Original Article

Exploring the Benefits of Preoperative Androgen Stimulation in Hypospadias Surgery: A Histological Analysis of Neovascularization

Abstract

Introduction: The administration of androgens prior to hypospadias surgery is recommended to enhance penile growth, improve neovascularization, and facilitate surgical correction, leading to improved cosmetic results. This study aimed to investigate the histological differences in neovascularization between hypospadiac patients who received preoperative testosterone and those who did not. **Materials and Methods:** A total of 33 boys aged 1–5½ years with anterior, medial, posterior penile or scrotal hypospadias were included in the study. Eighteen patients (Group A) received testosterone at a dosage of 25 mg intramuscularly every 4 weeks for 2–4 doses, with a maximum dose of 100 mg, as directed by an endocrinologist. Fifteen patients (control Group B) underwent hypospadias repair without androgen stimulation. During surgery, tissue samples were obtained from the prepuce and urethral plate (if possible). The samples were stained using immunohistochemical methods with anti-CD31 and anti-VEGF (Vascular Endothelial Growth Factor) antibodies. The number of microvessels with CD31 index and the intensity of VEGF expression in vessels, positive cells, and stroma were evaluated. **Results:** The microvessel count with CD31 index and the expression of VEGF in vessels and positive cells were significantly higher in hypospadiac patients who received preoperative testosterone compared to the control group ($P < 0.001$). **Conclusion:** These findings suggest that preoperative testosterone administration may enhance neovascularization in hypospadiac patients and should be considered in preoperative treatments, especially when using prepucial flaps. Further studies are needed to elucidate the role of vascularity in surgical repair and to validate these findings.

Keywords: *Androgen stimulation, cosmetic results, histology differences, hypospadias, neovascularization, surgical correction*

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Introduction

Hypospadias is a common congenital anomaly, accounting for 5%–8% of all such anomalies, and is caused by incomplete development of the anterior urethra during fetal life (Belman BA, 1985[5], Altwein, 1986[1], Bouty A, 2015[6]) The prepuce of hypospadiac patients is particularly important, as it can be used for neourethra reconstruction and penile skin closure during hypospadias surgery. The blood supply to the hypospadiac prepuce plays a crucial role in the surgical outcome. Androgen stimulation prior to hypospadias surgery has been recommended to improve penile growth, neovascularization, and cosmetic outcomes. This study aimed to investigate the effect of preoperative testosterone administration on neovascularization in hypospadiac patients. Our findings provide compelling evidence that preoperative testosterone administration significantly increases the number of microvessels and VEGF expression in vessels and positive cells in hypospadiac patients. These results suggest that testosterone may play an important role in blood vessel development in patients with hypospadias, potentially improving the success rate of surgical repairs. Further research is needed to confirm these findings and to better understand the role of vascularity in surgical repair.

Materials and Methods

The study protocol was approved by the institutional ethics committee with the reference number 267/October 14, 2011, and informed consent was obtained from the parents of all participating children. The study involved 33 boys aged 1–5½ years with anterior, medial, posterior penile or scrotal hypospadias. To assess the effects of androgen stimulation, the boys were

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divided into two study groups, with 18 boys in group A receiving intramuscular injections of testosterone 25 mg every 4 weeks, in 2–4 doses, with a maximum dose of 100 mg (Luo *et al*., 2003[8]), while the remaining 15 boys in group B did not receive any androgen stimulation and only underwent hypospadias repair.

During the operation, small tissue samples were taken from the prepuce and urethral plate, if possible, to evaluate the effects of androgen stimulation on the number of microvessels and VEGF expression in the tissue samples. Immunohistochemical staining was performed using anti-CD31 monoclonal mouse antibody (JC70A) Agilent Dako and anti-VEGF monoclonal mouse antibody (VG1) Agilent Dako with the avidin-biotin-peroxidase system. The CD31 index was used to count the number of microvessels, while the intensity of the expression of VEGF in the vessels, positive cells, and stroma was also assessed. The angiogenic index was determined by microvessel count/high power field ((Bastos *et al*., 2011[4]; Cree *et al*., 2021 [7])). The use of immunohistochemical methods allowed for the accurate and reliable measurement of these factors. By comparing the effects of androgen stimulation between the two groups, the study was able to assess the impact of androgen stimulation on neovascularization in hypospadiac patients.

Results

The results of the study showed that statistically significant differences were observed between the two patient groups in terms of foreskin CD31 index values ($P < 0.001$), with the testosterone-treated patients (Group A) having significantly higher microvessel count-CD31 values than the control patients (Group B) [Figures 6-9]. However, no statistically significant differences were observed in the CD31 index values in the urethral plate between the two groups ($P > 0.05$).

Regarding the expression of VEGF, statistically significant differences were observed between the two groups of patients in the intensity of the expression of the VEGF index of vessels and cells in the foreskin ($P < 0.001$), with the testosterone-treated patients (group A) [Figures 1 and 2] having significantly higher rates of strong (+++) VEGF expression in vessels and cells than the control patients (group B). However, no statistically significant differences were observed in the expression rates of VEGF in the stroma ($P > 0.05$) [Figures 3-5].

In the urethral plate, statistically significant differences were observed between the two groups of patients in the intensity of cell and stroma VEGF expression ($P < 0.001$), with the testosterone-treated patients (group A) having significantly higher rates of moderate/strong (+++) VEGF expression in cells and stroma compared to the control patients (group B). However, no statistically significant differences were observed in the expression rates of VEGF in the vessels and in the number of cells ($P > 0.05$).

The results of this Table 1 show that there is a statistically significant difference between the two groups in terms of CD31 marker expression. Group A had no markers expressed in the range of 5–9, while Group B had 10 markers expressed in that range (66.7%). Group A had 3 markers expressed in the range of 10–15 (16.7%), while Group B had 5 markers expressed in that range (33.3%). Group A had 14 markers expressed in the range of 16–20 (77.8%), while Group B had no markers expressed in that range. Finally, there were no markers expressed in either group in the range of >20.

In Table 2 the results of the CD31 index from the urethral plate indicate that Group A had 7 samples with values ranging from 5 to 9 (14.3%), 10–15 (28.6%) and 16–20 (42.9%) with one sample having a value greater than 20 (14.3%). Group B had 4 samples with values ranging from 5–9 (25.0%), 10–15 (25.0%) and 16–20 (50.0%) with no samples having values greater than 20 (0.0%). The P value for the comparison between the two groups was 0.856.

The results of this Table 3 show a significant difference between the expression of VEGF in Group A and Group B. In Group A, VEGF expression in vessels was 77.8% for strong expression (+++) and 22.2% for moderate expression (++), while in Group B, the expression of VEGF in the vessels was 33.3% for strong expression (+++) and 66.7% for moderate expression (++). In terms of cell expression, Group A had 88.9% for strong expression (+++) and 11.1% for moderate expression (++), while Group B had 0% for strong expression (+++) and 46.7% for moderate expression (++). The number of cells was also significantly different between the two groups, with Group A having 33.3%–38.9% for 16–30 cells and

Table 1: Foreskin CD31 values by group (*n*=33)

CD31 (number of vessels)	Group A (*n*=18)	Group B (*n*=15)	*P*
5–9	0	10 (66.7)	<0.001
10–15	3 (16.7)	5 (33.3)	
16–20	14 (77.8)	0	
>20	0	0	

Table 2: Urethral plate CD31 marker values by groups (*n*=11)

CD31 (number of vessels)	Group A (*n*=7)	Group B (*n*=4)	*P*
5–9	1 (14.3)	1 (25.0)	0.856
10–15	2 (28.6)	1 (25.0)	
16–20	3 (42.9)	2 (50.0)	
>20	1 (14.3)	0	

Group B having 40.0%–53.3% for 5–15 cells. The expression of VEGF in the stroma was also significantly different between the two groups, with Group A having 66.7% for weak expression (+) and 16.7% for moderate expression (++), and Group B having 53.3% for weak expression (+) and 46.7% for moderate expression (++).

The results of this Table 4 show that a significant difference exists in VEGF expression between the two groups in terms of vascular and cellular expression, as well as for the

Table 3: VEGF expression values in foreskin by groups (*n*=33)

VEGF	Group A (*n*=18)	Group B (*n*=15)	*P*
Vessels (expression)			
Week (+)	0	5 (33.3)	<0.001
Moderate (++)	4 (22.2)	10 (66.7)	
Strong (+++)	14 (77.8)	0	
Cells (expression)			
Week (+)	0	8 (53.3)	<0.001
Moderate (++)	2 (11.1)	7 (46.7)	
Strong (+++)	16 (88.9)	0	
Cells (number)			
5–9	0	6 (40.0)	<0.001
10–15	0	8 (53.3)	
16–20	6 (33.3)	0	
21–25	5 (27.8)	0	
26–30	7 (38.9)	1 (6.7)	
Stroma (expression)			
Week (+)	12 (66.7)	8 (53.3)	0.075
Moderate (++)	3 (16.7)	7 (46.7)	
Strong (+++)	3 (16.7)	0	

VEGF: Vascular endothelial growth factor

Table 4: VEGF expression values in urethral plate by groups (*n*=11)

VEGF	Group A (*n*=7)	Group B (*n*=4)	*P*
Vessels (expression)			
Week (+)	0	2 (50.0)	0.055
Moderate (++)	3 (42.9)	2 (50.0)	
Strong (+++)	4 (57.1)	0	
Cells (expression)			
Week (+)	0	2 (50.0)	0.017
Moderate (++)	1 (14.3)	2 (50.0)	
Strong (+++)	6 (85.7)	0	
Cells (number)			
5–9	0	3 (75.0)	0.060
10–15	5 (71.4)	1 (25.0)	
16–20	0	0	
21–25	1 (14.3)	0	
26–30	1 (14.3)	0	
Stroma (expression)			
Week (+)	0	4 (100.0)	0.004
Moderate (++)	4 (57.1)	0	
Strong (+++)	3 (42.9)	0	

VEGF: Vascular endothelial growth factor

number of cells between 5 and 15. In group A, the majority of vascular expression was moderate (++) and strong (+++) while in group B vascular expression was mainly low (+) and moderate (++). In terms of cellular expression, group A had a majority of strong (+++) expression while group B had a majority of low (+) and moderate (++) expression. As for the number of cells, group B had a majority of cell numbers between 5 and 9, while group A had a majority of cell numbers between 10 and 15. Finally, for stroma expression, group B had a majority of low (+) expression while group A had a majority of moderate (++) and strong (+++) expression.

Discussion

The use of androgen stimulation prior to hypospadias surgery is recommended to promote penile growth, improve neovascularization, and enhance surgical correction with better cosmetic results. The histological differences on neovascularization between hypospadias patients who receive preoperative testosterone and those who do not, have been studied extensively.

One such study conducted by Bastos *et al*. (2011)[4] examined the effects of topical testosterone treatment on the vascularization of the prepuce in hypospadias by measuring the number and volume density of blood vessels. Immunohistochemical staining for von Willebrand's factor was used to assess the number of vessels. The study found that the topical application of testosterone to prepuce tissue resulted in significantly higher neovascularization, increasing the absolute number of vessels and blood vessel volume density. This leads to better oxygenated tissue that is more prone to better cicatrization. Overall, this article provides an important contribution to the field of hypospadias research.

Another study by Savas *et al*. (2020)[10] aimed to determine the microvessel density of normal and hypospadiac prepuce.

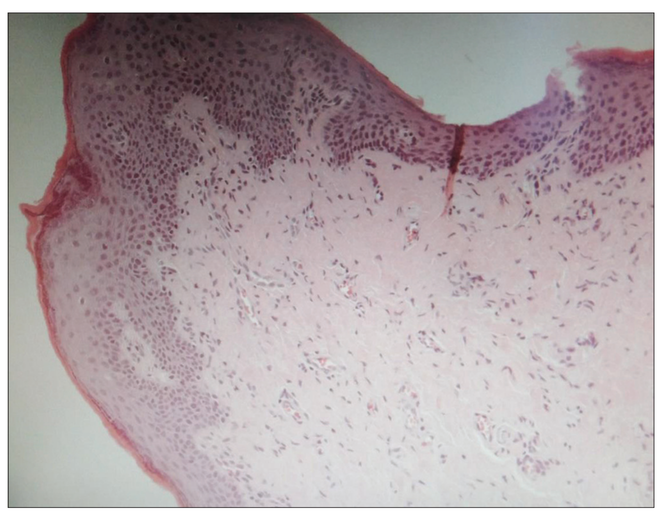

Figure 1: H and E, ×10, Urethral plate, Testosterone (+) Satisfactory epithelial thickness

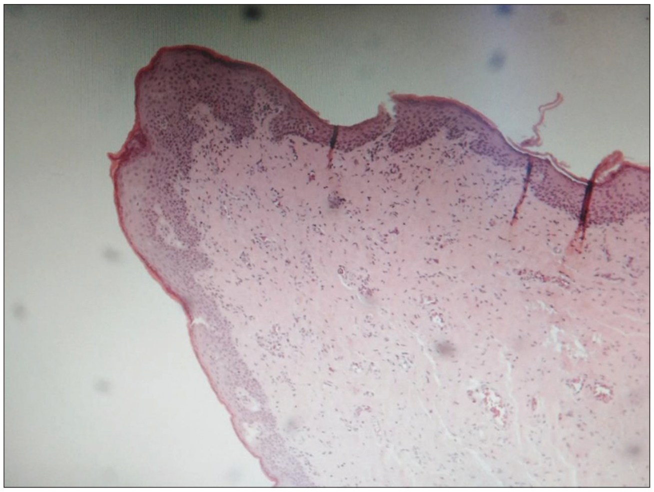

Figure 2: H and E, ×4, Urethral plate, Testosterone (+) Satisfactory epithelial thickness

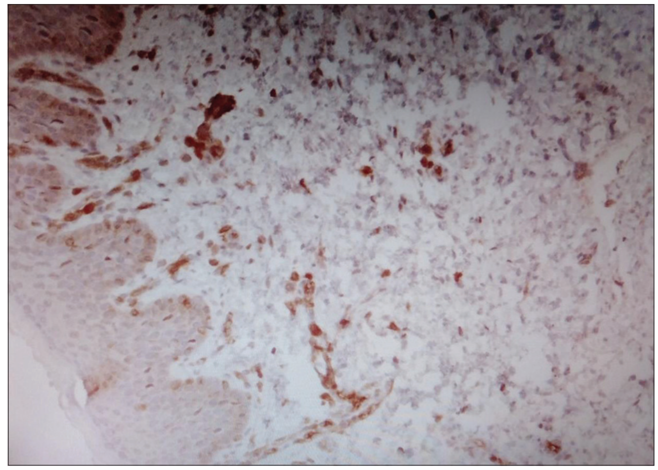

Figure 3: VEGF, ×20 Foreskin, Testosterone (+) Strong to moderate in vessels (++/+++) and weak in stroma (+). The antibody is also distinguishable here in brown

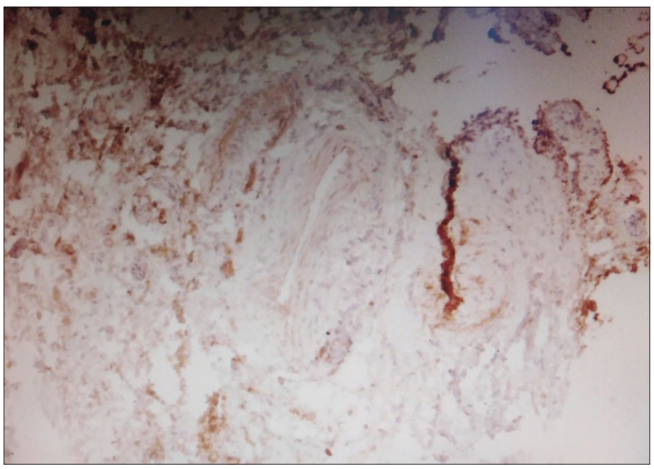

Figure 4: VEGF, ×40, Foreskin, Testosterone (−). The antibody, brown in colour, is faintly visible in the vessels, especially in the vessel in the middle of the image

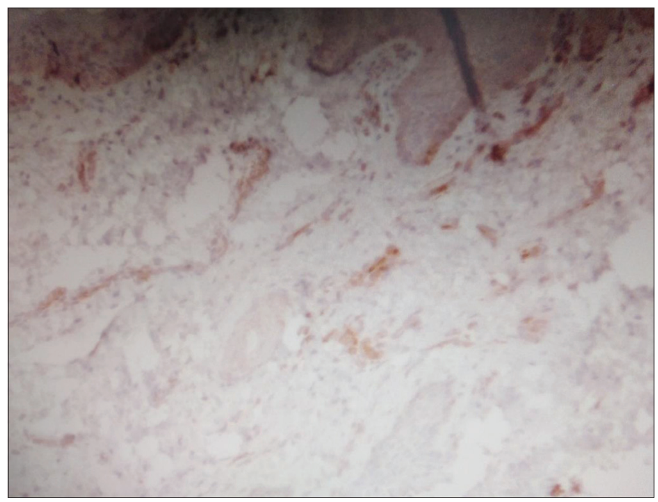

Figure 5: VEGF, ×20, Foreskin, Testosterone (−). The antibody, brown in colour, is faintly visible in the vessels, especially in the vessel in the middle of the image

The authors analyzed the microvessel density of hypospadiac prepuce in male children between the ages of 1–12 years and compared it with healthy age-matched controls. CD31 immunohistochemical staining was used to measure microvessel density. The study found that the microvessel density in hypospadiac prepuce was significantly lower than that in healthy prepuce. Additionally, the authors found that the microvessel density was negatively correlated with the severity of the condition. These findings have important implications for considering preoperative testosterone application treatment.

A systematic review and meta-analysis by Sembiring and Sigumonrong (2021)[11] provides an in-depth analysis of the efficacy of preoperative testosterone therapy in the treatment of hypospadias. The research question was whether preoperative testosterone therapy for hypospadias leads to better outcomes and lower risks of adverse events compared to those who did not receive preoperative testosterone treatment. The analysis found that patients who received preoperative testosterone had a decreased risk of complications such as glandular dehiscence. However, there was no significant difference in the reoperation rate, meatal stenosis, urethral-cutaneous fistula, and penile scarring between the testosterone-treated and control groups.

The prospective randomized study conducted by Babu and Chakravarthi (2018)[3] aimed to investigate the effects of preoperative intramuscular testosterone in improving functional and cosmetic outcomes in children undergoing hypospadias repair. The study included 200 boys, who were randomly assigned to either a placebo group or a testosterone group, with the latter further divided into subgroups based on their response to the treatment. The results showed that preoperative testosterone significantly increased the width of the glans, reduced complications, and lowered the need for reoperation, thereby improving cosmetic outcomes and parental satisfaction.

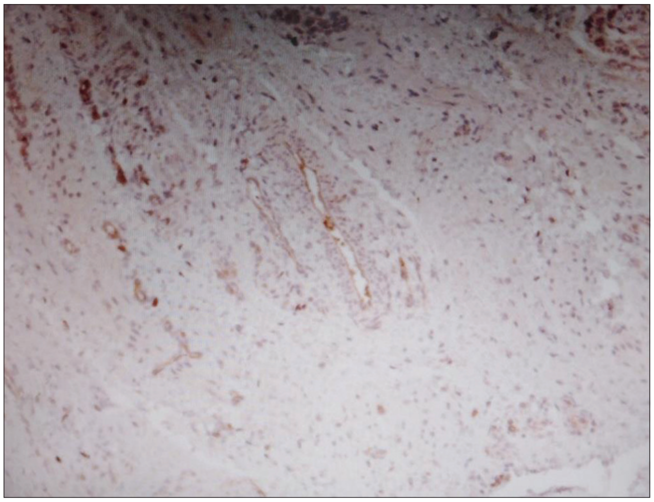

Figure 6: VEGF, ×20, Urethral plate, Testosterone (+) Staining with the antibody, in brown, is seen on the vessel wall. Moderate to strong staining in the vessels and weak staining in the stroma

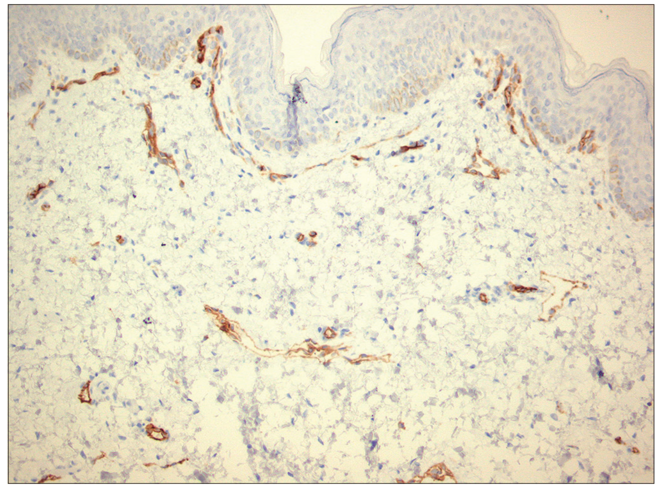

Figure 7: CD31, ×20, Foreskin, Testosterone (+). Staining with the antibody, brown in color, is seen on the vessel wall. Strong staining in the vessels

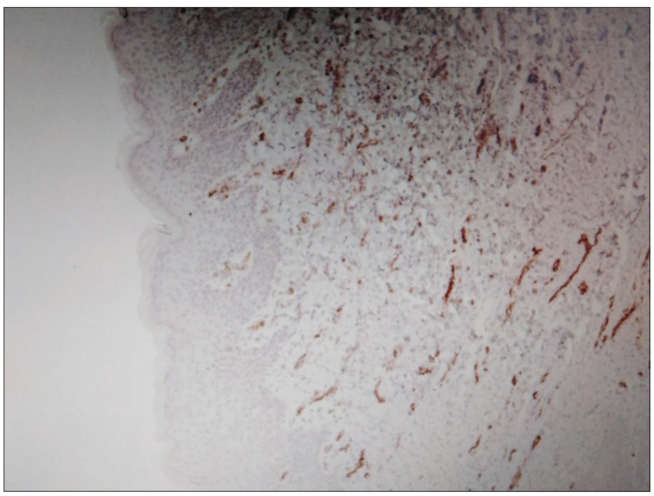

Figure 8: CD31, ×10, Foreskin, Testosterone (+). Staining with the antibody, brown in color, is seen on the vessel wall. Strong staining in the vessels

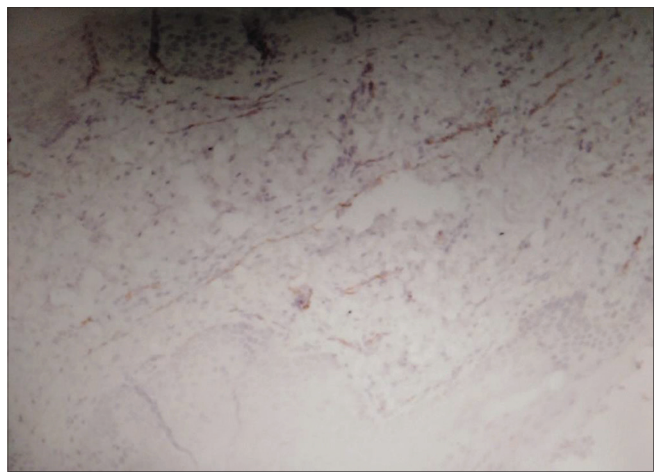

Figure 9: CD31, ×20, Foreskin, Testosterone (−). The antibody is weakly discernible in the vessel wall

In a study by Rynja *et al*. (2018)[9], the long-term outcomes of hypospadias surgery in adult men were investigated, with and without preoperative testosterone application. The study included 121 adult men who had undergone hypospadias repair between 1987 and 1993 at a single medical center in the Netherlands. It was compared height, penile length and penile cosmesis. The study found that complications occurred equally between patients with and without testosterone treatment, and that adult stretched penile length was negatively associated with proximal hypospadias and not with testosterone. Mean adult height was the same in patients with and without testosterone treatment. The authors suggested the need for further research to assess the long-term effects of testosterone administration in this population.

Asgari *et al*. (2015)[2] conducted a prospective, randomized, controlled study involving 182 patients who underwent hypospadias surgery and were followed up to 3 months postoperation. The results showed that preoperative testosterone administration decreased overall complication rates, which were significantly higher in the control group, and also reduced the need for reoperation and resulted in better cosmetic outcomes. These findings suggest that testosterone administration can be used to improve the efficacy of hypospadias surgery.

Sieveking *et al*. (2010)[12] examined the sex-specific role of androgens in angiogenesis in cardiovascular repair/regeneration in male and female endothelial cells (ECs) *in vitro*. They found that male ECs treated with dihydrotestosterone (DHT) demonstrated a dose-dependent increase in key angiogenic processes *in vitro*. The proangiogenic effect of androgens *in vitro* was VEGF-dependent, as exposure of male ECs to DHT produced a dose-dependent increase in the production of VEGF. These findings suggest that the proangiogenic effects of DHT in male ECs are VEGF-dependent, which is consistent with the results of our study, where the VEGF expression in testosterone-treated patients was higher than in the control group.

Conclusion

The present study provides strong evidence to suggest that preoperative administration of testosterone can significantly increase the microvessel count and VEGF expression in vessels and positive cells in hypospadiac patients. These findings are consistent with previous research indicating a positive correlation between testosterone and improved vascularity in various tissues. Therefore, testosterone may play a crucial role in the development of blood microvessels in hypospadiac patients. The increase in microvessels and VEGF expression could potentially enhance the success rate of surgical repairs in hypospadiac patients by providing better blood supply to the repaired area, which creates an optimal environment for wound healing and tissue regeneration. In addition, increased microvessels and VEGF expression could also improve the success rate of flap transfer, which is a widely used surgical technique for repairing hypospadiac patients. These findings highlight the importance of considering preoperative treatments and especially the use of prepucial flaps in hypospadiac patients. Further studies are required to elucidate the precise role of vascularity and its implications for surgical repair.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

How Valuable is Uroflowmetry in Children with Enuresis Nocturna?

Abstract

Objective: Enuresis nocturna is an important social and psychological problem in children. Uroflowmetry (UF) is a noninvasive urodynamic test that is performed in daily clinical practice to evaluate urinary function. In UF evaluation, urine amount, urination time, latency time, maximum urine flow rate access time, maximum urine flow rate, and mean urine flow rate are evaluated. The objective of the study was to evaluate the UF results of children with primary nocturnal enuresis (PNE). **Materials and Methods:** The UF findings of healthy and visualized children without any urinary symptoms and who were prospectively admitted to the urology and pediatric surgery outpatient clinic with the complaint of PNE were compared. Information and UF results of PNE and healthy children included in the study were recorded. In this research, we compared the clinical characteristics and features of bladder assessment: UF, postvoid residuals, and bladder wall thickness between boys and girls with PNE and the clinical characteristics and bladder assessment between children with primary and secondary PNE. **Results:** A total of 183 children, comprised 103 potty-trained children with PNE and 80 potty-trained healthy children were included in the study. There were 60 children in the PNE group and 62 children in the control group. There was no statistically significant difference between the groups in terms of age. When the UF findings of both groups were compared, it was found that only maximum flow was higher in the children with PNE. In other parameters, there was no difference between the two groups. The Qmax in the group with PNE and the control group was found to be 20.48 ± 6.57 ml/s and 17.22 ± 6.17 ml/s, respectively (P = 0.001). **Conclusions:** The present study reveals that there is no difference between patients with enuresis nocturna and healthy individuals in terms of UF. Therefore, UF is not recommended for use in differential PNE diagnosis.

Keywords: *Children, maximum urine flow rate, mean urine flow rate, postvoid residuals, primary nocturnal enuresis, uroflowmetry*

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Introduction

Enuresis is defined as the voluntary or involuntary leakage of urine for at least 3 consecutive months in the daytime and/or nighttime on clothes or the bed for children aged over 5 years old.[1] It is more common in boys than in girls. Until age 5, prevalence is 15%–20% and then declines to 1%–2% after the age of 17 years. Annual spontaneous remission ratios are approximately 14%.[2]

In enuresis pathophysiology, three factors play a significant role: (1) high urine production at night, (2) decreased bladder capacity (BC) or detrusor activity, and (3) impaired sleeping stimulation.[3] The excretion of nocturnal vasopressin is higher at nighttime than in the daytime under normal conditions. This situation causes 50% less urination at night.[4]

Uroflowmetry (UF) is a noninvasive urodynamic test that is performed in daily clinical practice to evaluate urinary function. It not only provides specific measurements but also ensures the graphical evaluation of the patient and plays a vital role in the diagnosis and management of urological diseases.[5] With UF, a straightforward and beneficial measurement method, the urine flow rate can be measured with simple flow measurements. In UF evaluation, urine amount, urination time, latency time, maximum urine flow rate access time, maximum urine flow rate, and mean urine flow rate are evaluated. Flow rate measurements provide information parallel to lower urinary tract (LUT) ultrasonography.[6]

Urodynamic studies usually suggest storage problems in patients with primary enuresis, such as low BC, decreased bladder compliance, and excessive detrusor activity.[1]

In males with LUT symptoms (LUTSs), having a drained volume over 150 mL and a urination time below 11.5 s have been

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accepted as normal.[7] UF results indicating that urination volume for children is >50 mL and that they have 50% of the capacity expected for their age ([years of age +1] × 30) are considered sufficient.[8]

The UF findings of children who applied to the urology and pediatric surgery outpatient clinic due to primary nocturnal enuresis (PNE) were prospectively evaluated.

Materials and Methods

Ethical committee approval was obtained from the Adana City Training and Research Hospital Clinical Research Ethical Committee with the protocol number 14.10.2021/1600 and the study was initiated with ClinicalTrials.gov ID: NCT05190601.

The UF findings of healthy and visualized children without any urinary symptoms and who were prospectively admitted to the urology and pediatric surgery outpatient clinic with the complaint of enuresis nocturna between January 2020 and July 2021 were compared.

The study population consisted of pediatric patients with PNE and healthy children without additional diseases aged 6–16 years.

Inclusion criteria

Patients with PNE, LUT disease (LUTD) diagnosis, without systemic and chronic diseases, >5 years of age, potty trained and fully completed 48-h voiding day and recurrent three UF measurements, and who had 50% of the capacity expected for their age ([years of age + 1] × 30) were included in the study.

Exclusion criteria

Patients with spina bifida, epispadias, hypospadias, vesicoureteral reflux, exstrophy vesica, kidney and liver diseases, genetic diseases and myopathy, neurological diseases, diabetes, epilepsy, cerebral palsy, urological surgery history, urological malignity, psychiatric disorders, active urinary tract infections, and those using any medications that could affect LUTSs were excluded from the study. This was an 18-month study, planned as a prospective cohort.

The highest urination volume obtained from a frequency–volume table for 2 days was accepted as the maximum BC (MBC). The Koff formula was used to measure the expected BC according to age (EBC): volume (mL) = (years of age +1 × 30).[8,9]

BC was expressed as a percentage according to the following formula: BC (%) = MBC/EBC. Nocturnal polyuria was calculated from the volume table, and urine >130% of the EBC according to age was defined as nocturnally produced. For the UF test, the children were asked to wait until they felt a strong urination desire. The UF test was consecutively performed two times and only the curves created after sufficient urination volume (>50% of the EBC) was analyzed. For normal and abnormal urine flow patterns, the categories suggested by the International Children's Continence Society (ICCS) were used: Normal urine flow is bell-shaped, and abnormal urine flow is tower, plateau, and on and off shaped. Bladder ultrasound was immediately performed after urination (within 5 min) using a 5 MHz suprapubic ultrasound. The residue after space was estimated with the following equation: Height × Width × Depth (of the bladder) × 0.52 mL.[1,7] It was accepted that in the empty bladder, the bladder thickness was increased by >4 mm.

Written informed consent forms were obtained for each patient from parents.

Statistics analysis

The independent samples test in IBM Corporation (Armonk, New York, ABD) SPSS Statistics version 25 (Statistical Package for the Social Sciences) was used to determine whether there was a statistically significant (significant) difference between enuresis and control group data. A $P < 0.05$ was considered statistically significant.

Results

The present study included a total of 183 children, 103 potty-trained children with PNE and 80 potty-trained healthy children. There were 60 boys and 43 girls in the PNE group and 62 boys and 18 girls in the control group. In the PNE group, the patient mean age was 9.45 ± 2.96 (6–16) years, while the patient mean age was 9.7 ± 3.07 (6–16) years in the control group. There was no statistically significant difference between the groups in terms of age. Other than the girls having higher Qmax speed in both groups, there was no difference between the sexes in terms of age, follow-up duration, maximum urination volume, or daily urination frequency.

When the UF findings of both groups were compared, only maximum flow was found to be higher in children with (Qmax) PNE. In other parameters, there was no difference between the two groups. Qmax values in the group with PNE and the healthy group were found to be 20.48 ± 6.57 mL/s and 17.22 ± 6.17 mL/s, respectively ($P = 0.001$). In the group with PNE, Qave, mean urination volume, and mean postvoid residual urine (PVR) were found to be 11.24 ± 3.98 mL/s, 198.87 ± 120.52 mL, and 1.71 ± 3.55 mL, respectively. In the control group, Qave, mean urination volume, and mean PVR were found to be 11.52 ± 2.98 mL/s, 207.50 ± 96.99 mL, and 0.95 ± 2.54 mL, respectively [Table 1 and Figure 1].

The fact that the urination amount increases with age attracted attention. In addition, no differences were seen in the group with PNE between the UF findings when compared in terms of sex [Figure 2].

Discussion

UF provides data regarding LUT function and the possible etiology of LUTD.[10]

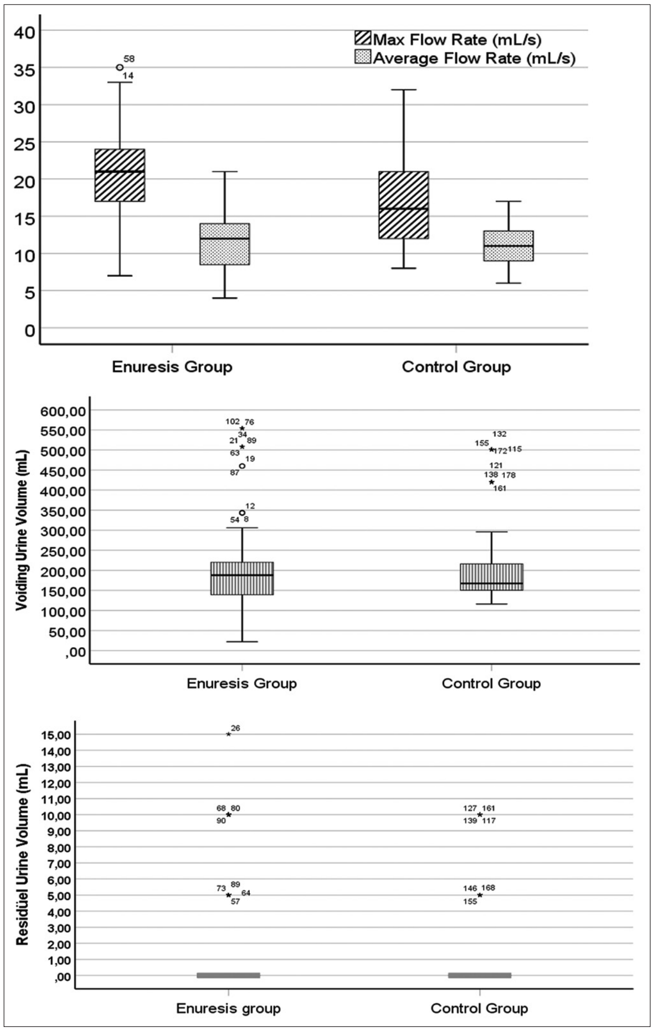

Figure 1: The box plots of data in enuresis and control groups

Since it is simple, noninvasive, and cheap, the UF test has been widely accepted as the first screening tool to evaluate urination function in children.[11] The UF curve model reflects the urination status in children.[12]

ICCS does not recommend bladder ultrasound as a prescreening diagnosis tool in enuresis nocturna. Recent studies have stated that PVR is the only noninvasive diagnostic test to estimate treatment results in children with nonneurogenic LUT dysfunction.[13-15]

UF is more commonly used in adults rather than children. Reasons for this, as documented in one study, include: (1) normal values for children were documented insufficiently, (2) most researchers give a compound value for the pediatric population including wide age ranges and combining the two sexes, and (3) many clinicians believe that children may be nervous during the uroflow, thus the values will not be representative.[10]

Studies conducted regarding UF in healthy children have established certain standards. With respect to the pediatric age group, UF studies regarding certain urinary system

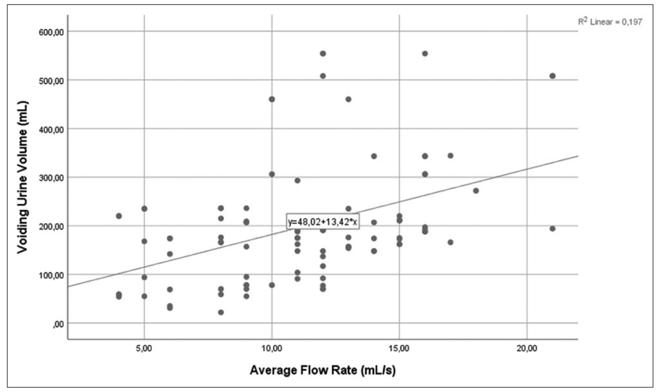

Figure 2: Regression plot of voided urine volumes with mean flow rates in children with enuresis

diseases have been conducted. However, there are a limited number of studies regarding enuresis nocturna. In this respect, importance was attached to this study and an attempt was made to obtain a wider series in terms of patient number. A scan of MEDLINE using the search terms "UF" and "children" yielded a result of 412 articles up to 2022. Similarly, eight articles were found using the terms "UF" and "enuresis." Only one of these eight articles was related to enuresis nocturna. In this study, it was shown that in children with and without enuresis nocturna, bladder function, ultrasonographic, and UF findings regarding upper urinary tract and urinary infection incidence were similar.[13]

UF monograms were drawn based on these positive correlations between the drained volume and flow rates.

While the mean Qmax in the PNE group of the present study was 20.48 ± 6.57 mL/s, another study determined this rate to be 18.9 ± 8.3 mL/s. In a study conducted on healthy children between 5 and 15 years of age (with a mean age of 9 years), mean urination volume and mean Qmax were found to be 220 ± 135 mL and 17.7 ± 6.2 mL/s, respectively.[16] When compared to the healthy group in the current study, similar results were obtained.

The higher Qmax value seen in the present study is considered to have been a result of the higher mean age (9.45 ± 2.96/8.5 ± 2.3 years).

There are studies evaluating the predictor factors for the response focusing on the problems in enuretic children, such as small BC, night polyuria, and stimulation problems.[17] In certain studies, it is explained that in patients with PNE, functional day and night bladder capacities are normal; however, increased urine production at night exceeds functional BC and causes involuntary leakage of urine.[18,19] Some authors argue that patients with PNE have a lower bladder functional capacity.[20]

However, the present study determined that the bladder capacities of children with PNE and healthy children were the same.

In the study of Cayan *et al*., it was found that monosymptomatic enuretic children did not have a

Table 1. Data of enuresis and control groups

	Enuresis Group (n=103) Mean±SD	Control Group (n=80) Mean±SD	t	P
Age (years)	9.45±2.96	9.70±3.7	0.54	0.588
Male/Female (M/F)	60/43	62/18	-	-
Max Flow Rate (mL/s)	20.48±6.57	17.22±6.17	3.41	0.001*
Average Flow Rate (mL/s)	11.24±3.98	11.52±2.98	0.52	0.598
Voiding Urine Volume (mL)	198.87±120.52	207.50±96.99	0.52	0.602
Residual Urine Volume (mL)	1.71±3.55	0.95±2.54	1.62	0.107

*P<0.001 (The Independent Samples Test)

significantly higher PVR compared to the control group.[13] However, no difference was observed between the PNE group and the healthy group in terms of PVR in the present research.

Limitations

The most important limitation of this study is the lack of data that were simultaneously obtained from pelvic floor electromyography as this could provide evidence of urination dysfunction. In addition, the small number of patients is another important limitation of the article.

We believe that in the future, more detailed studies, together with urodynamic studies and pelvic floor electrophysiological studies, will provide more detailed results on this subject.

Conclusions

The present study reveals that there is no difference between patients with enuresis nocturna and healthy individuals in terms of UF. Therefore, UF is not recommended for use in differential PNE diagnosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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A Prospective Study of Hyperbaric Oxygen as a Treatment Option for Radiation-induced Hemorrhagic Cystitis

Abstract

Introduction and Objective: Hemorrhagic cystitis (HC) is a diffuse bladder inflammation that causes hematuria and other urinary tract complaints. Noninfectious hemorrhagic cystitis most commonly occurs in patients who have undergone pelvic radiation. In cases with refractory disease and persistent hematuria, the bladder can be irrigated with a variety of agents. Hyperbaric oxygen (HBO) therapy has been used with some success in difficult cases. In the present article, the safety and efficacy of HBO was examined as the primary treatment choice for radiation-induced HC. **Evidence Acquisition:** Prospective data were collected among patients with HC and previous radiotherapy. HBO was applied as a primary treatment. The primary endpoint of our study was the incidence of complete and partial response to treatment, whereas a variety of secondary endpoints were examined including the duration of response, blood transfusion rate, the avoidance of surgery, and the overall survival. Moreover, the correlation between the interval between the onset of hematuria and initiation of therapy and the success of treatment was recorded. **Evidence Synthesis:** A total of 20 patients participated in the study. The complete and partial response rate was 85% and 15%, respectively. All patients completed therapy while the median number of sessions needed was 31. No complications were recorded during treatment. Patients with complete response received therapy within 3 months of the hematuria onset. One patient needed cystectomy, whereas 19 patients were alive at the end of follow-up. **Conclusions:** HBO consists of an effective and safe treatment option in the management of radiation-induced severe HC. Further prospective studies should be undergone in order to validate its efficacy and safety profile.

Keywords: *Hemorrhagic cystitis, hyperbaric oxygen, hyperbaric oxygen treatment, radiation cystitis*

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Introduction

Hemorrhagic cystitis is defined by lower urinary tract symptoms that include hematuria and irritative voiding symptoms. Several etiologic factors have been determined including infectious and noninfectious causes. It results from damage to the transitional epithelium and blood vessels while a wide spectrum of clinical presentation has been reported. Patients may develop asymptomatic microscopic hematuria or gross hematuria with clots, leading to urinary retention along with irritative lower urinary tract symptoms. In rare cases, it can be a life-threatening situation requiring challenging treatments with prolonged hospitalization. The use of hyperbaric oxygen (HBO) consists of a treatment modality of radiation-induced lesions. Although several studies have been published on HBO therapy for radiation cystitis, most of them use HBO as a secondary treatment while they are retrospective and not randomized or comparative studies. Herein, we present our updated results of a prospective study including patients diagnosed with severe radiation-induced hemorrhagic cystitis (HC) treated with HBO therapy as the first treatment option.[1]

Materials and Methods

Inclusion/exclusion criteria

Prospective data were collected among 20 patients diagnosed with severe Grade 3 or 4 radiation cystitis requiring transfusion (initially Grade 3 or 4 hematuria) according to the Common Terminology Criteria for Adverse Events (CTCAE) [Tables 1 and 2] since May 2021.[2] The study enrolled patients not previously treated for HC except for urethral catheter placement and bladder irrigation as initial and unique previous treatment. Patients with either infectious

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Table 1: Classification of hematuria according to the Common Terminology Criteria for Adverse Events

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

IV: Intravenous, ADL: Activities of daily living

Table 2: Classification of noninfectious cystitis according to the Common Terminology Criteria for Adverse Events

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia, or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

IV: Intravenous, ADL: Activities of daily living

or chemotherapy-induced cystitis were excluded from the study as well as cases with a history of severe chronic obstructed airway disease, spontaneous pneumothorax, spontaneous perforation of tympanic membrane, and uncorrected bleeding disorders.

Evaluation and treatment

Patients presented in our department most commonly complaining of hematuria and irritative symptoms. All patients underwent laboratory examinations including blood count and clotting and biochemistry profile measurements. Moreover, urine samples were collected for urinalysis, urine culture, and cytology. In all cases, imaging examination was performed most commonly using computed tomography. Afterward, cystoscopy examination was performed and bladder biopsies were taken by one surgeon (A.D). Pathology report confirmed the diagnosis of radiation-induced cystitis while excluding bladder malignancy. Patients were initially treated by the placement of urethral catheter (22F–24F) to secure prompt bladder irrigation as well as fluid and electrolyte resuscitation. In addition, HBO treatment was scheduled. Initially, patients underwent 30 HBO sessions in a walk-in multi-place hyperbaric chamber with intent to increase them up to 45 sessions until the hematuria resolved. The treatment protocol included the administration of 100% oxygen at a 1.8 atmospheres absolute pressure per session for 90 min/day, 5 days a week – Monday to Friday. When complete response to HBO was reached, the treatment was ceased. In refractory cases where worsening or relapse of hematuria was observed, HBO treatment was rescheduled. Treatment failure was determined as no recession of the symptoms observed after 45 sessions, severe complications occurred, or if patients declined further therapy. Treatment results were evaluated by the improvement of clinical symptoms while a cystoscopy was performed by the same surgeon within 4 weeks of treatment completion to compare with the pretreatment status. Bladder biopsy was reserved only for patients with subjectively abnormal bladder mucosa.

Study endpoints

The primary endpoint of our study was the incidence of complete and partial response to treatment. Complete responders' patients considered those with complete cessation of bleeding and the lack of need for transfusion in combination with the disappearance of endoscopic findings and concomitant normal bladder findings in repeat biopsies where available. On the other hand, the decrease in the grade of CTCAE scoring criteria and the existence of microscopic hematuria or mild macroscopic hematuria were the criteria of partial response. Meanwhile, the secondary endpoints measured included the duration of response, blood transfusion rate, the avoidance of surgery, the number of sessions needed to achieve success, and the overall survival.

Statistical analysis

Statistical analysis of the results performed using the SPSS 16 (SPSS Inc. Chicago, IL, USA) statistical package with $P < 0.05$ considered significant. Furthermore, the Chi-square and *t*-test were used, as appropriate.

Results

Since May 2021, 20 patients were enrolled in our study. Among them, 17 patients were male and 3 were female, with a mean age of 68.3 years. Patients had a history of previous radiation therapy due to prostate cancer, muscle-invasive bladder cancer, rectal cancer, and cervical cancer in 12, 5, 1, and 2 cases, respectively, with a mean radiation dose of 62.8 Gy (range: 32–80). The mean interval between completion of radiation therapy and onset of hematuria was 18.1 months (range: 1–210) and the mean interval between completion of radiation therapy and the onset of HBO therapy was 24.7 months (range: 2–months). Patients presented to our department after a mean time of 7 months from the onset of the hematuria and the interval among hematuria and HBO treatment was 7.4 months (range: 1–48). In the majority of cases, there was a need of blood transfusion with the median red blood cell packs calculated at 7.6 (range: 3–16).

Diagnosis was set upon pathology reports which included histological findings consistent with postradiation cystitis in all cases. Such findings include diffuse mucosal edema, submucosal hemorrhage, and interstitial or smooth muscle fibrosis. Another possible finding was severe ischemia of the bladder wall.

HBO treatment was well tolerated in all cases with no complications been reported during a mean follow-up period of 24.6 months (range: 5–73). The mean HBO therapy sessions were 31 (range: 24–73). Seventeen patients were characterized as complete responders whereas partial response was recorded in three cases. Patients with partial response experienced a marked improvement in their hematuria (Grade 2). Patients with complete response received therapy within 3 months of the hematuria onset, whereas in the remaining patients with partial response, the meantime interval was 8 months. All demographics and results of our study are detailed in Table 3. One patient from the complete response group had a recurrence of Grade 2 hematuria at 6 months of follow-up and received 18 additional HBO treatments. All aforementioned patients with complete response remained stable for the rest of the follow-up. Two patients experienced severe hematuria 6 months after the end of HBO therapy, and following full consent, one underwent cystectomy and urinary diversion, whereas the other was offered a successful embolization with sporadic episodes of low-severity macroscopic hematuria since then.

Table 3: Demographics and results of our study on hyperbaric therapy in the treatment of radiation-induced bladder complications

Variables	*n*
Patients	20
Men	17
Women	3
Age (years)	68.3
Indications	12 prostate cancer
	5 muscle-invasive bladder cancer
	1 rectal cancer
	2 cervical cancer
Radiation dose (Gys)	62.8 (32–80)
Interval between hematuria to HBO (months)	7.4 (1–48)
Interval between radiotherapy to HBO (months)	24.7 (2–212)
Interval between radiotherapy to hematuria (months)	18.1 (1–210)
Transfusion	7.6 (3–16)
Follow-up (months)	24.6 (5–73)
HBO sessions	31 (24–73)
Response	85% complete
	15% partial

HBO: Hyperbaric oxygen

Posthyperbaric treatment cystoscopy revealed a subjectively normal bladder mucosa in 18 patients. The pathologic examination of the cystectomy specimen revealed, apart from findings of radiation cystitis, a transitional T2G3 muscle-invasive bladder cancer. Regarding our study endpoints, the complete response rate was 85% and the partial response rate was 15%. Nineteen patients were alive at the end of follow-up [Table 3].

Discussion

Pelvic radiotherapy consists of a cornerstone treatment in a variety of diseases. Plenty of acute and chronic bladder complications have been documented during pelvic radiation therapy.[3] Radiation-induced HC is observed in 5%–10% of cases whereas radiation for prostate cancer may lead to moderate or severe hematuria in 3%–5% of cases.[4,5] Meanwhile, severe Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) Grade 3 or worse bladder morbidity has been reported at 1% at 5 years, 1.4% at 10 years, and 2.3% at 20 years following radiotherapy for cervical cancer.[6] The interval between radiotherapy and bladder complications varies between 2 months and more than 20 years with hemorrhage.[7]

Different modalities have been proposed as treatment options of severe radiation cystitis. Commonly, the first-line treatment consists of bladder irrigation with large urethral catheters. Other options include intravesical instillations with alum, silver nitrate, phenol, formalin, or hyaluronic acid. Last but not least, several oral agents have been used, such as aminocaproic acid, tranexamic acid, corticosteroids, estrogens, antibiotics, prostaglandins, and sodium pentosan polysulfate. However, most of the traditional treatments are based on nonrandomized underpowered trials. Furthermore, there are no prospective studies comparing oral, intravesical, and intravenous treatments between them or with HBO, apart from one randomized study between intravesical hyaluronic acid instillation and HBO therapy with similar results.[8] Moreover, some of the treatment options are characterized by serious side effects or may exacerbate bladder fibrosis.[8,9-16] In case of intractable hemorrhage, arterial embolization or ligation and/or cystectomy represent definitive treatment at the cost of increased morbidity.

Mechanism of action of radiotherapy is based on water radiolysis of urothelial cells. As a result, an increase of activated free oxygen radicals is noted that causes cell membrane injury by lipid peroxidation and immediate cell death. Radiation energy *per se* and free oxygen radicals result in replication failures and further cell death.[17] In addition, pelvic radiotherapy initially causes mucosal edema and inflammation as well as telangiectasia, submucosal hemorrhage, and interstitial fibrosis. Obliterative endarteritis of small blood vessels leads to acute and chronic ischemia of the bladder wall. The later chronic endarteritis is successfully described as “the three-H model.”[18,19]

HBO therapy is based on the enhancement of neovascularization on bladder wall as well as to an increase of oxygen supply.[20] In consequence, angiogenesis is stimulated by tissue macrophages responding to the steep oxygen gradient. Interestingly, the tissue oxygen could be noticed in normal levels for many years after HBO therapy, implying that the hyperoxia-induced angiogenesis is essentially permanent.[5] Last but not least, vasoconstriction and improvements of immune function constitute additional beneficial effects of HBO treatment.[21]

Indications of HBO therapy remain controversial and not well documented.[22] Especially, as far as radiation-induced HC is concerned, several series of patients treated with HBO have been published.[5,9-16,18,23-28] The vast majority are retrospective reviews and case series. Meanwhile, a limited number of prospective studies exist.[29] Furthermore, in all these studies, HBO was used as a secondary treatment option and not as a first-line option.

To the best of our knowledge, our study is the first prospective study using HBO as primary therapy for radiation-induced cystitis and severe hematuria. In our study, results on the absolute overall success rate of HBO as primary therapy seem really encouraging. The highest efficacy of our suggested method is further amplified by the fact that patients are stable with no or minor radiotherapy-induced morbidity and should be underlined that none of our patients had to discontinue therapy due to HBO side effects. As a result, we can therefore conclude that primary treatment with HBO has proved to be effective and safe. Finally, underlying causes such as malignancy should be considered in cases that HBO therapy fails.[9,10]

Several limitations of our study should be noted such as lack of randomization and the small size of the sample. However, since cystectomy represents the alternative definitive treatment for radiation cystitis, it will be difficult to randomize patients. In addition, as it is the only prospective study with severe HC patients, the number of patients enrolled in our study is relatively small.

Conclusions

HBO therapy as a first-line treatment modality in patients diagnosed with radiation-induced hematuria (especially within the first 6 months from the hematuria onset) is an effective and safe option with promising results. Larger prospective studies with longer follow-up are warranted to extract well-documented conclusions along with evidence-based guidelines.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Intracorporeal Urinary Diversion versus Extracorporeal Urinary Diversion during Robot-Assisted Radical Cystectomy

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Abstract

Background/Aim: Radical cystectomy (RC) is a fundamental step in the therapeutic plan of nonmuscle and muscle-invasive urinary bladder cancer. Open RC is a surgical procedure with high morbidity and as such robot-assisted RC (RARC) has been established as an efficient alternative. Although in the beginning, the urinary diversion step during RARC was mostly performed extracorporeally nowadays a preference of the intracorporeal approach is yearly increasing. The aim of this review is to compare these two techniques of urinary diversion and depict the latest trends of current research on this field. **Materials and Methods:** A literature search of MEDLINE database (March 26, 2022) was performed to retrieve the articles published in English that are dated between January 1, 2010 and February 28, 2022. The search strategy included terms: "intracorporeal," "vs," "extracorporeal," "urinary," "diversion," "comparison," "after," "RARC" and "or". **Results:** Intracorporeal urinary diversion (ICUD) is strongly associated with lower perioperative blood loss and blood transfusion needs compared with the extracorporeal urinary diversion (ECUD). ICUD prolongs the operative duration. However, when ICUD is performed by experienced surgeons or in high volume centers, operative duration is comparable for ICUD and ECUD. The two approaches are assessed as equal in respect of postoperative complications. **Conclusion:** The debate as to whether ICUD must replace ECUD and become the standard of care does not end with this review. Intracorporeal approach in most of the studies seems to be associated with prolonged operative duration, lower transfusion needs, and equal complication rates when compared with ECUD. However, the contradiction of the results and the low quality of the available data demand the conduction of randomized prospective studies comparing ICUD and ECUD in order to offer the best available treatment to the patient.

Keywords: *After, comparison, diversion, extracorporeal, intracorporeal, RARC, urinary, vs*

Introduction

Although often not recognized as such by the general population, urinary bladder cancer (UBC) is one of the most frequently diagnosed cancers. More specifically, in 2020, it was ranked as twelfth worldwide regarding the incidence with 573,278 new cases occurring.[1] In fact, recent data estimate that during 2022, UBC will cause the death of 30,000 and 10,000 male and female residents of countries-members of the European Union, respectively.[2]

Histologically, 75% of UBC cases present as pure urothelial carcinomas, whereas the remaining 25% is accounted to histological variants.[3] Tumor stage classification depends on the depth of the bladder wall invasion, and as a result, two major categories emerge; nonmuscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) with incidence rates as high as 70% and 30%, respectively.[4] Radical cystectomy (RC) remains as one of the mainstays in treatment of UBC.[5] More specifically, RC plays a central role in the treatment of very-high-risk and treatment refractory NMIBC. In the MIBC setting, RC is performed together with peri-operative chemotherapy and appropriate lymphadenectomy as part of the first-line therapy, while its role in locally advanced or metastatic UBC is limited.[6-9]

Open RC (ORC) is an extensive surgical procedure with high rates of short-term morbidity despite the implementation of enhanced recovery after surgery protocols in some cases.[10-12] Given that for many surgical procedures of the abdomen, the minimally invasive technics and especially robot-assisted procedures can enhance postoperative recovery and reduce peri-operative morbidity, numerous

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studies have been conducted to compare the ORC and the robot-assisted RC (RARC).[13-17] The majority of the studies indicated that RARC reduces blood transfusion needs and offers equal oncological results with ORC, but it fails to significantly decrease short-term complication rates and improve the patients' quality of life.[18-22]

It has been proven that when the urinary diversion is performed intracorporeally instead of extracorporeally during purely laparoscopic RC, not only lower transfusion rates and duration of hospital stay but also statistically significant differences regarding 30 days complications are observed.[23-25] Intracorporeal urinary diversion (ICUD) theoretically due to smaller incision will reduce pain and due to reduced expose of bowel to air will prevent paralytic ileus. In addition, thanks to lower third space loss of fluid ICUD will protect the patient from fluid imbalance.[26] Already since 2010, a small case series study comparing ICUD with extracorporeal urinary diversion (ECUD) after RARC manifested lower narcotic usage was required in the ICUD group.[27] Despite its potential advantages and the constantly increasing number of ICUDs performed worldwide, only few studies have been conducted to compare ICUD with ECUD.[28] The aim of this review is to further elucidate the possible superiority of ICUD against ECUD with regard to peri- and postoperative complications, surgical outcomes, and quality of life based on the data arising from studies comparing these two approaches.

Materials and Methods

A literature search of PubMed (March 26, 2022) was performed to perform this narrative review. The following terms were used in the search text fields: "intracorporeal vs. extracorporeal urinary diversion," "comparison of intracorporeal and extracorporeal urinary diversions," "urinary diversion after robot-assisted radical cystectomy" AND "intracorporeal or extracorporeal urinary diversion after robot-assisted radical cystectomy."

Published observational and interventional studies comparing extracorporeal to ICUD after RARC were included. Reviews, letters, commentaries, case reports, and articles whose text was not available in English were excluded.

The abstracts of all articles were screened and the full texts of all the relevant articles were examined for possible inclusion. Data collected included study and participants' characteristics, type of urinary diversion performed, peri-and postoperative complication rate, and surgical and functional outcomes. Operative time and estimated blood loss were identified as the primary outcomes because they ensure the feasibility of the method, while total complication rate, length of stay, functional outcomes, and postoperative renal damage are the secondary outcomes associated with the probable benefit to the patients. Figure 1 summarizes the study selection process.

Results

A summary of the included studies' characteristics along with some of their most important results is presented to provide a brief outlook on the available data before their more thorough review [Table 1].

One of the first studies ever conducted to compare ICUD and ECUD had a small sample size as low as 32 patients (12 ICUDs vs. 20 ECUDs). The retrospective and the nonrandomized nature of this study as well as the lack of long-term follow-up do not allow the extraction of reliable results which are more of a historical significance. According to them, the mean operative time was longer in ICUD group (5.3 h vs. 4.2 h $P < 0.001$), while the inpatient narcotic requirements (expressed in morphine sulfate equivalents) were lower in the intracorporeal cohort (57.6 vs. 93.2 $P = 0.042$).[27]

The same year Guru *et al*. presented their initial experience with intracorporeal ileal conduit. A total of 26 patients were enrolled in their study and were stratified based on the urinary diversion approach into two groups (13 ICUDs vs. 13 ECUDs). In this small comparative study neither intra-nor postoperative complications differed significantly between the two groups. Although the operative time was comparable 159 min and 120 min for ICUD and ECUD, respectively ($P = 0.058$), it is mentioned that the small sample size may be responsible for the false-negative result.[29]

The comparison between the two techniques was then further investigated by Kang *et al*. They conducted a comparative study with an ICUD group consisting of four patients and an ECUD group consisting of 36 patients with the two groups being demographically similar (ICUD patients seemed to be older; 69.5 vs. 62.2 $P = 0.194$). They further divided the groups based on the urinary diversion type (3 ilial conduits and 1 neobladders intracorporeally vs. 22 ilial conduits and 14 neobladders extracorporeally). They concluded that as regards the ilial conduit cases the mean total operative time and the urinary diversion time were significantly longer in the ICUD patients (510.0 vs. 420.8 min; $P = 0.01$, 200.7 vs. 118.9 min; $P = 0.01$ respectively), while no such difference was noticed in the neobladder cases.[30]

Similar results derive from a study published in 2021 by Iwata *et al*. in this retrospective study with a sample size equal to 46 patients (23 ICUDs vs. 23 ECUDs) the members of the ICUD group were significantly younger and received more often neoadjuvant chemotherapy as compared to those of the ECUD group ($P = 0.03$ and $P = 0.002$, respectively). There were no differences in the EBL or rate of blood transfusion and the rates of 30-and 90-day complications were comparable for both groups. Statistical significant difference was observed not only regarding the overall median operative time (416 min for

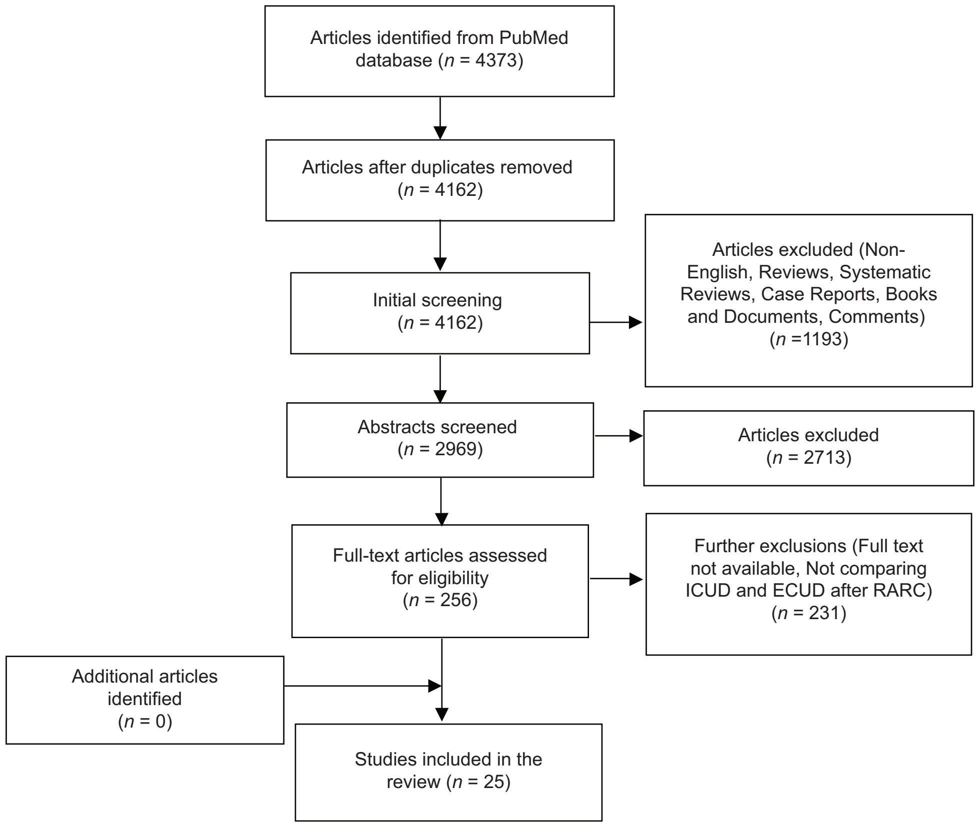

Figure 1: PRISMA flow diagram showing selection of articles for review

ECUD vs. 459 min for ICUD; $P = 0.003$) and the urinary diversion time (130 min for ECUD vs. 182 min for ICUD; $P < 0.0001$) but also in length of stay (23.5 vs. 18 days; $P = 0.02$). However, after taking in count the learning curve of both procedures, it has been shown that overall operative time did not differ significantly when it comes to the last 10 patients of both groups.[31]

Interesting results emerge from a study retrospectively analyzing the data of 52 patients who underwent RARC with either ECUD or ICUD (41 and 11, respectively) at Korea University Hospital from 2007 until 2014. The mean operative time for the ICUD cohort was prolonged (464 vs. 615 min $P < 0.001$), whereas ICUD was superior regarding estimated blood loss (269 mL vs. 165 mL $P = 0.003$). Furthermore, the incidence of minor complications (Clavien-Dindo grade I-II) was higher in the ECUD (48.8% vs. 9.1%) with the most common one being the transfusion. Notably after multivariable analysis estimated blood loss (>300 mL) and extracorporeal urinary diversion were identified as statistically significant predictors of total complications.[32]

Following the aforementioned retrospective study Pyun *et al*. conducted another similar retrospective analysis including now more ICUD cases (38 ECUDs vs. 26 ICUDs). The results do not refrain from the previous ones indicating longer operative time for ICUD cohort (468 ± 77.7 vs. 581 ± 76.3 min $P < 0.01$), lower estimated blood loss in favor of intracorporeal approach (265 ± 118.2 148 ± 62 mL $P < 0.01$) as well as higher incidence of minor and total complications for the ECUD group. It is mentioned that the teaching nature of the hospital makes the addition of new trainees and assistants part of everyday practice, something that probably affects the operative times.[33]

In Carrion *et al*.'s study, 43 patients (21 ICUDs vs. 22 ECUDs) who underwent RARC by a single surgeon between 2015 and 2018 were enrolled. The patients were diagnosed with either MIBT or high-risk NMIBT and they had a median follow-up of 27.7 months. The data that were collected were retrospectively reviewed. Preoperatively, there were no significant differences between the ICUD and the ECUD group except for the fact that more patients in the ICUD group received neoadjuvant chemotherapy ($P < 0.001$). According to the results, no significant differences were observed regarding perioperative complications, operative time, and hospital stay, but a lower risk of developing uretero-ileal and urethro-neobladder strictures in favor of the intracorporeal approach has been detected (45.5% vs. 14.3%; $P = 0.026$ and 33.3% vs. 0%; $P = 0.044$).[34]

In partial disagreement with the above results comes a small retrospective study designed to investigate the relationship between the surgical approach of urinary diversion and the incidence of benign ureteroenteric stricture after cystectomy. After a multivariable Cox proportional hazards model was

Table 1: Studies comparing intracorporeal urinary diversion with extracorporeal urinary diversion

Studies	Type of study	Type of UD	ICUDs	ECUDs	OPerative time (min)	EBL (mL)	Total complication (%)	LOS (days)
Pruthi *et al*.	Retrospective	IC/NB	12	20	318 versus 252 *P*<0.001	221 versus 266 *P*=0.564	-	
Guru *et al*.	Retrospective	IC	13	13	391 versus 387 *P*=0.869	315 versus 454 *P*=0.126	-	-
Kang *et al*.	Retrospective	IC/NB	4	38	510.0 versus 420.8 *P*=0.01 (only IC)	400.3 versus 370.1 *P*=0.398	25 versus 42.1 *P*=0.217	-
Iwata *et al*.	Retrospective	IC	23	23	459 versus 416 *P*=0.003	340 versus 300 *P*=0.9	48 versus 30 *P*=0.4	18 versus 23.5 *P*=0.02
Pyun *et al*.	Retrospective	IC/NB	11	41	615 versus 464 *P*<0.001	165 versus 269 *P*=0.003	3 versus 23 *P*=0.092	18.7 versus 16.9 *P*=0.531
Pyun *et al*.	Retrospective	IC/NB	26	38	581 versus 468 *P*<0.001	148 versus 265 *P*<0.001	8 versus 22 *P*=0.33	15 versus 16.7 *P*=0.393
Carrion *et al*.	Retrospective	IC/NB	21	22	355 versus 360 *P*=0.655	-	76.2 versus 86.4 *P*=0.391	10 versus 13.5 *P*=0.586
Faraj *et al*.	Retrospective	IC/NB	39	197	359 versus 367 *P*<0.001	-	-	6 versus 5 *P*<0.001
Ericson *et al*.	Retrospective	IC	307	382	-	-	-	-
Mistretta *et al*.	Retrospective	NB	57	44	520 versus 455 *P*=0.02	400 versus 500 *P*=0.9	75.4 versus 72.7 *P*=0.9	11 versus 12 *P*=0.5
Khan *et al*.	Retrospective	NB	20	20	-	-	-	-
Asil *et al*.	Retrospective	IC	42	19	403 versus 347 *P*=0.004	183.5 versus 305.2 *P*<0.001	28.6 versus 36.8 *P*=0.536	11 versus 15 *P*=0.001
Khalil *et al*.	Retrospective	IC/NB	14	21	457.14 versus 388.29 *P*=0.073	250 versus 450 *P*=0.05	64.3 versus 71.4 *P*=0.656	6.29 versus 8.1 *P*=0.168
Lenfant *et al*.	Retrospective	IC/NB	74	34	320 versus 285 *P*=0.4	400 versus 500 *P*=0.04	47.3 versus 38.2 *P*=0.4	4 versus 8 *P*=0.006
Ahmed *et al*.	Retrospective	IC/NB	167	768	414 versus 414 *P*>0.05	-	35 versus 43 *P*=0.07	9 versus 8 *P*=0.086
Hussein *et al*.	Retrospective	IC/NB	1094	1031	357 versus 400 *P*<0.001	300 versus 350 *P*<0.001	57 versus 43 *P*<0.001	9 versus 8 *P*<0.001
Hussein *et al*.	Retrospective	IC/NB	486	486	355 versus 401 *P*<0.01	250 versus 400 *P*<0.01	66 versus 58 *P*=0.01	9 versus 8 *P*<0.01
Dalimov *et al*.	Retrospective	NB	264	147	435 versus 431 *P*=0.56	-	67 versus 68 *P*=0.81	8 versus 12 *P*<0.001
Teoh *et al*.	Retrospective	IC/NB	307	249	362.8 versus 329.3 *P*=0.002	423.08 versus 541.30 *P*=0.002	51.3 versus 47.8 *P*=0.327	15.7 versus 17.81 *P*=0.002
Bertolo *et al*.	Prospective	IC	60	66	420 versus 360 *P*=0.0004	380 versus 350 *P*=0.6	12 versus 11 *P*=1	7 versus 8 *P*=0.2
Tan *et al*.	Prospective	IC	59	68	330 versus 375 *P*=0.019	300 versus 425 *P*=0.035	48.4 versus 71.4 *P*=0.008	8 versus 8 *P*=0.166
Kingo *et al*.	Prospective	IC	38	12	311 versus 332 *P*=0.002	185.4 versus 524.1 *P*<0.0001	-	10.89 versus 8.17 *P*=0.366
Kingo *et al*.	Prospective	IC	9	13	296.56 versus 341.23 *P*<0.0001	127.8 versus 546.0 *P*<0.001	-	8 versus 8 *P*=0.063
Lone *et al*.	Retrospective	IC/ NB/IP	191	260	412.4 versus 443.4 *P*<0.001	397 versus 676 *P*<0.001	47 versus 52 *P*=−0.64	-
Mazzone *et al*.	Retrospective	IC/NB	162	105	350 versus 350 *P*=0.1	300 versus 350 *P*=0.02	35.2 versus 42.9 *P*=0.2	11.5 versus 13 *P*=0.02

UD: Urinary diversion, EBL: Estimated blood loss, LOS: Length of stay, IC: Ileal conduit, NB: Neobladder, IP: Indiana pouch, ICUDs: Intracorporeal urinary diversions, ECUDs: Extracorporeal urinary diversions

fitted ICUD was found not to be significantly associated with lower risk of ureteroenteric strictures (UES), although the incidence of UES in this group was the lowest as compared to the other groups (2.6% for ICUD vs. 9.6% for ECUD vs. 8% for ORC). However, the small sample size of patients who underwent RARC combined with ICUD (39 patients) indicates the possibility of a type II statistical error.[35]

A larger analysis including now 968 patients who underwent RC (279 open, 382 robotic extracorporeal, and 307 robotic intracorporeal) was designed to answer the same question. Although the Chi-square analysis found no significant difference between these surgical techniques and the UEAS incidence, in multivariate analysis, ICUD was indicated as an independent factor for UEAS. However, in the ICUD cohort, stricture incidence trended down as surgeons gained experience. In fact, prior to a surgeon's 75th case, the stricture incidence was 17.5%, but after 75 cases, the same percentage declined 4.9%.[36]

One retrospective study compares the extracorporeal with the intracorporeal approach of the same reconstruction technique, the orthotopic neobladder. This study included 101 patients (57 ICUD vs. 44 ECUD) with the only difference between the two groups being the higher rate of neoadjuvant chemotherapy in ICUD cohort (49.1% vs. 20.5% $P < 0.01$). This study addressed that the only statistically significant distinctions between them is the higher operative time present in the ICUD group (520 min vs. 455 min; $P = 0.02$). Surgical and functional outcomes as well as early (<30 postoperative days) and late complications (>30 postoperative days) were similar for these two urinary diversion approaches.[37]

Another recently published study included only patients who obtained orthotopic neobladder after RARC. This study tried to compare intracorporeal neobladder (ICNB) with extracorporeal neobladder (ECNB) from an innovative point of view; Khan *et al*. tried to clarify the relationship between ICUD and ECUD regarding the functional outcomes of the neobladder. In order to answer this question, they compared 20 ICUD with 20 ECUD neobladder cases in respect of continence and urodynamic assessment. The only differentiation between the groups was that ICUD patients attained continence a little earlier without any statistical significance being detected. Both groups achieved urodynamically proven adequate capacity, compliance, good flow rate, and acceptable residual urine. Thus, the study concluded that there is no perceived superiority of ICNB over ECNB.[38]

A retrospective study conducted by Asil *et al*., which included now patients who underwent RARC only with intracorporeal ileal conduit, compared them with both RARC with extracorporeal ileal conduit and ORC with ileal conduit. Ninety-two cases of radical cystectomies performed by two surgeons who had already performed the minimum amount of cystectomies for their learning phase were enrolled in the study. Estimated blood loss, transfusion rates, and complications did not differ significantly between ICUD and ECUD groups. On the other hand, length of hospital stay was significantly shorter in the ICUD group ($P < 0.001$).[39]

Khalil *et al*. conducted a study with a relatively small sample (14 ICUD cases vs. 21 ECUD cases) to compare a single-institution cohort of patients undergoing intracorporeal and extracorporeal diversions with the unique feature that patients underwent cystectomy as part of their therapeutic plan against benign or malignant conditions. The ICUD was associated with longer operative time (457.14 ± 103.91 vs. 388.29 ± 110.17 min $P = 0.07$) and lower EBL (250 vs. 450 mL $P = 0.05$). There was no difference in readmission or reoperation rates in 30 days and, although no statistically significant relationship has been proven, a trend in favor of ICUD has been detected regarding the 90-day complication rates.[40]

In the first multi-institutional retrospective study with a sample size equal to 108 (34 ECUDs vs. 74 ICUDs), the cases derived from five referral centers in France. The patients' stratification was based on the surgical approach for urinary diversion and no significant difference was spotted between the two teams except for higher ASA score in patients receiving ECUD. Through the comparison of these two techniques, it has emerged that ICUD is associated to lower estimated blood loss and transfusion rates (500 vs. 400 cc, $P = 0.04$ and 23.5 vs. 5.4%, $P = 0.006$, respectively). Notably, it is mentioned that in the ICUD cohort, higher percentage of early minor and major complications was present, although it did not reach statistical significance, while ECUD group faced more late complications. However, these two last features might reflect two of the limitations of this specific study which are the impact of the learning curve on ICUD cohort and the statistically significant longer follow-up of the ECUD group ($P = 0.04$).[41]

The first study based on the results from the International Robotic Cystectomy Consortium comparing ICUD with ECUD was published in 2014 and included 935 patients from 18 institutions who underwent RARC and PLND (167 ICUDs vs. 768 ECUDs). The study addressed no significant differences regarding the demographic data of the patients, the median total operative time, the estimated blood loss, and the length of stay. The readmission rate was higher for the ECUD cohort both after 30 and 90 days (5% vs. 15% $P \leq 0.001$ and 12% vs. 19% $P = 0.016$, respectively). More specifically, gastrointestinal complications and postoperative infections were significantly lower in the ICUD group ($P < 0.001$ and $P = 0.035$, respectively). Furthermore, the 90-day mortality events were higher in the ECUD group (4.9% vs. 1.6% $P = 0.043$). After univariable and multivariable analysis, ECUD was a predictor of more frequent transfusions.[42]

In 2018, Hussein *et al*. performed a similar retrospective study including 2125 patients (1094 ICUDs vs. 1031 ECUDs). This study indicated the yearly increasing transition from ECUD to ICUD. More specifically, ICUD increased from 9% of all urinary diversions in 2005-97% in 2016. Preoperatively, ICUD cohort included fewer patients with ASA score of 3 or greater (44% vs. 53% $P < 0.001$) but received neoadjuvant chemotherapy more frequently (25% vs. 17% $P < 0.001$). ICUD was associated with shorter operative time (357 vs. 400 min), less estimated blood loss (300 vs. 350 ml), and lower blood transfusion rates (5% vs. 13% all $P < 0.001$). Patients receiving ICUD were more prone to complications (57% vs. 43% $P < 0.001$), especially 30 day complications (31% vs. 19% $P < 0.001$). However, it should be noted that yearly the high grade complication rates after ICUD decreased from 25% in 2005-6% in 2015 ($P < 0.001$) whereas it remained stable for ECUD, reflecting the effect of the steep learning curve of ICUD. Furthermore, after multivariable analysis, ICUD was not identified as a predictor of neither high grade complications nor readmissions. As regards the oncologic outcomes, they were comparable for the two groups.[43]

Hussein *et al*. in 2020 conducted another relevant retrospective analysis based on more recent data. It was a large multi-institutional retrospective study where 972 patients were enrolled (476 ICUDs vs. 476 ECUDs). First of all, ICUD was associated with shorter operative time (355 vs. 401 min $P < 0.01$), lower estimated blood loss (250 vs. 400 mL $P < 0.01$), and less frequent transfusion rates (9% vs. 15% $P < 0.01$). In addition, ICUD patients stayed 1 day longer in hospital (9 vs. 8 days $P < 0.01$) and experienced more complications (66% vs. 58% $P = 0.01$). More specifically, they had significantly more infectious complications (30% vs. 23% $P = 0.03$) and urinary tract infections (14% vs. 8% $P < 0.01$). Last but not least, higher readmission rates were observed in the ICUD cohort (27% vs. 17% $P = 0.01$).[44]

Contradicting to the above results emerge from a large retrospective review with a sample size as high as 411 patients (264 ICNBs vs. 147 ECNBs) deriving from 19 institutions extracted some interesting conclusions about this comparison. First of all, intracorporeal approach was mostly selected during the last RARC eras ($P < 0.0001$) for older patients (61 vs. 57 years $P < 0.001$) who received more frequently neo-adjuvant chemotherapy (35% vs. 8% $P < 0.001$) and underwent cystectomy in institutions with higher annual neobladder volume, ICUD volume, and ICNB volume. When it comes to perioperative outcomes surprisingly, techniques were assessed as equal regarding operative time, estimated blood loss, and transfusion rates. Furthermore, patients receiving ICNB had longer ICU stay (2 vs. 1 day $P < 0.001$) but shorter overall hospital stays (8 vs. 12 days $P < 0.001$) while they were less likely to experience reoperations within 30 days (9% vs. 13% $P = 0.02$) and to receive adjuvant chemotherapy (10% vs. 19% $P = 0.018$). Although there was no significant difference regarding complications, ICUD cohort was associated with more frequent readmissions (36% vs. 24% $P = 0.03$) and had higher readmission rates within 30 days (30% vs. 15% $P = 0.006$) and 90 days (41% vs. 18% $P < 0.001$). In fact, after multivariate analysis, ICNB was significantly related to readmission rates.[45]

The most recently published multicenter study comes from Teoh *et al*. and comprises 556 patients (307 ICUDs vs. 249 ECUDs) deriving from nine centers in Asia. The two groups had similar demographic characteristics with the only differentiations being the higher ASA score in ECUD cohort (19.2% vs. 9.2%; $P < 0.001$) and the fact that ileal conduit was more frequently performed in the ICUD group (48.4% vs. 29.5%; $P < 0.001$). Although the ECUD was associated with shorter operative time (362.8 ± 94.9 vs. 329.4 ± 147.8 min; $P = 0.002$), the ICUD cohort had less blood loss and shorter hospital stay (423.1 ± 361.1 vs. 541.3 ± 474.3 mL; $P = 0.002$ and 15.7 ± 12.3 vs. 17.8 ± 11.6 days; $P = 0.042$). In spite the fact that ICUD experienced lower rates of overall complications, no level of statistical significance was achieved.[46]

One of the few prospective studies comparing ICUD with ECUD was conducted by Bertolo. There were two surgeons, one for the ECUD group and the other for the ICUD group. The complications were evaluated within 30 and 90 days postoperatively and the oncological follow-up took place at 1 and 3 months, every 6 months for 2 years and then annually or as clinically indicated. The two groups differed significantly regarding the age (69 for ICUD vs. 73 for ECUD, $P = 0.009$). Both techniques had comparable perioperative, 30- and 90-days complication rate. However, extracorporeal fashion of urinary diversion was associated to shorter operative time ($P = 0.0004$).[47]

Another prospective study was conducted by an institution during their transition from ECUD to ICUD following RARC 127 patients were enrolled (68 ECUD cases and 59 ICUD cases). Through their transition, intracorporeal approach reduced the estimated blood loss (300 vs. 425 mL $P < 0.035$), the 30-day overall complication rates (48.4 vs. 71.4% $P = 0.008$), and surprisingly, the overall operative time (330 vs. 375 min $P = 0.019$). The relatively small sample and the nonrandomized nature of the study which might insert a selection bias as well as the shorter follow-up time for ICUD patients (4 vs. 14 months $P < 0.001$) are the limitations of this study.[48]

Kingo *et al*. designed a study aiming to compare open surgery with robot-assisted combined with ECUD and robot assisted combined with ICUD in respect to inflammatory response. Although RARC with ICUD was the technique associated with the highest CRP levels from postoperative day two until the seventh postoperative day, no significant difference was observed between the two robotic groups. Furthermore, it is stated that the higher CRP concentration is not necessarily associated with more extensive trauma, but it might be explained by the longer operative time and the consequent longer duration of pneumoperitoneum.[49]

Another similar prospective study by Kingo *et al*. examined the relationship between the extracorporeal and intracorporeal approach of urinary diversion in respect of the induced inflammatory response. The sample consisted of 13 patients receiving ECUD and 9 patients receiving ICUD. First of all, between these two groups, no differences emerged regarding estimated blood loss, transfusion rates, operative time, and total anesthesia time. At postoperative day 2, the levels of the preinflammatory cytokine interleukin (IL)-6 were marginally higher in the ICUD cohort (P = 0.052), although right after the procedure, they were lower in the ICUD group (probably reflecting a lower EBL). However, MCP-1 levels appeared to be significantly lower in the ICUD group at postoperative day 0 (P = 0.036), whereas the levels of the anti-inflammatory cytokine IL-10 were significantly higher for ICUD during postoperative days 0, 1, and 2 (probably reflecting the counteraction against the high IL-6 levels to maintain a balance between pro- and anti-inflammatory cytokines).[50]

Once ICUD automatically means longer duration of pneumoperitoneum which has been identified as a risk factor for acute kidney injury in robot-assisted surgeries, a retrospective study was conducted to compare ICUD with ECUD in respect of kidney injury. It has been proven that the urinary diversion type does not affect neither the median renal function decline free survival rate (eRARC: 2.2 years iRARC: 2.3 years) nor the rates of postoperative development of chronic kidney disease 3B or worse. Only preoperative CKD stage 3A, pathologic T3 disease, and ureteroenteric anastomotic strictures were identified as the independent risk factors of renal function decline after RC.[51]

An interesting result can be derived from a retrospective study were 267 patients who underwent RARC in a single center were enrolled. This study attempted to investigate whether RARC with ICUD is associated with lower risk of perioperative complications, length of stay, and readmission rate and whether this kind of surgical approach is more beneficial to special subgroups. In fact, no statistically significant differences were monitored regarding the previously mentioned characteristics, but it was found that with the increase of baseline Age-adjusted Charlson Comorbidity Index, patients with ICUD had lower risk of Clavien Dindo ≥ 2 relative to those with ECUD.[52]

Discussion

Many studies published during the last decade proved the superiority of RARC over ORC regarding not only the peri- and postoperative outcomes, such as blood loss and length of stay but also the oncological outcomes and safety.[53-55] It is a fact that the minimally invasive approach as an alternative of ORC would be a challenging procedure, but it was made much more feasible by the introduction of robotic surgery.[56] These data constituted the foundation of the safe transition from ORC to RARC resulting in an enormous increase of RARC procedures.[57-59]

The RC as a procedure comprises three major steps: cystectomy, lymph node dissection, and urinary diversion.[60] In contrast with ECUD which requires a minilaparotomy wound for bowel manipulation, ICUD is expected to further reduce trauma and gastrointestinal complications.[61-63] On the other hand, others support the opinion that this theoretical benefit is marginally significant and cannot justify the ICUD in respect of cost and learning curve.[64] Thus, the comparison of ECUD with ICUD still remains a key research point.

One of the main reasons why most surgeons were skeptical about the adoption of ICUD is the steep learning curve that results in longer operative time.[65] This feature combined with the fact that RARC is not a high volume surgery addresses that it may ultimately take years to achieve this learning curve.[66-68] Moreover, longer operative time has been associated in other robotic-assisted surgical procedures with higher rates of 30-day perioperative complications, deep-venous thrombosis, and pulmonary embolism.[69,70] More specifically about RC, Faraj *et al*. proved that patients who underwent a surgical procedure of longer duration, especially over 479 min, had higher risk of deep-venous thrombosis, pulmonary embolism, urinary tract infection, readmission, and blood transfusion.[71] Although many of the studies presented in this review indicated that ICUD results in prolonged operative duration, larger multi-center studies addressed that ICUD can even shorten the duration of this surgical procedure.[30-34,37,42-45] These data might suggest that higher volume and experience may help overcome probable technical difficulties and reduce operative duration. This assumption may be also supported by Iwata *et al*. study, which addressed that for the last 10 patients of each cohort, the operative times did not differ significantly.[31]

Through this review, it has been clear that ECUD is associated with higher blood loss when compared with ICUD.[31,33,39,43,44,48,50] The reduced estimated blood loss in intracorporeal approach might reflect the longer pneumoperitoneum time that serves as an invisible tourniquet. This, also, explains the decreased needs for blood transfusions in the postoperative period for patients receiving ICUD. In previous studies, it has been shown that lower blood transfusion rates have a positive impact on cancer recurrence and survival following RC.[72,73]

As ICUD is a complex surgical procedure, one of the main concerns in its adoption regards the complication rates. No reliable results regarding complications can be derived from this review, because the studies presented do not come to agreement and most of them assess these surgical approaches as equal. It is important to report that one of the few studies that showed higher 30 day complication rates for ICUD group mentioned that the incidence of complications in ICUD was yearly decreasing, while the incidence of complications in ECUD remained stable. This shows the impact of the ICUD learning curve on the results.[43] Previous studies have shown that laparoscopic surgeries have shorter postoperative ileus compared to open surgeries probably because open surgeries expose the peritoneum to air.[74] In agreement with this past literature come the results from the International Robotic Cystectomy Consortium which address fewer gastrointestinal and infection complications postoperatively in the ICUD cohort.[42] In fact, gastrointestinal complications and more specifically ureteroileal complications and bowel obstruction are identified as the most common causes of reoperations after RARC.[75] This might be the cause of the lower readmission rates in ICUD group reported in three studies.[34,43,47]

Given that anastomotic strictures are a common late complication of RC and their management might require an additional surgery with inherent risks several studies aimed to investigate whether ICUD offers some kind of protection against this complication. Carrion *et al*. concluded that the patients receiving a urinary diversion in intracorporeal fashion experienced the lower rates of uretero-ileal and urethro-neobladder anastomotic strictures (45.5% vs. 14.3%; $P = 0.026$ and 33.3% vs. 0%; $P = 0.044$).[34] Faraj *et al*. failed to statistically prove the superiority of ICUD regarding UEAS due to the small sample size that probably inserted a type II statistical error.[35] To complete disagreement with the aforementioned results comes a larger analysis by Ericson *et al*. which identifies ICUD as an independent risk factor for UEAS. However, this study manifests that during the surgeons' transition through the learning curve, the UEAS rates are reduced.[36] Thus, the advantage of ICUD over ECUD in respect of the risk of anastomotic strictures formation still remains a controversial issue.

However, it is of vital significance to solve the issue mentioned above as Lone *et al*. identified anastomotic strictures as one of the major independent risk factors for renal injury after RARC. In fact this study indicated that ICUD cannot sufficiently increase the renal function decline-free survival.[51] Apart from anastomotic strictures that can cause renal damage another possible factor that can be responsible of renal function decline after RC is the efficiency of the neobladder due to probable urine retention. Khan *et al*. attempted to investigate whether the type of urinary diversion approach affects the neobladder function and concluded that both groups reached an adequate level of capacity, compliance, urine flow, and acceptable residual volume.[38]

As the oncologic part of the operation, meaning the cystectomy and the lymph node dissection, are completed before the urinary diversion it is unlikely that the urinary diversion technique has any effect on the oncological outcomes. In a large retrospective study published by Hussein *et al*., a significant difference in recurrence-free survival and disease-specific survival between the two approaches emerged. However, it is mentioned that survival outcomes after cystectomy are mainly driven by disease-specific features, such as pT stage, nodal status, and positive surgical margins.[76-79] Moreover, in this study, ICUD group had a worse overall survival which was however associated with the higher complication rate.[43]

The limitations of this review include that most of the studies presented have a nonrandomized and retrospective nature. These two features introduce a selection bias in these studies. Furthermore, the fact that many studies were multi-institutional means that there are differentiations between the established protocols regarding reporting of complications and follow-up. Last but not least, the different experience of the surgeons and the steep learning curve significantly reduce the reliability of the results.

Conclusion

In order to end the debate as to whether ICUD after RARC has to offer more benefits compared with the extracorporeal approach, two fundamental questions have to be answered; first, is it technically possible to execute this complex procedure as part of everyday practice without increasing the complication rates and second is it more beneficial to the patient? This review aimed to answer these two essential questions. In respect of operative time, intracorporeal approach seems to be associated with longer operative duration, but high volume institutions and experienced surgeons seem to significantly decrease this duration. A strong association between ICUD and lower estimated blood loss and thus less transfusion needs seems to exist in most of the studies. As regards the 30- and 90-day complications, the two techniques have comparable results. There is a need for randomized prospective studies to conclude which approach is superior in respect of oncologic and perioperative outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Current Trends in Metabolic Evaluation of Patients with Urinary Tract Lithiasis

Abstract

Urolithiasis is one of the most frequent disorders of the urinary tract with a high prevalence among the general population. The etiology is multifactorial and is related primarily with, race, age, gender, occupation, hygienic-dietetic issues, lifestyle factors, geographic and climatic aspects, hereditariness, and metabolic changes. Therefore, for prevention of the disease, the metabolic causes responsible for stone formation should be addressed before and particularly after treatment. Key point for the metabolic evaluation is to perform stone analysis and to classify patients into low- and high-risk group. In low-risk patients, basic metabolic evaluation is proposed comprising basic urine and blood tests. Spot urinalysis should include red cells, white blood cells, nitrite, urine pH, urine microscopy, and culture if indicated. Basic blood testing includes blood cell count, creatinine, uric acid, ionized calcium, sodium, potassium, and C-reactive protein if indicated. In high-risk stone formers, apart from the basic workup, analysis of two 24-h urine samples should be examined for evaluation of the total urine volume as well as the concentration of creatinine, calcium, phosphate, oxalate, urea nitrogen, uric acid, citrate, magnesium, sodium, and if indicated of cystine. Further examination should be based on the composition of stone. The follow-up of stone formers is still matter of debate, but most experts agree that the follow-up should be individualized according to stones composition, the underlying metabolic cause, and the treatment that has been offered.

Keywords: *Evaluation, lithiasis, metabolic*

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Introduction

Urolithiasis is the third most frequently encountered disorder among urinary tract diseases. It is anticipated that almost 9% of people in the USA (prevalence of 10.6% and 7.1% for men and women, respectively) will be diagnosed with urinary stone at least once during their lifetime.[1,2] Calcium-containing stones (calcium oxalate (COX), calcium apatite, and brushite) represent approximately 75% of upper tract stones, and the remaining 25% contain struvite, cystine, uric acid, and other stones.[3-5]

The etiology of this disorder is multifactorial and is related primarily with genetic or dietary factors and poor physical activity. To be more specific, race, age, gender, occupation, hygienic–dietetic issues, lifestyle factors, geographic and climatic aspects, hereditariness, and metabolic changes may predispose the general population to stone formation.[2,6,7] The assessment of the aforementioned factors, and particularly the diagnosis and interpretation of the underlying metabolic disorders, might play a crucial role toward the elimination of the disease or of its recurrences. Hypercalciuria, hyperphosphaturia, hyperoxaluria, hypocitraturia, hyperuricosuria, hypomagnesuria, cystinuria, low urinary output, and defect of urinary acidification are only some of the metabolic changes responsible for the lithiasic disease.[6,8]

In general, 50%–75% of patients without prophylactic intervention their disease is expected to recur within 5 years and about ten percent of patients experience up to three or more recurrences during their lifetime, particularly if any relevant metabolic disorder remains untreated.[7,9] Therefore, for the prevention of the disease, the metabolic causes responsible for stone formation should be understood and the appropriate treatment should be offered to the patients. Key point for the metabolic evaluation of lithiasic patients is to perform stone analysis and to classify patients into low- and high-risk group.[7-10]

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Materials and Methods

Who should be assessed?

The optimal determination of stone composition is performed with X-ray crystallography, infrared spectrophotometry, or polarization microscopy, with an anticipated error rate of approximately 10%.[11] Chemical analysis is not considered accurate enough for decision-making in lithiasic disease. Although stone examination is unpopular among physicians, it is now considered one of the most crucial steps for the correct metabolic evaluation of stone formers determining the next diagnostic steps.[12] Further metabolic evaluation should be based on patients' risk factors for recurrence and of other comorbidities associated with stone formation. The high-risk group includes patients with one or more of the following:[10,13-15]

1. Diseases causing or related to stone formation, mainly hyperparathyroidism (HPT), impairment of Vitamin D metabolism, gastrointestinal diseases causing malabsorption (Crohn's disease, jejuno-enteric bypass, bowel resection, pancreatic deficiency, etc.), sarcoidosis, osteoporosis, and neurogenic bladder. Chronic bacteriuria related to urea-splitting strains should also be considered
2. Genetic diseases that cause stone formation, including renal tubular acidosis (RTA), cystinuria, hyperoxaluria, xanthinuria, hyperuricemia, etc. Genetic diseases may predispose to lithiasis in young ages, early recurrence after successful treatment, and familial clustering of cases
3. Consumption of drugs related to stone formation including indinavir, calcium and magnesium components, Vitamin D, ascorbic acid (Vitamin C), allopurinol, triamterene, amoxicillin, sulfonamides, ceftriaxone, and quinolines. Chronic consumption of laxatives and antiacid drugs containing aluminum–magnesium may also predispose to stone formation
4. Impairment or obstruction of the urinary collecting system: these lesions include tubular ectasia, ureteral stenosis, urethral stricture, bladder outlet obstruction, vesicoureteral reflux, and any other endogenous or exogenous factors affecting urinary flow. Special consideration should be applied to patients with chronic kidney disease (CKD) and solitary kidney
5. Specific environmental factors including sun exposure and geographical characteristics relevant to people's access to water resources.

How should patients be assessed?

Basic metabolic evaluation

The basic metabolic evaluation comprises urine and blood tests and should be restricted only to patients with none of the five aforementioned risk factors. Spot urinalysis should include red cells, white blood cells, nitrite, urine pH, urine microscopy, and culture if indicated.[7,13] The microscopic examination of morning urinary sediment may reveal crystals of characteristic shape, like cystine and struvite stones. The detection of COX crystals, on the other hand, is not of great importance however because they can be collected from healthy population as well.[16] Basic blood testing includes blood cell count, creatinine, uric acid, ionized calcium, sodium, potassium, and C-reactive protein if indicated.[7] Albeit it is not recommended by the European and American Urologic Association, some authors propose the addition of serum glucose in the panel of basic metabolic evaluation.[13]

Specific metabolic evaluation

Besides the basic workup, the specific metabolic evaluation should be performed to all high-risk stone formers and should also comprise analysis of 24-h urine. Ideally, the bottle should be instilled with 5% thymol or with boric acid and should be kept in the refrigerator so as the crystallization of the content to be avoided.[17] The 24-h urine examination should comprise urine volume as well as concentration of creatinine, calcium, phosphate, oxalate, urea nitrogen, uric acid, citrate, magnesium, sodium, and if indicated of cystine.[7,13,18] Due to the considerable variation of the examined parameters in the urine collected by the same patient, it is proposed that at least two 24-h urine collections should be obtained by each patient in regular physical activity and diet for reliable results to be extracted.[17,18] The monitoring of pH with dipstick should be intensified in high-risk group with at least four pH measurements per day of urine specimens. In cases of persistently elevated urine pH above 5.8, blood gas analysis should be performed (for the detection of RTA disorder).[7,16] Further specific metabolic examination should be based on the type of stone according to the stone composition as the following:

Calcium oxalate stones

This group of stones may be related to one or more of the following: high calcium, oxalate and uric acid urine levels, and low citrate or magnesium levels.[14] In cases of remarkably elevated hyperoxaluria (persistently >1 mmol/d, normal value <0.50 mmol), patients may harbor genetic defect (primary hyperoxaluria Type I or II).[7] The next step of specific evaluation is based on the calcium concentration in blood.

- In patients with hypercalcemia (and hypercalciuria) primary HPT, hyperthyroidism, Vitamin C excess intake, and malignant or granulomatous disorders should be considered for the etiology of stone formation[7,13,14]
- Normocalcemia with hypercalciuria is indicative of idiopathic disease, granulomatous disease, or excessive Vitamin D consumption. Should a persistently low urine pH (approximately 5.8) with metabolic acidosis is detected, RTA should be suspected[7]
- COX may coexist with hyperuricosuria and hyperuricemia related primarily to gout, with

consumption of purine-rich dietary products and conditions related to excessive cell lysis (hemolysis or treatment for malignancies)[14]

- In COX with hyperoxaluria, the stone formation may be related to consumption of oxalate-rich foods and with minimum calcium intake. Calcium has the ability to form a complex with the oxalate molecule in the bowel and this complex is removed with the stools. In cases with low calcium consumption or loss of enteric calcium due to chronic diarrheal syndrome, the formation of this complex is minimal and the enteric oxalate is absorbed into the systematic circulation and is excreted in the urine. This absorption is responsible for hyperoxaluria and therefore of oxalate stone formation[13]
- In patients with hypocitraturia, RTA or chronic diarrhea should be considered and managed properly[14]
- Furthermore, COX may be related to low serum magnesium lever (hypomagnesemia), probably related to low magnesium intake with the food or with poor absorption or loss of magnesium from the intestine (malabsorption and chronic diarrhea, respectively).[14]

Calcium phosphate stones

This group of stones is frequently encountered among the stone former population. The assessment of serum calcium ion level (or of total calcium level related to albumin concentration in the serum) and the urine pH are fundamental during the metabolic workup. Patients should mainly be examined for HPT and RTA and specific treatment should be offered according to the findings. A persistently elevated pH >6.8 is associated with carbonate apatite stones, while the maximum crystallization of brushite stones is encountered in ranges between 6.5 and 6.8. In patients with infection stones, carbonate apatite is frequently identified. In chemolysis with alkalizing agents, the achievement of a urine pH persistently <7.4 increases the odds of calcium phosphate stone formation.[7]

Uric acid stones

The three main determinants of uric acid stone formation are: persistently low pH (<6), low urine volume and hyperuricosuria, although low urine pH is the most important contributing factor.[14] All the patients with uric acid and ammonium urate calculi are high risk of recurrence. Several dietary and metabolic factors are related to uric acid stone (UAS) formation. High purine intake, high animal protein consumption, metabolic syndrome, and resistance to insulin may increase the risk. Gout is closely related to hyperuricosuria and hyperuricosuria and the episodes of this disease should be restricted to minimum with appropriate diet and medical therapy.[7] Proliferative diseases, particularly blood malignancies, as well as treatment of malignancy with antiproliferative agents may predispose to stone formation. These conditions should be considered during the evaluation of patients with UAS.[19]

Cystine stones

Cystinuria is an autosomal recessive disorder characterized by a defect in intestinal and renal tubular transport of dibasic amino acids, resulting in excessive urinary excretion of cystine. Cystine is poorly soluble in urine. Hence, precipitation of cystine and subsequent stone formation occur at physiologic urine. These stones are considered very hard and are difficult to be treated. The stone analysis may reveal typical hexagonal crystals, but this finding is encountered in the minority of the patients (one out of four).[9,14]

Infection stones

All infection-stone formers experience frequent recurrences. Struvite stones are consisted of magnesium ammonium phosphate ions and are produced by urea-splitting bacteria during urinary tract infection. Under these conditions, urease, a bacterial enzyme, hydrolyses the urinary urea to ammonia, increasing therefore the urine pH at levels above 7.[9] The alkaline environment of the urine further promotes phosphate dissociation and allows formation of magnesium ammonium phosphate stones. Albeit the treatment of stones is beyond the scopes of this review, it should be emphasized that the management of infection stones requires the combination of urine acidification with antibiotic treatment and stone removal.[20,21]

Stones related to rare specific genetic disorders

- Genetic disorders of the normal metabolic pathway of transformation of adenine to AMP may lead to formation of 2,8-dihydroxyadenine vast product. The excessive secretion of 2,8-dihydroxyandenine in the urine may easily cause precipitation and therefore stone formation. The definite diagnosis of this rare condition relies upon the stone analysis and the determination of the genetic defect without the need of any other specific metabolic examination[22]
- Patients with xanthine stones are considered to be at high risk of recurrence due to the related genetic defect of xanthine-oxidase enzyme. The high concentration of xanthine in the urine causes the formation of stones. Following stone removal, the recurrences may be alleviated with low purine diet.[23]

When should patients be assessed?

The resent EAU guidelines suggest that for the initial specific metabolic workup, the patient should stay on a regular self-determined diet under normal daily conditions and should ideally be stone free for at least 20 days. Follow-up studies are necessary in patients taking medication for the prevention of recurrence. The first follow-up with 24-h urine measurement is suggested 8 to 12 weeks after starting pharmacological prevention of stone recurrence.[10]

Following the initial investigation, the metabolic spectrum of 24-h urine study, the number of 24-h urine studies, and the rest of metabolic tests that should be performed are all still matters of debate among experts,[15,16] but most of them agree that the follow-up should be individualized to the patient in dependence on the type of stones, the underlying cause, and the treatment that is being followed. A comprehensive metabolic workout, including 24-h urine collection, is proposed be repeated after 3–4 weeks after the stone passage on the grounds of an unobstructed and bacterial-free urinary tract.[15] In addition, patients on dietary and selective medical therapy should also be monitored regularly in time intervals between 3 and 12 months from the beginning of treatment to assess the compliance of the patient and/or the medical response as well as to detect adverse effects. However, considering that high-quality trials relevant to the metabolic follow-up are lacking, there is a great variability on the monitoring schedules among the medical centers and the expert physicians.[15]

The implementation of metabolic evaluation accompanied by the modification of the respective risk factors and the relevant therapeutic treatment may reduce the recurrence rate up to 85% in long-term basis.[24] However, the metabolic evaluation is rather considered unpopular among most of the physicians and the patients due to the ignorance of stone formation physiology and the complexity of the specific metabolic algorithm. The compliance of the patients to the proposed scheme is often poor, while the laboratory tests are anticipated to increase the financial burden of primary health-care providers. The cost-effectiveness of the metabolic workup of stone formers should therefore be evaluated in future studies.

Conclusions

It is the responsibility of the physician to properly evaluate the stone-former patient, to detect the underlying metabolic disorder, and to assess the risk of disease recurrence. In all of the lithiasic patients, the stone composition should be determined as the first-line evaluation. Further metabolic workup relies upon the patient's classification into low- or high-risk group. In low-risk group, only basic metabolic evaluation should be performed. However, in high-risk patients, a more detailed metabolic analysis should be offered. The composition of stone dictates the specific features of the recommended evaluation.

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Conflicts of interest

There are no conflicts of interest.

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Vesicoureteral Reflux – Insights into Diagnosis and Management

Abstract

Vesicoureteral reflux (VUR) is the most common congenital condition of the urinary tract. A plethora of imaging methods and treatment plans are described in literature and are used in clinical practice. The aim of this article is to analyze the available diagnostic tests and the pharmaceutical, endoscopic, and surgical options of our therapeutic armamentarium. A literature search on the PubMed database was conducted by two writers. Randomized controlled trials and meta-analyses were included, all published in PubMed and in the English language from 2011 to this day. After reviewing the full texts, we excluded duplicates, papers regarding secondary disease and those without a pediatric reference population. Regarding the mostly used imaging tests, voiding cystourethrography is considered the reference method for the diagnosis and grading of the disease, but it entails exposure of patients to ionizing radiation. Voiding urosonography has a similar sensitivity but is highly dependent on the operator's experience. Renal scintigraphy with dimercaptosuccinic acid remains a useful test for detecting renal scars. As far as management is concerned, continuous antibiotic prophylaxis, though previously doubted, remains a valid therapeutic option, especially for lower grades of VUR. Open surgical techniques and their modern–laparoscopic and robotic–variations are useful for dealing with high-grade disease, while endoscopic methods have sufficient efficacy and are utilized more and more. The diagnosis and treatment of VUR are constantly evolving areas. New diagnostic methods are replacing the older ones, while the treatment algorithm is individualized.

Keywords: *Antibiotic prophylaxis, imaging, surgery, vesicoureteral reflux*

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Introduction

Vesicoureteral reflux (VUR) is the most common urologic abnormality, with a prevalence of 1%–2% among the pediatric population worldwide. Most common presentations include recurrent febrile urinary tract infections (FUTI) in children, whereas prenatally a common sign is evidence of hydronephrosis. It has been estimated that up to one-third of children with VUR will experience a urinary tract infection (UTI) until the age of 2 years.[1] Acute pyelonephritis associated with VUR can lead to renal scarring and ultimately chronic/end-stage kidney disease known as reflux nephropathy.[1] Continuous antibiotic prophylaxis (CAP) is conventionally the initial treatment option, as it is considered effective for lower VUR grades, although its efficacy has previously been questioned. Definitive treatment strategies, such as endoscopic injections and surgery are often utilized for higher grades, but there is still a discussion in literature surrounding their indications in individual cases. This review aims to discuss existing evidence regarding the available diagnostic tests and management alternatives for this condition.

Methods

Two databases (PubMed [MEDLINE], Scopus) were searched by 2 independent reviewers. The terms used were "vesico-ureteral reflux and diagnosis "vesico-ureteral reflux and diagnostic imaging" "vesico-ureteral reflux and diet therapy" "vesico-ureteral reflux and drug therapy" "vesico-ureteral reflux and epidemiology" "vesico-ureteral reflux and microbiology" "vesico-ureteral reflux and prevention and control" "vesico-ureteral reflux and surgery" "vesico-ureteral reflux and therapy." The included studies were randomized controlle d trials (RCTs), reviews, systematic reviews, and meta-analyses from 2011 until today. Duplicates, studies that were not related to primary VUR and studies that also included nonpediatric populations were excluded.

Diagnostic evaluation

The initial detection of primary VUR is in

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many cases prompted by the diagnosis of a febrile UTI.[2] In children with complicated/febrile UTI and/or comorbidities, VUR is considered a significant possible diagnosis that is worth actively searching for to be treated. Prompt diagnosis and treatment of UTI are essential as it reduces the risk of renal scarring. The assessment of grade is also highly important as children with higher grades of VUR and UTI are at increased risk for developing pyelonephritis and renal scars. In case of recurrent UTIs, the diagnostic evaluation should be appropriately escalated, including a voiding cystourethrogram (VCUG).[2] VCUG is considered the gold standard but due to its cost and concerns of exposure to ionizing radiation, other imaging modalities that are less expensive and are related to less exposure to radiation, such as the contrast-enhanced US, have been explored as a tool for the assessment of VUR.[3] We will briefly analyze the most important imaging modalities used for the diagnosis and follow-up of VUR.

Voiding cystourethrogram

Voiding Cystourethrogram (VCUG) with fluoroscopy remains the gold standard in the detection and evaluation of VUR among children, as it yields images of the bladder and urethra and in addition enables grading of the reflux.[3] The disadvantages mainly include the need for bladder catheterization and the possibility of infection as well as the risk of radiation.[4] In addition, it is difficult to predict which subset of patients will develop renal scarring. It has been suggested that there are features of the VCUG that could predict the possibility of spontaneous resolution of VUR, as well as for the risk of FUTI recurrence, such as calculated ureteral diameter ratio and the bladder volume at the onset of reflux which are more predictive than reflux grade alone.[5] VCUG has been proposed by a recent consensus as an option for all children with antenatal dilatation of the urinary tract but is indicated in those with more severe dilatation or other abnormalities.[2] According to the updated AAP guidelines, it is recommended that in infants with initial febrile UTI, a VCUG should be carried out only in the presence of abnormal sonographic findings (i.e., hydronephrosis, scarring) or in atypical clinical circumstances.[2]

Radionuclide indirect-direct cystography

Indirect radionuclide cystography has the advantage that catheterization is not required and may offer images of renal parenchyma, as well as examine the urine drainage from the kidney to the bladder. One limitation is that it can only be used in toilet-trained children. Direct radioisotope cystography can also be done and could be an option for babies and infants, but bladder catheterization is required and does not provide any information for the bladder and the urethra.[4]

Renal and bladder ultrasound

Ultrasound is recommended by widely used clinical practice guidelines as the initial diagnostic testing for the first UTI in children with high suspicion of VUR.[3,6] It is widely used as it is often comforting to the family to have a safe, noninvasive exam with less exposure to radiation.[5] However, ultrasonography has not been proven to be either sensitive or specific in detecting reflux. Several publications have concluded that sonography remains an inferior screening test in children with febrile UTI as it is technician dependent, does not provide assessment of renal function and is not sensitive enough to detect all scarring.[2] Therefore, renal and bladder ultrasound (RBUS) results do not significantly alter the treatment plan. Clinical practice guidelines do recommend US as the initial diagnostic test but the VCUG, due to its ability for precise anatomic illustration, remains the gold standard.[3] RBUS and VCUG should, therefore, be considered complementary studies, as they each provide important, but different, information to the clinician.

Voiding urosonography

Voiding urosonography is more sensitive and specific than RBUS. It is an investigation of the urinary tract with intravesical administration of contrast agents. Advantages include that there is no exposure to radiation and there are not many side effects of contrast agents and it offers the opportunity of better assessment of grade.[4]

Dimercaptosuccinic acid

99 mTc-dimercaptosuccinic acid (DMSA) scintigraphy is a radionuclide scan performed to detect pyelonephritis and renal scars and is considered the gold standard.[1] DMSA is now the gold standard to assess for kidney injury and persistent renal scars. According to the results of a recent meta-analysis, neither RBUS nor DMSA have been shown to have sufficient accuracy in assessing the grade in VUR, to be used as a screening tool, as the specificity is low.[5]

Contrast-enhanced voiding urosonography-harmonic imaging/contrast-enhanced voiding urosonography-harmonic imaging

Contrast-enhanced voiding urosonography-harmonic imaging (CEVUS-HI) is also considered highly accurate in detecting VUS among children. Contrast-enhanced ultrasound (CEUS) could be an alternative to VCUG as it eliminates exposure to radiation while maintaining the same diagnostic accuracy.[3] Among the limitations is that it still requires urethral catheterization, is operator dependent and requires expertized sonographers.[5]

A pilot study demonstrated that CEUS can detect parenchymal defects in children with a history of VUR nephropathy. It has been shown that CEUS shows defects that are apparent on other forms of imaging including DMSA with the advantage of being less expensive, as well as the fact that there is no need for sedation or exposure to radiation.[1]

The use of harmonic imaging in VUS has shown an increase in the sensitivity and specificity and therefore shows improved accuracy with the superior evaluation of the retrovesical space and renal pelvis, bladder neck, and urethra compared with CEVUS. However, the use of CEVUS-HI as an alternative primary diagnostic modality to detect VUR cannot yet be strongly recommended due to the low–moderate quality of evidence of existing meta-analyses.[7]

Magnetic resonance urography

Magnetic resonance urography (MRU) can differentiate congenital renal dysplasia from acquired renal damage thanks to the improved spatial and contrast resolution, and also offers the opportunity of grade assessment as there is a proven association between damage in MRU and VUR grade.[5] However, patients often need sedation to obtain optimal images, and magnetic resonance imaging is the most expensive imaging modality.[1]

Management

The ultimate goal on which VUR management should be focused has been a long-debated issue. Some publications insist on the anatomical correction or improvement of reflux *per se*, while others highlight the importance of reducing the morbidity of recurrent UTIs and the long-term sequelae of renal damage. It is evident through literature that there seems to have been a recent yet dynamic shift in thinking toward the latter approach. For this purpose, the treatment options are many and the therapeutic algorithm is becoming more individualized.

Conservative measures

Managing VUR through avoidance of invasive treatment is based on the high rates of spontaneous resolution. The condition resolves with an annual rate of 28%,[8] while the mean overall spontaneous resolution rate is 68%, though even higher in Grades I-III.[9] The factors that have been identified to affect VUR resolution are VUR grade, clinical presentation, age, sex, laterality, and lower urinary tract (LUT) dysfunction.[10] Some authors recommend the VUR index as a useful tool to calculate the possibility of resolution, thus helping in cases of clinical dilemmas.[9]

Active surveillance

The watchful waiting approach was useful when the benefits of continuous antibiotic prophylaxis were controversial. In light of recent evidence through RCTs; However, in light of recent evidence through RCTs, the validity of CAP as a therapeutic option is not doubted anymore.[11] Therefore, active surveillance is no longer indicated. However, some authors mention that it could be offered to compliant families that can seek medical care when UTI symptoms appear.[9,10]

Continuous antibiotic prophylaxis

The long-term use of a low-dose antibiotic scheme is one of the oldest treatment options for VUR. Utilizing CAP for most cases is a safe option,[12] considering we are still unable to accurately discern the subset of children susceptible to the negative consequences of VUR, such as renal scarring.[10,13] Although its effectiveness has been questioned in the past, some recent RCTs and meta-analyses show adequate results.

When it comes to reducing the morbidity of UTIs, the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial found a hazard ratio (HR) of 0.50 and a longer time interval to recurrence for the prophylaxis group.[11] The treatment failure rate was almost double for the placebo group and the calculated number needed to treat was 8.[11] Similarly, the Swedish reflux trial showed a marked reduction in febrile UTIs in girls in the prophylaxis group compared to the surveillance group, though no difference was detected between treatment groups in boys.[8] Concerning VUR grades, the meta-analysis by De Bessa *et al*. found CAP to be beneficial for both high and low grades of VUR.[14] Correspondingly, the systematic review by Wang *et al*. found CAP to have a pooled OR for febrile or symptomatic UTIs of 0.63 and an even lower one for the studies at lower risk of bias, which further reinforces the argument for CAP.[15] Conversely, a Cochrane meta-analysis found CAP makes little to no difference in the risk of symptomatic or febrile UTI compared to no treatment or placebo, though considerable heterogeneity between included studies was noted.[16]

As far as renal parenchymal abnormalities are concerned, there is currently no evidence of benefit from the use of CAP.[16] RIVUR reported similar percentages in both the prophylaxis and placebo group,[11] whereas the Swedish reflux trial found that, the difference in new renal damage percentages was not statistically significant.[10] Nonetheless, CAP reducing the risk of renal scarring is a pathophysiologically sound hypothesis. With this in mind, some authors note that no trials have been designed with renal scarring as the primary endpoint, thus the follow-up period could be too short to detect such damage.[13,15] Furthermore, participant recruitment and monitoring could be to blame.[15] With regard to anatomical resolution or improvement of VUR, there does not seem to be any advantage from the use of CAP, as evidenced by available trials[8] and systematic reviews.[16]

Moreover, there is currently an effort to distinguish which patients are at a greater risk of VUR sequelae, which plays a crucial role in reaching the goal of individualized management. Wang *et al*. reevaluated the RIVUR trial results by applying a risk stratification method, separating patients to high- and low-risk groups, based on their VUR grade and bladder and bowel dysfunction (BBD), and circumcision status.[17] They found that there was no statistically significant difference between treatment groups in low-risk patients, while, in the high-risk group, the UTI recurrence rate was significantly lower for the prophylaxis arm.[17] These findings suggest that children categorized as low risk may not benefit from CAP enough to justify prescribing it to them, though this cannot be conclusively stated based on such a small sample size.[17]

Of equal importance are several concerns that arise from the prolonged use of antibiotics. Primarily, as expected, CAP increases the probability of resistant bacterial UTIs, as evidenced in the RIVUR trial[11] and later systematic reviews.[15,16] On the other hand, the incidence of antibiotic-related adverse events does not seem to be increased by CAP.[11,15,16] Furthermore, adherence to treatment is not routinely evaluated in studies;[14] thus many authors raise the question of how generalizable their results truly are.[13,16] Finally, the duration of CAP is still not clarified in the literature.[10]

Bladder and bowel dysfunction/lower urinary tract dysfunction

BBD/lower urinary tract dysfunction (LUTD) is the presence of symptoms such as urgency, wetting, constipation, or holding maneuvers and is characterized by abnormal bladder function variables. BBD/LUTD and VUR are interdependently associated. In the Swedish reflux trial, baseline PVR was an independent factor of not only recurrent UTIs and renal damage but also VUR persistence in both the prophylaxis and the endoscopic treatment groups.[18] Similarly, the RIVUR trial found that patients with BBD at entry benefitted more from CAP (HR 0.21) compared to those without BBD.[11] As expected, the detection and management of this condition are highlighted as priority in official guidelines.[12]

Invasive treatment

The common objective of all definitive treatment options is the anatomical correction of VUR. Taking into consideration that the resolution of reflux seems to no longer be the ultimate goal, assessing both the necessity and the success of these procedures and tailoring the available options for the needs of each patient is crucial.

Indications

Definitive treatment is strongly recommended for persistent high-grade (IV/V) VUR, yet there is no consensus on proper timing.[12,19] Furthermore, most authors agree with the traditional approach of shifting from conservative to invasive treatment once new renal scars or breakthrough UTIs appear.[19,20] However, this strategy is currently challenged, as the evaluation of scar progression is highlighted.[19] Finally, other indications include antibiotic intolerance or allergies, noncompliance, and parental preference.[19]

Endoscopic injections

Endoscopic injections of bulking agents aim at increasing the coaptation of the ureteral orifice, thus minimizing reflux. It is a minimally invasive option, which has become progressively more popular due to the ambulatory nature of the procedure, high rates of parental satisfaction,[21] low complication rate, and short learning curve.[20]

The reported success rates vary widely among studies since success can either be interpreted as reflux resolution or defined clinically. A recent RCT in infants with high-grade VUR found endoscopic injection to have significantly higher rates of resolution and downgrading of VUR, compared to CAP.[22] Similarly, the Swedish reflux trial found that VUR status improvement for the endoscopic arm was superior to that of the surveillance and prophylaxis arms.[8] Regarding clinical success, the same study reported a Hazard Ratio (HR) of 0.28 for recurrent UTIs compared to surveillance in girls,[8] while a Cochrane meta-analysis found a Risk Ratio of 0.55.[16] Nonetheless, the durability of this procedure is questioned, as evidenced by the 20% recurrence after 2 years in the Swedish reflux trial,[8] which is explained by possible migration or absorption of the agent. Finally, most authors agree that endoscopic treatment should be reserved for lower grades of reflux since its effectiveness is reduced as VUR grade increases,[10,20,23-25] which is reflected in official guidelines.[12]

With the evolution of endoscopic treatment throughout the years, different injection methods have been developed. The three most prominent ones are the subureteral transurethral injection (STING), the hydrodistention implantation technique (HIT) and the double HIT. Yap *et al*. found HIT to be superior to STING in correcting both low- and high-grade VUR,[25] a finding supported by other authors.[23] A modified version of the HIT, the Double HIT was reported to have higher success rates than HIT,[24] even comparable to those of open surgery.[23]

Surgery

The surgical correction of VUR is one of the oldest available treatment options, which aims at lengthening the intramural part of the ureter, thus strengthening the anti-reflux mechanism. With continuous technological advancements in surgery, different techniques have emerged.

Open ureteral reimplantation is still considered the gold standard for definitive treatment of VUR, with success rates in the anatomical correction that consistently surpass 95%.[10,23] There are two main approaches · the extravesical one, named Lich-Gregoir, and the intra-vesical one. The latter includes three versions · the cross-trigonal or Cohen's technique, which is the most widely used, the suprahiatal or Politano-Leadbetter and the infrahiatal or Glenn-Anderson, both of which are utilized less and less nowadays.[12,23] Open surgery, though often considered outdated, has a proven effectiveness in treating high-grade VUR; hence, it being recommended for this purpose in official guidelines,[12,20] though its higher morbidity should be noted.[23] One RCT showed a 100% resolution rate for Grades II, III, and IV with open surgery compared to 87.5% with endoscopic injections, though the difference was not statistically significant,[26] while another reported 93.75% and 80% correction rates, respectively.[27] Regarding clinical success, there does not seem to be any difference in UTI resolution posttreatment.[28]

Laparoscopic versions of the forementioned techniques have been used in clinical practice and studied thoroughly, with success rates comparable to[20] or surpassing those of open surgery. A recent meta-analysis reported a 96.7% resolution rate with the laparoscopic extravesical approach compared to 93.7% with the open transvesicoscopic technique.[29] Other advantages include less postoperative overall morbidity, shorter hospital stay and faster recovery,[10,20,29] though its steeper learning curve must be noted.[10] Finally, the extravesical approach is generally preferred over the intravesical one,[10] due to the technical difficulties of the latter.[20]

Robotic ureteral reimplantation has seen a rise in popularity, as expected, over the past decade. It offers lower overall morbidity, a shorter hospital stay,[10,23] and multiple degrees of freedom of movement for the surgeon.[9] On the other hand, it requires a longer operative time[20] and has a steep learning curve,[9,10] while its significant financial cost and limited availability[9] are to be considered. With robotics, the extravesical approach is most often used[20] because the intravesical version is technically challenging.[20] Regarding its success rate, the data vary widely between studies, ranging from 77% to 100%,[10] as expected due to the scarceness of studies on this fairly new treatment option. A recent systematic review and meta-analysis showed a slightly lower success rate of 93.4% in VUR resolution with robotic extravesical surgery, compared to 96.7% with the laparoscopic counterpart.[30]

Despite the multiple benefits laparoscopic and robotic surgery supposedly offer, their advantage over open surgery is still debated, so no general recommendation for them is currently included in official guidelines.[10,12]

Conclusion

VUR is the most common congenital abnormality of the urinary tract and its diagnosis and treatment are rapidly evolving fields. The most usual first presentation is febrile UTI and newer guidelines suggest the US as the initial diagnostic test in these cases. VCUG remains the gold standard for diagnosis, but other methods that do not involve exposure to radiation are under evaluation. Continuous antibiotic prophylaxis is often the first choice for treatment, while open surgery remains a helpful option for high-grade diseases. As technological advancements gain more ground, endoscopic injections and laparoscopic and robotic surgery are becoming increasingly popular. More large-scale studies that compare these techniques concerning their effectiveness and safety are required.

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Conflicts of interest

There are no conflicts of interest.

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Primary Urethral Carcinoma Manifested as a Perineal Abscess

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Abstract

Primary urethral cancer is a rare but highly aggressive malignancy. Risk factors include chronic inflammation and irritation of the urethra. In early stages, this type of cancer presents with nonspecific symptoms, which can be misleading and associated with urethral strictures. We report a case of a 66-year-old male with a history of urethral stricture who presented with a perineal abscess of unknown origin. During the process of treatment, he was diagnosed with primary urethral carcinoma. Salvage therapy immediately followed, including surgery and radiation, but during the follow-up, the patient developed distant metastases and died 2 years after initial diagnosis.

Keywords: *Perineal abscess, urethral carcinoma, urethrotomy*

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Introduction

Primary urethral carcinoma is considered one of the rarest malignancies of the urogenital tract.[1] It occurs almost three times as often in males than in females, and the incidence rises in the elderly (>75 years old).[2] Risk factors for primary urethral carcinoma include chronic irritations of the urethra due to catheterization, chronic inflammation secondary to infection, radiation, urethral diverticulum, and strictures. Although rare, primary urethral carcinoma is highly aggressive and becomes more difficult to treat if diagnosed in advanced stages, as in most cases reported in the literature.[3] We report a case of a man who presented with a perineal abscess as a result of urethral carcinoma.

Case Report

A 66-year-old male presented febrile to the emergency department with a large abscess in the perineum. The patient reported admission to another hospital for the same reason 2 months ago. At that time, a surgical drainage of the abscess took place and a suprapubic bladder catheter was placed afterward. A recent pelvic magnetic resonance imaging (MRI) revealed a perineal abscess with multiple compartments that extended anteriorly to the apex of the prostate, with a diameter of 6.5 cm and was in contact with the base of the penis, the bulbar urethra, and the scrotum. Medical history included arterial hypertension, type 1 diabetes, and an optical urethrotomy due to urethral stricture 5 years ago. He was also cured from Hodgkin’s lymphoma after receiving six cycles of chemotherapy 22 years ago.

A new pelvic MRI was performed, setting a suspicion of a fistula between the urethra and the left side of the perineal abscess, along with the enlarged inguinal lymph nodes (LNs). A computed tomography (CT) urethrography was performed and revealed the progression of the contrast media up to 13 cm from the urethral meatus, entering the perineal abscess [Figure 1].

The patient was subsequently operated. He was placed in the standard lithotomy position. The optical urethrotome was introduced and reached the point of the stricture, and then multiple biopsies were taken from the area [Figures 2 and 3].

At this point, an Amplatz dilator set was used though the suprapubic tract up to 24 Fr, and an access sheath was placed. The cystoscope was then used to enter the bladder through the suprapubic access. Both ureteral orifices were recognized, and a retrograde pyelography followed. Ureteral double-J stents were then placed *in situ* and diverted through the suprapubic tract [Figure 4]. Finally, a Couvelaire 18 Fr catheter was placed through the urethra.

A new pelvic MRI performed 15 days postoperatively showed a decreased size

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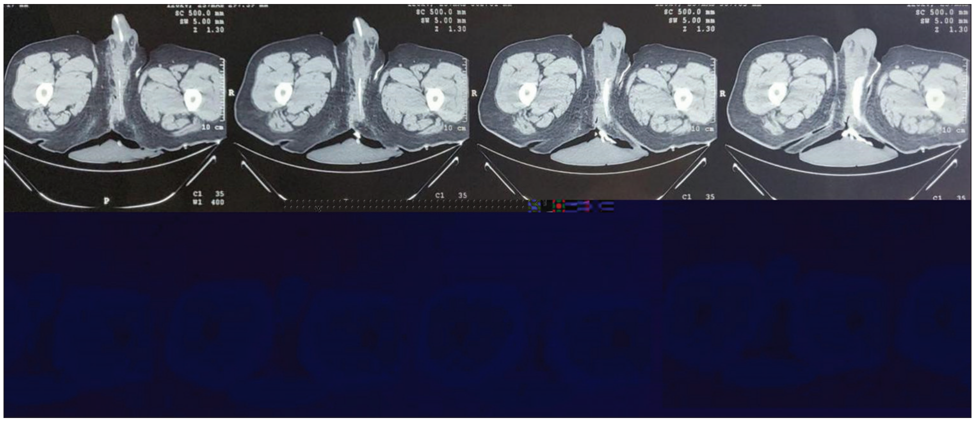

Figure 1: Computed tomography urethrography

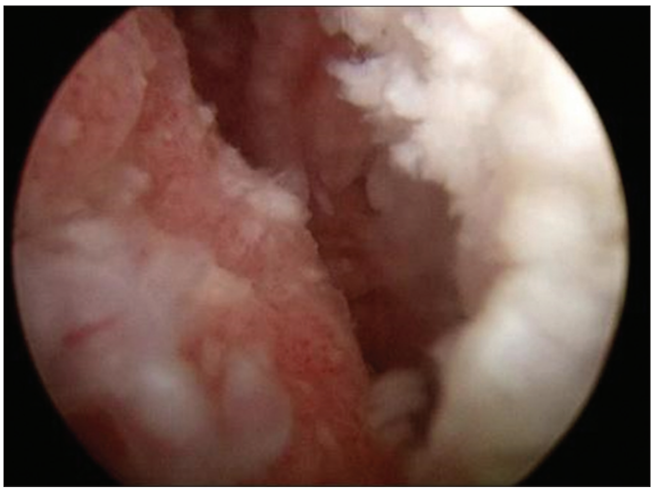

Figure 2: Point of the stricture (endoscopic view)

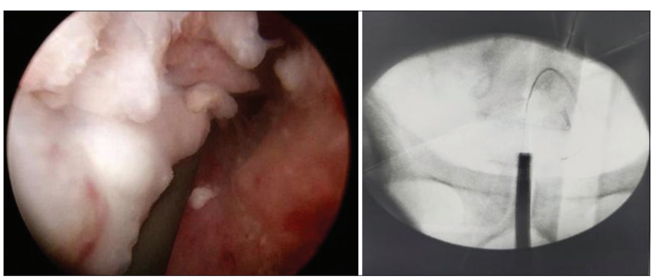

Figure 3: Use of the guidewire navigating the urethra

of the perineal abscess. The pathology report revealed a high-grade primary urethral squamous cell carcinoma. In light of this diagnosis, the patient was scheduled for extirpative surgery after a multidisciplinary team meeting. He underwent radical penectomy. During the surgery, the tissues of the right testis and the apex of the prostate were macroscopically invaded. Rapid biopsies confirmed neoplastic infiltration, and subsequently, radical (right) orchiectomy and radical prostatectomy followed. Finally, a suprapubic cystostomy was performed, and a 20 Fr Foley was placed. The patient recovered uneventfully and was discharged after 10 days. The pathology report revealed squamous cell carcinoma infiltrating the penis, prostate, periurethral tissues, and the right testicle. Furthermore, the removed LNs were affected. The limit of the resected tissue remained disease free.

A multidisciplinary meeting followed, scheduling the patient for two cycles of platinum-based chemotherapy and thirty sessions of radiotherapy. The cycles were completed uneventfully, and the patient was inducted to a very strict follow-up plan due to the complexity of the disease. Unfortunately, 2 years after the initial diagnosis, the patient developed pulmonary metastases along with metastatic ascites and died.

Discussion

Patients suffering from primary urethral carcinoma, commonly report symptoms such as hematuria or lower urinary tract obstruction, which can also be accompanied by extraurethral mass, irritative symptoms, or pelvic pain.[4] Up to 50% of men with urethral cancer have a history of urethral stricture disease and almost 25% report a history of sexually transmitted infections. The diagnosis requires a high level of suspicion and requires history and physical examination, laboratory evaluation, direct visualization, and imaging to assess the extent of the disease.[2] Known preexisting pathologies (e.g., stricture, infection, and urethritis) can often delay treatment of the patients, as they continue to be treated based on the assumption that their symptoms are caused by the preexisting disease.[5]

The current studies in literature are mostly retrospective analyses with small sample sizes.[3] Given this, there are limited data to guide diagnostic and treatment strategies. While surgery and radiation therapy remain the main treatment options for localized or early-stage disease, advanced-stage disease requires multimodal treatment.[2]

The European Association of Urology guidelines on the primary urethral carcinoma recommend diagnostic urethrocystoscopy accompanied by biopsies for primary assessment.[6] The location and extend of the tumor constitute crucial information, as well as the subtype

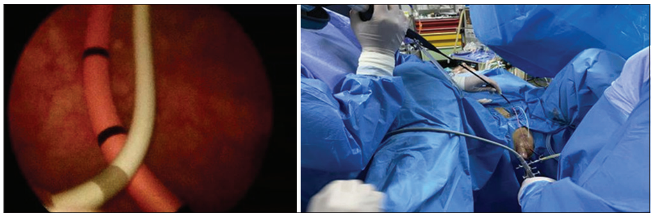

Figure 4: Diversion of the ureteral stents

classification that can be determined through the histological workup.[7] The primary urethral carcinoma is very unlikely to occur in adults under the age of 45 years, and its highest incidence rate is often reported in individuals 75 years and older.[3] Symptoms such as fistula or abscess formation, ulceration, and induration must be alarming.[6]

Radiological imaging of urethral carcinoma aims to assess local staging and to detect lymphatic and distant metastatic spread.[8] Imaging workup should include CT of the chest, abdomen, and pelvis for staging, including CT urography with delayed phases for optimal urothelial evaluation.[6] MRI can be used to evaluate tumor location and size, as well as local tumor extent and the presence of regional LN metastases, focusing, in particular, on inguinal and pelvic LNs. For local staging, there is evidence that MRI is an accurate tool for monitoring tumor response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease before any extirpative surgery.[8,9]

Prognostic factors for survival in primary urethral carcinoma include age, race, tumor stage, and grade.[10] According to the RARECARE project, the 1- and 5-year overall survival (OS) rates in patients with urethral carcinoma are 71% and 54%, whereas cancer-specific survival rates at 5 and 10 years were 68% and 60%, respectively.[10] OS rates do not substantially differ between both sexes.[6]

Conclusions

This case report describes a case of a primary urethral carcinoma, which is an uncommon malignancy. A more comprehensive investigation is often required if there is a discrepancy between clinical symptoms and the underlying disease. Pathology workup is necessary for accurate diagnosis because a tumor's appearance can be misleading. Salvage therapy is likely to improve oncological outcomes, warranting a multidisciplinary approach to therapy based on the current evidence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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