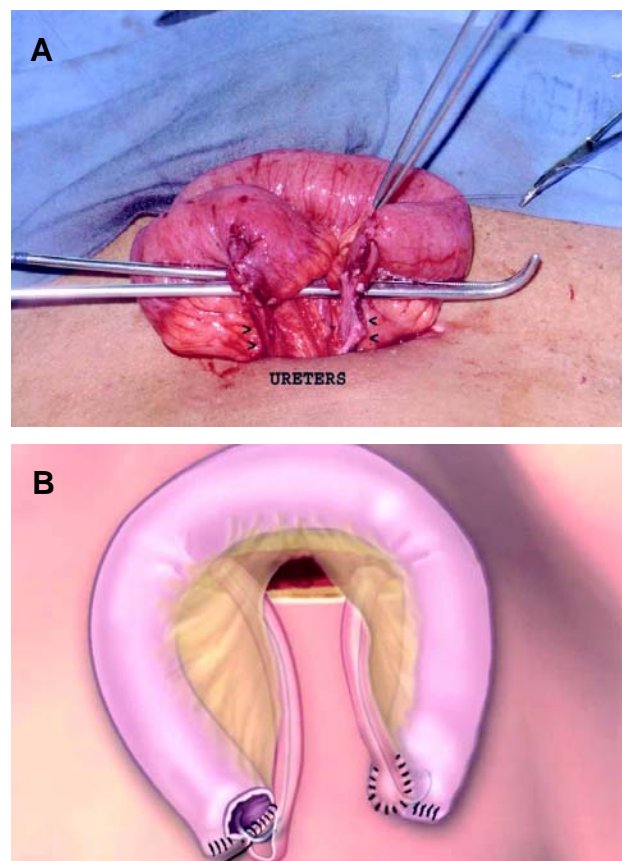


Figure 2 – A) Photograph showing the ureters (arrowheads) being directly anastomosed to the open ends of the limbs of the neobladder; B) Schematic drawing.

were brought together and detubularized with 2 sequential firings of a 80 x 3.5 mm and 60 x 3.5 mm non-absorbable mechanical stapler (Multifire GIA - US Surgical) inserted through an opening made at the lowest point of the neobladder on its anti-mesenteric border (Figure-3). The recently created neobladder was reinserted inside the abdominal cavity and the 5-cm Pfannenstiel incision was closed. Pneumoperitoneum was re-established and the Y-neobladder was anastomosed to the urethra with four interrupted 2-0 monocryl sutures over a 22F Foley catheter, using intracorporeal laparoscopic free-hand suturing. The 2 limbs of the neobladder were then fixed to the psoas muscles. A suction drain was left in the deep pelvis.

PATIENTS AND RESULTS

Two male patients diagnosed with muscle invasive transitional cell carcinoma of the bladder consented and were scheduled to a laparoscopic assisted radical cystoprostatectomy with orthotopic Y-shaped ileal neobladder. Metastatic workups with chest x-rays and abdominal CTs were negative in both patients. There were no signs of enlarged pelvic nodes. Demographic, intraoperative and postoperative data are presented in Table-1.

A retrograde cystogram was performed with 200 cc of contrast on postoperative day 3 and postoperative day 7 in the first and second cases respectively, showing no signs of contrast media extravasation (Figure-4). In both cases, bladder catheter was removed on postoperative day 21. In both cases, cystoscopic viewing in the second postoperative month did not reveal any stones at the staple lines, which were almost entirely covered by the intestinal mucosa, except by a single spot where 3 staples could be visualized in the first case (Figure-5). We used a smaller 5-cm Pfannenstiel incision (Figure-6) to perform the bowel work, the Y-shaped orthotopic ileal neobladder and the ureteral re-implantation, thus further improving cosmesis and perhaps further decreasing surgical morbidity. Pathology revealed a T2G3 transitional cell carcinoma (TCC) of the bladder with negative surgical margins in the first case and a T3aG3 TCC of the bladder in the second case. Lymph nodes were negative in both cases.

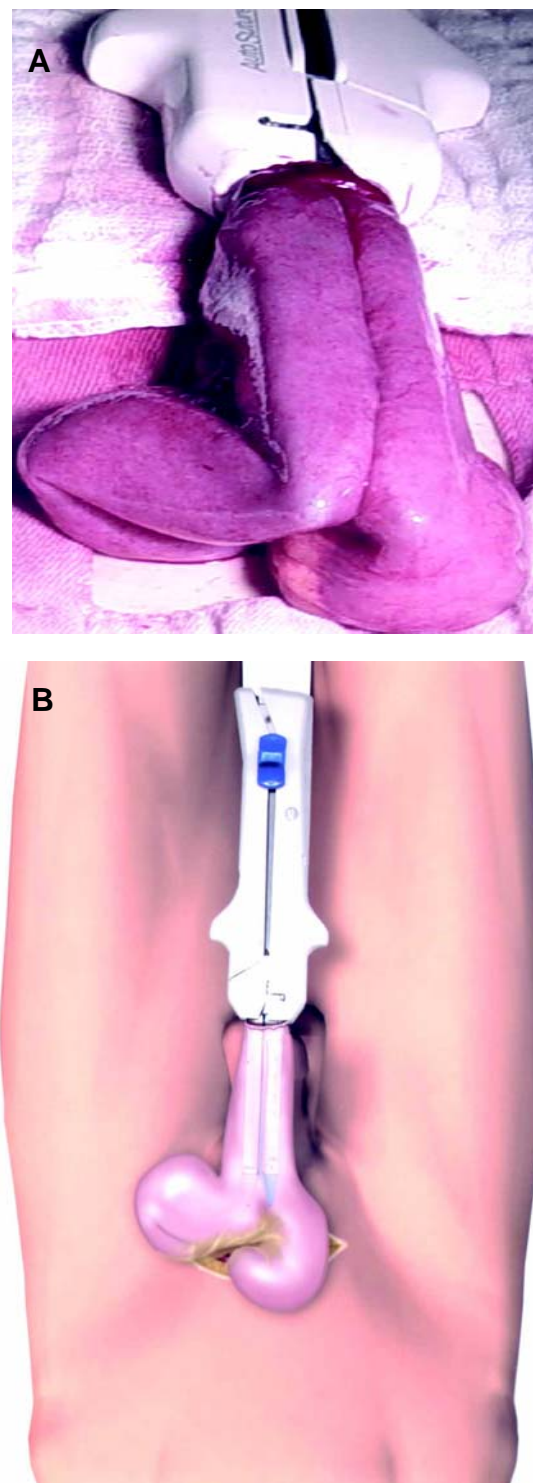


Figure 3 – A) Photograph showing the Y-shaped neobladder being created with non-absorbable titanium staples; B) Schematic drawing.

Table 1 – Demographics, intraoperative and postoperative data.

	Case #1	Case #2
Age (years)	64	59
ASA	2	2
OR Time		
• Total (hrs)	5.0	6.5
• Radical cystectomy and pelvic lymphadenectomy (hrs)	3.5	4.5
• Bowel work and neobladder construction (min)	45	40
• Ureteral re-implantation (min)	25	25
Urethro-intestinal anastomosis (min)	20	55
Blood loss (cc)	250	550
Blood transfusion (units)	—	1
Complications	—	—
Oral fluids intake (POD)	2	3
Cystogram without leak (POD) *	3	7
Hospital stay (days)	5	7

* 200 cc of contrast

COMMENTS

Over the past decade, a few studies have reported that the use of non-absorbable titanium staples inside the urinary tract may be safe and secure (4-9). The corrosive resistant nature, low toxicity and excellent tissue and fluid biocompatibility of titanium may explain why such non-absorbable staples are well tolerated here. In fact, in 1993, Kerbl and colleagues from Washington University have reported the initial encouraging laboratory and clinical data with laparoscopic stapled (titanium staples) bladder closure (4). However, this article was criticized by reviewers at that time, who used comments such as: "...just because it is new, rapid and easy to use does not mean that it should be used in a cavalier fashion;" and "... sutures are less expensive than staples and less likely to result in stone formation." However, in 2000 this same group discussed its follow up research conducted over a more than 10-year period, and attesting to the safety of using non-absorbable titanium staples to secure the bladder cuff during laparoscopic nephroureterectomy (5), and demonstrating that no stones have ever been observed at the titanium staple line even when the staples were not entirely covered by the vesical mucosa.

In 2004, an Italian group from Piedmont reported an acceptable 6% rate of stones formation when fifty Y-shaped orthotopic ileal neobladders were created in open surgical procedures with non-absorbable titanium staples in a mean follow up of 20 months (total follow up range: from 8 to 47 months) (7). Encouraged by the Fontana and colleagues study, we recently performed and documented the first orthotopic ileal neobladder constructed totally intracorporeally using non-absorbable titanium staples exclusively (8). Although the procedure was possible, it took a long time (approximately 10 hours) and it required a considerable amount of disposables (8 stapler loads) to complete it. In an attempt to overcome these difficulties, we sought to incorporate Fontana's idea of creating an ileal neobladder with non-absorbable titanium staples with the technique discussed by Basillote and colleagues of laparoscopic assisted radical cystectomy (2). Basillote et al. have demonstrated that when radical cystectomy is performed laparoscopically and the neobladder is performed open surgically with conventional techniques through a Pfannenstiel incision, the patient has the benefits of a minimally invasive approach, including decreased post-operative pain and quicker recovery, without a significant increase in operative time (2). Therefore,

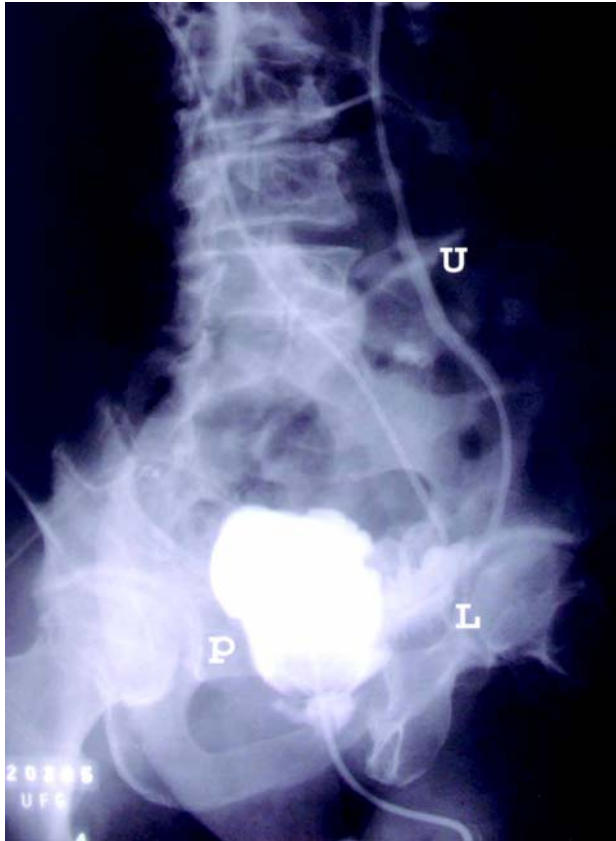


Figure 4 – Retrograde pouchgram with 200 cc performed on post-operative day 7 showing no signs of contrast extravasation, but free reflux of contrast from the limbs (L) of the pouch (P) to the ureters (U).

we performed 2 cases of laparoscopic assisted radical cystoprostatectomy wherein the Y-shaped orthotopic ileal neobladder was created extracorporeally using non-absorbable titanium staples.

Although longer follow-up is required to fully evaluate the safety of this approach, we believe that our initial results are encouraging. It is also worth noting the mean overall surgical time of 5.7 hours, mean blood loss of 375 cc and mean total hospital stay of 5 days. Moreover, over a very short period ranging from 3-7 days post-operatively, we were able to demonstrate that there were no signs of contrast extravasation during retrograde pouchgram performed with 200 cc of contrast. Furthermore, cystoscopy performed in the second post-operative month did not reveal any stones at the staple line, and only a few

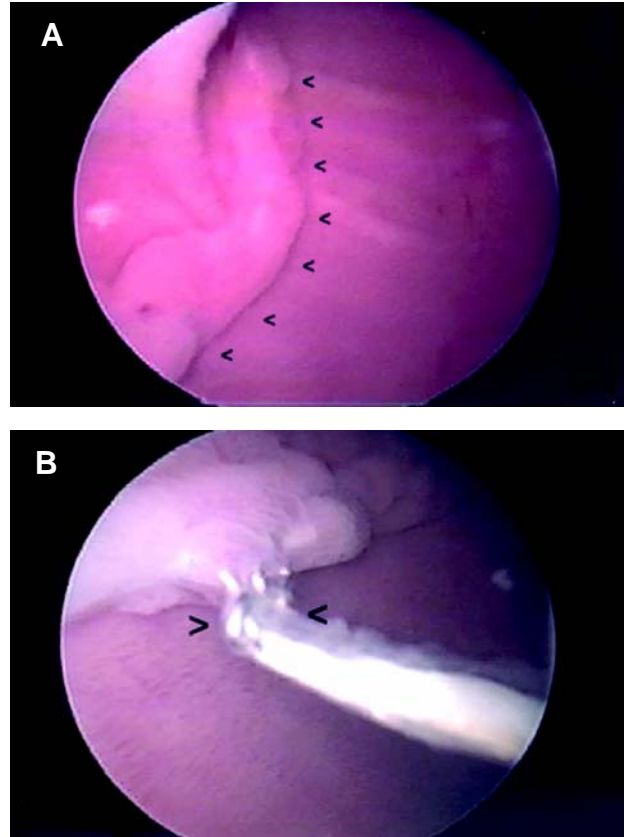


Figure 5 – A) Photograph showing the staple line (multiple arrows) covered by the intestinal mucosa; and B) Single spot where 3 staples were viewed within the reservoir (there is mucus adherent to the staples).



Figure 6 – Photograph of port site incisions and 5-cm muscle-splitting Pfannenstiel incision.

staples were visualized within the neobladder while the remainder of the staple line was recovered by the intestinal mucosa.

We differed from the technique described by Basillote et al., who used a 15-cm Pfannenstiel incision to perform bowel work, Studer orthotopic ileal neobladder, ureteral re-implantation and the urethral-ileal anastomosis (2). As reported, we used a smaller 5-cm Pfannenstiel incision to perform the bowel work, Y-shaped orthotopic ileal neobladder and ureteral re-implantation, thus further improving cosmesis and perhaps further decreasing surgical morbidity. In our approach, the urethral-ileal anastomosis is performed using free-hand laparoscopic suturing after the recently fashioned neobladder is pushed back into the abdominal cavity, the extraction incision is closed and pneumoperitoneum is re-established.

Moreover, our approach to the bilateral ureteral re-implantation was different from that originally described by Fontana et al. In their report, the ureters were spatulated anteriorly and were anastomosed to the dorsal aspect of the two limbs of the Y with 5-0 sutures using the direct (end-to-side) Nesbit technique. Subsequently, the previously placed ureteral stents were brought out through the distal portions of each chimney and then through the anterior abdominal wall. In our procedure, the ureters were freshened and spatulated for approximately 1.5-cm, and then directly anastomosed (end-to-end) to the already open ends of the 2 limbs with 4-0 sutures over previously placed double J ureteral stents, resulting in a wide patent anastomosis. We thus avoided the presence of external ureteral stents and did not have to close the open ends of the limbs or create 2 new openings in the chimneys in order to implant the ureters, thus saving some time and perhaps decreasing the chances of developing a urinary fistula in the reservoir.

CONCLUSION

Laparoscopic assisted radical cystoprostatectomy with Y-shaped orthotopic ileal neobladder constructed using non-absorbable titanium staples through a 5-cm Pfannenstiel incision is feasible and our preliminary results are encouraging. Continued surveillance will be necessary to determine

the lithiasis-inducing potential of these titanium staples within the urinary tract.

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EDITORIAL COMMENT

The authors are to be congratulated for achieving the advanced laparoscopic procedure of radical cystoprostatectomy. This procedure has started to gain interest worldwide, with more institutions performing the procedure. As with any new oncologic procedure, one must look at the outcomes in order to assess efficacy of the procedure. The margin status must be reported together with surveillance follow-up imaging studies. In the open cystectomy literature, 5 year survival is 87-89% for organ confined node negative disease compared to 50-62% for locally extravesical non-metastatic disease (1).

The limits of an extended pelvic lymph node dissection have been another area of discussion. An extended lymph node dissection should include the distal para-aortic and paracaval lymph nodes as well as the pre-sacral nodes, known anatomic sites of lymph node drainage from the bladder. An extended dissection may provide a survival advantage in patients with node-positive and node-negative tumors without significantly increasing the morbidity or mortality of the surgery (2). Recently, a multi-institutional study reviewed their series of where positive lymph nodes were most commonly found (3). This mapping study demonstrated positive lymph nodes were found most commonly in the obturator spaces and adjacent to the iliac vessels. Interestingly, 16% of lymph node metastases also included nodes above the aortic bifurcation, whereas 8% of lymph node metastases involved the presacral region.

Performing the ureteral reimplantation into the neobladder extracorporeally is a reasonable

method to decrease operative time; however, one must be conscious of avoiding excessive tension when the ureters are pulled up through the incision, as this can lead to early strictures.

The use of non-absorbable titanium staples to create the neobladder is a balance between time saving maneuvers and decreasing the morbidity of the procedure. While stones have been reported at a rate of only 6% where titanium staples were used to construct the neobladder, one wonders if this is comparable with the baseline stone formation rate where mucus is a nidus of stone formation.

Clearly, laparoscopic radical cystectomy will continue to play a role in urologic oncology. It is currently at the infancy of institutions' experience, and differs from the experience of laparoscopic radical prostatectomy in that fewer cases are performed due to the incidence of muscle invasive transitional cell carcinoma compared to prostate cancer, as well as the average age and health status of the patients. Longer follow-up outcome data however is needed in order to insure optimal results.

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EDITORIAL COMMENT

The authors should be commended for presenting a hybrid procedure combining a novel open technique, the Y-shaped orthotopic ileal neobladder, and a minimally invasive laparoscopic approach. As with any hybrid procedure, the urologist will need broad surgical skills. Urologists using this approach must possess advanced laparoscopic skills, as they must perform a laparoscopic cystoprostatectomy and complete the urethrovesical anastomosis laparoscopically. Similarly, the creation of the Y-shaped neobladder requires experience with urinary diversion, and specifically care must be taken to avoid twisting or rotating the ureter or blood supply to the neobladder during the procedure through the 5 cm incision.

It is evident that careful patient selection will be critical when using this technique. Patients having prior abdominal procedures, or with aggressive disease may be better suited to an alternative

approach. Similarly, morbidly obese patients may prove challenging, specifically when managing the open neobladder creation through the smaller Pfannenstiel incision. Although convalescence data and long-term follow-up are lacking, this procedure should prove effective and beneficial. The authors diligently state the need for long-term follow-up of the neobladder for stone disease, although most experts would agree this would not be problematic.

In 2005, cystoprostatectomy and neobladder creation remains an open operation in most centers, despite the fact that many bladder cancer patients would benefit from the improved convalescence and cosmesis of the minimally invasive approach. Moreover, a more rapid recovery would be beneficial for bladder cancer patients requiring adjuvant chemotherapy. This report adds nicely to the growing body of literature supporting minimally invasive cystoprostatectomy and urinary diversion.

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TREATMENT OF PHIMOSIS WITH TOPICAL STEROIDS AND FORESKIN ANATOMY

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ABSTRACT

Objectives: To correlate topical steroidal treatment of stenosed foreskin with the different degrees of glans exposure and the length of time the ointment is applied.

Materials and Methods: We studied 95 patients with phimosis, divided according to the degree of foreskin retraction. Group A presented no foreskin retraction, group B presented exposure of only the urethral meatus, group C presented exposure of half of the glans, and group D presented exposure of the glans, which was incomplete because of preputial adherences to the coronal sulcus. Patients were submitted to application of 0.05% betamethasone ointment on the distal aspect of the prepuce twice daily for a minimum of 30 days and a maximum of 4 months.

Results: Of 95 patients, 10 (10.52%) abandoned the treatment and 15 patients in groups C and D were excluded from the study. Among the remaining 70 patients, only 4 patients (5.7%) in group A did not obtain adequate glans exposure after treatment. In group A (38 patients), fully retractable foreskins were obtained in 19 patients (50%) after 1 month of treatment. In group B (28 patients), fully retractable foreskins were obtained in 18 patients (64.2%) after 1 month.

Conclusions: Treatment was successful in 94.2% of patients, irrespective of the type of foreskin anatomy. The improvement may require several months of treatment. Patients with impossibility of urethral meatus exposure present around 10% treatment failure.

Key words: penis; phimosis; anatomy; steroids; circumcision

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INTRODUCTION

Circumcision is frequently performed in the United States and Canada, although in a variety of locations around the world, such as Europe and South America, this procedure is not done on a routine basis. When it is not done routinely, the incidence of pathological phimosis is increased (1). Pathological phimosis results when there are adherences to the fibrotic foreskin ring that make it impossible to expose the penis glans (1). This situation hinders adequate penis hygiene, which favors the occurrence of foreskin infections, repeated urinary tract infections, sexu-

ally transmitted diseases and, in adults, carcinoma of the penis (2).

The correction of phimosis in infancy is performed with general anesthesia, a procedure that is not without risks, with a complication rate that may reach 34% (3). The main complications following circumcision are hemorrhage, stenosis of the urethral meatus and the foreskin ring, and even amputation of the glans (4). In addition, this procedure presents considerable costs (5).

Recently, clinical treatment of phimosis using topical corticosteroids has been proposed as an alternative to surgery with good results (6-8). Regard-

less of the patient's age, the results are encouraging, with success rates ranging from 67 to 95% of cases (2,8,9).

There are several classifications for the position of the phimotic ring (1,2,9,10), although only Kayaba et al. (11) demonstrated the form and degree of retractability of the prepuce. Studies that correlate foreskin anatomy with topical treatment using corticosteroids in patients with phimosis are rare, or even inexistent.

The objective of this work is to correlate topical treatment of 0.05% betamethasone in the stenosed foreskin with the different degrees of exposure of the glans and the length of application needed for the foreskin to become fully retractable.

MATERIALS AND METHODS

Between January 2001 and October 2003, we evaluated 95 patients with phimosis for possible circumcision. The patients ranged in age from 19 months to 14 years (mean age 7.7 years). The Human Research Committee at our institution approved the investigation. An informed consent form was obtained from the parents (mother or father) of each patient.

The patients were divided into groups according to the degree of foreskin retraction (11) (Figure-1). Group A consisted of patients who presented no foreskin retraction, group B presented exposure of the urethral meatus only, group C presented exposure of half of the glans, and group D presented incomplete exposure of the glans due to preputial adhesions to the coronal sulcus.

After classification into one of the groups, the patients were submitted to application of 0.05% betamethasone ointment on the phimotic ring (distal aspect of the prepuce). Parents were instructed to gently apply traction to the foreskin until the ring appeared, applying a thin layer of cream twice daily for a minimum of 30 days and a maximum of 4 months, in association with correct hygiene of the penis. These children were followed every month in our outpatient service.

Therapy was considered successful when the prepuce was fully retractable with total glans exposure. Failure was considered when it was impossible to achieve glans exposure, when there was no alteration in the degree of stenosis after more than 4 months, and if there was infection during the treatment. In such cases, circumcision would be indicated.

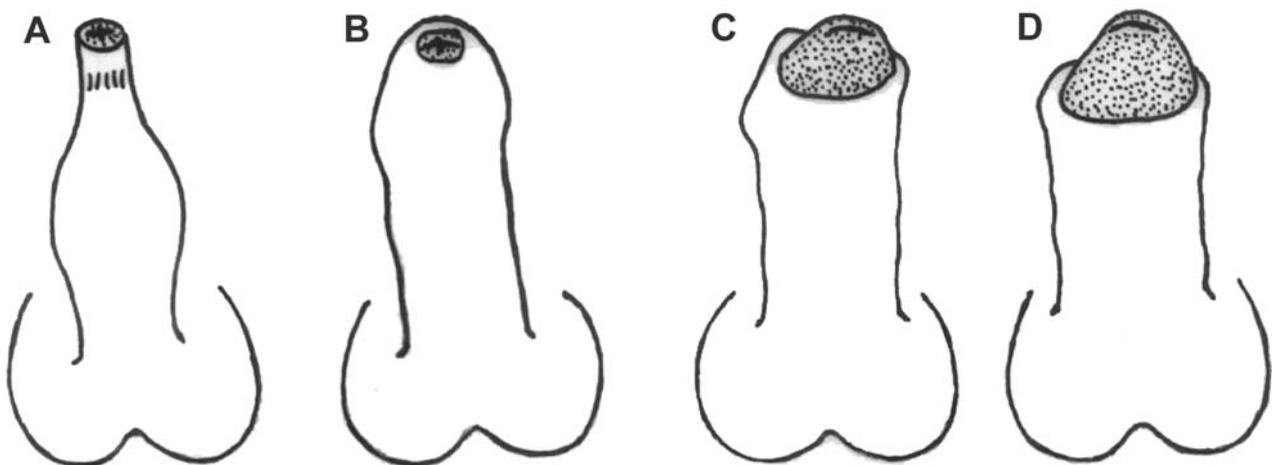


Figure 1 – Diagram based on the work by Kayaba et al. (11) showing the 4 types of foreskin according to the position of the phimotic ring and the retraction ability, as well as the incidence found in the present study. Group A - no foreskin retraction, group B - exposure of the urethral meatus, group C - exposure of half of the glans, and group D - incomplete exposure of the glans due to preputial adhesions to the coronal sulcus.

For statistical analysis, we used the chi-squared test. $P < 0.05$ indicates statistically significant differences (12).

RESULTS

The type of foreskin anatomy found in the 95 children is shown in Table-1. There was a predominance of group A (43 children - 45.2%) and group B (34 - 35.7%). Groups C (6 - 6.3%) and D (12 - 12.6%) presented a lower incidence. Of the 95 patients, 10 (10.52%) abandoned the treatment and 15 patients in groups C and D were excluded from the study because they were not strictly considered as having phimosis. Among the patients who abandoned treatment, one presented the foreskin anatomy of group A, 6 of group B and 3 of group D. Among the remaining 70 patients, only 4 patients (5.7%) in group A did not obtain adequate exposure of the glans after treatment.

Of the 66 patients (94.2%) who did obtain adequate exposure of the glans after treatment (fully retractable prepuce), 38 (57.5%) were in group A and 28 (42.5%) were in group B. The response to topical treatment for the groups studied in relation to the length of time the ointment was used is shown in Table-2.

Table 1 – Incidence of the different types of foreskin anatomy found in the present study.

Foreskin Anatomy	Patients	%
Group A	43	45.2
Group B	34	35.7
Group C	6	6.3
Group D	12	12.6
Total	95	100

Table 2 – Therapeutic success rate for groups A and B in relation to the length of time the ointment was applied.

Groups	Month 1	Month 2	Month 3	Month 4	Total
A	19 (50%)	5 (13.1%)	9 (23.6%)	5 (13.1%)	38 (57.6%)
B	18 (64.2%)	6 (21.4%)	1 (3.5%)	3 (10.7%)	28 (42.4%)
Total	37 (56%)	11 (16.6%)	10 (15.1%)	8 (12.1%)	66 (100%)

In group A, 8 patients (21%) were ≤ 3 years old and 30 patients (79%) were > 3 year old. Of the patients who responded to treatment in group A (38 of 42 patients - 90.4%), fully retractable foreskins were obtained in 19 patients (50%) after 1 month of treatment, in 5 patients (13.1%) after 2 months, in 9 patients (21.6%) after 3 months, and in 5 patients (13.5%) after 4 months.

In group B (28 patients), 4 patients (14.2%) were ≤ 3 years old and 24 patients (86%) were > 3 year old. All patients in group B responded to treatment and fully retractable foreskins were obtained in 18 patients (64.2%) after 1 month, in 6 patients (21.4%) after 2 months, in 1 patient (3.5%) after 3 months, and in 3 patients (10.7%) after 4 months.

Independently of the group they were classified, 37 of the patients (56%) achieved glans exposure within 30 days of treatment. Only 8 patients (12.1%) required 4 months of treatment to obtain a fully retractable prepuce. No adverse side effects were observed from the topical betamethasone treatment. There was no statistically significant difference in satisfactory response to treatment over the course of the months between groups A and B.

COMMENTS

Physiological phimosis affects 96% of newborns and its incidence diminishes with age. At 3 years old, 10% of boys present phimosis and by the age of 14 years, this incidence decreases to 1% (13).

In Australia at the beginning of the 1990s, Kikiros et al. (10) attested to the efficacy of topical corticosteroids in the treatment of preputial stenosis. Since then, several authors have shown satisfactory results (67% to 95%) with the topical use of betamethasone, clobetasol, sodium diclofenac, 0.05% mometasone furoate and triamcinolone acetonide (8-10).

Betamethasone is one of the steroids that present the best improvement rates (13,14), and this was the reason the drug was used in this study. Corticosteroids act by reducing the arachidonic and hydroxyeicosatetraenoic acids in proliferative inflammatory disease of the skin, thereby inhibiting prostaglandin release and increasing the activity of dismutase superoxide. Additionally, they have the potential to release antioxidants (13). Collateral effects may occur, such as the suppression of the hypothalamus-hypophysis-adrenal axis or cutaneous atrophy. However, the doses utilized in topical treatment of phimosis are not large enough to lead to these types of complications (1). In our study, we did not observe any adverse effects in our patients.

We obtained a success rate of 94.2% from the treatment with 0.05% betamethasone ointment, which is similar to what has been found in recent studies in the literature (1,2,13,15-18). All patients were advised to continue retracting the foreskin to maintain penile hygiene. We observed parent satisfaction when the decision to pursue conservative treatment was made. Topical treatment using corticosteroids has been shown to have low risk with an absence of side effects and good adherence to treatment when those responsible for the child have been well briefed.

Monthly follow-up for observation of the evolution of the phimotic ring has been shown to be fundamental in the assessment of the time at which the therapy utilized is having its effect, or whether it is ineffective. Therapy can be stopped at any time and surgery can then be indicated.

All 4 patients (5.7%) who showed no improvement after using the ointment and required a surgical procedure were in group A. Among the patients in group A who responded to topical treatment, 35% obtained the desired result only after 3 or 4 months of treatment. The patients without any foreskin retraction (group A) presented an approximately 10% chance of not benefiting from clinical treatment, even after a long period of ointment use, and such patients will require circumcision. In group B, 70% of the patients showed the desired result within the first two months of ointment application. These results are very significant at the time of indicating the treatment, especially for patients unable

to have foreskin retraction (group A), which was the most frequent situation among our patients (incidence of 45%). Patients with foreskin anatomy in groups B presented a high chance of obtaining the desired result with treatment duration of less than 60 days.

In conclusion, topical treatment of phimosis using 0.05% betamethasone ointment presented a success rate of 94.2%, regardless of the form and degree of foreskin retraction. Most previous reports have described one month of treatment; nevertheless, we found that the desired improvement might take several months of treatment.

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EDITORIAL COMMENT

These authors have confirmed successful treatment of phimosis in children with betamethasone ointment as has been shown in other studies. In addition, they have demonstrated success with lower dose betamethasone ointment (0.05% instead of 0.1%) and that only one month treatment is needed in about half of the cases. However, they do not report on long term follow-up to determine if recurrence is a problem. Ashfield et al. (Reference 18 in article) also did not report long term follow-up but they examined patients six weeks following cessation of treatment, which should have at least detected early recurrences.

The more important point on this topic to consider is when this treatment is indicated. From

the results in this study, this would seem the best treatment for phimosis causing ballooning of the prepuce with voiding and/or when phimosis is thought to be causing recurrent infections. These authors do not note that any of these boys had symptoms. While these authors and others have shown resolution of phimosis with steroid ointment, they have not demonstrated that treating asymptomatic phimosis in pre-pubertal boys has any medical benefit.

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MALE INFERTILITY IN SPINAL CORD TRAUMA

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ABSTRACT

Every year there are 10 thousand new cases of patients victimized by spinal cord trauma (SCT) in the United States and it is estimated that there are 7 thousand new cases in Brazil. Eighty percent of patients are fertile males. Infertility in this patient group is due to 3 main factors resulting from spinal cord lesions: erectile dysfunction, ejaculatory disorder and low sperm counts. Erectile dysfunction has been successfully treated with oral and injectable medications, use of vacuum devices and penile prosthesis implants. The technological improvement in penile vibratory stimulation devices (PVS) and rectal probe electro-ejaculation (RPE) has made such procedures safer and accessible to patients with ejaculatory dysfunction. Despite the normal number of spermatozoa found in semen of spinal cord-injured patients, their motility is abnormal. This change does not seem to be related to changes in scrotal thermal regulation, frequency of ejaculation or duration of spinal cord damage but to factors related to the seminal plasma. Despite the poor seminal quality, increasingly more men with SCT have become fathers through techniques ranging from simple homologous insemination to sophisticated assisted reproduction techniques such as intracytoplasmic sperm injection (ICSI).

Key words: spinal cord injuries; semen; infertility, male; ejaculation; paraplegia
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INTRODUCTION

In the United States, there are approximately 300,000 patients with sequelae from spinal cord trauma (SCT), and there are a reported 10,000 new cases every year (1). In Brazil, an estimated 7 thousand new cases occur every year. Approximately 80% of the affected patients are males of reproductive age. Men with SCT often present fertility problems related to the neurological lesion. This patient group faces 3 main problems concerning this issue (1-5): first, erectile dysfunction, where both medical and surgical treatment has provided a high resolution in-

dex; second, ejaculatory dysfunction, present in up to 90% of the cases and requiring the use of resources for inducing semen release; and finally, low sperm counts. The number of spermatozoa in the ejaculate of spinal cord-injured patients is generally within normal ranges. However, motility is low, approximately 20% as compared to the 70% rate usually found in healthy patients. Infertility among spinal cord-injured patients usually results from the sum of all these factors. This present report aims to provide a critical analysis of each involved factor, the pathophysiology and the currently available treatment modalities.

ERECTILE DYSFUNCTION

The change of erectile quality in the spinal cord-injured patient is directly related to the lesion level and the extent of impairment. Two components act together in the erectile physiology: the reflex and the psychogenic components (6). The reflex component is induced by tactile stimulation of the genital organs; impulses run through the pudendal nerve (somatic innervation) until they reach the sacral erection center. The parasympathetic nuclei are activated and erection is achieved through the cavernous nerves. On the other hand, psychogenic stimulation results from audio-visual or imaginary stimuli and depends on the modulation of the spinal erection centers (T11-L2 and S2-S4). In order to activate the erection process, cerebral impulses are transmitted through the sympathetic (inhibiting norepinephrine release), parasympathetic (releasing nitric oxide and acetylcholine) and somatic (releasing acetylcholine) tracts.

When the lesion occurs at the sacral level, the psychogenic erection component is preserved but the reflex mechanism is not. Under these circumstances, the cerebral stimulus is transmitted through sympathetic fibers thus inhibiting the norepinephrine release, while acetylcholine and nitric oxide are released through synapses existing in somatic and postganglionic parasympathetic neurons. When compared with sacral fibers, the lower number of synapses between thoracic-lumbar fibers and postganglionic parasympathetic neurons results in partial erection. In patients with spinal cord lesion above the T9 level, psychogenic erection is usually absent (1,6).

Treatment of Erectile Dysfunction

The first step consists of orientating the patient about the impact of SCT on sexual dysfunction and the types of erection he can possibly achieve.

Before treatment, it is fundamental that patients be instructed to empty their bladders prior to initiating the sexual stimulation. This maneuver aims to avoid the occurrence of autonomic dysreflexia (AD) (7,8).

Therapeutic options for erectile dysfunction (9-20) in these patients include the use of oral medi-

cation, intracavernous injection, vacuum devices and penile prostheses. The selection of the type of treatment depends on adaptation and individual response to the selected modality, though it should always start with the less invasive methods.

Sildenafil, an oral medication introduced in the market approximately 6 years ago, is a potent inhibitor of type-5 phosphodiesterase (PDE5), responsible for degradation of cyclic guanosine monophosphate (cGMP). Sildenafil enhances the relaxing effect of nitric oxide (NO) released in response to sexual stimulation by increasing cGMP concentrations in the cavernous body. This results in increased penile rigidity and tumescence. Success rates among spinal cord-injured patients range from 75 to 94% (10-12). For the majority of writers, the best results are achieved by patients with partial neurological damage. On the other hand, Sanchez Ramos et al. (11) demonstrated that there was no difference in the response to medication when comparing either the severity of neurological impairment or the level of spinal cord lesions. Adverse effects resulting from Sildenafil use among patients with SCT do not differ from those observed in the general population and range from 10 to 42%. Headaches (17%) and face rubor are among the most frequent side effects (12). Tadalafil and vardenafil, 2 other inhibitors of phosphodiesterase that have been more recently used, produce effects similar to Sildenafil in spinal cord-injured patients (9,10,13).

Apomorphine, a dopaminergic agonist, acts by stimulating the D2 receptors in the paraventricular nucleus of the hypothalamus. This activates pro-erectile central pathways involving NO and oxytocin, thus leading to erection (10,14). The only study on the efficacy of apomorphine for erectile dysfunction in spinal cord-injured patients was performed by Strebel et al. (14). Only 2 out of 22 patients presented satisfactory erections following the use of sublingual apomorphine.

Intracavernous injections of vasoactive substances provide a success rate of 95%, defined by achievement of an erection suitable for penetration (15,16). Treatment should start with low dosing due to the risk of priapism (papaverine 7.5 mg, or prostaglandin E1 2 μ g). In addition to priapism, other po-

tential complications for this treatment modality include penile excoriation, infection and fibrosis of the cavernous body.

Vacuum devices (17,18) promote an increase in penile blood flow due to the negative pressure they generate. Once the erection is obtained, a constriction ring is placed at the base of the penis. Patients should not keep this ring in place for more than 30 minutes due to the risk of ischemic penile damage. Denil et al. (17) assessed 20 patients with SCT using vacuum devices. After 3 months, 93% of the men reported proper erections, but this index decreased to 41% after 6 months, with the most frequent complaint being early loss of erection rigidity. Its use is contraindicated in patients with blood dyscrasias, or those using anticoagulants due to complications such as ecchymoses, skin edema and abrasions.

The implantation of a penile prosthesis (19) is usually the last therapeutic option, and is attempted when all previously described techniques have failed. There is a wide range of materials and models that adapt to each patient's condition and needs. Semi-rigid prostheses have the advantage of easy implantation, a low mechanical failure rate and low cost. The disadvantages are that the penis remains constantly in an erect position, in addition to presenting a higher risk of penile erosion. Inflatable prostheses promote an appearance more resembling that of a normal erection, however their implantation is more laborious and costs are quite high. In patients with SCT, the penile prosthesis aims also to assist in the management of urinary incontinence, making the adaptation of external penile collectors easier (20). Kimoto & Iwatsubo (20) assessed 82 spinal cord-injured patients. Follow-up time ranged from 1 to 10 years (mean 4 years) and obtained a satisfaction rate of 64% for sexual function and 93% for adaptation of the urine collector. Complications occurred in 13.3% of cases, with the most frequent being extrusion of the prosthesis and cavernous infection.

EJACULATORY DYSFUNCTION

Ejaculatory dysfunction is one of the main factors for infertility in patients victimized by SCT

(1,3-5,21). In 1948, Horne et al. (3) reported that ejaculation was present in only 18% of the 84 patients under study whose spinal cord trauma occurred above the sacral level. Talbot (4) assessed 408 patients and found an even lower value – only 10% of reported antegrade ejaculation.

Normal ejaculatory function, a primarily sympathetic phenomenon, consists in a complex and coordinated sequence of striated and smooth muscular contractions, which results in the antegrade emission and expulsion of sperm. The dorsal nerve of the penis transmits the afferent impulse produced by the tactile stimulation through the pudendal nerve to the cerebral centers. The efferent stimulus follows, occurring through the anterolateral column of the spinal cord until it reaches the sympathetic ganglionic chain (T10 to L2), the hypogastric plexus anterior to the aorta. Short postganglionic fibers divide into branches and reach the prostate, vasa deferentia and seminal vesicles. Adrenergic neurons stimulate the emission of sperm into the posterior urethra, while the bladder neck closes simultaneously, which prevents retrograde ejaculation. Through the somatic innervation (S2-S4), involuntary contractions of the periurethral musculature (bulbocavernosus and ischiocavernosus muscles) and the pelvic floor cause the expulsion of seminal fluid through the distal urethra distal, thus completing the ejaculatory event.

Methods for Assisted Ejaculation

Penile vibratory stimulation (PVS) and rectal probe electro-ejaculation (RPE) are methods currently used for this purpose (3,22-27). The vibratory stimulation was first reported by Sobrero et al. (23) in 1965 as a method for inducing ejaculation in humans. In PVS, a vibratory device is placed in contact with the glans and frenulum preputii in order to stimulate ejaculation. Devices with high-amplitude movement (> 2.5 mm) have shown better results when compared with low amplitude devices (< 2.5 mm), with success rates of 60% to 80% and 30% to 40% respectively (28,29). Since it is a non-invasive method, the process can be used at home by the patient himself, with no need for medical assistance. Due to the low local tactile sensitivity, patients should be instructed

towards intermittent and non-prolonged use to avoid penile damage. The PVS shows better results in men with spinal cord lesion located above the thoracic-lumbar efferent center (T10-L2); that is, when the ejaculatory reflex arc remains intact.

Electro-ejaculation was described by Horne et al. (3) in 1948 and is used in cases where PVS fails. It has a higher success rate than PVS – about 90% to 100%. It consists in introducing a rectal probe and applying direct electric stimulation on the sympathetic efferent fibers of the hypogastric nerve through the anterior rectal wall. The procedure is usu-

ally well tolerated and only 5% of patients require sedation or anesthesia for reducing the discomfort. Inadvertent damage to rectal mucosa can occur, and the performance of rectosigmoidoscopy before and after the procedure is routinely recommended. An additional disadvantage is the fact that the procedure's execution is restricted to outpatient/hospital regimen and provides low quality semen (30) (Table-1).

In the presence of retrograde ejaculation, pH changes and potential infections make the vesical environment hostile to the ejaculate, thus demanding urine alkalinization 24-48 hours before the procedure. For

Table 1 – Results with vibratory ejaculation (PVS) and electro-ejaculation (RPE) for obtaining semen and pregnancy rate in patients with spinal cord trauma.

Author	N	Lesion Level	Method	Ejaculation Rate	Pregnancy Rate
Rutkowski et al. (22)	113	NR*	PVS RPE	67% 97%	55% (17/31)
Heruti et al. (25)	84	Cervical - 29 Thoracic - 50 Lumbar - 05	RPE	100%	70% (18/23)
Nehra et al. (26)	78	Cervical Thoracic	PVS RPE	44% 95%	63% (17/27)
Hultling et al. (32)	25	C2 - L3	PVS RPE	NR NR	64% (16/25)
Sonksen et al. (59)	28	-	PVS RPE	79% 100%	32% (9/28)
Brindsen et al. (60)	56	C5 - L1	PVS RPE	17,8% 62,5%	51% (18/35)
Kolletis et al. (61)	27	Cervical - 10 Thoracic - 16 Lumbar - 1	RPE	100%	40% (2/5)
Shieh et al. (62)	10	T3-T12-9 C6 - 1	RPE	100%	80% (8/10)
Buch et al. (63)	18	-	RPE	89%	50% (3/6)
Bennett et al. (64)	37	Thoracic	RPE	53%	40% (4/10)

*NR = non-reported data.

this, sodium bicarbonate is orally administered the day before surgery, or a conservative medium, such as modified human tubal fluid (HTF), is instilled into the bladder after its emptying. Retrograde ejaculate is collected by bladder catheterization (24). Patients undergoing RPE or PVS and with lesions located above the T6 level are more susceptible to autonomic dysreflexia and require continuous monitoring or previous prophylaxis, such as administration of 20 mg of nifedipine 15 minutes before performing the procedure (31).

Alternative methods, such as sperm aspiration from the epididymis or testis by microsurgery or puncture, can be used as well (MESA - microsurgical epididymal sperm aspiration, PESA - percutaneous epididymal sperm aspiration, TESE - testicular sperm extraction, TESA - testicular sperm aspiration). They have the inconvenience of obtaining a small seminal volume and a low number of spermatozoa in relation to ejaculate, and these methods are reserved for cases with obstructive azoospermia or when both PVS and RPE have failed (32,33).

SPERM QUALITY

The quality of the ejaculate is yet another additional obstacle for patients with SCT, even following successful sperm collection by the several methods described above. Despite the absence of agreement among authors, the number of spermatozoa in spinal cord-injured patients is believed to be normal and, contrary to the previous thinking, there is no progressive decline over the years following trauma if the men have proper urological follow-up. Brackett et al. (34) conducted one study with 125 patients victimized by SCT. They analyzed spermograms collected at intervals of 1 to 12 weeks, with an average of 5 samples per patient, over 24 months. This study found no differences in the concentration, total number and motility of spermatozoa in the ejaculate in relation to the time lapsed. However, other authors have reported increased sperm fragility, low motility (mean of 20% in comparison with 70% in healthy patients) and the presence of necrospemia. No correlation was demonstrated between these findings and the lesion level, patient's age, time since the trauma, or frequency of ejaculations (35,36). The exact moment where the seminal quality starts to de-

cline is still an issue for further investigation; however, it can possibly occur during the first months following the spinal cord lesion. It is difficult to assess the patients during the acute phase of SCT because they lack the emotional and physical conditions that would allow them to participate in assisted reproduction procedures. Brackett et al. (35) described a low success index in assisted ejaculation for patients at less than 1 year from the trauma, and once the semen was obtained, there was a small amount of spermatozoa, making the assessment difficult during the acute period. In a prospective study, Mallidis et al. (37) assessed 7 men with SCT and identified a decline in semen quality starting 16 days after SCT, thus recommending seminal cryopreservation in the acute phase. Padron et al. (38) found that the effects of sperm freezing were similar both in healthy patients and those with SCT; that is, there was decreased motility ranging from 60% to 80% after thawing. Due to the inferior seminal quality in spinal cord-injured patients, there is no apparent advantage with routine seminal cryopreservation in this group of patients. The process would be indicated in specific cases, such as the patient's personal wish, difficulty of transporting the ejaculate to the assisted reproduction centers, or limitations in time coordination between sample collection and use (33).

Causes of Low Sperm Quality

The main hypotheses formulated to explain the low sperm quality in spinal cord-injured patient are increase in scrotal temperature, aggression resulting from methods used in bladder emptying, infrequent ejaculations, altered hormonal environment, leukospermia, urinary tract infections and factors in seminal plasma that regulate sperm motility (39-57).

Scrotal Temperature

The similarity in seminal changes observed among patients with SCT has stimulated the search for common factors that could explain them. The increase in scrotal temperature is basically due to a scrotal thermoregulatory change by the autonomic nervous system and to the long periods which such patients remain seated in wheelchairs. Early studies have established a correlation between the increase in scrotal temperature and the low motility of sper-

matozoa. Wang et al. (39) identified an initial scrotal temperature 1.2° C higher among spinal cord-injured patients compared to the control group. On the other hand, Brackett et al. (40) analyzed 66 patients with SCT and 21 controls and did not identify any differences in scrotal temperature or in seminal quality.

Frequency of Ejaculation

Siosteen et al. (41) reported an increase in seminal volume and the total number of motile spermatozoa in 16 patients who presented repeated ejaculations for a period of 4 to 6 months. On the other hand, Sonksen et al. (36) did not identify any changes in seminal quality when assessing 19 patients for a 1-year period on a weekly PVS program.

Method of Urinary Bladder Drainage

Rutkowski et al. (42) evaluated the ejaculate of patients with SCT and identified a better percentage of sperm motility in patients who used intermittent bladder catheterization compared to other methods (indwelling bladder catheter and suprapubic drainage), probably due to the lower rate of urinary infection.

Endocrine Dysfunction

Normality of the hypothalamus-pituitary-gonad axis is fundamental for normal sperm production. Brackett et al. (43) identified a normal hormonal pattern in spinal cord-injured patients. In turn, Naderi et al. (44) identified decreased LH and FSH levels, suggesting that this contributed to the seminal changes to some degree. However, Morton (45) suggested that such changes could be caused by sleep apnea, which is present in 40% of patients with SCT, and associated with hypogonadotropic hypogonadism.

Leukospermia and Urinary Tract Infections

Bacteriuria was described in 60-70% of annual tests in patients with SCT. Wolff et al. (46) reported the association between leukospermia and a decrease in the number and motility of spermatozoa. Ohl et al. (47) have also verified the association between urinary infections and poorer sperm quality. However, seminal improvement is limited following treatment, still maintaining lower levels than healthy patients.

Seminal Plasma

Several authors have investigated the role of seminal plasma as the cause of poor sperm quality. When mixed with spermatozoa from normal men, seminal plasma from patients with SCT promotes a decrease in their motility. Contrarily, the addition of seminal plasma from normal men improves sperm motility in patients with SCT (48). Spermatozoa collected from the vas deferens of patients with spinal cord lesions show higher motility when compared to those obtained from the ejaculate and seminal vesicles, suggesting that the worsening quality could be associated with factors that are present in prostate or seminal vesicle secretions (49,50). Changes in the seminal plasma have been found following SCT installation, such as reduced levels of fructose levels, albumin, glutamic oxaloacetic transaminase, alkaline phosphatase and prostate-specific antigen (PSA), and increased levels of chloride (51,52), reactive oxygen species (ROS) (53) and cytokine (54,55). The low fructose concentration in the semen from patients with SCT, which is a major energy source for the spermatozoa, has been pointed out as a co-factor in asthenospermia. Reactive oxygen species such as superoxide anion, hydrogen peroxide, peroxy and hydroxyl are being correlated with low viability and morphological changes in spermatozoa (56). High cytokines (54) indicate an immunological ground for infertility. Cohen et al. (55) reported improvement in sperm motility following cytokine inactivation by monoclonal antibodies. Anti-sperm antibodies have also been reported as a potential cause of low seminal quality due to their high titers in such situations (57).

ASSISTED REPRODUCTION TECHNIQUES

Due to their low seminal quality, spinal cord-injured patients undergoing sperm collection usually require assistance for achieving fecundation and consequently, fatherhood. Factors that help determine the method to be employed are the patient's seminal parameters, their partner's age, their wife's health conditions and the procedure costs. The most frequently used techniques are intrauterine insemination (IUI), in vitro fertilization (IVF), gamete intrafallopian trans-

fer (GIFT) or zygote intrafallopian transfer (ZIFT) and intracytoplasmic sperm injection (ICSI) in the oocyte (58).

In IUI, the semen is processed and the spermatozoa are separated from the seminal plasma. The partner is monitored by ultrasound or urine tests in order to detect the moment when ovulation occurs. Spermatozoa are introduced into the uterus through a catheter. The seminal concentration should be superior to $5.0 \times 10^6/\text{mL}$ following processing so that the technique can be used. Pregnancy rates oscillated from 8% to 12% per cycle. When seminal concentration is between 2 and 5 million, IVF, GIFT or ZIFT must be preferred. In IVF, spermatozoa are left with the ovules and, following fertilization, the embryos are transferred to the uterus, with pregnancy rates of 20% to 40%. GIFT and ZIFT consist of transferring gametes or the zygote into the uterine tube. Due to the procedure's more invasive nature, they are currently little used. ICSI is the injection of a single spermatozoon into the ovule, with subsequent transfer to the maternal uterus following embryo formation. It is indicated in cases where the previously mentioned methods have failed and in those where the seminal concentration is lower than $2 \times 10^6/\text{mL}$. The success rate (by pregnancy) is also around 20% and 40%. Few studies have reported pregnancy rates (pregnancy/number of couples), or fecundation rates (pregnancy/number of pregnancy trials) in spinal cord-injured patients with assisted reproduction methods, ranging from 32% to 80% (22,25,26,32,59,60-64) (Table-1).

CONCLUSION

Difficulties leading the patient with SCT to infertility are being progressively transposed due to advances in research and technology area. Methods for treating erectile dysfunction (oral and injectable medication, vacuum devices and prosthesis) and ejaculatory dysfunction (PVS, RPE, MESA, PESA, TESA and TESE) have contributed to this. Current studies have tried to establish factors existing in the seminal plasma as being responsible for the low sperm quality, even if there are no definitive results as yet. Currently, assisted ejaculation and reproduction have

tried to answer this deficiency and increase the chances of patients with SCT in reaching their goal of fatherhood.

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CALCIUM CHANNEL BLOCKER AND RENAL MITOCHONDRIAL FUNCTION IN WARM RENAL ISCHEMIA

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ABSTRACT

Objective: Ions, particularly calcium ions, play an important role in ischemia-reperfusion cell injury. In this study, we investigated the action of verapamil on the mitochondrial function of kidneys submitted to ischemia without blood reperfusion in order to study isolated early and late ischemic effects.

Materials and Methods: 44 rats were submitted to bilateral warm renal ischemia for 30 minutes. The kidneys were then immediately reperfused with saline or Euro-Collins (EC) solution, with and without previous administration of 0.35 mg/kg of verapamil. Mitochondrial function was assessed at the end of renal perfusion and after 24 hours of cold preservation.

Results: In kidneys perfused with saline, verapamil allowed a significant early preservation of state III mitochondrial respiration, a result that was no longer evident after 24 hours. In kidneys perfused with EC solution, verapamil did not change state III for either early or late evaluations. Comparison of the groups showed that the results obtained for kidneys perfused with EC were always superior to those obtained for the saline group, except for the initial analysis of kidneys treated with saline and verapamil, which showed results similar to those obtained with EC perfusion alone.

Conclusion: Administration of verapamil before warm ischemia provides partial and short-lasting functional protection of the mitochondrial function in kidneys perfused with sodium rich saline. With Euro-Collins solution, verapamil did not show any additional beneficial effect. This fact permits us to conclude that protective action is effective only under conditions that facilitate increased sodium uptake and/or potassium loss.

Key words: kidney; mitochondria; ischemia; function; verapamil

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INTRODUCTION

Despite the care taken to preserve vital functions in brain dead patients and candidates for organ donation, organs removed from them may pass through a variable period of hypoxia and/or ischemia secondary to a low renal blood flow with a conse-

quent deleterious effect on renal cell metabolism that may affect function after transplantation (1).

In an attempt to reduce renal cell damage, kidney preservation for transplantation currently consists of arterial perfusion with solutions whose composition is similar to that of the intracellular medium used at low temperature. Hypothermia is mandatory

because it decreases the cellular metabolic rate, reducing the renal oxygen demand by 84% at 20° C and by 95% at 10° C (2).

In addition of hypothermia and different preservation solutions, several drugs have been used to maintain cell integrity and to preserve the organs for transplantation (3,4). Among them, calcium channel blockers have shown reduction of cell damage induced by oxygen deprivation. Verapamil has shown a protective effect on renal function in animal models, specifically acute ischemic renal failure when administered before an ischemic episode ranging from 40 to 60 minutes, usually with blood reperfusion after the period of ischemia (5-9), as well as in renal transplantation (10). In addition, there is an anti-oxidant protective effect against tissue injury attributable to oxidative stress (11).

Considering these aspects, the objective of the present study was to assess the action of verapamil on the mitochondrial function in kidneys of rats submitted to 30 minutes of warm ischemia and then immediately perfused with two different solutions at low temperature with no blood reperfusion of the kidney in order to study isolated early and late ischemic effects.

MATERIALS AND METHODS

This study was approved by the Institution Committee on Animal Research, following the recommendations for animal research by the National Institute of Health.

Forty-four male Wistar rats weighing 300 to 345 g were used. Of these, 37 underwent bilateral warm renal ischemia and were divided into 4 groups (A, B, C and D).

Warm renal ischemia: after thionembatal anesthesia (40 mg/kg, intra-peritoneal) and laparotomy, the aorta and vena cava were dissected and renal arterial blood flow was interrupted for 30 minutes by placing vascular clamps in the aorta above the emergence of the renal arteries. Groups B and D animals received 0.35 mg/kg of verapamil intravenously 15 minutes before the beginning of ischemia. After that, the aorta and the vena cava were ligated above and below the renal vessels. A small incision was made

in the vena cava and in situ renal perfusion was started with 20 mL of a solution stored on ice and slowly injected by puncturing the aorta. The injected solution varied between groups, as described below. The incision in the vena cava permitted the drainage of blood and perfusion fluid. One of the kidneys was then randomly removed in order to obtain mitochondria and determine their function. The contralateral kidney was removed and kept in a flask immersed in ice (0 to 4° C), which contained the solution with which the kidney had been perfused. This organ was used 24 hours later for a new determination of mitochondrial function.

Perfusion solutions: Groups A (n = 8) and B (n = 5) - saline (0.9% NaCl); Groups C (n = 12) and D (n = 12) - Euro-Collins® solution. Seven additional rats were used for the determination of control mitochondrial function. Euro-Collins was used in this study due to its frequent use as the main solution for organ perfusion in cadaveric and live donor kidney transplant at our institution.

Determination of mitochondrial function: to obtain the mitochondrial fraction, the kidney is washed in 0.9% saline solution conserved on ice and then fragmented in appropriate medium (0.25 M sucrose, 1 mM EDTA, 1 mg/mL albumin, pH 7.4) using a Potter Elvehjem blender 3 times for 3 seconds at 1 minute intervals. The fraction containing the mitochondria is obtained by centrifugation of this tissue, first at 750 x g for 3 minutes, and then twice at 15000 x g for 10 minutes. All centrifugations were done at 4° Celsius. A Himac CR21 refrigerated Hitachi® centrifuge was used. The final precipitate was suspended and used to determine the protein content and the respiratory activity of mitochondria. The protein concentration was assayed by means of the biuret modified reaction (12,13). The polarographic method involving oxygen electrodes using a Gilson oxygraph was applied to determine the respiratory activity of mitochondria (14).

The parameters of mitochondrial function studied were state III (oxygen consumption in the presence of ADP) and state IV (basal respiration after the mitochondria had converted to ATP all the ADP available in the assay). With these two parameters, the respiratory control ratio (RCR) was calculated for

each respiratory assay. This ratio measures the coupling of oxidative phosphorylation and is used as the quality control of the mitochondrial preparation. In the present study, the only data used were obtained in the experiments in which the RCR of the control mitochondrial preparation presented a value higher than 3.5.

The paired and unpaired Student t-test was used for parametrical variables and the Wilcoxon-Mann-Whitney test for non-parametric variables, with level of significance set at 5%.

RESULTS

Data of mitochondrial function obtained for 73 organs were used, considering the mitochondrial RCR as the quality control of the preparations.

Kidneys perfused with saline and verapamil showed a significant preservation of state III mitochondrial respiration in the evaluation performed immediately after the perfusion period when compared with kidneys without verapamil ($p < 0.05$). However, this difference was not observed after 24 hours of cold kidney preservation.

In organs perfused with Euro-Collins® solution, the administration of verapamil before ischemia did not significantly alter the state III values either at the immediate or at the 24-hour evaluation periods. However, there was a tendency to higher values of these parameters in the animals that received this drug.

When the groups were compared, the results obtained after perfusion with Euro-Collins® solution were always superior to those obtained for the kidneys perfused with saline ($p < 0.05$), except for the animals which received verapamil in combination with saline, whose results were similar to those obtained with perfusion of Euro-Collins® alone ($p > 0.05$).

State III and RCR values are listed in Table-1.

COMMENTS

In aerobic organisms, oxidative phosphorylation is the major source of ATP for all vital processes needing a supply of chemical energy. The variation in free energy to maintain these processes originates from carbon substrates and from the correspond-

Table 1 – Data concerning state III of mitochondrial respiration and respiratory control ratio (RCR) (mean \pm standard error).

Experimental Groups	Time	State III	RCR
A (S)	I	130*, ** \pm 11.7	3.17 \pm 0.38
	L	163.2** \pm 12.5	2.47 \pm 0.33
B (S + V)	I	256.8* \pm 5.8	3.97 \pm 0.40
	L	184.7** \pm 10.2	2.55 \pm 0.38
C (EC)	I	235.1 \pm 12.7	4.77 \pm 0.57
	L	229.6 \pm 17.1	3.75 \pm 0.28
D (EC + V)	I	278.1 \pm 17.8	3.65 \pm 0.38
	L	270.0 \pm 15.2	4.87 \pm 0.43
Control		390 \pm 7.8	5.21 \pm 0.71

$p < 0.05$ - level of significance; * saline group difference with/without verapamil, ** different from Euro-Collins group in the same experimental condition. I = evaluation at the end of perfusion, L = evaluation 24 hours after perfusion, S = saline, EC = Euro-Collins® solution, V = verapamil. State III data are reported as nAtoms O_2 /min. mg prot.

ing electron transport in the respiratory chain that occurs inside the mitochondrial membrane. Oxygen is required as the final electron receptor for the maintenance of these metabolic processes. During ischemia, anoxia prevents this efficient form of ATP production, consequently impairing cell functions.

The cause-effect relationship between the processes for obtaining chemical energy is still quite obscure and depends on membrane integrity (such as integrity of the mitochondrial membrane) and on renal function, which depends on cell organization. In the kidney, one of the consequences of ischemia is the loss of tubular cell polarity and the redistribution of the Na^+ , K^+ ATPase enzyme, which represents cellular disorganization and compromises renal function. The relation of this disorganization to the fall in ATP levels has been proposed by other investigators (15). In the absence of oxygen, the anaerobic glycolytic pathway is activated, with glycogen degradation, lactate and H^+ production, increase in the number of particles with a consequent increase in osmotic pressure, and development of cellular edema (16,17). Not only the lack of oxygen but also the interruption of tissue removal of metabolites contributes to this condition.

Several studies have indicated an important contribution of calcium ion to cell damage in the process of renal ischemia-reperfusion (18,19). Usually, the rapid accumulation of H^+ permits the exchange of this ion with Na^+ and concomitantly the exchange of Na^+ with Ca^{++} . The ion calcium activates phospholipases and proteases (17,20) and a further increase in plasma membrane permeability with a massive calcium influx into the cytoplasmic and the mitochondrial compartments. This process leads to irreversible cell injury.

The beneficial effects of verapamil in the processes of kidney ischemia-reperfusion have been demonstrated. However, this protection may be due both to its vasodilating action and to its effect as a calcium channel blocker (5). Electron microscopy studies have shown that verapamil also acts to preserve the ultra structure of the mitochondrial membrane (21), and possibly reducing the infiltration of neutrophils into the ischemic kidney (22). In the present study, we assessed the action of verapamil on the mitochondrial

function of renal cells when administered in combination with two different perfusion solutions. Any vasodilating effect was excluded, since nephrectomy was performed with no blood reperfusion of the kidney.

The evaluation performed at the end of perfusion showed that in organs perfused with saline, the administration of verapamil before ischemia allowed a significant preservation of state III mitochondrial respiration compared to the group that did not receive the drug. This beneficial effect may correspond to the maintenance of structural membrane integrity observed by Alvarez et al. (21). In addition, the similarity in state III values for groups B and C ($p > 0.05$) in the evaluation performed immediately after nephrectomy suggest that the protection of the mitochondrial membrane provided by Euro-Collins® perfusion was qualitatively similar to that obtained with verapamil.

These data confirm the inadequacy of sodium saline solution alone for renal preservation (allowing for the manifestation of the action of verapamil) and, more importantly, indicate that the ionic effect, i.e., the short duration effect, may be exerted by both the verapamil and the Euro-Collins® solution. This suggests that the prevention of the sodium increase by EC is as beneficial as the initial prevention of the increase in calcium, without synergistic effects of the two maneuvers on prolonged preservation. In acute and short duration episodes of ischemia during which the effects of the changes in ATP levels affecting the functioning of the cellular ion pumps may be initially and partially prevented by the anaerobic production of ATP, the use of verapamil may permit renal membrane preservation in addition to preserving vascular endothelium obtained with the use of sodium rich saline (23).

The disappearance of the protective effect of verapamil on organs assessed 24 hours after renal perfusion with saline may suggest that the action of the drug is short lasting, or that blockade of calcium entry by verapamil occurs only initially. Thus, if sodium continues to be offered through the 0.9% saline solution, the ischemic injury will increase and cell and mitochondrial function will fall over time even under conditions of hypothermia.

The results obtained for the kidneys perfused with the Euro-Collins® solution showed higher values of state III mitochondrial respiration after previous administration of verapamil. These values did not reach a statistically significant level, but may indicate a protective tendency of the drug in addition to that provided by the Euro-Collins® solution. The analysis performed after 24 hours of cold ischemia revealed the persistence of this tendency and favors the hypothesis that the results obtained for the group perfused with saline solution may really represent a worsening of cell injury. It should be pointed out that by not permitting renal reperfusion, we limited the action of verapamil exclusively to the period of ischemia.

This aspect of the experimental design permits us to exclude from the discussion some blocking action of the drug on the calcium elicited phenomena and its eventual vasodilating effects that might be observed at the time of reperfusion. Administration of verapamil before warm ischemia provides partial- and short-lasting functional protection of the mitochondrial fraction in kidneys perfused with sodium rich saline. When the kidneys were perfused with Euro-Collins®, a high potassium solution similar to the intracellular medium, verapamil did not show any additional beneficial effect. This fact allows for the conclusion that the protective action of verapamil is effective only under conditions that facilitate increased sodium uptake and/or potassium loss.

Values of state III mitochondrial respiration closer to those observed in controls suggest that the mitochondrial membranes were functionally more efficient with a greater capacity for synthesis, and therefore were able to re-establish, at least theoretically, ATP stores after organ reperfusion, contributing to the return of cell function.

Recently, the study of prolonged periods of total ischemia in skeletal muscle whose dimensions were maintained in order to preserve energy metabolism (24,25) showed that the variation in state III respiration was a more sensitive indicator of mitochondrial damage than the membrane potential, basal mitochondrial respiration (state IV), or RCR (25). However, the last index (RCR) still seems to represent a

relatively simple and reliable form of evaluating the quality of mitochondrial preparations.

In conclusion, analysis of these results as a whole indicates that the administration of verapamil before the ischemic episode provides only partial- and short-lasting functional protection of mitochondrial function and this protection is superimposed on that promoted by renal perfusion with Euro-Collins® solution before ischemia. On the other hand, early events occurring during the initial period of ischemia may include a possible direct sodium effect upon mitochondrial function. Therefore, this possibility may deserve further investigation when the role of kidney function upon ionic homeostasis is taken into account.

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STONE DISEASE

Shock wave lithotripsy at 60 or 120 shocks per minute: a randomized, double-blind trial

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Purpose: The rate of shock wave administration is a factor in the per shock efficiency of shock wave lithotripsy (SWL). Experimental evidence suggests that decreasing shock wave frequency from 120 shocks per minute results in improved stone fragmentation. To our knowledge this study is the first to examine the effect of decreased shock wave frequency in patients with renal stones.

Materials and Methods: Patients with previously untreated radiopaque stones in the renal collecting system were randomized to SWL at 60 or 120 shocks per minute. They were followed at 2 weeks and 3 months. The primary outcome was the success rate, defined as stone-free status or asymptomatic fragments less than 5 mm 3 months after treatment.

Results: A total of 220 patients were randomized, including 111 to 60 shocks per minute and 109 to 120 shocks per minute. The 2 groups were comparable in regard to age, sex, body mass index, stent status and initial stone area. The success rate was higher for 60 shocks per minute (75% vs 61%, $p = 0.027$). Patients with larger stones (stone area 100 mm² or greater) experienced a greater benefit with treatment at 60 shocks per minute. The success rate was 71% for 60 shocks per minute vs 32% ($p = 0.002$) and the stone-free rate was 60% vs 28% ($p = 0.015$). Repeat SWL was required in 32% of patients treated with 120 shocks per minute vs 18% ($p = 0.018$). Fewer shocks were required with 60 shocks per minute (2,423 vs 2,906, $p < 0.001$) but treatment time was longer (40.6 vs 24.2 minutes, $p < 0.001$). There was a trend toward fewer complications with 60 shocks per minute ($p = 0.079$).

Conclusions: SWL treatment at 60 shocks per minute yields better outcomes than at 120 shocks per minute, particularly for stones 100 mm² or greater, without any increase in morbidity and with an acceptable increase in treatment time.

Editorial Comment

Over the last decade, lithotripter technology has been disappointingly stagnant. Indeed, current lithotripters are less effective at stone fragmentation than the original Dornier HM3 lithotripter. As a result, endoscopic stone management, which has advanced substantially during this same time frame, has become an increasingly attractive option for the treatment of renal calculi. Recent efforts, however, have been underway to improve SWL efficacy and efficiency through optimization of treatment parameters.

Paterson and colleagues first demonstrated in a novel porcine model that slowing the rate of shock wave delivery improved stone fragmentation (1). In the current study, Pace and co-workers report the first prospective, randomized clinical trial comparing slow with fast shock wave delivery on SWL outcomes. Among 220 patients with > 5 mm renal calculi randomized to slow (60 shocks/minute) versus fast (120 shocks/minute) shock wave delivery, "success rates" (defined as stone free or asymptomatic fragments less than 5 mm) were superior in the slow shock wave group. When stratified by stone size into smaller and larger stones (< 100 mm² or ≥ 100 mm²), the difference in success rates and stone free rates between the 2 treatment groups was more pronounced in the larger stone group.

While small stones are generally successfully fragmented under most conditions, larger stones have been less successfully treated, particularly with newer generation lithotripters. Therefore, slowing the rate of

shock wave delivery may provide a means of achieving acceptable outcomes with SWL for stones which are increasing being treated by endoscopic means. The small increase in treatment time associated with slower shock wave delivery should be more than compensated for by the less frequent need for retreatment and the fewer complications associated with poorer fragmentation. Perhaps with optimization of SWL treatment parameters, non-invasive management will once again become the preferred treatment option for renal calculi.

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Randomized controlled study of mechanical percussion, diuresis, and inversion therapy to assist passage of lower pole renal calculi after shock wave lithotripsy

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Urology. 2005; 65: 1070-4

Objectives: To determine whether mechanical percussion, diuresis, and inversion (PDI) therapy after shock wave lithotripsy (SWL) improves the clearance rates of lower pole renal stones.

Methods: In this single-blind study, 108 patients who underwent SWL treatment for lower pole renal stones with a total diameter of 2 cm or less were prospectively randomized into two groups. One group (n = 49) received SWL only and the other group (n = 59) received a median of four sessions of PDI therapy (range 1 to 12), 1 to 2 weeks after each SWL session. PDI therapy was performed as follows. Patients drank 500 mL of water 30 minutes before therapy; they then lay in a prone Trendelenburg position on a 45 degrees -angle couch, and received continuous 10-minute manual mechanical percussion applied over the flank. Stone clearance was documented with plain abdominal radiography, with additional imaging, if indicated, 1 and 3 months after initial SWL therapy.

Results: The patients from both groups were comparable in terms of total stone diameter, infundibular neck diameter, infundibular length, caliceal height, infundibular-pelvic angles, infundibular-ureteral angles, infundibular-vertebral angles, lower pole cortical thickness, and caliceal number. All patients underwent a maximum of four SWL treatments. For all assessable patients, the radiologically documented complete stone clearance rate at 3 months for the SWL-alone group was 35.4% and for the SWL plus PDI group was 62.5% (chi-square test, P = 0.006).

Conclusions: PDI therapy is a valuable adjunct in assisting passage of lower pole renal stone fragments after SWL therapy.

Editorial Comment

The dependent location of the lower pole calyces has been shown to constitute an impediment to passage of fragments after SWL. Other anatomic factors, such as the length, width and angle of the lower pole infundibulum also likely contribute to the probability of fragment clearance. Pace and colleagues previously

showed in a randomized trial that a regimen of percussion, diuresis and inversion therapy in patients left with residual < 4 mm lower pole calyceal fragments after SWL resulted in an additional 40% of patients clearing fragments from the kidney compared with no further clearance in the observation group (1).

In the current study, Chiong and associates randomized patients with lower pole stones to undergo 4 formal sessions of percussion, diuresis and inversion therapy starting 1-2 weeks after SWL versus no additional therapy and found a significant improvement in stone free rates in the treated group compared with the control group (63% versus 35%). Although the mean stone size in the 2 groups was 1 cm in the control group and 0.8 cm in the treated group, patients with stones up to 2 cm in size were included, a group that has previously been shown to respond poorly to SWL (2). As such, this regimen offers promise for improving stone free rates in a group of patients who have historically done poorly with SWL. Perhaps combining these mechanical maneuvers with pharmacotherapy using potassium citrate, which has been shown in a randomized trial to improve clearance of residual fragments after SWL of lower pole stones (3), will further improve treatment outcomes in this problematic patient group.

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ENDUROLOGY & LAPAROSCOPY

Laparoscopic rectovesical fistula repair

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J Endourol. 2005; 19: 603-7

Background and Purpose: Rectovesical fistula (RVF) is a rare complication of radical prostatectomy. A 62- year-old man with clinically localized prostate cancer underwent open radical prostatectomy that was complicated by rectal injury and subsequent RVF development. Conservative management failed, and the patient was referred for surgical correction.

Technique: The operative steps consisted of (1) cystoscopy, (2) RVF catheterization, (3) ureteral catheterization, (4) five-port transperitoneal laparoscopic approach, (5) cystotomy, (6) opening of the fistulous

tract, (7) dissection between the bladder and the rectum, (8) closure of the rectum, (9) interposition of omentum, (10) suprapubic cystostomy placement, (11) bladder closure, and (12) colostomy creation.

Results: The operative time was 240 minutes. The hospital stay was 3 days. The urethral catheter was kept indwelling for 4 days. At 8 weeks postoperatively, the suprapubic tube was removed and the colostomy reversed. At 1-month follow-up, the patient remains free of fistula recurrence.

Conclusion: Laparoscopic rectovesical fistula repair is feasible and represents an attractive alternative to the standard approaches.

Editorial Comment

Rectovesical fistula is a rare complication after radical prostatectomy but when it occurs, it is very frustrating for the patient and the surgeon involved. The authors describe a novel laparoscopic approach to a problem that traditionally has been managed with complex reconstructive open surgery. This manuscript demonstrates the universally well known attractive benefits of minimally surgery, including faster recovery and better cosmetic results.

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Outpatient laparoscopic pyeloplasty

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Urology. 2005; 66: 41-3; discussion 43-4

Objectives: To assess the feasibility of ambulatory laparoscopic pyeloplasty. Laparoscopic pyeloplasty aims to reproduce the excellent functional outcomes of open pyeloplasty while diminishing procedural morbidity.

Methods: Six patients fulfilled specific inclusion criteria for outpatient laparoscopic pyeloplasty: informed consent, body mass index of 40 kg/m² or less, primary ureteropelvic junction obstruction, uncomplicated laparoscopic surgery completed by 12:00 pm, and postoperative pain control by oral analgesics. All patients had a double-J ureteral stent placed cystoscopically before laparoscopic access. No drains were placed postoperatively.

Results: All 6 patients successfully underwent laparoscopic dismembered pyeloplasty (3 left, 3 right) using the retroperitoneal (n = 5) or transperitoneal (n = 1) approach. The average patient age was 22 years. The mean surgical time was 223 minutes (range 165 to 270), the mean blood loss was 82 mL (range 10 to 250), and the mean postoperative hospital stay was 359 minutes (range 226 to 424). Postoperative analgesia comprised a mean of 6 mg morphine sulfate and 32 mg of ketorolac. No complications or readmissions occurred postoperatively. Intravenous urography and Lasix technetium-99m mercaptoacetyl triglycine renal scans documented resolution of obstruction. With long-term follow-up (mean 38.4 months), no recurrences have developed.

Conclusions: We report our initial series of ambulatory laparoscopic pyeloplasty. In this well-selected patient population, outpatient pyeloplasty was feasible and safe.

Editorial Comment

Advancement in the area of laparoscopy allowed better and minimally invasive management of ureteropelvic junction obstruction, departing from the less cosmetic but highly successful open technique. Other less invasive surgical techniques (i.e.; retrograde and anterograde endopyelotomy and Acucise endopyelotomy) offered an attractive outpatient setting but the success rates remained less than optimal. This article reveals that we have not explored all the benefits of minimally invasive laparoscopic surgery with an important caveat demonstrating that great results and low morbidity can only be achieved in high volume and experienced centers in laparoscopic surgery.

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IMAGING

Use of extended pattern technique for initial prostate biopsy

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Purpose: An extended prostate biopsy schema has been advocated at initial prostate biopsy to decrease the rate of false-negative cancer cases. However, critics have raised concerns that this may lead to the greater detection of clinically insignificant cancers. We examined the impact of using an extended pattern schema on cancer detection and also on the finding of smaller and clinically insignificant cancer.

Materials and Methods: Clinical data, including patient age, race, prebiopsy prostate specific antigen (PSA), digital rectal examination, prostate volume, number of needle cores and biopsy findings were abstracted from the medical records of all patients who underwent prostate biopsy in a 5-year period. Extended pattern prostate biopsy was defined as more than 10 cores. Clinically insignificant cancer was defined as a maximal tumor dimension of 1.0 cm or less, Gleason sum 6 or less and organ confined disease at radical prostatectomy. Adjusted regression models were developed to assess the independent effects of using an extended biopsy pattern on the detection of cancer overall and on the detection of clinically insignificant cancer.

Results: A total of 740 men with a mean age of 62.6 years were referred for prostate biopsy. Median PSA was 5.7 ng/ml and prostate volume was 39.7 cc. The OR for detecting prostate cancer was 1.55 (95% CI 1.09 to 2.19) for the extended pattern compared with standard biopsy. Of the subset of 136 patients who underwent radical prostatectomy 12.6% had clinically insignificant cancer. However, in contrast to overall cancer detection, extended pattern prostate biopsy was not found to be associated with an increased risk of detecting smaller or clinically insignificant cancer. PSA density was the single parameter found to be independently associated with the detection of clinically insignificant cancer (95% CI 0.20 to 0.98).

Conclusions: Using an extended prostate biopsy pattern involving more than 10 cores increases the likelihood of detecting prostate cancer. A significant association between more needle cores at initial prostate biopsy and finding smaller and clinically insignificant cancer was not apparent.

Editorial Comment

There is a worldwide tendency to perform an extended biopsy for the initial evaluation of a patient suspecting of prostate cancer. When both scheme of biopsy (sextant and extended) are performed in the same group of patients overall yield of prostate cancer detection varies from 0 to 35%. When we compare the results of both schemes in distinct group of patients the yield is still significant. In a recent review of our clinical database we had a 24.6% detection rate in a group of 2,647 patients submitted to sextant biopsy and a 39.7% detection rate in the group of 1,000 patients who underwent a 12-cores-scheme of biopsy (yield of 15.1%). We have to consider that in the last group many patients were biopsied because their PSA level was > 2.5 ng/mL. The authors reviewed the results of initial prostate biopsy performed in a group of 740 patients in which 136 patients with prostate cancer were treated by radical prostatectomy. The extended pattern prostate biopsy technique (more than 10 cores) increased the cancer detection rates when compared with the sextant scheme, without a significant increase in clinically insignificant disease. Clinically insignificant cancer was defined as cancer with maximal dimensions of 1.0 cm or less at prostatectomy (i.e. a diameter of 1.0 cm or less, corresponding to a volume of 0.5 cc or less), Gleason sum 6 or less and organ confined disease. This article brings us an important information about an intriguing phenomenon, which is related to the potential increasing in the number of clinically insignificant tumors by increasing the number of cores. Similarly to others studies the authors report that they found the lack of an association between an extended biopsy technique and the detection of smaller or clinically insignificant tumors. From a practical point of view one limitation of this study is that the authors used the surgical pathology results for define clinically insignificant cancer. It would be interesting to have this information before surgery. But this issue is also controversial since there are different criteria to predict insignificant prostate cancer on prostate needle biopsy (1): needle biopsies with prostate carcinoma in fewer than 3 cores (from a 6-core biopsy sample), absence of Gleason grade (pattern) 4 or 5, no more than 50% prostate carcinoma involvement in any of these cores, stage T1c and PSA density < 0.15 ng/mL (2) and focal carcinoma on sextant biopsy defined as < 3 mm in length in only one core, no Gleason grade (pattern) 4 or 5, and PSA density (PSAD) cut-off level of < 0.10 ng/mL (3). Other new information is related to PSAD, which was found to be the single parameter independently associated with the detection of overall cancer and clinically insignificant cancer. The authors found that at lower PSAD prostate cancer was less likely to be detected but a greater proportion of them were insignificant cancers and that PSAD greater than 0.2 was the threshold at which there was a lower likelihood of detecting insignificant cancer. Beyond PSAD greater than 0.3 all cancers detected were clinically significant. The authors state that the simple calculation of PSAD may be useful for determining whether the cancer detected by extended biopsies is potentially insignificant disease. Unfortunately, at least in our experience, the majority of patients submitted to the initial biopsy has PSAD < 0.2. This finding is even more pronounced when we biopsy patients with PSA level > 2.5 ng/mL.

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MDCT urography of upper tract urothelial neoplasms

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Objective: The purpose of our study was to review the MDCT urography appearance of pathologically proven transitional cell carcinomas of the renal collecting system and ureter and to correlate the MDCT urography findings with pathology findings.

Materials and Methods: Of 370 MDCT urography examinations performed over an 18-month period, 18 patients were diagnosed with 27 renal collecting system or ureteral urothelial neoplasms at endoscopic biopsy (n = 8) or surgery (n = 19). Initial MDCT reports were reviewed to determine the sensitivity of original reviewers in detecting these neoplasms. Two radiologists also retrospectively reviewed these scans and characterized the CT appearance of the neoplasms on both axial CT and 3D reformatted images. Findings at retrospective review were correlated with pathology results to determine whether any CT features could be used to predict tumor grade.

Results: Eighteen of 27 neoplasms were prospectively identified on MDCT urography, and an additional six neoplasms were detected on retrospective review. Three ureteral neoplasms could not be visualized. The 24 retrospectively detected neoplasms had three distinct MDCT appearances: circumferential urothelial wall thickening (n = 14), small masses (> 5 mm in maximal diameter) (n = 5), and large masses (> 5 mm in maximal diameter) (n = 5). All detected lesions could be seen on axial excretory phase images provided wide window settings were reviewed; however, only six were detected on 3D reconstructions. MDCT urography appearance did not correlate with tumor grade.

Conclusion: MDCT urography is a promising technique for detecting upper urinary tract neoplasms. The static 3D reconstructions used in this study are insufficient for visualization. Axial image review remains essential for tumor identification.

Editorial Comment

Multidetector CT (MDCT) urography has been shown to be a promising and effective single comprehensive examination in the evaluation of patients with hematuria or with risk for the development of urothelial malignancies. During MDCT urography the images are obtained in the unenhanced phase (detection of calculi), nephrographic-phase (detection of renal masses) and excretory-phase (detection of urothelial lesions).

The authors nicely presents the imaging findings of 24 neoplasms retrospectively detected in 18 out 370 patients submitted to the "state of the art" MDCT urography. In this investigation 89% of malignant upper tract foci were detectable with this relatively new technique. One of the several important contributions showed by this study was the possibility of detecting small tumors. These small tumors, similarly to larger ones, were both papillary and flat and both high grade and low grade. The authors were able to retrospectively detect small (< 5 mm) tumors. Similarly to larger lesions, these tumors appeared as intraluminal masses and ureteral wall thickening. Most of these small lesions were seen only on the axial images and with wide window settings.

Our early experience with MDCT has also been rewarding since we have been able to prospectively detect some cases of small urothelial malignancies, two of these confirmed as carcinoma in situ. The use of virtual endoscopy in both of these cases was useful to confirm the presence of such small lesions and to differentiate them from ectopic or prominent papillae. Additional information was also offered to the surgeon when endoscopic resection was the modality of treatment.

As pointed out by the authors MDCT will not identify all urothelial tumors due to either its peculiar location or small size or more frequently due to technical problems (lack of opacification of the pelvicalyceal system and ureter).

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UROGENITAL TRAUMA

Management of penile fracture

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J Trauma. 2004; 56: 1138-40

Background: Penile fracture is not a frequent event. It consists of rupture of the tunica albuginea of the corpora cavernosa. Fracture occurs when the penis is erect, as the tunica is very thin and not flexible.

Methods: This prospective study was carried out over a period of 1 year and included 12 patients presenting with penile fracture.

Results: Diagnosis was made clinically, and there was no need to perform cavernosography in any case. The most common cause of fracture was trauma to the erect penis during intercourse. Mean age of patients was 29.5 (+/- 8.96) years, and mean time of presentation was 15.5 (+/- 8.04) hours. Subcoronal circumferential degloving incision was done in all cases. Nine patients were operated on, and three patients refused surgery and were treated conservatively. Repair consisted of evacuation of hematoma and repair of the tunical defect with absorbable sutures. The mean operative time was 33.9 (+/- 8.2) minutes. Preoperative and postoperative antibiotics were used, and all operated cases were discharged on the second postoperative day. All operated cases were able to achieve full erection with straight penis except one, in whom mild curvature and pain during erection was observed.

Conclusion: Penis fracture is a true urologic emergency. It should be treated surgically as early as possible to ensure a better outcome.

Editorial Comment

This Egyptian study is a nice review that emphasizes the importance of prompt surgical repair for the management of penile fractures. Fractures that were repaired had no organic impotence and had straight, painless erections. Those who were managed conservatively developed penile nodules and plaques, and/or penile curvature and erectile dysfunction. Penile fracture is the result of axial forces to the erect penis that result in a tear in the tunica and/or Buck's fascia of the penis. The tear in the fascia is typically transverse, involves the mid to proximal penis and is on ventral to lateral aspect. The tear can be close to or travel under the urethra, and in rare instances can extend into the corpus spongiosum or into urethra (partial or complete transactions). Patients with blood at the meatus or any degree of hematuria and penile fracture need to have the urethra evaluated for concomitant injury. This can be done preoperatively with a retrograde urethrogram or intraoperatively by flexible cystoscopy or by injecting blue-tinged saline retrograde and evaluating for extravasation. The diagnosis of

penile fracture is based on history and physical examination. In rare instances, rupture of the dorsal vein can mimic a penile fracture. Otherwise, the diagnosis is often easy to make. Cavernosography is cumbersome, invasive, rarely ever performed, and generally unnecessary to make the diagnosis. In equivocal cases, magnetic resonance imaging may have a role in the diagnosis of penile fracture, since it is a noninvasive and sensitive and specific modality.

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Treatment of pelvic fracture-related urethral trauma: a survey of current practice in the UK

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BJU Int. 2005; 96: 127-30

Objective: To quantify experience of pelvic fracture-related urethral trauma (PFUT), a condition not often encountered and managed by urologists.

Methods: The consultant urologists of the UK and Ireland were contacted informally to establish their experience with PFUT and its management, both immediate and delayed. In addition, particular individuals thought to have a specific interest in PFUT were targeted for more data.

Results: The overall response rate was 49% (235 responders), representing 78% of urological departments, including all the targeted individuals. Of the responders, 129 (55%) had never seen PFUT in 1-25 years of consultant practice. Only four urologists (2% of responders) saw three or more cases a year. Another four (2%) saw one or two cases per year and the remaining 98 (41%) saw PFUT less frequently. Acutely, 69% of urologists who treated PFUT did so by placing a urethral catheter. Subsequent strictures were treated endoscopically for as long as this was possible. The other 31% inserted a suprapubic catheter and referred the patient for reconstructive surgery if needed. Those who used urethroplasty for strictures after PFUT were identified and targeted; half used urethral mobilization and spatulated anastomosis alone. Only three surgeons performed more than five procedures a year.

Conclusion: Whatever a specialist reconstructive unit might do, practice in the wider urological community is different. Even within specialized units, PFUT is rare and the surgical management is often significantly different from published 'expert' opinion.

Editorial Comment

This British paper eloquently states what those of us who specialize in trauma and urethral reconstructive surgery have experienced in practice for years. Despite a wealth of literature supporting that managing urethral distractions by a "reconstructive ladder" is antiquated and prone to failure, this is the most common method practiced by contemporary British and Irish urologists. Furthermore, most UK urologists manage only a handful of urethral distraction injuries their entire career, and even fewer have performed a posterior urethroplasty. It is this general lack of experience and knowledge of the literature that makes minimally invasive methods of management disproportionately popular. Posterior urethral injury from pelvic fracture is a distraction injury where the space between the separated ends of the urethra fills with scar. Thus, posterior urethral distraction

injuries are not really urethral strictures, and thus minimally invasive methods and “cut to the light” procedures do not have any durable success.

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PATHOLOGY

Prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens

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Scand J Urol Nephrol Suppl. 2005; 216: 20-33

The information provided in the surgical pathology report of a prostate needle biopsy of carcinoma has become critical in the subsequent management and prognostication of the cancer. The surgical pathology report should thus be comprehensive and yet succinct in providing relevant information consistently to urologists, radiation oncologists and oncologists and, thereby, to the patient. This paper reflects the current recommendations of the 2004 World Health Organization-sponsored International Consultation, which was co-sponsored by the College of American Pathologists. It builds on the existing work of several organizations, including the College of American Pathologists, the Association of Directors of Anatomic and Surgical Pathologists, the Royal Society of Pathologists, the European Society of Urologic Pathology and the European Randomized Study of Screening for Prostate Cancer.

Editorial Comment

This consensus meeting was held in Stockholm in 2004 and sponsored by the World Health Organization. I will emphasize some topics of interest for the urologist.

1. Histopathologic type: greater than 99% of all carcinomas are acinar. The remain types include urothelial, ductal (endometrioid), mucinous, signet ring cell, adenosquamous, small cell carcinoma and sarcomatoid carcinoma. Although uncommon, the aggregate data on these variants suggest that they may have diagnostic, prognostic or therapeutic importance. Urothelial carcinoma is not hormone dependent. Small cell carcinoma (with or without neuroendocrine differentiation) is usually associated with widespread, often concurrent, metastasis (frequently to unusual locations) and rapid acceleration of clinical course. Sarcomatoid carcinoma (carcinosarcoma) of the prostate, like small cell carcinoma, has an extremely poor prognosis with a median survival of 3 years.

2. Gleason score: it predicts findings in radical prostatectomy (pathologic stage), biochemical progression, local recurrences, and lymph node or distant metastasis. The most significant recommendation is to separately report the Gleason score for each recognizable core irrespective of whether the cores are individually submitted (in individual container signifying specific anatomic location), or submitted together. Another important change is the recognition and reporting of the tertiary pattern of higher grade in needle biopsies. A case with primary pattern 3, secondary pattern 4, and tertiary pattern 5 should be assigned a Gleason score $3 + 5 = 8$.

3. Extent of involvement of needle core: there is lack of consensus in the literature and, hence, to some extent in clinical practice as to the best method of reporting the extent of tumor involvement. It is recommended that the report should provide the number of involved cores, the percentage estimate of involvement of each of the cores derived by visual estimation and the linear length in increments of 0.5 mm.

4. Local invasion: the prostate has not a true fibrous capsule. Terms such as “capsular invasion” or “capsular penetration” should not be used. The proper term is extraprostatic extension. Only exceptionally rarely is fat present within the normal prostate. Hence, tumor in adipose tissue in a needle biopsy specimen can safely be interpreted as extraprostatic extension.

5. Perineural invasion: although perineural invasion in needle biopsy specimens is not an independent predictor of prognosis when Gleason score, serum PSA and extent of cancer are factored in, some studies indicate that its presence correlates with extraprostatic extension. The data are conflicting. Clinicians should be aware that all cases of perineural invasion on needle biopsy would not necessarily have extraprostatic extension.

6. Reporting of atypical foci suspicious but not diagnostic of malignancy: atypical small acinar proliferation (ASAP) is not a diagnostic entity and is not synonymous with high-grade prostatic intraepithelial neoplasia (HGPIN). It represents descriptive diagnostic terminology in which there is architectural and/or cytologic atypia that does not reach an individual pathologists' threshold required for the diagnosis of cancer. The term ASAP may be confusing for the urologist. The committee members recommended designating atypical biopsies as either suspicious or highly suspicious for cancer. These patients should have a close clinical follow-up and re-biopsied.

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Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens

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Scand J Urol Nephrol Suppl. 2005; 216: 34-63

This paper, based on the activity of the Morphology-Based Prognostic Factors Committee of the 2004 World Health Organization-sponsored International Consultation, describes various methods of handling radical prostatectomy specimens for both routine clinical use and research purposes. The correlation between radical prostatectomy findings and postoperative failure is discussed in detail. This includes issues relating to pelvic lymph node involvement, detected both at the time of frozen section and in permanent sections. Issues of seminal vesicle invasion, including its definition, routes of invasion and relationship to prognosis, are covered in detail. The definition, terminology and incidence of extra-prostatic extension are elucidated, along with its prognostic significance relating to location and extent. Margins of resection are covered in terms of their definition, the etiology, incidence and sites of positive margins, the use of frozen sections to assess the margins and the relationship between margin positivity and prognosis. Issues relating to grade within the radical prostatectomy specimen are covered in depth, including novel ways of reporting Gleason grade and the concept of tertiary Gleason patterns. Tumor volume, tumor location, vascular invasion and perineural invasion are the final variables discussed relating to the prognosis of radical prostatectomy specimens. The use of multivariate

analysis to predict progression is discussed, together with proposed modifications to the TNM system. Finally, biomarkers to predict progression following radical prostatectomy are described, including DNA ploidy, microvessel density, Ki-67, neuroendocrine differentiation, p53, p21, p27, Bcl-2, Her-2/neu, E-cadherin, CD44, retinoblastoma proteins, apoptotic index, androgen receptor status, expression of prostate-specific antigen and prostatic-specific acid phosphatase and nuclear morphometry.

Editorial Comment

This is a long paper of the Consensus meeting held in Stockholm in 2004 and sponsored by the World Health Organization. I will emphasize only some of the topics of interest for the urologist.

1. Seminal vesicle invasion: this finding in a radical prostatectomy specimen markedly diminishes the likelihood of cure. In contemporary series of men with positive seminal vesicles and negative pelvic lymph nodes, 5-year biochemical progression-free rates range from 5% to 60%. The diagnosis of invasion should be restricted to invasion of the muscle layer of the seminal vesicle that is a structure exterior to the prostate. Cases that some have diagnosed as invasion of the “intraprostatic portion” of the seminal vesicle should be regarded as invasion of the ejaculatory duct. Possible routes of seminal vesicle invasion are: 1) extension into soft tissue adjacent to the seminal vesicle and then into the muscle layer; 2) invasion via the sheath of the ejaculatory duct and extending up into the seminal vesicle muscle layer; and 3) discontinuous metastases. There are conflicting studies as to whether the first or second method is most common. Metastases are the least common mode of spread.

2. Extraprostatic extension: because the prostate lacks a discrete capsule, the term extraprostatic extension should be used instead of “capsular” penetration to describe tumor that has extended out of the prostate into periprostatic soft tissue. Prognosis has relation to extraprostatic extent. This evaluation, however, is controversial. Unfortunately, the most prognostic method to substratify the degree of extraprostatic extent remains the subjective designation of focal versus nonfocal.

3. Margins of resection: the pathological definition of positive margins of resection is “tumor extending to the inked surface of the prostatectomy specimen which the surgeon has cut across”. There are two causes for positive margins: transection of intraprostatic tumor (iatrogenic incision) and non-iatrogenic. Tumors in stage T2 with positive surgical margins are designated stage T2+. This is because the pathologist cannot evaluate if the tumor in the area with positive margin is confined to the gland or has extraprostatic extension. The pathology report should also indicate the presence of normal prostate tissue at the resection margin level. This might help the urologist explain why the serum PSA in patients with such a feature remains detectable after radical prostatectomy. In fact, the serum PSA value, even though very low, is not linked to tumor recurrence and persistence, but to incomplete resection of the prostate gland.

4. Gleason score: is a very powerful predictor of progression following radical prostatectomy. Gleason scores 2-4 are rarely seen. Most of the cases were tumors incidentally found on transurethral resection (stages T1a and T1b). All men with only Gleason scores 2-4 tumor at radical prostatectomy are cured. The prognosis of Gleason scores 5-6 shows a spectrum in its biologic behavior depending on other variables such as margin status and organ-confined status. Gleason score of 7 have a significantly worse prognosis than those with Gleason score 6. It is controversial the prognostic significance of Gleason score 3 + 4 versus Gleason score 4 + 3. Gleason scores 8-10 account for only 7% of the grades seen at radical prostatectomy. Typically, these tumors are highly aggressive and present at an advanced stage such that are not amenable to localized therapy.

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INVESTIGATIVE UROLOGY

Pelvic floor exercises for erectile dysfunction

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BJU Int. 2005; 96: 595-7

Objective: To examine the role of pelvic floor exercises as a way of restoring erectile function in men with erectile dysfunction.

Patients and Methods: In all, 55 men aged > 20 years who had experienced erectile dysfunction for ≥ 6 months were recruited for a randomized controlled study with a cross-over arm. The men were treated with either pelvic floor muscle exercises (taught by a physiotherapist) with biofeedback and lifestyle changes (intervention group) or they were advised on lifestyle changes only (control group). Control patients who did not respond after 3 months were treated with the intervention. All men were given home exercises for a further 3 months. Outcomes were measured using the International Index of Erectile Function (IIEF), anal pressure measurements and independent (blinded) assessments.

Results: After 3 months, the erectile function of men in the intervention group was significantly better than in the control group ($P < 0.001$). Control patients who were given the intervention also significantly improved 3 months later ($P < 0.001$). After 6 months, blind assessment showed that 40% of men had regained normal erectile function, 35.5% improved but 24.5% failed to improve.

Conclusion: This study suggests that pelvic floor exercises should be considered as a first-line approach for men seeking long-term resolution of their erectile dysfunction.

Editorial Comment

The first time that pelvic floor exercise was discussed and documented as a realistic alternative for treatment of erectile dysfunction was in 1993 by Claes & Baert, for patients with mild degrees of venous leakage (1). The authors randomized a group of 150 consecutive male patients with erectile dysfunction and proven venous leakage to surgery or to a program of pelvic floor training. Surgery was not superior to the pelvic floor training program either subjectively or objectively. 42% of patients was satisfied with the program and refused surgery (1). Since then, a couple of works have been done on this subject, with somewhat good results (2,3).

Doctor Grace Dorey and co-workers have been extensively working in this field, examining the role of pelvic floor muscle exercises (focusing on the bulbocavernosus and ischiocavernosus muscles) as a key to restoring erectile function. The present work is one more important contribution from this group. The authors concluded that pelvic floor muscle exercises should be considered as a first-line approach for erectile dysfunction. This might be more important in men seeking long-term resolution of erectile dysfunction without acute pharmacological and surgical interventions, which can cause significant side-effects.

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Apoptosis and proliferation in human undescended testes

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Objective: To study apoptosis and proliferation in the testes of children with undescended testes; the degree to which undescended testes contributes to a patient's ultimate fertility is debatable, but undescended testes have fewer germ cells, and some have proposed that apoptosis is an important cause.

Patients and Methods: Testis biopsies were taken at the time of orchidopexy in a consecutive series of children undergoing surgical repair for undescended testes. Immunohistological techniques were used to detect apoptosis and proliferation, and the numbers of cells undergoing apoptosis or proliferation per 50 seminiferous tubules were recorded.

Results: Inguinal testes had less apoptosis than abdominal testes, with a mean (sd) of 0.71 (1.31) vs 1.63 (1.95) apoptotic cells per 50 seminiferous tubules ($P < 0.02$). Similarly, there was less apoptosis in children aged > 1 years than in children aged < 1 years (0.68 (1.40) vs 1.35 (1.56); $P < 0.03$). Proliferation was very limited in all cryptorchid testes. In contrast to cryptorchid testes, five autopsy controls had many more apoptotic cells, (10.60 (1.34) per 50 seminiferous tubules), and many more proliferating cells, (8.40 (6.43) per 50 seminiferous tubules).

Conclusion: In contrast to animal studies, neither apoptosis nor proliferation was common in undescended testes from 6 months of age onward. However, apoptosis was more common in abdominal testes and in children aged < 1 year. It is likely that, if substantial apoptosis occurs in human undescended testes, it occurs before 6 months of age.

Editorial Comment

Apoptosis has been implicated in testicular germ cell loss in experimental models of cryptorchidism. Using the rat as an experimental model, it was demonstrated that apoptosis is the predominant mechanism of germ cell death rather than atrophy and necrosis in cryptorchidism (1,2). The mechanisms of germ cell apoptosis have been associated with oxidative stress or testicular exposure to elevated temperature, and there are evidence that endothelial nitric oxide synthase plays a functional role in mouse spermatogenesis in cryptorchidism-induced apoptosis (3).

In the present elegant and well designed study, doctor Kogan and his group, by the first time, showed us that surprisingly and different from animal studies, neither apoptosis nor proliferation was common in undescended testes from children with more than 6 months of age. The authors discussed that this unexpected result is probably due to the timing of the biopsies, as significant apoptosis might have taken place before the typical time of surgical intervention (6 months).

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RECONSTRUCTIVE UROLOGY

An artificial somatic-autonomic reflex pathway procedure for bladder control in children with spina bifida

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J Urol. 2005; 173: 2112-6

Purpose: Neurogenic bladder is a major problem for children with spina bifida. Despite rigorous pharmacological and surgical treatment, incontinence, urinary tract infections and upper tract deterioration remain problematic. We have previously demonstrated the ability to establish surgically a skin-central nervous system-bladder reflex pathway in patients with spinal cord injury with restoration of bladder storage and emptying. We report our experience with this procedure in 20 children with spina bifida.

Materials and Methods: All children with spina bifida and neurogenic bladder underwent limited laminectomy and a lumbar ventral root (VR) to S3 VR microanastomosis. The L5 dorsal root was left intact as the afferent branch of the somatic-autonomic reflex pathway after axonal regeneration. All patients underwent urodynamic evaluation before and after surgery.

Results: Preoperative urodynamic studies revealed 2 types of bladder dysfunction- areflexic bladder (14 patients) and hyperreflexic bladder with detrusor external sphincter dyssynergia (6). All children were incontinent. Of the 20 patients 17 gained satisfactory bladder control and continence within 8 to 12 months after VR microanastomosis. Of the 14 patients with areflexic bladder 12 (86%) showed improvement. In these cases bladder capacity increased from 117.28 to 208.71 ml, and mean maximum detrusor pressure increased from 18.35 to 32.57 cm H₂O. Five of the 6 patients with hyperreflexic bladder demonstrated improvement, with resolution of incontinence. Urodynamic studies in these cases revealed a change from detrusor hyperreflexia with detrusor external sphincter dyssynergia and high detrusor pressure to nearly normal storage and synergic voiding. In these cases mean bladder capacity increased from 94.33 to 177.83 ml, and post-void residual urine decreased from 70.17 to 23.67 ml. Overall, 3 patients failed to exhibit any improvement.

Conclusions: The artificial somatic-autonomic reflex arc procedure is an effective and safe treatment to restore bladder continence and reverse bladder dysfunction for patients with spina bifida.

Editorial Comment

A successful but not rewarding patient treatment of malfunctioning bladders with spina bifida became possible with both the introduction of sphincterotomy of the external urethral sphincter and intermittent clean self-catherisation in order to protect and preserve the upper urinary tract.

In the last two decades there was no real breakthrough in the treatment options for pediatric spina bifida patients. The most commonly used drugs in adults were not approved for children. This includes the direct injection of Botulinum toxin into the detrusor or the external sphincter (1-3).

Through the extraordinary work of Shapiro et al., it was recognized that in patients with spinal cord changes apart from lower urinary tract malfunction, fetal muscle and innervation changes could be seen (4). The “defect in the development” of the lower urinary tract is complete by the 20th week of pregnancy, but that there is no correlation between the smooth muscle cell mal-development and the severity of the spinal cord defect.

It is stunning to see in the present paper that surgery on the spinal roots might be a treatment solution for the malfunction of the lower urinary tract (5). Xiao et al. presented initially their work by creating an artificial somatic-autonomic reflex pathway to treat neurogenic bladder in spinal cord injured patients (6).

They have now apparently found a way for a successful treatment using the same technique in spina bifida patients (7).

In the present study they enrolled 20 children with spinal bifida and performed intradural anastomoses of the ventral root of the L5 with the ventral root of S3. Twelve of 14 patients with a former areflexic bladder improved their bladder pressure from 18.35 to 32.57 cm H₂O. Five of the 6 patients with a detrusor-sphincter dyssynergia increased their bladder capacity from 94.33 to 177.83 mL and postoperatively decreased the post voiding residual from 70.17 to 23.67 mL within 8 to 12 months.

Most of these children (12 male, 8 female; 5 - 14 years) had successful results and were able to void voluntarily (n = 16), whereas one had to scratch the skin dermatome of L5 to initiate the micturation (n = 1). In 17 (85%) patients, they noted improved bladder function (the young patients had an increased bladder storage and bladder sensory in the emptying function and maintained the ability to sense for a full bladder and felt the desire to void). However, some possible side effects might be the partial loss of the L5 motor function.

The surgical option to improve the neurogenic bladder of young patients with spina bifida will increase possibilities in their future life. Because of the success rate, specialized groups should confirm these results with an equivalent follow-up. It seems to be possible that this surgical approach will teach us that the pathology described by Shapiro et al. might be reversible, partial or complete, up to a certain age (4).

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Combined buccal mucosa graft and local flap for urethral reconstruction in various forms of hypospadias

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Purpose: Hypospadias is one of the most common congenital deformities in the male urogenital system. Although there are more than 250 techniques for treating hypospadias, it is often difficult to repair severe hypospadias using conventional methods.

Materials and Methods: We combined a buccal mucosa graft with a local onlay flap for urethral reconstruction in cases of severe hypospadias or a failed previous operation. A total of 162 patients with hypospadias (glandular 11, penile 40, penoscrotal 49, scrotal 34 and perineal 28) were treated between July 2000 and November 2003. For patients whose urethral meatus was perineal 2 treatment steps were taken. First, we used the aforementioned method to construct the penile urethra, and then we constructed the scrotal and perineal urethra with a local flap.

Results: Of the 134 nonperineal cases 127 were managed successfully in 1 stage, and 26 of 28 perineal cases were managed successfully in 2 stages. Most patients had a satisfactory penile appearance. A urethral fistula resulted in 8 cases, of which 4 closed spontaneously within 1 month postoperatively. Meatal stenosis occurred in 1 case.

Conclusions: This technique is simple, safe and reliable, especially in cases of failed previous operation or for salvage hypospadias repair with deficient local tissue.

Editorial Comment

The reconstruction of the pediatric urethra requires knowledge of the anatomical system, specifically of blood supply of both the native urethra and a pedicled flap as well as other peculiarities of certain flaps e.g. hair growth after puberty, thickness of the basement membrane etc. Whereas buccal mucosa has become a frequent way of urethral reconstruction in circumcised adult patients, its use in pediatric patients is rare for various reasons. The data presented in this paper of more than 160 patients deals with the use of a combination of buccal mucosa with a pedicled flap to resolve different forms of severe or previously unsuccessfully operated hypospadias.

Various techniques exist both for the simple as well as the complicated cases of urethral malformations. It has been shown like in many other fields of reconstructive surgery that the best results may be obtained with the simplest possible technique and the use of a pedicled instead of a free flap.

In our experience, the distal hypospadias reconstruction can be performed with an excellent outcome by the MEMO technique (meatus-mobilization technique) (1) with an acceptable surgery time (mean 85 minutes in this series), and no need for a tissue transfer. If necessary a lengthening of the penile shaft is possible in some cases by reconstruction of the penile skin.

Why do we want to mention this paper then? Not always do we have enough pedicled epithelial tissue for a single stage reconstruction, especially in the previously operated penoscrotal or scrotal hypospadias cases. Although we are not totally convinced that pedicled tissue flaps combined with buccal mucosa may be best solution despite the good results presented here, the recent progress with urothelial cell cultivation (2) may be the future in desperate cases. Instead of harvesting buccal mucosa and transposing it to the urethra, expanded urothelium applied to well vascularized flaps may cause less foreign reaction and less morbidity.

This paper is a good preparation for applying tissue engineering in combination with pedicled flaps for complicated urethral reconstruction. Such a combination for the time being is probably the best way to successfully introduce tissue engineering into urologic surgery.

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UROLOGICAL ONCOLOGY

External beam radiation therapy after radical prostatectomy: efficacy and impact on urinary continence

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Introduction and Objectives: The efficacy of adjuvant and salvage external beam radiation (AXRT+SXRT) for prostate cancer after radical prostatectomy (RP) has been debated because of the inability to rule out systemic occult metastasis, uncertainty that radiation eradicates residual local disease and the potential of exacerbating impotency and incontinence. To characterize the effectiveness and treatment morbidity a retrospective review was performed.

Methods: In all, 38 patients received AXRT and 91 received SXRT. The SXRT group was stratified by PSA level, age, race, pathologic stage, margin status, worst Gleason sum, radiation dose and pelvic field. Complications evaluated were impotence and incontinence. Median follow-up was 60.2 months.

Results: The 5-y disease-free survival (DFS) rate was 61.3% for AXRT and 36.3% for SXRT. Multivariate analysis of the SXRT cohort showed Gleason score, pathologic stage and pre-XRT PSA to be predictors of disease recurrence. After XRT 26% had worsened continence.

Conclusions: Patients who recur after RP whose pathologic stage is pT2 or pT3c, Gleason score of 8 or higher or pre-XRT PSA is > 2.0 ng/dL may have microscopic metastatic disease and a decreased chance of cure with SXRT alone. Continence was further impaired after XRT.

Editorial Comment

A current treatment option for positive margins after radical prostatectomy (RP) (required by up to 35% within 5 years after RP) is adjuvant external beam radiation (AXRT), if PSA progression already has occurred salvage external beam radiation (SXRT) often is performed. Outcomes and side effects of these approaches have been documented in the current paper from two large institutions.

The AXRT group had a 5-year disease-free survival (DFS) rate of 61.3%; the SXRT group DFS was 36.3%. Post-RP PSA below 2 ng/mL was a significant determinant of success.

Most interesting are data on side effects of this approach. In all groups a significant deterioration of continence occurred. After XRT 10% of previously continent patients became incontinent and 14% became partially incontinent. These data are even worse in partially continent patients after RP.

Thus, additional radiation treatment should be advocated with a note of caution to patients with PSA progression, and benefits should be weighted against disadvantages.

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FEMALE UROLOGY

Sexual function in women with pelvic organ prolapse compared to women without pelvic organ prolapse

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J Urol. 2005; 173: 1669-72

Purpose: We compared sexual function in women with pelvic organ prolapse to that in women without prolapse.

Materials and Methods: We collected sexual function data using a standardized, validated, condition specific questionnaire. The study group consisted of 30 women with pelvic organ prolapse and it was compared with 30 unmatched controls without evidence of prolapse.

Results: The 2 groups were similar in age, race, parity and postmenopausal hormone use. Subjects in the study group were more likely to have undergone previous pelvic surgery. Mean total Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire scores +/- SD were lower in the study group compared with controls (81.4 +/- 7.3 vs 106.4 +/- 15.5, $p < 0.001$). In the study group total questionnaire scores in women with prior pelvic surgery were similar to those in women without prior pelvic surgery (79.3 +/- 14.9 vs 82.9 +/- 10.2, $p = 0.61$).

Conclusions: Pelvic organ prolapse appears to have a significant negative impact on sexual function.

Editorial Comment

The authors report on a comparison of sexual function in women with pelvic organ prolapse and women without pelvic organ prolapse. They utilized an excellent statistical analysis involving a Likert scale as well as the PISQ (a validated, condition-specific, self-administered questionnaire that evaluates sexual function in women with pelvic organ prolapse and/or urinary incontinence). Statistical planning was utilized to identify the appropriate size study groups to detect a difference if present between the controls and the patients with prolapse.

This is a noteworthy paper that covers an issue, which is not frequently discussed in the medical office but is never far from the thoughts of a large portion of the population. The study's strength lies in the use of a validated self administered questionnaire as well as excellent statistical analysis. It did exclude women younger than 35 years perhaps to obtain a greater degree of similarity between the two groups. In addition, it only involved patients presenting for gynecological evaluation or therapy and not the general population. Several key points on which the paper may educate the reader include the findings that there was no significant difference in dyspareunia rate between women with and without previous hysterectomy as well as in women who have undergone anti-incontinence surgery those who did not. This fact will allow the urologic surgeon to clearly

respond to patients who wonder about their sexual function after their anti-incontinence operation. The publication helps characterize the sexual habits and desires of patients with prolapse compared to the general population including: observing that both groups were able to find a man when needed; both groups felt their men were sexually satisfied to the same degree; both groups wanted sex to the same degree; and both groups attempted to self pleasure at that same rate and had identical rates of anorgasmia. Differences between the two groups that were highlighted did include that women with prolapse, though masturbating at the same degree, were not able to achieve orgasm with the same degree of efficacy and that though both groups desired sexual activity to the same degree, women with prolapse were not able to participate in coitus at the same level of desired frequency.

This is an excellent paper, which should be read and appropriately digested. It would have been of extreme interest if the authors had been able to comment if there was an increased rate for women with prolapse utilizing different sexual techniques or acts of pleasure in order to allow their partner to achieve the same rate of partner satisfaction as those without prolapse in view of their altered vaginal anatomy. I recommend this article for all physicians actively involved in prolapse surgery.

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Experience with the orthotopic ileal neobladder in women: a mid-term follow-up

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Objective: To report our experience with orthotopic bladder reconstruction in women, as currently the ileal orthotopic neobladder is the diversion of choice for women requiring a bladder substitute at our institution.

Patients and Methods: From February 1995 to March 2001, 29 women with muscle-invasive bladder carcinoma underwent a nerve-sparing radical cystectomy and had an orthotopic ileal neobladder reconstructed. The outcome was evaluated at 2 and 6 months and then yearly, by a clinical history, physical examination, voiding diary, stress test and estimate of functional neobladder capacity.

Results: All patients were followed for at least 14 months (mean 27.5); there were no major complications related to the surgery. The mean (range) neobladder capacity 2 months after surgery was 250 (190-320) mL; at 6 months it increased, remaining stable for the remaining follow-up, at 450 (350-700) mL. Four patients (14%) had nocturnal incontinence and one stress urinary incontinence, associated with using three pads per day. Three patients (10%) required catheterization for a postvoid urinary residual of > 100 mL. Of the 29 patients, seven died with metastatic disease and three from causes unrelated to the reservoir or bladder cancer. Currently, 19 patients (65%) are alive and disease-free, with a mean follow-up of 35 months.

Conclusion: Orthotopic neobladder reconstruction in women, using 40 cm of ileum, is safe and gives high continence and low urinary retention rates. Therefore, it should be advised as the first option in women with good renal function and a tumour-free bladder neck.

Editorial Comment

The authors reviewed their experience with orthotopic ileal neobladder in a population of 29 women. The mean long term follow-up was 27.5 months. The authors point out their results as well as their specific technique and commentary on same. They noted that the bladder capacity stabilized at an appropriate volume at

six months with 14% of patients having nocturnal incontinence, 10% of patients requiring self intermittent catheterization to empty their reservoir and 2.5% of the study group having stress urinary incontinence.

This is an excellent review and instructional presentation by these authors. The paper is extremely strong in the area of voiding dysfunction. The use of a voiding diary and the strict criteria of urinary incontinence should be applauded. The authors' notations on their surgical technique and its positive effects should be carefully read by others performing this type of surgery and reconstruction. The very surgically precise technique including nerve sparing has done nothing but reward these physicians with excellent postoperative results. In addition, their explanation of the use of 40 cm of ileal segment for reconstruction and its positive results should be noted. A reader may question why this group required their patients with a residual > 100 cc to undergo clean intermittent catheterization. Perhaps these patients had recurring urinary tract infection or voiding dysfunction that was not clearly stated. In view of this excellent study group and their notations on the quality of life of patients after cystectomy, the authors if able should consider performing a sexual function questionnaire such as the PISQ and report their results on the sexual habits of this group that have had undergone a major yet successful urinary reconstruction. This may have a great value. The study group had a very low level of postoperative stress urinary incontinence. The authors' opinion on options for this subgroup would be of keen interest in view of other reports describing postoperative catastrophes at the time of sub urethral sling placement (1). Would they consider a trans obturator technique in view of its extra peritoneal position? The ileal conduit has been used for an extended period of time, even much to the surprise of the original describers (2). With excellent publications such as this, ileal neo-bladders will continue to increase in use when appropriate thus potentially one day surpassing ileal conduits as the most frequent urinary diversion in women. If dismissive of the orthotopic ileal neobladder, one should not discount the complications associated without diversion including stomal problems, peristomal dermatitis, stomal ischemia, peristomal hernias as well as stomal prolapse (2).

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PEDIATRIC UROLOGY

Routine voiding cystourethrography is of no value in neonates with unilateral multicystic dysplastic kidney

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Objectives: To determine if two successive ultrasound examinations could rule out the presence of clinically significant contralateral anomalies in neonates with multicystic dysplastic kidney (MCDK), thereby avoiding unnecessary voiding cystourethrography (VCUG).

Study Design: We followed 76 newborn infants with antenatally discovered MCDK. Two successive neonatal renal ultrasound examinations were performed, one within the first week and one at around 1 month of life. VCUG and isotopic studies were performed in all infants.

Results: Urologic anomalies of the contralateral kidney were present in 19 of 76 children (25%): vesicoureteral reflux (VUR) in 16 (21%), ureteropelvic junction obstruction in 2 (3%), and renal duplex kidney in 1 (1%). Sixty-one infants (80% of total) had normal contralateral urinary tract on the 2 successive neonatal renal ultrasound scans. Among them, 4 of 61 (7%) infants presented with low-grade VUR on VCUG that had resolved spontaneously before 2 years of age. The sensitivity, specificity, positive predictive value, and negative predictive value of two successive ultrasound scans in the neonatal period to predict contralateral urological anomalies on VCUG were 75%, 95%, 80%, and 93%, respectively.

Conclusions: In infants with antenatally diagnosed MCDK, two successive normal neonatal renal ultrasound scans will rule out clinically significant contralateral anomalies, thereby rendering the need for a neonatal VCUG unnecessary.

Editorial Comment

The authors reviewed retrospectively their experience since 1990 with prenatally diagnosed multicystic kidney disease. They look specifically at the need for a VCUG. They show that about 21% of patients had reflux. This number is comparable to that seen in the literature. Mostly the reflux was low grade, although 7 of 16 had reflux of Grade III, IV or V. The authors show that all cases of high grade reflux, and most of those with low grade reflux, had an abnormal ultrasound. They propose that VCUG should not be done routinely; only when the ultrasound is abnormal.

This is an interesting and somewhat controversial proposal. In general, little severe pathology occurs in the contralateral kidney of a neonate with an isolated multicystic kidney, making the author's proposal attractive. On the other hand, the authors provide no data on the use of prophylactic antibiotics and the rate of urinary tract infection (either with or without antibiotics). Although I intuitively agree with the concept, the data behind the proposal are, in my mind, limited. If they demonstrated that there were no UTIs, even without antimicrobials, this would provide data that diagnosing reflux is truly unimportant in the great majority of cases.

An even more interesting question is the cost-benefit of annual ultrasound examinations. Presumably, these are performed in order to follow the size of the kidney and to rule out a neoplasm. On the other hand, the size of the kidney is largely irrelevant and in the absence of symptoms (extremely rare), there is little need to know the size. Moreover, the disease does not exist in adulthood; hence, virtually all multicystic kidneys must involute over time. Neoplasm is vanishingly rare and even in that rare instance; will an annual ultrasound pick it up in reasonable time? Hence, on theoretical grounds, annual ultrasound is unnecessary. A formal study of this would be valuable.

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Myogenic bladder decompensation in boys with a history of posterior urethral valves
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BJU Int. 2005; 96: 140-3.

Objective: To investigate whether myogenic bladder decompensation in patients treated for congenital posterior urethral valves (PUV, the most serious cause of infravesical obstruction in male neonates and infants) may be secondary to bladder neck obstruction, as despite prompt ablation of PUV these patients can have dysfunctional voiding during later childhood or adolescence, the so-called 'valve bladder syndrome'.

Patients and Methods: The study comprised 18 boys (mean age 14 years, range 6.2-18.5) who had had successful transurethral ablation of PUV between 1982 and 1996, and had completed a follow-up which included serial assessment of serum creatinine, completion of a standard voiding diary, ultrasonography with measurement of urine before and after voiding, a urodynamic examination with simultaneous multichannel recording of pressure, volume and flow relationships during the filling and voiding phases, coupled with video-cystoscopy at least twice. The mean (range) follow-up was 9.3 (6-17) years.

Results: Urodynamic investigation showed myogenic failure with inadequate bladder emptying in 10 patients; five with myogenic failure also had unstable bladder contractions. On video-cystoscopy the posterior bladder neck lip appeared elevated in all patients but in those with myogenic failure it was strongly suggestive of hypertrophy, with evidence of obstruction. At the last follow-up one patient with myogenic failure who had had bladder neck incision and four others who were being treated with alpha-adrenergic antagonists had a significant reduction of their postvoid residual urine.

Conclusion: Despite early valve ablation, a large proportion of boys treated for PUV have gradual detrusor decompensation, which may be caused by secondary bladder neck obstruction leading to obstructive voiding and finally detrusor failure. Surgical or pharmacological intervention to improve bladder neck obstruction may possibly avert this course, but further studies are needed to validate this hypothesis.

Editorial Comment

The authors review their experience treating 18 boys with posterior urethral valves, diagnosed from 1982-1996. Many of the children eventually developed myogenic failure. The authors propose that this is due to secondary bladder neck obstruction.

The observation of progressive myogenic failure in these patients is not new and is increasingly observed as valve patients get older. Clearly this is something that all clinicians should be aware of. The etiology of this is, no doubt, multifactorial, but among the causes is high urine flow and infrequent voiding. The proposal that bladder neck obstruction contributes is intriguing and suggests a potential treatment. However, the data presented are quite limited. Fluro-urodynamic studies are key to the diagnosis and unfortunately no urodynamic data are presented in the paper! The authors present cystoscopic findings, but this condition can not be diagnosed during cystoscopy under anesthesia (or even local anesthesia for that matter). Moreover, the bladder neck musculature is connected to the bladder muscle and it is during bladder contraction that the bladder neck opens. In the case of myogenic bladder decompensation, the bladder neck would not be expected to open. Hence this condition is even more difficult to diagnose once myogenic failure has developed.

Nonetheless, the proposal to consider alpha-adrenergic antagonist therapy in these patients has some merit. Careful documentation of urodynamic function in patients before and after pharmacological intervention would be very interesting. However, this study should be done early on, before myogenic failure. The ultimate would be to demonstrate that years of alpha-adrenergic antagonist therapy prevents myogenic failure, but this will require a large multi-center, long-term study and probably is not realistic.

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ERRATUM

RESORBABLE EXTRACELLULAR MATRIX GRAFTS IN UROLOGIC RECONSTRUCTION Volume 31, Number 3: pp. 192-203, 2005.

In Table-1 there was an incorrect reference. Bard is listed as the manufacturer of SIS, which is incorrect. This product is produced and distributed by Cook Urological.