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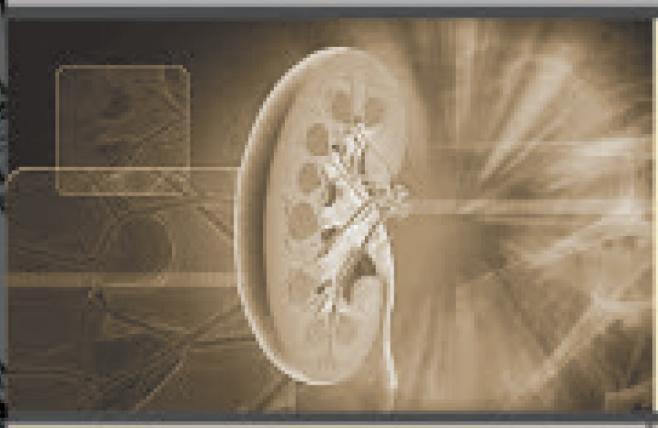

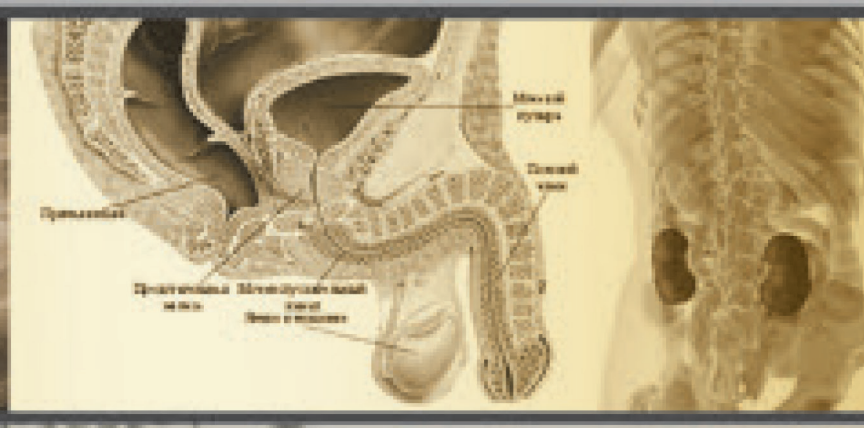

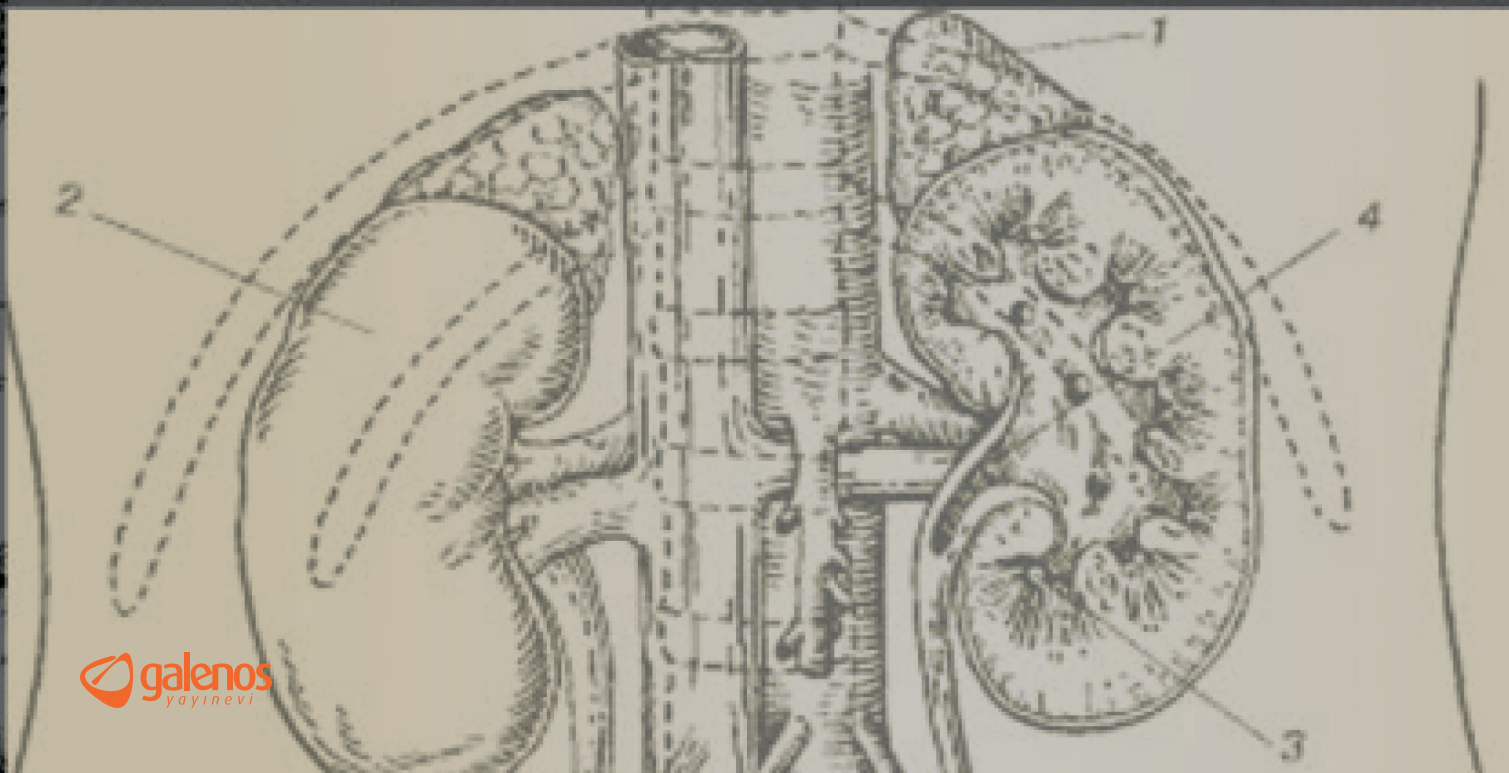

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Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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ORIGINAL RESEARCH
General Urology

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Journal of Urological Surgery, 2019;6(1):1-6

Supine PCNL is the Way Forward, with Reduced Anesthesia and Operative Times As Compared to Prone PCNL, Along with Comparable Blood Loss and Stone Free Rates

Supin PCNL ile Karşılaştırıldığında, Supin PCNL, Anestezi ve Operasyon Süreleri Azaltılarak İleriye Doğru İlerliyor

Adnan Siddiq Awan, Salman Khalid, Shariq Anis Khan, Shoaib Mithani, Jahanzeb Shaikh, Imran Sharif

The Kidney Centre Postgraduate Training Institute, Department of Urology, Karachi, Pakistan

What's known on the subject? and What does the study add?

Since the advent of prone percutaneous nephrolithotomy (PCNL) in 1976, it is a widely accepted procedure of choice for renal stones >2 cm. Supine PCNL has been realized as even better modality than prone PCNL but is still not being performed frequently due to a fear factor of colonic injury. Another factor is that surgeons acquainted with prone PCNL do not want to acquire a new modality with fear of rough transition. Supine PCNL keeps its promise of reduced operative and anesthesia time.

Abstract

Objective: The aim of this study is to compare safety and efficacy of supine versus prone percutaneous nephrolithotomy (PCNL) in terms of stone-free rate, operative time, anesthesia time and blood loss in a retrospective case-control trial.

Materials and Methods: Fifty patients underwent supine PCNL during the study period (group A). Equal number of patients, who underwent prone PCNL during same period with similar demographic and clinical attributes, were taken as controls (group B). Demographic details, such as gender and age, and body mass index, stone size, stone location and stone laterality were comparable between the two groups. Pre- and post-operative hemoglobin (Hb) levels in patients in both groups were tabulated. Variables analyzed to compare the groups included operative time, anesthesia time, fall in Hb, blood transfusion, stone clearance and need for auxiliary procedure.

Results: The median operative time (minutes) in patients of group A [35; interquartile ratio (IQR): 25], was significantly different from group B (70; IQR: 40) (p=0.000). The median anesthesia time (minutes) in patients in group A (50; IQR: 25) was significantly different from group B (85; 45) (p=0.000). The median fall in Hb (g/dL) in patients in group A (1.700; IQR: 1.2) was significantly different from group B (1.200; IQR: 2.4) (p=0.967). Two patients in group A and 7 in group B needed blood transfusion (p=0.080). Thirty two patient in group A and 34 in group B achieved stone-free status (p=0.833). Eleven patients in group A and 6 in group B needed auxiliary procedure in the form of extracorporeal shockwave lithotripsy (p=0.287).

Conclusion: Supine PCNL is as safe and effective as conventionally performed prone PCNL, with an added benefit of decreased operative and anesthesia time.

Keywords: PCNL, Supine, Prone, Valdivia

Öz

Amaç: Bu çalışmanın amacı retrospektif bir olgu kontrol çalışmasında supin perkütan nefrolitotomi (PCNL) ve pron PCNL'yi taşsızlık oranı, operasyon süresi, anestezi süresi ve kan kaybı bakımından karşılaştırmaktır.

Gereç ve Yöntem: Çalışma süresince 22 hastaya supin PCNL yapıldı (grup A). Aynı dönemde benzer demografik ve klinik özellikleri olan ve pron pozisyonda PCNL uygulanan eşit sayıda hasta kontrol grubu (grup B) olarak çalışmaya dahil edildi. İki grup arasında cinsiyet, yaş, vücut kitle indeksi, taş boyutu, taş yeri ve taş lateralitesi gibi demografik detaylar benzerdi. Her iki gruptaki hastaların ameliyat öncesi ve sonrası hemoglobin (Hb)

Correspondence: Adnan Siddiq Awan MD, The Kidney Centre Postgraduate Training Institute, Department of Urology, Karachi, Pakistan
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düzeyleri tablolandı. İki grubun karşılaştırılması için analiz edilen değişkenler arasında ameliyat süresi, anestezi süresi, Hb'de düşüş, kan transfüzyonu, taş klirensi ve yardımcı prosedür ihtiyacı sayılabilir.
Bulgular: Grup A'daki hastaların (35; 26) operasyon zamanı medyan ve çeyrekler açıklığı (IQR) değerleri grup B'den (87,5; 45) anlamlı olarak farklıydı (p=0,000). Grup A'da anestezi süresi, medyan ve IQR (35; 26), grup B'den (87,5; 45) anlamlı olarak farklıydı (p=0,000). Grup A'daki (1,700; 1,2) Hb'li hastaların Hb'deki fallen medyan ve IQR değerleri grup B'den (1,400; 2,4) anlamlı olarak farklıydı (p=0,613). Grup A'da 1 hasta, grup B'de 3 hastada kan transfüzyonuna ihtiyaç vardı (p=0,294). Grup A'da 14, grup B'de 15 hastada tam taş açıklığı saptandı (p=0,500). Grup A'da 5 hasta, grup B'de 2 hastada ekstrakorporeal şok dalgası litotripsi şeklinde yardımcı prosedür gerekti (p=0,206).
Sonuç: Supin PCNL, geleneksel olarak yapılan pron PCNL kadar güvenli ve etkilidir, ancak azaltılmış operasyon ve anestezi süresinin ek bir yararı vardır.
Anahtar Kelimeler: PCNL, Supin, Pron, Valdivia

Introduction

Fernström and Johansson (1) described the first percutaneous nephrolithotomy (PCNL) in 1976 performing it in the prone position and adopting it as a standard surgical procedure for renal stones larger than 2 cm. Prone PCNL became widely popularized and totally replaced open surgery for renal stones and emerged as the gold standard procedure for 2 decades.

In prone PCNL, the patient is initially placed in dorsal lithotomy position to insert ureteric catheter and then the position is changed to prone for the remaining procedure. This results in an unnecessary delay and also harbors risk of damaging nerves, limbs, neck, and eyes of the patient under anesthesia. Furthermore, prone position is not favorable in morbidly obese patients, compromised cardiac index or those with cardiopulmonary diseases (2).

In 1987, PCNL in the supine position was first described by Valdivia et al. (3), aiming to reduce patient-, anesthesia- and surgery-related inconveniences of the prone position, but supine position did not attract much popularity for lots of years to come. Later on, the Valdivia position was improved further by Ibarluzea et al. (4) by adding a modified lithotomy arrangement, giving origin to a new position called Galdakao-modified supine Valdivia position. Supine PCNL gained popularity due to many pros in contrast to prone position in terms of reduced operative time, avoiding injuries resulting from patient repositioning, reduced radiation exposure to surgeon, anesthesia-related complications, and ability of surgeon to perform surgery in sitting position (5). Limited exposure of the flank area for renal puncture is considered to be the major disadvantage of this position. Kumar et al. (6) made some modifications in the supine position resulting in better exposure of flank area. Falahatkar et al. (7) performed the procedure in a complete supine position without using towel roll or changing leg position and found it to be feasible yet safe.

Despite these advantages, the popularity of supine PCNL among urologists worldwide remains modest and is still considered a "new" rather than an alternative position (8,9). Another reason why many experienced surgeons are not very eager to embrace supine position is because they are afraid that this radical change may be cumbersome and may impact surgical outcomes during the learning curve. This is something that an established surgeon does not want to experience (10). Nevertheless, some authors should be congratulated because they confuted this concept, demonstrating that changing position is not cumbersome and the learning curve is rather short, yielding similar or even better outcomes, rather quickly (11).

The importance of this study is to kill the fear factor which resides in minds of many experienced urologists. Hiding behind the false paradigms, which is translated by statements like "supine PCNL is not my thing", the way forward cannot be paved. This study aims to establish safety of supine PCNL, emphasizing the improved efficacy in the process.

Materials and Methods

This retrospective case-control study was done at the Kidney Centre Postgraduate Training Institute, Karachi, Pakistan. Patients enrolled in the study were those who got operated from October 2017 to May 2018, the reason being that supine PCNL was started at that time in the institute. Prior to performing the study, the ethics committee approval was obtained by the Kidney Centre Ethical Review Committee (date: February 2018, reference number 64-URO-022018).

Fifty patients underwent supine PCNL during the study period (group A). An equal number of patients, who underwent prone PCNL during the same period and bearing similar demographic and clinical attributes, were taken as controls (group B). Therefore, a sample size of 100 was taken consisting of 50 patients as group A and 50 as group B. This was also comparable to the sample size calculated by OpenEpi™ sample size calculator by obtaining means and standard deviations of a similar study performed (12).

All adult patients (>14 years), who were electively admitted for PCNL and underwent the procedure in either supine or prone procedure, were analyzed in the study. Demographic details, such as gender and age, and data on body mass index (BMI),

stone size, stone location and stone laterality were comparable between the two groups. Pre- and post-operative hemoglobin (Hb) levels in patients in both groups were also tabulated. Variables analyzed to compare the two groups included operative time, anesthesia time, fall in Hb, blood transfusion, stone clearance and need for auxiliary procedure.

Access acquired with a spinal needle in the prone position was performed using the "triangulation" technique under fluoroscopic guidance, after performing rigid cystoscopy, ureteric catheter placement and retrograde urography in dorsal lithotomy position. Patients, who underwent supine PCNL, had their cystoscopy and ureteric catheter placement also performed in the supine position, instead of dorsal lithotomy position. All procedures were performed by the same urologist. All supine PCNLs were performed in the Valdivia position.

Tract dilatation in both groups was achieved by Alkin's metallic dilators up to 27 Fr and a 30 Fr Amplatz sheath was used. Stone fragmentation was achieved in all patients with pneumatic lithoclast. Nephrostomy tube was not placed in any patient among the two groups. None of the patients required double J stent insertion.

Statistical Analysis

Normality was checked for all the recorded data. Normally distributed variables were described in terms of mean and standard deviation for continuous variables (age, BMI, residual stone) and parametric testing was performed by the independent samples t-test. Not normally distributed data (stone size, operative time, anesthesia time, pre-operative and post-operative Hb and fall in Hb) was described in terms of median and interquartile ratio (IQR) and was tested using the Mann-Whitney U test. Categorical variables (gender and stone location and laterality) were described in terms of "n number" and were compared between the two groups applying a chi-square test. Data were analyzed using SPSS version 20. A p value of less than 0.05 was taken as statistically significant.

Results

Forty seven males and 3 females underwent supine PCNL (group A) and 38 males and 12 females underwent prone PCNL (group B) (p=0.023) (Table 1).

There was no significant difference in mean age between patients in group A (39.52+10.463) and group B (36.66+11.241) (p=0.191) (Table 1).

There was no significant difference in mean BMI in patients in group A (23.590+4.959) was and group B (24.471+5.400) (p=0.398) (Table 1).

The median stone size in patients in group A (2.20; IQR: 1.0), was not significantly different from group B (2.35; IQR: 1.1) (p=1.000) (Table 1).

Thirty five patients in group A and 39 in group B had pelvic stone; 15 patients in group A and 11 in group B had lower calyceal stone (p=0.495) (Table 1).

Twenty six patients in group A and 20 in group B had right-sided stone(s); 24 patients in group A and 30 in group B had left-sided stone(s) (p=0.316) (Table 1).

The median operative time in patients in group A (35; IQR: 25) was significantly different from group B (70; IQR: 40) (p=0.000) (Table 2).

The median anesthesia time in patients in group A (50; IQR: 25) was significantly different from group B (8; 45) (p=0.000) (Table 2).

The median pre-operative Hb in patients in group A (14.750; IQR: 1.5) was significantly different from group B (13.900; 2.0) (p=0.000) (Table 2).

The median post-operative Hb in patients in group A (13.200; IQR: 1.2), was significantly different from group B (12.600; 3.2) (p=0.000) (Table 2).

Table 1. Baseline demographics and clinical characteristics

	Group A (Supine PCNL)	Group B (Prone PCNL)	
	Number of patients (n)	Number of patients (n)	p values
Gender			
Male	47	38	p=0.023
Female	03	12	
Age (years)			
Mean	39.52	36.66	p=0.191
Standard deviation	+10.463	+11.241	
BMI (kg/m²)			
Mean	23.590	24.471	p=0.398
Standard deviation	+4.959	+5.400	
Stone size (cms)			
Median	2.20	2.35	p=1.000
Interquartile range	1.0	1.1	
Stone location			
Pelvis	35	15	p=0.495
Lower calyx	39	11	
Stone laterality			
Right side	26	24	p=0.316
Left side	20	30	

PCNL: Percutaneous nephrolithotomy, BMI: Body mass index

Table 2. Investigative and operative parameters

	Group A (Supine PCNL)	Group B (Prone PCNL)	
	Number of patients (n)	Number of patients (n)	p values
Operative time (minutes)			
Median	35	70	p=0.000
Interquartile range	25	40	
Anesthesia time (minutes)			
Median	50	85	p=0.000
Interquartile range	25	45	
Pre-operative hemoglobin (gm/dL)			
Median	14.750	13.900	p=0.000
Interquartile range	1.5	2.0	
Post-operative hemoglobin (gm/dL)			
Median	13.200	12.600	p=0.000
Interquartile range	1.2	3.2	
Fall in hemoglobin (gm/dL)			
Median	1.700	1.200	p=0.967
Interquartile range	1.2	2.4	
Blood transfusion			
Transfusion done	02	07	p=0.080
Stone clearance			
Complete	32	34	p=0.833
Partial	18	16	
Residual stone size (cms)			
Mean	0.216	0.200	p=0.805
Standard deviation	+0.324	+0.322	
Auxiliary procedure (number of patients)			
Shockwave lithotripsy	11	06	p=0.287

PCNL: Percutaneous nephrolithotomy

The median fall in Hb level in patients in group A (1.700; IQR: 1.2) was significantly different from group B (1.200; 2.4) (p=0.967) (Table 2).

Two patients in group A and 7 patients in group B needed blood transfusion (p=0.080) (Table 2).

Thirty two patient (64%) in group A and 34 patients (68%) in group B achieved complete stone clearance (p=0.833) (Table 2).

There was no significant difference in mean residual stone size between group A (0.216+0.324) and group B (0.200+0.322) (p=0.805) (Table 2).

Eleven patients in group A and 6 patients in group B needed auxiliary procedure in the form of extracorporeal shockwave lithotripsy (p=0.287) as shown in Table 2.

Discussion

Prone PCNL has dominated renal stone surgery ventures for the past 3 decades now. After the advent of prone PCNL in the developed world, most of the developing countries have also developed the necessary armamentarium and expertise to acquire this procedure. Since renal stone disease affects a larger chunk of urological patient population, PCNL has become one of the frequently performed procedures in the world. Any renal stone of >2 cm should be treated with PCNL wherever available and feasible, according to the recent American and European urology guidelines. With passing time, whilst urologists have developed a stable learning curve for this procedure, new techniques and innovations have revolutionized PCNL procedure vastly. A good example for this notion is the advent of supine PCNL which grants the urologists immunity from adverse effects resulting from previously popular modality of prone PCNL. These adverse effects included changing of patient position causing unnecessary delay, risk of damage to patient's neck, limbs, nerves and eyes; not to forget the least favorable position in morbidly obese patients and those with compromised cardiopulmonary system (2). These outcomes resulted in experimentation of PCNL procedure and thus, supine PCNL was invented by Valdivia back in 1987 (3).

Many trials have demonstrated the benefits of supine PCNL along with its good safety profile. Some of the benefits include reduced operative and anesthesia time and reduced surgeon's fatigue. Falahatkar et al. (7) from Iran conducted a clinical trial on 117 patients who underwent PCNL in the supine position between January 2009 and January 2010. He reported a stone-free rate (SFR) of 77.77% and also mentioned potential advantages including better urethral access, better control of the airway, less positioning of patients, reduced operative time, a relatively comfortable surgeon, and more rapid access to airway especially in patients with morbid obesity and compromised cardiopulmonary function.

A retrospective study conducted from 2011 to 2016 by Sofer et al. (11) revealed a trend toward shorter operative time (138 vs 150 minutes), anesthesia time (174 vs 192 minutes) and hospitalization (2.2 vs 2.6 days) in the supine PCNL group, without significantly different SFRs as compared to prone PCNL group. The same study also demonstrated that implementation of supine PCNL in their centre reached 96% in 3 years. The reason was that both anesthesiologists and urologists expressed their unanimous preference for supine position over the prone one.

Another retrospective study by Sohail et al. (12) conducted from January 2011 to December 2015 on 197 patients showed that the mean operative time in supine PCNL was 32.3+6.6 min shorter than that in the prone position (p<0.001). They also

noted that the mean hospital stay was 1.2+0.75 days shorter for the supine vs the prone position ($p<0.001$).

Abdel-Mohsen et al. (13) conducted a prospective study from October 2008 to March 2010 in Zagazig University, Egypt, in which 77 patients with renal stones were randomized into two groups: group A (39 patients) were operated using the free-flank modified supine position, and group B (38 patients) in the prone position; SFR, operative time and complication rates were compared. The results revealed that SFRs were 84.6% and 84% in group A and B, respectively. Furthermore, operative time was significantly longer in group B (prone) than in A (free-flank modified supine) and there was no significant difference between the groups in terms of complications.

Our study demonstrated comparable results with the aforementioned literature in many ways. Operative as well as anesthesia times were significantly reduced in patients undergoing supine PCNL whereas there was no difference in stone clearance rate between supine (64%) and prone (68%) PCNL cases.

Study Limitations

The prominent limitation of the study is its retrospective nature and future prospective trials would be more beneficial in establishing stronger evidence. Another limitation of the study is its small sample size which can be addressed after further prospective trials in the future. Another limitation could be the use of only single type of supine position (Valdivia) and this limitation can be tackled by experimenting on Galdakao (modified Valdivia) position in future trials.

Conclusion

Supine PCNL is as safe and effective as the conventionally performed prone PCNL, but with an added benefit of decreased operative and anesthesia time due to nullification of changing of patient's position during the procedure. Furthermore, the surgeon's as well as anesthetist's comfort associated with supine position is a contrasting advantage in the scope of ergonomics during this very common urological procedure.

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Primary investigator or patients did not have any conflict of interest. Institutional grant was approved and used for the extra routine investigations.

Ethics

Ethics Committee Approval: This study was approved by the Kidney Centre Ethical Review Committee (date: February 2018, reference number 64-URO-022018).

Informed Consent: Not applicable because this was a retrospective study of patients' clinical and surgical records.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S.A., S.E.K., S.A.K., S.M., Concept: A.S.A., Design: A.S.A., Data Collection or Processing: A.S.A., S.A.K., J.S., I.S., Analysis or Interpretation: A.S.A., Literature Search: A.S.A., Writing: A.S.A.

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Our Multiple Single-step Access Results in Percutaneous Nephrolithotomy

Perkütan Nefrolitotomide Multipl Single-step Akses Sonuçlarımız

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What's known on the subject? and What does the study add?

In some patients, percutaneous nephrolithotomy (PNL) may require more than one access into the kidney due to stone burden. There is no publication that shows the success and complication rates of multiple access single step PNL. Therefore, despite our limitations, our work is valuable in this respect.

Abstract

Objective: The aim of this study is to evaluate the success and complication rates of percutaneous nephrolithotomy (PNL) with multiple single step access in patients with staghorn kidney stones.

Materials and Methods: A total of 118 patients with staghorn kidney stones, who underwent PNL in our clinic between 2008 and 2015, were included in the study. All patients were examined with non-contrast abdominal computed tomography before the operation. Demographic data of patients, operation details, intra- and postoperative complications and additional interventions were evaluated.

Results: The mean age of the patients included in the study was 49.6 years. The mean operative time was 139.4 minutes and the mean fluoroscopy time was 126.9 seconds. Postoperative residual stone was detected in 28% of the patients. Postoperative fever was observed in 19 patients (16.2%), and sepsis developed in 3 (2.5%) of them. Additional postoperative procedures were required in 11 patients (9.3%). No patient was lost due to complications. Operation success and complication rates were compatible with the literature.

Conclusion: For staghorn stones, PNL with multiple single step dilatation technique can be used as an effective and safe method in adult patients.

Keywords: Percutaneous nephrolitotomy, Single-step dilatation, Multiple access

Öz

Amaç: Bu çalışmada amacımız, staghorn taşı olan hastalarda yapılan single-step multipl akses perkütan nefrolitotomi sonuçlarımızı değerlendirmektir.

Gereç ve Yöntem: Kliniğimizde, 2008-2015 yılları arasında staghorn taşı olup PNL yapılan 118 hasta çalışmaya dahil edildi. Operasyon öncesi tüm hastalar kontrastsız batın bilgisayarlı tomografi ile değerlendirildi. Hastaların demografik verileri, operasyon bilgileri, intra/postoperatif komplikasyonlar ve ek girişim gerekliliği ayrıca incelendi.

Bulgular: Çalışmaya katılan hastaların ortalama yaşı 49,6 yıldı. Ortalama operasyon zamanı 139,4 dakika ve ortalama fluoroskopi süresi 126,9 saniyeydi. Hastaların %28'inde rezidü taş izlendi. On dokuz hastada (%16,2) postoperatif ateş yükseliği, 3 hastada (%2,5) sepsis görüldü. On bir hastada (%9,3) ek girişim gerekliliği oldu. Hiçbir hasta komplikasyonlar nedeniyle ölmedi. Başarı ve komplikasyon oranlarımız literatür ile uyumluydu.

Sonuç: Staghorn taşı olan ve PNL planlanan hastalarda, multipl single-step dilatasyon tekniği güvenle uygulanabilir.

Anahtar Kelimeler: Perkütan nefrolitotomi, Single-step dilatasyon, Multipl akses

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Introduction

Percutaneous nephrolithotomy (PNL) is known as the standard surgical treatment for large stones with high success and low complication rates (1). Establishment of the nephrostomy tract is one of the most important steps of PNL. A tract dilatation of 25-30 Fr following 6 Fr dilatation in one session was described as the single step dilatation with a view to reduce operative and fluoroscopy times (2). Although, it has been mentioned in large-scale studies that single step dilatation techniques can be used as an alternative dilatation technique (3), there is no information about increased complications associated with this method in PNL patients requiring multiple access. The aim of this study was to retrospectively evaluate the success and complication rates of treatment with multiple access using the single-step technique in patients with staghorn kidney stone.

Materials and Methods

Records of 1150 patients who underwent PNL between 2008 and 2015 were retrospectively reviewed. Written informed consent was obtained from the patients. Patients younger than 18 years and those having urinary system anomalies were excluded from the study. All patients were examined with non-contrast abdominal computed tomography (CT) before the operation. A total of 118 patients having only staghorn kidney stones were included in the study. The period from the injection of contrast medium to the insertion of the Malecot catheter was recorded as the operative time. The surgery was performed in the prone position. Important data such as fluoroscopy time, number of access and intraoperative complications during the operation were also recorded.

At the end of the surgery, a 14 Fr nephrostomy catheter was placed at one access site in all patients. The incisions were closed primarily at other access sites. Malecot catheter was removed on postoperative day 1-3 and the patients without complications were discharged. Postoperative complications and additional interventions were recorded.

All patients were reevaluated with a non-enhanced CT taken at postoperative 1st month. Determining stone-free status or having fragments ≤4 mm was considered treatment success (4). Stone analysis is not being done routinely in our country.

Results

Data of 118 patients with a mean age of 49.6±1.69 years, who met the study criteria, were reviewed. Of the patients, 76 (64.4%) were male and 42 (35.6%) were female. Sixty patients (50.8%) were operated on the left kidney and 58 patients (49.2%) on the right kidney. In 96 of the 118 patients (81.3%), two accesses were sufficient and in 22 patients (18.7%), 3 accesses were performed. The mean operative time was 139.4±5.03 minutes. The mean fluoroscopy time was 126.9±6.9 seconds. Postoperative residual stones were observed in 33 patients (28%) (Table 1).

Three patients (2.5%) received blood transfusion due to intraoperative hemodynamic instability. Except hemorrhage, no other intraoperative complications were observed.

Ten patients (8.5%) received blood transfusion due to postoperative hemodynamic instability, none of them needed more than 2 units. Fever over 38 °C was detected in 19 patients (16.2%) before discharge (first 24-72 hours). Three patients (2.5%) required intensive care due to sepsis (Table 2). They were followed up in the intensive care unit and discharged without any problem. None of the patients died from operation-related complications.

The patients were also evaluated for additional intervention in the postoperative period. Three patients (2.5%) were placed

Table 1. Preoperative data of the patients

	Number of patients (n)	Percent (%)
Average age (years)	49.6±1.69	-
Gender (%)		
Male	76	64.4
Female	42	35.6
Operation time (minute)	139.4±5.03	-
Fluoroscopy time (second)	126.9±16.9	-
Operation side		
Right	60	50.8
Left	58	49.2
Number of access		
Two	96	81.3
Three	22	18.7
Stone-free status/success	85	72

Table 2. Complications during and following percutaneous nephrolithotomy

	Number of patients (n=118)	Percent (%)
Intraoperative transfusion (%)	3	2.5
Postoperative transfusion (%)	10	8.5
Postoperative fever (%)	19	16.2
Sepsis and need for ICU (%)	3	2.5
Additional interventions		
URS	8	6.7
DJS	3	2.5

ICU: Intensive care unit, URS: Ureterorenoscopy, DJS: Double j stent

double j stent due to wound site discharge and severe colic pain. Ureterorenoscopy (URS) was performed in 8 patients (6.7%) upon detection of ureteral stone at the same side (Table 2).

Discussion

Since the publication of the first PNL series of Wickham and Kellet (5) in 1981, application of open stone surgery lost popularity and it has practically become an outdated method today. Such a wide-scale application of PNL raised concerns among surgical team regarding exposure to radiation during the procedure. Travis et al. (2) described the single-step dilatation method which is an acute dilatation reaching to 25-30 Fr after 6 Fr dilatation and providing reduced operative time as well as reduced radiation exposure. Amjadi et al. (6) reported that the single-step dilatation method with low radiation exposure can be used in almost all adult patients.

We could not find any study in the literature evaluating the success and complication rates for patients with single step access and required more than one access. We evaluated in this study our success and complication rates regarding the single-step access method performed in our patient group who required two or more access due to staghorn kidney stones.

Success rates during PNL vary between 76% and 84%, depending on the stone size (7). In this study, our success rate was found to be 72% which was close to the indicated rates in the literature.

Bleeding during and after PNL was always recognized as an important problem. Although insignificant amount of bleeding requiring no transfusion was not considered a complication for PNL, transfusion requiring bleeding in PNL was reported in large series at a frequency of 0-20% (1). In our study, blood transfusion was needed in a total of 13 patients (11%); in 3 patients (2.5%) intraoperatively and in 10 patients (8.5%) postoperatively, compatible with the literature.

The rate of bleeding requiring selective angioembolization has been reported to be between 0% and 1.5% (1). It has been reported that the presence of staghorn stones in particular was actually a risk factor for bleeding requiring embolization (8). In this study, in patients with staghorn stones, none of our patients required embolization.

It has been reported that post-PNL fever was the most common (22%) complication (9), and a short-term antibiotic therapy could be sufficient for treatment. In our study, fever was determined in 19 patients (16.2%) and sepsis developed in 3 of them (2.5%) in whom intensive care was needed. Post-PNL urosepsis was noted as a rare complication with a rate of 0.3-1.1% (1). The high rate of urosepsis in our study can be explained by the inclusion of patients having only staghorn stones, and urosepsis might be due to infection-induced stones in a significant proportion of these patients, although there is no stone analysis available leakage of urine to some extent is generally considered normal until the healing of the tract following withdrawal of the nephrostomy tube. Intervention may be required if leakage continues in the long term in the presence of blood clots or stones in the ureter and associated obstruction.

Post-PNL fistula has been reported to occur in 1.5%-3% of patients. Due to prolonged drainage after PNL, double j stent was placed in 3 patients, and due to stones causing ureteral obstruction, URS was performed and double J stent was implanted in 8 patients (6.7%) (10). In our study, the rate of additional interventions after PNL was determined to be higher with respect to the literature, and this was correlated with initially high stone burden.

Our study is not a comparative study. Thus, we cannot mention about the advantages of multiple single step dilatation comparatively in terms of operative time and radiation exposure. Nevertheless, this technique has been reported to shorten the operative time and reduce radiation exposure (11).

Study Limitations

The retrospective design of the study and the absence of comparative design are the main limitations of our study. Moreover, the rate of infection-induced stones which may explain the higher rate of sepsis in our patients is undetermined because stone analysis information was not available.

Conclusion

Despite these limitations of our study, acceptable rates were determined in terms of treatment success and complications of PNL with multiple single step dilatation technique applied for staghorn stones. In this regard, prospective studies with large-scale series are needed to reach definitive conclusions.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.S.İ., Concept: Y.Ö.İ., Design: C.S.İ., Data Collection or Processing: C.S.İ., Analysis or

Interpretation: Y.Ö.İ., Literature Search: C.S.İ., Writing: C.S.İ., Y.Ö.İ.

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Does Hued Lubricant Jelly Prevent Stone Migration/Retropulsion During Semi-rigid Ureterorenoscopy and Pneumatic Lithotripsy?

Renkli Lubrikant Jel Yarı Rijit Üreterorenoskopi ve Pnömatik Litotripsi Sırasında Taş Migrasyonunu/Retropülsiyonunu Önler mi?

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What's known on the subject? and What does the study add?

Retropulsion of calculus during rigid ureteroscopy is a known outcome and various mechanisms have been tried to prevent it including jelly. However, because the jelly is a colorless fluid, it is not easy to visualise it after instillation. We have used jelly mixed with methylene blue so as to make both the stone and jelly to be visualised easily simultaneously.

Abstract

Objective: The aim of this study is to study the efficacy of hued lubricating jelly instillation proximal to the upper ureteral stone during intracorporial pneumatic lithotripsy using semi-rigid ureteroscope for the prevention of migration of the stone.

Materials and Methods: We enrolled 60 subjects with ureteral stone in this prospective, controlled clinical trial. Alternate patients were assigned to the hued lubricating jelly instillation group A (n=30) and control group B (n=30). Ureteroscopy was performed according the standard protocol, using 7.5 F semi-rigid ureteroscope and stone fragmentation by pneumatic lithotripter. In the group A patients, a 5 Fr catheter was inserted into the ureter under fluoroscopy and 3-5 mL of hued lubricant jelly was dispensed above the stone. Retropulsion and the presence of residual fragments were evaluated with computed tomography of kidneys, ureters and bladder, X-ray and ultrasonography at 24 hours and at two weeks. The migrated stones were treated with shock wave lithotripsy. Any adverse event was reported and graded as per the modified Clavien classification system.

Results: The two groups had comparable demographic and stone characteristics. There was a statistically significant difference in retropulsion rate between the lubricating jelly instillation group and control group (6.67% vs 26.67%, p=0.04). No statistically significant complications were noted amongst the two groups. All patients were stone-free at 2-week follow-up.

Conclusion: Instillation of hued lubricating jelly proximal to ureteral calculi during pneumatic lithotripsy is an effective method of preventing retrograde stone migration.

Keywords: Ureteroscopy, Lithotripsy, Retropulsion, Migration, Lubricating jelly instillation

Öz

Amaç: Bu çalışmada intrakorporial pnömotik litotripsi sırasında taş migrasyonunun önlenmesi için semi-rijit üreteroskop kullanılarak, proksimal üst üreter taşına renkli lubrikant jel instilasyon etkinliğinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif, kontrollü çalışmaya üreter taşı olan 60 kişiyi dahil ettik. Alternatif hastalar, renkli lubrikant jel instilasyon grubu A (n=30) ve kontrol grubu B'ye (n=30) ayrıldı. Üreteroskopi, standart protokole göre 7,5 F semi-rijit üreteroskop ve pnömatik litotriptör ile taş parçalama yöntemi kullanılarak yapıldı. A grubundaki hastalara, üreter içerisine floroskopi altında 5 Fr kateter yerleştirildi ve 3-5 mL renkli lubrikant jel taş üzerine dağıtıldı. Retropülsiyon ve kalan parçaların varlığı 24 saatte ve iki haftada böbrekler, üreterler ve mesane düz bilgisayarlı tomografisi, X-ray ve ultrasonografi ile değerlendirildi. Migrate olan taşlar şok dalga litotripsi ile tedavi edildi. Her bir advers olay modifiye Clavien sınıflama sistemine göre rapor edildi ve derecelendirildi.

Bulgular: İki grup benzer demografik ve taş özelliklerine sahipti. Lubrikant jel instilasyon grubu ve kontrol grubu arasında retropülsiyon oranları (%6,67'ye karşı %26,67, p=0,04) açısından istatistiksel olarak anlamlı farklılık vardı. İki grup arasında istatistiksel olarak anlamlı bir komplikasyon görülmedi. Bütün hastaların iki haftalık takip sonrasında taşı yoktu.

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Sonuç: Pnömatik litotripsi esnasında proksimal üretral taşa renkli lubrikant jel instilasyonu yapılması, retrograd taş migrasyonunu önlemede etkili bir yöntemdir.
Anahtar Kelimeler: Üreteroskopi, Litotripsi, Retropülsiyon, Migrasyon, Lubrikant jel instilasyonu

Introduction

The rising incidence of ureteric stones has made the procedure of ureterorenoscopy (URS) common in recent times (1,2). The success of URS depends upon various factors such as stone size, location, degree of proximal hydronephrosis, and the energy source used to break the stone (pneumatic lithoclast/laser) (3). One of the important variable remains migration or retropulsion of stone during the procedure (4). Various studies have reported that 28% to 48% (5,6,7) of proximal ureteric stones and 3% to 15% (8,9) of distal ureteric stones undergo migration during URS. The migration of the calculus will warrant an additional procedure in the form of extra-corporeal shock wave lithotripsy (SWL) or flexible URS and laser lithotripsy. Stone migration results in decreased stone clearance rates, increased operative time and additional costs and morbidity of second procedure (10,11). In the era of rising health-care expenses, any advancement to make the procedure cheaper and effective is welcome. Various novel devices, such as stone cones, gels, trapping devices etc., have been described to prevent stone migration (3,4,5,6,7,8,9,10,11,12) with differing efficacy rates. However, the costs and availability of these is a major issue (3,4,5,6,7,8,9,10,11,12).

We studied the effectiveness of a hued lubricant gel (lubricating jelly mixed with methylene blue), an easily available and cheap gel, in preventing the retropulsion of upper ureteric (at or above the level of L5 lumbar vertebral transverse process) stone during URS while using pneumatic lithoclast.

Materials and Methods

From June 2016 to December 2017, after institutional review board approval (approval number: MDC/DOME/495, JNMC Institutional Ethics Committee on Human Subjects Research) and obtaining written informed consent from the participants, 60 patients with upper ureteral stones (7-15 mm) requiring ureteroscopy were enrolled in this study.

All patients were evaluated by history taking, physical examination, laboratory investigations, including urinalysis, full blood count, and renal function test. Preoperative radiographic imaging studies, including X-ray of kidneys, ureters and bladder (KUB), ultrasound, and computed tomography (CT) scan were performed and stone size, location, opacity, and degree of obstruction were documented.

All patients diagnosed to have calculus present in the upper ureter (defined as calculus present at or above the level of L5 vertebral transverse process) were eligible for the study.

Exclusion criteria included patients below 18 years, those having active urinary infection, obstructive uropathy, underlying chronic kidney disease, and impacted calculus.

Patients were divided into two treatments groups: group A of 30 patients who received hued jelly instillation before intracorporeal lithotripsy using pneumatic lithoclast and group B of 30 patients who were treated with conventional method without jelly. Alternate patients were allocated to group A and group B. The operation was performed under general anesthesia and all patients received a single broad-spectrum antibiotic parenterally at the time of induction.

Ureteroscopy and stone fragmentation were performed using a 7.5 Fr Olympus semi-rigid ureteroscope and Swiss LithoClast. Saline was used as the irrigation fluid. A colorless lubricant jelly was hued by mixing with methylene blue. 8 mL of lubricant jelly (K-Y Jelly, Johnson&Johnson, USA) was mixed with 2 mL of methylene blue in a sterile container and then loaded in a 10 mL syringe for instillation. Cystoscopy and retrograde urography were routinely performed and a guide-wire was passed to the renal pelvis. Prior to stone fragmentation, in the group A patients, 5 Fr catheter was inserted into the ureter over a guide-wire under fluoroscopy and 3-5 mL of hued jelly was dispensed above the stone and the catheter was removed (Figure 1). In the group B patients, no anti-retropulsion device was used. The Swiss LithoClast was used for stone fragmentation with

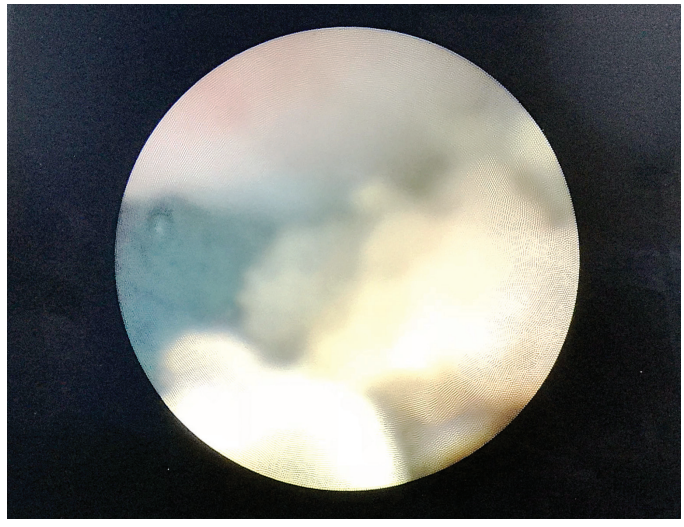

Figure 1. Endoscopic view of stone after instillation of hued lubrication jelly

300 kPa pressure and a 3.5 Fr rod. The stones were fragmented to approximately 1-3 mm particles and were allowed to pass spontaneously. The remaining jelly was washed out with saline at the end of the procedure. In all patients, a 5 Fr double J (DJ) stent was inserted and left in place for 2 weeks. A Foley catheter was inserted in all of our patients and was removed on the next day. Operative time was calculated from the time of cystoscope insertion to the completion of the procedure.

CT scan of the KUB was performed after 24 hours to exclude stone migration and confirm stone clearance. Stone migration was defined as stone retropulsion into the pelvicalyceal system. Patients who had stone migration were subjected to SWL treatment. The patients were discharged on the first postoperative day or 24 hours after SWL treatment and were advised to take oral antibiotic for 5 days. All patients were followed up for 2 weeks and underwent DJ stent removal after radiological confirmation of stone clearance with KUB X-ray, ultrasound and CT. For all the subjects, any adverse events were assessed and reported at 24 hours postoperatively and at the 2-week follow-up visit.

A sample size of 54 patients was calculated using comparing two proportion formulas. It was estimated to yield 80% power (type 2 or beta error of 0.20%) to detect a difference of 20% or more between the two groups (40% migration rate in no jelly group and 20% migration in the hued jelly group), allowing 5% of type 1 error. Totally, 60 patients were enrolled in the study.

Statistical Analysis

All data were analyzed using SPSS 20 (SPSS, Chicago, IL, USA) software. Continuous variables with normal distribution were presented as mean ± standard deviation and were compared by the independent samples t-test and paired t-test. Nominal variables were taken as counts (or frequencies) and were compared by a chi-square test. The stone migration rates and the stone-free rates in the two groups were compared by the cross tabulation analysis. All statistical tests were reported based on two tailed probability. A p value of less than 0.05 was considered statistically significant.

Results

A total of 30 patients underwent URS with deployment of hued lubricating jelly in group A and 30 without in group B. The patient profiles were similar in both groups regarding age, mean largest dimension of the stone (Table 1). The mean time to deploy hued jelly was 146.5 seconds (standard deviation: 34.57). The mean lithotripsy time was 13.7 minutes in group A and 13 minutes in group B. All the procedures were completed within one hour. Stone retropulsion occurred in 2 cases (6.67%) in group A and in 8 (26.67%) patients in group B (p=0.04) (Table 2). All patients having retropulsion of the calculus were successfully treated with SWL. Patients with retropulsion had to stay one day more than planned treatment. Two patients each from the gel arm and the control group had fever in the postoperative period needing paracetamol, while 1 patient in group B had hematuria which resolved spontaneously. However, no serious complications such as ureteral perforation, avulsion or ureteral stricture occurred in either group. All patients were stone-free at the time of DJ stent removal.

Discussion

Stone migration during ureteroscopy remains a concern and has the potential to increase operative time, need for additional procedure and the health-care cost of the treatment (3,4,12). Moreover, residual stone fragments can act as a nidus for recurrent stone formation, recurrent urinary tract infection, and renal colic (13). A number of novel accessory instruments, devices, and strategies have been introduced into the field of ureteroscopic lithotripsy to address the problem of proximal stone migration. The currently available anti-retropulsion devices are either: 1) mechanical, wire based; 2) mechanical, balloon based; or 3) gel based (3,4,12).

While the mechanical devices like stone cone, NTrap and balloons achieve some level of effectiveness in preventing stone migration, they use mechanical elements that can potentially cause trauma to the ureter or interfere with the safe working of the energy source (12,14). They require that a wire remain in the ureter, encumbering the operative field and potentially

Table 1. Patient demographics and stone size

	Group A (n=30)	Group B (n=30)	p values
Gender			
Male	19	14	0.15
Female	11	16	
Mean age (years)	41+/-16	40+/-15	0.88
Stone size (mm)	9.39+/-2.39	9.17+/-1.9	0.72

Table 2. Intraoperative and postoperative outcomes

	Group A (n=30)	Group B (n=30)	p values
Jelly deployment time (seconds)	146.5 (SD: 34.57)	-	-
Total procedure time (minutes)	33.83+/-6.62	30.00+/-6.47	0.027
Stone migration	2 (6.67%)	8 (26.67%)	0.04
Adverse events	2 (6.67%)	3 (10%)	0.50

SD: Standard deviation

inhibiting ureteroscope maneuverability, and may allow smaller fragments to migrate (12).

Similar to mechanical devices, different gel-based barriers have been tried to prevent stone migration. Ali et al. (15) instilled lubricant gel proximal to the ureteric calculus before applying kinetic energy and were successful in adequately fragmenting and preventing stone migration in 7 patients they treated. Mohseni et al. (16) found lubricating jelly to be an effective method of preventing retrograde stone displacement when instilled proximal to the ureteral stone during lithotripsy in 16 patients. However, they found no significant difference in the stone-free rates when compared to control group.

Zehri et al. (17) used 2% lidocaine gel for instillation in 25 patients and reported a statistically significantly lower rate of stone migration in those patients. They also noted that the use of lidocaine jelly had the potential to impair visibility during ureteroscopy (17). In a similar study using lidocaine gel, Saad et al. (18) noticed a decreased migration rate and also a significantly higher stone-free rate in patients of the lidocaine group at 1-month follow-up.

A randomized trial using BackStopTM, a reverse-thermosensitive gel, conducted by Rane et al. (12) found stone retropulsion in 8.8% of 34 patients who were randomized to BackStopTM group and in 52.9% of 34 controls (p=0.0002). The use of BackStopTM was not associated with any short-term adverse events while four cases in the control group had complications including one incident of ureteral stricture (12).

In the present study, we deployed hued jelly proximal to the stone prior to fragmentation. The advantage of coloring the jelly was that the presence of the jelly and the stone fragments being stopped from getting migrated by the colored gel were easily visualized during ureteroscopy. In our study, use of hued lubricant jelly resulted in a statistically significantly lower stone migration rate of 6.6% compared to 26.6% in controls (p=0.04). The mean operation time in the jelly group was 33.8 minutes while it was 30 minutes in controls (p=0.027). Though minor adverse events were noted in both groups, they were not statistically significant. However, all the subjects in the study were free of stones at 2-week follow-up and underwent DJ stent removal. In the present study, we had to increase the intensity of the light during the procedure as some of it was getting absorbed by the colored jelly, however, the stone and the gel were visualized distinctly in all the cases. Also, we had to be cautious with irrigation during the procedure as to not dislodge the jelly.

Study Limitations

Our study was a single center trial. Multicenter trials are needed to assess the ease of preparing the colored jelly and its deployment proximal to the stone. Also, we have not addressed the operative time and procedure-related cost in the present study.

Conclusion

During ureteroscopy using a pneumatic lithotripsy device to treat ureteric stones, instillation of hued lubrication jelly proximal to the stone prior to lithotripsy is effective in preventing stone retropulsion. However, its effect on improving the stone-free rate was not significant in our study.

Ethics

Ethics Committee Approval: The approval was taken from JNMC Institutional Ethics Committee on Human Subjects Research (number: MDC/DOME/495, date: 14.03.2016).

Informed Consent: It was taken in the vernacular language spoken by the patient (Kannada, Marathi and Hindi).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.N., A.P., S.P., Concept: S.N., Design: S.N., Data Collection or Processing: S.N., A.P., S.P., Analysis or Interpretation: S.N., Literature Search: S.N., A.P., Writing: S.N., A.P.

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The Effect of One-shot Multi-access Percutaneous Nephrolithotomy on Complications

Çoklu Access Perkütan Nefrolitotominin Komplikasyonlara Etkisi

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What's known on the subject? and What does the study add?

We hypothesized that peri- and postoperative complications may increase in multi-access percutaneous nephrolithotomy cases due to multiple damage to the kidney.

Abstract

Objective: Kidney stones can be seen as single and pelvic stones as well as complex and multiple calculi. For this reason, single-access is not always sufficient for the treatment of kidney stones and multi-access percutaneous nephrolithotomy (PCNL) may sometimes be necessary for stone removal. In this study, we aimed to investigate the effect of multi-access PCNL using the one-shot dilation technique on kidney functions and related complications.

Materials and Methods: The effects of access number on the hemoglobin and creatinine alterations, duration of operation, need for transfusion, postoperative fever, and length of hospital stay were investigated in patients who underwent PCNL due to renal stones.

Results: Single- and multi-access PCNL using the one-shot technique was performed in 329 and 79 patients, respectively. Duration of operation, duration of scopy, and length of hospital stay as well as alterations in hemoglobin and creatinine values were found to be statistically higher in the multi-access group.

Conclusion: One-shot multi-access PCNL can be safely performed for complex kidney stones due to its high stone-free rates, despite some potential complications.

Keywords: Multiple tract, Single tract, Renal stone, Transfusion

Öz

Amaç: Böbrek taşları her zaman tek ve pelvis taşı değil kompleks ve multipl taşlar şeklinde görülebilmektedir. Bu nedenle böbrek taşlarının tedavisinde her zaman tek access yeterli olmamakta ve çoklu access taşların temizlenmesi için gerekebilmektedir. Bu çalışmamızda çoklu accessin böbrek fonksiyonları ve komplikasyonlara etkisini incelemeyi amaçladık.

Gereç ve Yöntem: Böbrek taşı nedeniyle perkütan nefrolitotomi (PCNL) yapılan hastalarda access sayısının hemoglobin ve kreatinin değişimi, operasyon süresi, transfüzyon ihtiyacı, postoperatif ateş yüksekliği ve hastanede kalış sürelerine etkisi incelendi.

Bulgular: Tek access ve çoklu access PCNL yapılan, sırasıyla 329 ve 79 hasta incelendi. Operasyon süresi, skopi süresi, hastanede yatış süresi, hemoglobin değişimi ve kreatinin değişimi çoklu access grubunda istatistiksel anlamlı daha yüksek bulundu.

Sonuç: Kompleks böbrek taşları için çoklu access PCNL olası bazı komplikasyonlarla birlikte yüksek taşsızlık oranları nedeniyle güvenle uygulanabilecek bir yöntemdir.

Anahtar Kelimeler: Çoklu giriş, Tek giriş, Böbrek taşı, Transfüzyon

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Introduction

Percutaneous nephrolithotomy (PCNL) is a method with proven surgical efficacy and it is performed in kidney stones over 20 mm with high success and minimal morbidity rates (1,2). However, kidney stones are not always seen in standard and normal structure kidneys but also in anomalous kidneys. Also, kidney stones are not always single and pelvic but can be complex and multiple. For this reason, single-access is not always sufficient for the treatment of kidney stones and multi-access is sometimes required for stone removal. The effect of multi-access on renal functions, as well as complications, such as low hemoglobin (Hb) values and postoperative infection, is a controversial issue (3,4).

Patients who underwent PCNL in our clinic were reviewed retrospectively to evaluate the effects of one-shot single- and multi-access PCNL on complications during and after the procedure. We hypothesized that peri- and postoperative complications may increase in patients undergoing multi-access PCNL due to multiple damages to the kidney.

Materials and Methods

PCNL operations performed in our clinic between January 2015 and May 2018 were retrospectively reviewed. The surgical operations were performed by three different surgeons. Detailed information on age, gender, stone-skin distance, body mass index, number, size and location of stones, complete blood count, complete urine analysis, bleeding profile, preoperative blood biochemistry and creatinine clearance were taken from the patient records. For stone diameter, the longest diameter was measured on non-contrast computed tomography (CT) images (5). Perioperative complications, alterations in hematocrit and creatinine values, operation and scopy duration, transfusion status, postoperative fever and length of hospital stay were evaluated. After the placement of a guide catheter, tract was created by first dilating using a 6F Amplatz dilator set, then with one-shot method by using 25-30F dilator. Percutaneous access to the kidney was obtained under fluoroscopic guidance. A 26-Fr rigid nephroscope was inserted through a 30-Fr sheath. The stones were broken up using a pneumatic or ultrasonic litotripter and the small pieces were taken out with foreign body holders. If the stone burden could not be effectively removed via 1 tract, additional tracts were obtained at the surgeon's discretion. Due to its unavailability in our clinic, we did not use flexible nephroscope and we made another access. A nephrostomy tube was placed at the end of the procedure and all patients were monitored overnight. Perioperative complications were defined as hemorrhage during PCNL that may reduce vision, hypotension, extravasation and collecting system perforation. In patients without complications, the nephrostomy tube was removed on postoperative day 1. Also, hematocrit measurement and serum biochemistry were performed and creatinine clearance was calculated on the first postoperative day.

The presence of residual stones and kidney functions were evaluated during the first postoperative month by spiral CT. Stone-free status or presence of asymptomatic, non-infectious, non-obstructive stones that are smaller than 4 mm (clinically insignificant residual fragmentations) was considered surgical success.

Statistical Analysis

IBM Statistical Package for Social Sciences (Chicago, IL) version 20 was used for statistical analysis. Differences between the groups were assessed by a chi-square test for categorical variables, by Student's t-test or Mann-Whitney U test for continuous variables. A p value of less than 0.05 was considered statistically significant.

Results

One-shot single-access and multi-access PCNL were performed in 330 and 79 patients, respectively. Two accesses was performed in 50 (63.3%) patients, 3 accesses in 21 (26.6%) and 4 accesses in 8 (10.1%). The mean age of the patients in single-access and multi-access groups was 49.02±14.2 years and 51.06±13.3 years, respectively, with no significant difference between the two groups (p=0.25). The male-to-female ratio in single-access and multi-access group groups was 215/115 and 52/27, respectively. According to the chi square test, there was no statistically significant difference in gender distribution between the two groups (p=0.91).

There was no statistically significant difference in stone location between the groups (p=0.9). The stones were mostly located in the pelvis and calyx in the multi-access group in comparison to the other group (p=0.003) (Table 1).

As for the duration of operations and duration of the scopies, both were significantly longer in the multi-access group (p=0.0001, p=0.0001). Similarly, the length of hospital stay was significantly longer in the multi-access group than in single-access group (p=0.034) (Table 2). Reoperative creatinine level was significantly higher (1.55 mg/dL vs 1.09 mg/dL, p=0.04) and creatinine clearance was lower (75.7 mL/min vs 90.1 mL/min; p<0.05) in the multi-access group than in the single-access group. Similarly, postoperative creatinine level and change in creatinine clearance were significantly increased in the multi-access group than in the single-access group (0.43 mg/dL vs 0.1 mg/dL, p<0.05, 10.8 mL/min vs 3.4 mL/min; p<0.05) (Table 3).

Preoperative Hb was lower in the multi-access group in comparison to single-access group (11.5 g/dL vs 13.1 g/dL, p<0.05) and postoperative decrease in Hb was more significant

Table 1. Patient characteristics

	Single access	Multiple access	p values
Age (year)	49.02±14.2	51.06±13.3	0.25
Gender (%)			910
Female	115 (34.8)	27 (34.1)	-
Male	215 (65.2)	52 (65.9)	-
Stone site (%)			0.9
Right	166 (50.3)	41 (51.8)	-
Left	164 (49.7)	38 (48.2)	-
Stone location (%)			3
Calyx	49 (14.8)	16 (20.2)	-
Pelvis	96 (29)	8 (10.2)	-
Calyx + pelvis	185 (56.2)	55 (69.6)	-
Stone size (mm^2)	892.17±700.3	1238.35±1240.4	3
SSD (mm)	84.33±22.9	86.86±21	0.27
BMI	28.39±5.6	27.1±4.8	326
Operative time (minute)	80.99±143.7	113.67±55.3	0.0001
Scopy time (second)	146.02±143.8	198.83±132.6	0.0001

BMI: Body mass index, SSD: Stone-skin distance

Table 2. Analysis of demographic data and operative data of patients

	Single tract	Multiple tract	p values
Perioperative complications			0.97
Positive	36 (10.9)	7 (8.8)	-
Negative	294 (89.1)	72 (91.2)	-
Malecot period (day)	1.54±1.8	1.68±1.4	0.125
Postoperative fever			0.160
Positive	33 (10)	12 (15.1)	-
Negative	297 (90)	67 (84.9)	-
Rezidal stone			0.053
Positive	61 (18.4)	7 (8.8)	-
Negative	269 (81.6)	72 (91.2)	-
Postoperative hospital stay			0.984
Positive	29 (8.7)	7 (8.8)	-
Negative	301 (91.3)	72 (91.2)	-
Total hospital stay (days)	1.86±2.4	2.60±2.4	0.034*

*Statistically significant

in the multi-access group (3.6 g/dL vs 0.9 g/dL, p<0.05). In the multi-access group, 8 (10%) patients needed transfusion and a total of 17 units of erythrocyte suspension were administered. In the single-access group 12 (3%) patients needed transfusion and a total of 19 units of red blood cells were transfused (p=0.04) (Table 4).

Table 3. Comparison of creatinine and creatinine clearance levels in the two groups in patients before and after percutaneous nephrolithotripsy

	Single tract	Multiple tract	p values
Mean serum creatinine preoperative (mg/dL)	1.55±1.3	1.09±0.38	0.04
Mean serum creatinine postoperative (mg/dL)	1.98±1.59	1.21±0.61	<0.05
Change	0.43±0.54	0.1±0.32	<0.05
Mean creatinine clearance preoperative (mL/min)	75.7±40.8	90.1±42.1	<0.05
Mean creatinine postoperative (mL/min)	66.9±38.2	86.7±43.1	0.01
Change	10.8±10.2	3.4±12.2	<0.05

Table 4. Comparison of hemoglobin levels in the two groups in patients before and after percutaneous nephrolithotripsy

	Multi tract	Single tract	p values
Mean preoperative Hb (g/dL)	11.50±2.51	13.10±2.11	<0.05
Mean postoperative Hb (g/dL)	8.90±1.87	12.20±2.03	<0.05
Drop in Hb (g/dL)	3.60	0.90	<0.05
Number of patients transfused (%)	8 (10)	12 (3)	0.04

Hb: Hemoglobin

Discussion

PCNL is the treatment method of choice for large and complex renal stones. Occasionally, more than one access may be required to completely clear the kidney stones so that a second intervention will be avoidable. It has been reported that multi-access in PCNL was not associated with any adverse effects on kidney function (3). However, there are data in some reports showing that multi-access would increase blood loss (6,7). In addition, Cho et al. (3) demonstrated that multi-access was as safe and effective as single-access in small stones, as a versatile method which can also be used for complex stones. The American Urological Association (AUA) guideline also suggested that PCNL with multiple tracts was a safe and effective way for treating staghorn stones, with monotherapy stone-free rate of 79%, and acute complication rate of 15% (8). We studied the outcomes of PCNL incorporating the use of multiple tracts and single tract. In this study, most patients required three tracts to gain access to the calculi in the various calices. Patients with multi-access PCNL had a stone-free rate of 91.2%. Patients who underwent single-access PCNL had a stone-free rate of 89.1%. This result parallels the high stone-free rate achieved by PCNL monotherapy highlighted in the AUA panel report (9). Since the parenchyma is injured more than one point in multi-access PCNL, both the amount of and the risk of bleeding is expected to be

greater than in single-access. It has been shown that the need for blood transfusion was more common in patients undergoing multi-access PCNL than in those having single-access PCNL (9,10,11,12). On the contrary, there were also studies reporting that multi-access did not increase the need for transfusion (4). In our study, however, the need for blood transfusion was statistically significantly more in the multi-access group than in the single-access group. Blood transfusion was usually needed on the second and third postoperative days. That is to say, blood transfusion was not needed urgently but electively. None of our patients needed embolization due to bleeding. The rate of Hb drop in our study was slightly higher than in the literature. This may be due to the high number of patients undergoing three and four access.

There was no difference between the two groups in our study in terms of postoperative fever. Hegarty and Desai (13) also found no difference in terms of postoperative infectious complications between patients with multi- and single-access PCNL.

The mean preoperative creatinine level was higher in the multi-access group (1.55 mg/dL) than in the single-access group (1.09 mg/dL). This may be attributed to a previous stone-related infection and renal injury due to obstructive stones. Postoperative creatinine values displayed a statistically significant difference between the two groups. Multiple access in PCNL was thought to be responsible for having negative effects on renal functions, with a significant increase in creatinine values in many reports (4,13). There were also studies claiming the opposite, that it had no impact on kidney functions (3). In our study, however, multiple accesses were shown to cause significant variations in creatinine and the clearance of creatinine. Operative time is expected to be longer in multi-access PCNL due to the size of the stones and their dispersion. In our study too, the duration of operation was longer in the group with multiple accesses, consistent with other studies in the literature (4,13). Despite longer duration of the operations, a second operation can be avoided with a high stone-free rate. The length of hospital stay showed an increase in parallel to the number of accesses. We attributed this to the higher incidence of decreased Hb levels and increased need for blood transfusion in the multi-access group. Again, the need for analgesia was more in the patients of this group. For these reasons, the length of hospital stay was statistically significantly longer in the multi-access group, compatible with the literature (13).

Study Limitations

As for the limitations of our study, its retrospective design, differences in demographic features of the patients in multi-access and single-access study groups and its moderate sample size can be mentioned. We could not find any study in the literature evaluating the success and complication rates in patients with one-shot single-access and those requiring more than one access. The patients who underwent one-shot access PCNL in our clinic were reviewed retrospectively to evaluate its effects on complications during and after single- and multi-access PCNL.

Conclusion

It was shown in patients who underwent PCNL due to kidney stones that one-shot multi-access decreased Hb level statistically significantly in comparison to one-shot single-access and that the need for blood transfusion was more in the multi-access group. Besides that, multi-access caused significant variation in the length of hospital stay and alterations in creatinine clearance. On the other hand, it was shown to be safe with high stone-free rates.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.T., E.A., Concept: S.Ü., E.A., A.S.Ö., Design: H.T., S.Ü., Data Collection or Processing: H.T., E.A., Analysis or Interpretation: A.S.Ö., Literature Search: E.A., H.T., Writing: E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Course of Renal Function After Radical Cystectomy with Ileal Conduit Diversion for Bladder Cancer

Mesane Kanserinde Radikal Sistektomi ve İleal Kondüit Diversiyon Sonrası Böbrek Fonksiyonlarının Seyri

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What's known on the subject? and What does the study add?

Renal function deterioration is one of the important adverse events related to radical cystectomy with ileal conduit diversion. However, most of the previous studies have evaluated change in renal function using serum creatinine values. In the present study, we retrospectively analyzed the yearly changes in the renal function assessed by the estimated glomerular filtration rate, more reliable parameter, in order to identify potentially modifiable risk factors associated with worsening of the renal function.

Abstract

Objective: We evaluated the course of the renal function and potential risk factors for renal deterioration in patients who had undergone radical cystectomy with ileal conduit diversion.

Materials and Methods: A retrospective study evaluated 121 patients, including 114 male and 7 female who underwent radical cystectomy with ileal conduit diversion. Estimated glomerular filtration rate (eGFR) was calculated and postoperative changes in renal function were reviewed. The clinical variables influencing renal function were evaluated.

Results: The median follow-up period was 35.6 months (range, 12.2 to 139.6 months). The mean eGFR was 78.37±27.58 mL/min/1.73 m^2 before surgery and 90.14±29.68 mL/min/1.73 m^2 at 5 years postoperatively. The comparison of preoperative eGFR and the last follow-up eGFR showed the no statistically significant difference (p=0.195). Statistical analysis showed that development of postoperative urinary tract obstruction and postoperative urinary tract infection were significant adverse factors (p=0.008, p=0.026, respectively).

Conclusion: Thirty two patients (53.3%) developed renal deterioration during the follow-up period. Development of urinary tract obstruction and urinary tract infection in the postoperative period were found to be significant adverse factors affecting renal function.

Keywords: Renal insufficiency, Urinary bladder neoplasms, Cystectomy, Urinary diversion

Öz

Amaç: Bu çalışmada mesane kanseri nedeniyle radikal sistektomi ve ileal kondüit diversiyon uygulanan hastalarda böbrek fonksiyonlarındaki değişiklik ve böbrek fonksiyon kaybı için potansiyel risk faktörleri değerlendirildi.

Gereç ve Yöntem: Retrospektif çalışmada radikal sistektomi ve ileal kondüit diversiyon yapılan 114 erkek ve 7 kadın, 121 hasta değerlendirildi. Tahmini glomerüler filtrasyon hızı (eGFR) hesaplandı ve postoperatif böbrek fonksiyon değişiklikleri gözden geçirildi. Böbrek fonksiyonlarını etkileyen klinik değişkenler değerlendirildi.

Bulgular: Medyan izlem süresi 35,6 ay (dağılım 12,2-139,6 ay) idi. Ortalama eGFR, ameliyat öncesi 78,37±27,58 mL/dakika/1,73 m^2 ve ameliyat sonrası 5. yılda 90,14±29,68 mL/dakika/1,73 m^2 idi. Ameliyat öncesi eGFR ile son takipteki eGFR k arşılaştırması istatistiksel olarak anlamlı bir fark göstermedi (p=1,95). İstatistiksel analiz postoperatif üriner sistem tıkanıklığı gelişiminin ve postoperatif üriner sistem enfeksiyonunun anlamlı olumsuz faktörler olduğunu gösterdi (sırası ile p=0,008, p=0,026).

Sonuç: İzlem süreci boyunca, 32 hastanın (%53,3) böbrek fonksiyonlarında azalma görüldü. Postoperatif üriner sistem tıkanıklığının böbrek fonksiyonlarını etkileyen önemli bir olumsuz faktör olduğu bulundu.

Anahtar Kelimeler: Böbrek yetmezliği, İdrar kesesi tümörleri, Sistektomi, Üriner diversiyon

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Introduction

Radical cystectomy (RC) and urinary diversion are the optimal treatment for muscle-invasive and high-grade non-muscle-invasive bladder cancer (1,2). Ileal conduit diversion (ICD) and orthotopic bladder substitution (BS) are two most frequently used urinary diversions after RC (3). Although BS has recently become more popular for urinary diversion, ICD is still believed to be appropriate for urinary diversion in most patients because of its relative simplicity, acceptable complication rate and satisfactory postoperative quality of life (4).

Deterioration in renal function is one of the most important adverse events related to RC and urinary diversion. Several studies have reported a high incidence of renal impairment in ICD patients. However, most of the previous studies have evaluated renal function using serum creatinine values, whereas estimated glomerular filtration rate (eGFR), in addition to serum creatinine, is a more accurate parameter for the measurement of renal function because it takes into account other relevant factors such as age, race and gender (5).

In the present study, we retrospectively analyzed the year-by-year changes in the renal function assessed by eGFR in order to identify potentially modifiable risk factors associated with worsening of the renal function in patients with primary bladder cancer who underwent RC with ICD.

Materials and Methods

A total of 121 (114 male and 7 female) patients, who had undergone RC with ICD for primary bladder cancer between March 2001 and July 2017, were identified. In this period, patients with RC and BS for bladder cancer were not included in the study because there were only 2 patients. The patient's desire and the surgeon's preference are major determinants for choice of urinary diversion methods. Cases of non-primary bladder cancer (direct extension of adenocarcinoma of the rectum in 1 patient), non-urothelial bladder cancers (carcinosarcoma in 1 patient and fibrosarcoma in 1 patient) and non-malignant bladder conditions (emphysematous cystitis in 1 patient and eosinophilic cystitis in 1 patient) were excluded. All data were obtained in accordance with the privacy protection policy of our institution. This study was approved by Başkent University Institutional Review Board (project no: KA16/16) and was supported by Başkent University Research Fund.

All patients underwent RC using standard techniques through the open approach. For urinary diversion, an ileal segment 15-20 cm long was isolated approximately 25 cm proximal to the ileocecal valve. The ureters were split and anastomosed to the proximal end of the ileum using the Wallace technique (6).

The primary outcome measure of this study was eGFR. Changes in renal function were examined using eGFR. eGFR was calculated using the modification of diet in renal disease (MDRD) equation: GFR (mL/min per 1.73 m^2)=186 x (serum creatinine, mg/dL)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) (7,8). Renal deterioration was defined as a reduction in the eGFR >1 mL/min/1.73 m^2 annually after RC. This definition, consistent with previous studies, is based on the fact that physiologic age-related GFR decreases 1 mL/min/1.73 m^2 per year (9,10).

Evaluated clinical variables that might influence renal function included age, gender, pathological tumor-node-metastasis stage, a prior history of hypertension or diabetes mellitus and renal function status, American Society of Anesthesiologists class risk, anatomical or functional solitary kidney, presence of preoperative urinary tract dilatation, postoperative febrile urinary tract infection, development of postoperative urinary tract obstruction, and presence of systemic chemotherapy. Patients with systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg were regarded as hypertensive, patients with diabetes mellitus were defined as those who met the relevant diagnostic criteria and required glycemic control. Febrile urinary tract infection was defined as a febrile episode (>38 °C axillary) with a positive urine culture (bacteriuria of >10^5/mL colony-forming units) in the absence of another indication for the cause of fever (1). Dilation encountered during upper tract imaging in patients with or without documentation of ureteroenteric or stomal obstruction was accepted as urinary tract obstruction (2). Solitary functioning kidney was defined as the presence of a contralateral non-functional kidney (uptake <10% in dimercaptosuccinic acid scan) (11). The renal function status of patients was determined according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. KDOQI guidelines stratify chronic kidney disease (CKD) into five stages according to eGFR level (Table 1) (12).

Statistical Analysis

Statistical analyses were performed using the statistical package SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). For each continuous variable, normality was checked by the Kolmogorov-

Table 1. Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

GFR: Glomerular filtration rate

Smirnov test, Shapiro-Wilk test and histograms. The categorical variables between the groups were analyzed using a chi-square test or Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 62.03±7.37 years. The median follow-up period after RC with ICD for patients alive at the last visit was 35.6 months (range, 12.2 to 139.6 months). Table 2 summarizes the characteristics of the 121 patients included in this study. The overall survival rate was 43.2% (35/81) at 5 years. Forty patients who were lost-to-follow-up were excluded from the overall survival assessment.

Figure 1 shows the median eGFR course. A decrease in eGFR was documented in 32 of 60 patients (53.3%) who could be followed at least one year. At 5 years postoperatively, the median eGFR had increased from 77.43 mL/min/1.73 m^2 to 79.2 mL/min/1.73 m^2. The change in eGFR was statistically insignificant.

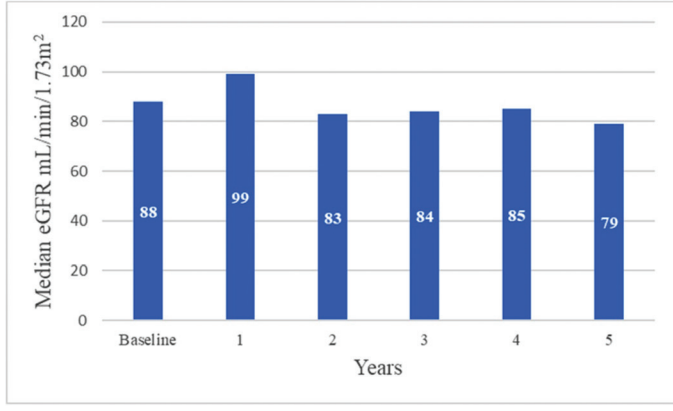
The patients were evaluated with the CKD classification; in 14 (23.3%) patients, CKD stage was found to be worsened (Table 3). Moreover, preoperative and postoperative CKD stage was similar (p=0.80).

Statistical analysis showed that the development of postoperative urinary tract obstruction and postoperative urinary tract infection were significant adverse factors for

Table 2. Patient characteristics

Characteristic	n (%)
Gender	
Female	7 (5.8)
Male	114 (94.2)
Comorbidity	
Hypertension	27 (22.3)
Diabetes mellitus	16 (13.2)
Preoperative hydronephrosis	35 (28.9)
Solitary kidney	14 (11.6)
pTNM stage	
Tcis	7 (5.8)
Ta	1 (0.8)
T0	13 (10.7)
T1	10 (8.3)
T2	28 (23.1)
T3	28 (23.1)
T4	34 (28.1)
CKD stage	
1	41 (33.9)
2	48 (39.7)
3	27 (22.3)
4	2 (1.7)
5	3 (2.5)
ASA class	
1	7 (5.8)
2	74 (61.2)
3	39 (32.2)
4	1 (0.8)

pTNM: Pathological tumor-node-metastasis, CKD: Chronic kidney disease, ASA: American Society of Anesthesiologists, Tcis: Carcinoma *in situ*



	Baseline	1st Year	2rd	3rd	4th	5th
No. pts with RF deterioration	0	32	18	13	7	7
No. pts evaluated	121	60	38	25	19	17

Figure 1. Change in median estimated glomerular filtration rate after radical cystectomy with ileal conduit diversion across the postoperative period

eGFR: Estimated glomerular filtration rate, RF: Renal function, Pts: Patients

Table 3. Postoperative course of renal function according to chronic kidney disease stage

CKD stage	Preoperative n (%)	Postop alteration of renal function (n)	Last follow-up n (%)
1	41 (33.9)	Worsening: 7 To stage 2: 5 To stage 3: 2	16 (26.7)
2	48 (39.7)	Worsening: 7 To stage 3: 6 To stage 4: 1 Improvement: 1 To stage 1: 1	30 (50)
3	27 (22.3)	Improvement: 4 To stage 1: 1 To stage 2: 3	13 (21.7)
4	2 (1.7)	-	1 (1.6)
5	3 (2.5)	-	-

CKD: Chronic kidney disease

deterioration of kidney function. The other risk factors did not affect the renal function outcomes (Table 4).

Of the 21 (17.3%) patients with postoperative urinary tract dilatation, 8 (38.1%) had ureteroileal stricture, 4 (19%) had ureteral recurrence, 1 (4.8%) ureteral compression secondary to a metastatic lymph node, and 1 (4.8%) had ureteral stone. For 7 patients (33.3%), no cause for the upper urinary tract dilatation was found. The location and approach towards urinary tract dilatation are summarized in Table 5.

Discussion

Renal function is one of the most important points to be assessed after RC and urinary diversion and, protection of the renal function is an essential goal after RC and urinary diversion.

In the literature, there is no consensus on how to assess renal function after RC. GFR is widely accepted as the best marker of renal function (13). Although urinary inulin clearance is considered the gold standard measurement for GFR, the use of inulin is expensive, invasive, complex and has limited use in routine clinical settings (14,15,16). The creatinine-based eGFR equations are alternative non-invasive methods for easily assessing renal function because of their simplicity (16,17,18).

Table 4. Analysis of clinicopathological variables and complications associated with renal function deterioration

	Renal function outcome p value
pTNM stage	0.453
Preoperative urinary tract dilatation	0.397
Chemotherapy	0.271
Postoperative urinary tract dilatation	0.008
Postoperative urinary tract infection	0.026
Diabetes mellitus	0.109
Hypertension	0.312
Solitary kidney	1
ASA	0.715

pTNM: Pathological tumor-node-metastasis, ASA: American Society of Anesthesiologists

The MDRD equation is one of these equations and has gained widespread acceptance (17). Serum creatinine measurement, intravenous urography and radioisotope renography also have been used to evaluate renal function (1,3,16,19,20,21). Serum creatinine is the most commonly used biochemical marker of renal function, but is not a sensitive marker to assess deterioration of renal function (3,18,22). This marker is affected by numerous factors such as age, gender, race, hydration level and muscle mass (2,23).

Definition of renal deterioration is also unclear. When we look at the small number of studies available in the literature which have used eGFR, we see that there are different definitions such as CKD stage changes, 25% decline in eGFR from baseline and a decrease in eGFR by >1 mL/min/1.73 m^2 per year (1,2,3,24). In this study, we used the eGFR and annual change in eGFR.

Our study shows that 53.3% of patients who underwent RC with ICD experienced renal deterioration during the follow-up period. However, the changes in renal function were not statistically significant. In a study by Osawa et al. (1), the renal deterioration rate was 29% in 25 patients who underwent RC with ICD for bladder cancer. In the report by Osawa et al. (1), the definition of renal deterioration was described as a >25% decrease in eGFR compared to the preoperative renal function. However, in our study, we described renal deterioration as any decrease from the expected GFR. Thus, this difference may explain why this ratio is lower than ours (29% vs 53.3%). Jin et al. (3) reported that 36% of 50 patients (42 of them had bladder cancer), who underwent RC with ICD, experienced renal function decline in a follow-up period of more than 10 years. In this study, deterioration in renal function was defined as a decrease in GFR by >10 mL/min/1.73 m^2 in 10 years (3). In another study with a follow-up of 10 years, the rate of renal deterioration in 73 patients, who underwent RC with ICD for bladder cancer, was reported as 71%. This rate has been reported as 26% in the first year of the follow-up and 54% in the fifth year of follow-up (2). In a study by Rouanne et al. (10), these rates were reported as 39.3% and 20.3%, respectively. In our study, renal function deterioration was seen in 53.3% of patients in the first year and 41.1% of patients in the fifth year.

Table 5. Location and management of urinary tract dilatation

		Side			Treatment					
	n	Left	Right	Bilateral	Ntp	Nux	Nux + Uc	Ntp + SWL	Follow-up	Lost-to follow-up
Stricture	8	4	1	3	7	-	-	-	1	-
Tumor	4	1	-	3	1	1	1	-	-	1
Compression	1	-	1	-	1	-	-	-	-	-
Stone	1	1	-	-	-	-	-	1	-	-
No cause	7	4	-	3	1	2	-	-	4	-

Ntp: Nephrostomy tube placement, Nux: Nephroureterectomy, Uc: Ureterocutaneostomy (contralateral), SWL: Shock wave lithotripsy

Jin et al. (3) reported that 13 of 50 patients (26%) developed stage 3-5 CKD in more than 10 years after RC with ICD for bladder cancer. In our study, 9 patients (15%) developed stage 3-5 CKD during the follow-up period. Although we have detected a worsening in the CKD stage in 23.3% of patients during the follow-up period, this was not statistically significant. Considering that the median follow-up in our study was 35.6 months, a longer follow-up period might reveal if worsening of CKD is time-related.

Urinary diversion-related and -unrelated potential factors which may affect renal function deterioration include age, gender, a prior history of hypertension or diabetes mellitus, preoperative renal function, presence of preoperative urinary tract dilatation, postoperative febrile urinary tract infection, development of postoperative urinary tract obstruction, and systemic chemotherapy (1,2,3,24,25,26,27). Although the preoperative and postoperative eGFR values were statistically insignificant, the development of postoperative urinary tract obstruction and postoperative urinary tract infection were the only significant risk factors for renal deterioration.

The pathophysiology of urinary obstruction resulting from inflammatory process, apoptosis and fibrosis is highly complex (28). The effect of urinary obstruction on renal function depends on numerous factors, such as the duration (acute or chronic), side (unilateral or bilateral) and degree (partial or complete) of dilatation, contralateral kidney function, age, compliance of ureter and renal pelvis, pyelolymphatic backflow, presence of accompanying urinary tract infection and use of nephrotoxic agents and medications (29). The relief of obstruction for the improvement or the stabilization of the renal function is almost universally accepted. However, in practice, it may not be easy to separate the obstructive dilatation from the non-obstructive (30).

Ureteroileal anastomosis technique is controversial. Selection of anastomosis technique is generally based on surgeon's preference. Bricker and Wallace remain the two most common surgical techniques of ureteroenteric anastomosis for ileal conduit (31). These techniques are proven to be reliable and safe. In terms of ureteroileal stricture, both techniques provide similar and acceptable rates (31,32). We cannot make a comparison because only Wallace technique was used in our study.

Study Limitations

The limitations of this study include its retrospective and non-randomized design and small sample size. The lack of a control group was a limiting factor for assessing the effect of RC with ICD on the renal function.

Conclusion

In the current study, statistically insignificant reduction of renal function developed in 32 patients (53.3%) during the follow-up period after RC with ICD. We identified development of postoperative urinary tract obstruction and postoperative urinary tract infection as risk factors for deterioration of renal function. Recognition of these potential risk factors and early intervention for urinary tract obstruction and prevention of urinary tract infection may help preserve the postoperative renal function in patients undergoing RC with ICD.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (project no: KA16/16) and was supported by Başkent University Research Fund.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., M.R.G., T.E., F.K., S.G., Concept: C.O., M.R.G., Design: C.O., M.R.G., Data Collection or Processing: C.O., Analysis or Interpretation: C.O., M.R.G., Literature Search: C.O., Writing: C.O., M.R.G., T.E.

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Comparison of Ultrasonography and Cystoscopy in the Evaluation of Hematuria

Hematüri Değerlendirilmesinde Ultrasonografi ve Sistoskopinin Karşılaştırılması

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What's known on the subject? and What does the study add?

Hematuria is a prevalent symptom and it may be an occult sign of genitourinary abnormality. It is necessary to find the underlying cause of hematuria. In some of patients, malignancy can be detected during the evaluation of hematuria. In this study, we compared the results of ultrasonography and cystoscopy in the evaluation of hematuria. When the literature is examined, there is no study that examines the relationship between the number of red blood cells in urinalysis and the requirement of cystoscopy procedure.

Abstract

Objective: Every day, many patients visit hospital due to hematuria. Ultrasonography and/or cystoscopy are performed in the initial evaluation and management. In this study, we compared ultrasonography and cystoscopy in the evaluation of microscopic or macroscopic hematuria.
Materials and Methods: A total of 55 patients, who presented to our clinic with the complaint of hematuria between July 2016 and October 2017, were enrolled in this study. After obtaining informed consent, the patients were directed to urinary ultrasonography and cystoscopy for the evaluation of hematuria.
Results: Ultrasonography showed 45 (81.8%) normal bladder and 10 (18.2%) masses, and cystoscopy detected 39 (70.9%) normal bladder and 16 (29.1%) masses in the bladder (p=0.001). Ultrasonography was able to report only 8 (50%) of 16 masses detected via cystoscopy. Two (20%) of 10 masses reported by ultrasonography were not confirmed through cystoscopy. The sensitivity and specificity of ultrasonography in detecting and excluding masses in the bladder were calculated to be 50% and 94.9%, respectively. Ultrasonography failed to detect lesions at the posterior, dome and right side and bladder neck. The cut-off value for blood cell count in urine to refer the patient to a cystoscopy procedure was detected to be 15 with 60% sensitivity and 50% specificity.
Conclusion: With low sensitivity, ultrasonography could not offer enough knowledge about the bladder masses as sufficient as cystoscopy.
Keywords: Cystoscopy, Hematuria, Ultrasonography

Öz

Amaç: Birçok hasta her gün hematüri nedeniyle hastaneye gitmektedir. İlk değerlendirme ve yönetimde ultrasonografi ve/veya sistoskopi yapılmaktadır. Bu çalışmada, mikroskopik veya makroskopik hematüri değerlendirilmesinde ultrasonografi ve sistoskopi sonuçları karşılaştırıldı.
Gereç ve Yöntem: Temmuz 2016 ve Ekim 2017 tarihleri arasında, hematüri hastası olan toplam 55 hasta çalışmaya dahil edildi. Hastaların rızası alındıktan sonra hastalar hematüri değerlendirmesinde üriner ultrasonografi ve sistoskopi işlemine yönlendirildi.
Bulgular: Ultrasonografide hastaların 45'inde (%81,8) normal mesane ve 10'unda (%18,2) kitle saptanırken sistoskopide ise hastaların 39'unda (%70,9) normal mesane ve 16'sında (%29,1) mesane içinde kitle saptandı (p=0,001). Ultrasonografi; sistoskopi ile tespit edilen 16 kitlenin sadece 8'ini (%50) rapor edebildi. Ultrasonografide rapor edilen 10 kitleden 2'si (%20) sistoskopi ile doğrulanmadı. Ultrasonografinin mesanedeki kitleleri saptamak ve dışlamak için duyarlılığı ve özgüllüğü %50 ve %94,9 olarak hesaplandı. Ultrasonografide mesanenin posterior, kubbe, sağ yan duvar ve mesane boynundaki lezyonlar tespit edilemedi. Hastayı bir sistoskopi prosedürüne yönlendirmek için idrardaki eritrosit sayımının kesme değeri %60 duyarlılık ve %50 özgüllük ile 15 olarak tespit edildi.
Sonuç: Düşük duyarlılık ile ultrasonografi, sistoskopi kadar mesane kitleleri hakkında yeterli bilgi sağlayamadı.
Anahtar Kelimeler: Sistoskopi, Hematüri, Ultrasonografi

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Introduction

Hematuria is a common clinical finding and it can be a sign or symptom of an important disease in the practice of urology. The prevalence of hematuria is variable but estimated at 2.5% to 20% in the adult patients (1). Hematuria is described as the presence of an abnormal number of red blood cells (RBCs) in a urine sample and it can be classified as microscopic or macroscopic (gross) hematuria (2). According to the latest American Urological Association guidelines, microscopic hematuria can be defined as more than 3 RBCs per high-power field (hpf) in a properly collected urine sample (3). In most cases of microscopic hematuria, there is no etiology or pathology and this condition is called as asymptomatic microscopic hematuria with a prevalence ranging from 0.9% to 18.0% (3,4). There are many causes for microscopic hematuria, but the most common pathologies include urinary tract infection, benign prostatic enlargement, urolithiasis, urethral stricture disease, urologic malignancy, renal cystic disease, and renal disease (3,4,5). Male gender, age over 35 years, smoking history, analgesic abuse, and exposure to chemicals are the most common risk factors for urinary tract malignancy in patients with microscopic hematuria (5). Macroscopic hematuria can be described as a visible discoloration due to the presence of blood in the urine (2). In the diagnosis of macroscopic hematuria, the use of various medicines and foods that discolor urine should be investigated.

A detailed history should be taken in patients presenting with hematuria. Tobacco and anticoagulant drug use should be questioned. A physical examination involving the urogenital system should be performed. All patients are evaluated with whole blood count, renal function tests, urine analysis, and urine culture. Intravenous urography has been used to evaluate microscopic hematuria in the past, but now it is not preferred due to its low sensitivity (3). Ultrasonography (USG), computed tomographic urography and magnetic resonance imaging are more frequently preferred because they provide detailed images in the evaluation of microscopic hematuria (3,5). Upper urinary tract can be examined by radiological methods but cystoscopy should be done especially for lower urinary tract evaluation (1). Cystoscopy should be recommended to hematuria patients with risk factor for urinary system malignancy, such as male gender, age over 35 years, and tobacco use (3,6). Although cystoscopy is an invasive procedure, it continues to be a reference standard in the evaluation of patients with asymptomatic microscopic hematuria (7). USG is considered the imaging method of choice for hematuria and it has an indisputable role in the evaluation of hematuria. Since contrast media and radiation are not applied during USG, it is a less risky diagnostic method for hematuria patients (2).

Every day, many patients visit hospital due to hematuria. In some of these patients, malignancy can be detected during the evaluation of hematuria. USG and/or cystoscopy are performed in the initial evaluation and management. In this study, we compared USG and cystoscopy in the evaluation of microscopic or macroscopic hematuria.

Materials and Methods

Patient Selection

This study was approved by the Gülhane Training and Research Hospital Ethical Committee (approval number: 18/88, date: 5 April 2018) and followed the Institutional Review Board for Human Subjects Researches Guidelines.

This is a retrospective study. The sample size was calculated with the help of sample size calculator at www.calculator.net and examining >50 patients were found to be enough for this study. A total of 55 patients who presented to our clinic with the complaint of hematuria between July 2016 and October 2017 were enrolled in this study. The patients, who were included in the study, had no history of upper urinary tract or bladder malignancy. After obtaining informed consent, the patients were directed to urinary USG and cystoscopy for the evaluation of hematuria.

All patients underwent a complete physical examination especially for costovertebral tenderness. After physical examination, all patients were evaluated by urinalysis, urine culture, measurement of hemoglobin, serum urea and creatinine, and kidneys, ureters, and bladder (KUB) X-ray. Patients, who had positive urine cultures, were treated according to the reported antibiogram results until the urine cultures became sterile. All procedures were done when the urine cultures were sterile. A second urinalysis was taken for the presence of blood and to investigate white cell count in the urine after sterile urine culture was obtained. Firstly, urinary system USG was used for diagnosis. Then, cystoscopy was applied to investigate any mass in the bladder. Patients with negative urine cultures had a single-dose oral antibiotic with a first-generation cephalosporin or quinolone for cystoscopy procedures.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences 20.0 software (SPSS 20.0 for MAC). Descriptive statistics of nominal samples were expressed with numbers and percentiles. Descriptive statistics of scale samples were expressed as mean ± standard deviation (minimum-maximum). The Shapiro-Wilk test and Kurtosis and Skewness test were used to assess normality of the variables. Cross-tabs were used to detect sensitivity and specificity. A chi-square test was used

to compare the independent nominal parameters. The paired samples t-test was used to compare the independent scale parameters with normal distribution. A p value of less than 0.05 was considered statistically significant.

Results

Of 55 patients included in the study, 39 (70.9%) were female and 16 (29.1%) were male. The mean age of the patients was 62.43±14.79 (21-91) years. Nine patients (16.3%) had a history of tobacco smoking at the time of interview. None of the patients had costovertebral tenderness. The mean hemoglobin, urea, and creatinine levels were 12.9±1.5 (10.50-16.73) g/dL, 30.43±5.3 (17-48) mg/dL, and 1.07±0.2 (0.74-1.79) mg/dL, respectively. Thirty-two patients had urinary infection at first visit, and they were treated according to antibiogram results. None of our patients had active urinary tract infections, and urine samples and urine cultures were normal before USG and cystoscopy procedures. The mean blood and white cell count, when the urine culture, was sterile was 82.23±62 (0-1249) and 15.81±13.2 (0-364), respectively.

USG reported 45 (81.8%) normal bladder, and 10 (18.2%) masses; and cystoscopy detected 39 (70.9%) normal bladder, and 16 (29.1%) masses in the bladder (p=0.001). USG was able to report only 8 (50%) of 16 masses detected by cystoscopy. Two (20%) of 10 masses reported by USG were not confirmed via cystoscopy (Table 1). The sensitivity and specificity of USG to detect and exclude masses in the bladder were calculated to be 50% and 94.9%, respectively. The positive and negative likelihood ratios of USG to detect masses in the bladder were 8.3 and 0.53, respectively. There was a statistically significant difference in examining the location of the lesions in the bladder between USG and cystoscopy (p=0.001). USG failed to detect lesions at the posterior, dome, and right side, and bladder neck (Table 2). The mean lesion diameter detected by USG and cystoscopy was 13.62±16.16 (0-47) mm, and 20±13.9 (5-50) mm, respectively (p=0.007).

Calculating the receiver operating characteristic curve using the blood cell count in urine sample, there was a 0.534 area under curve value. This meant that blood cell count in urine sample could be a moderately (not very useful) used parameter for the diagnosis of any lesion in the bladder (Figure 1). The

Table 1. Lesions in cystoscopy and ultrasonography

			Lesions in USG		
			Total	No	Yes
				Count (%)	Count (%)
Lesions in cystoscopy	No	Count (%)	37 (94.9)	2 (5.1)	39
	Yes	Count (%)	8 (50.0)	8 (50.0)	16
	Total		45 (81.8)	10 (18.2)	55

USG: Ultrasonography

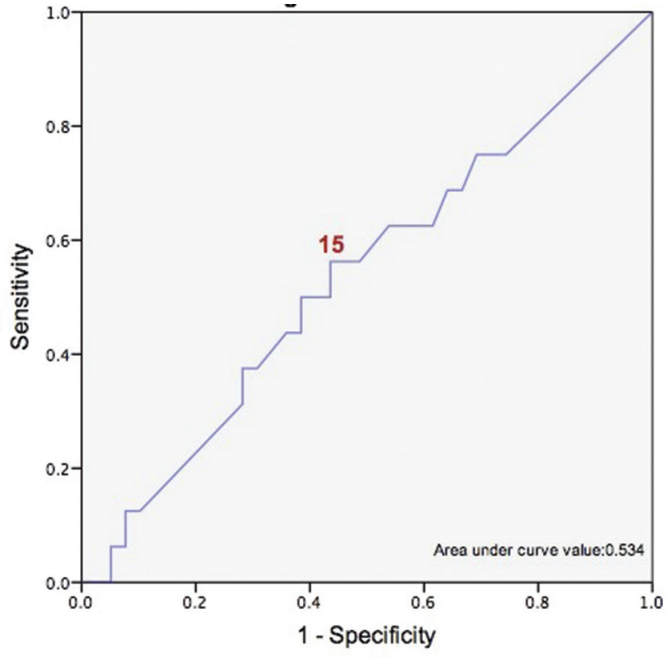

Figure 1. Receiver operating characteristic curve using urine blood cell count

Table 2. Localization of lesions in ultrasonography and cystoscopy

		Localization of lesions in cystoscopy							Total
		No	Trigon	Posterior	Dome	Right side	Left side	Bladder neck	
Localization of lesions in ultrasonography	No	37	0	1	1	4	0	2	45
	Trigon	1	0	0	0	0	0	0	1
	Posterior	1	0	2	0	0	0	0	3
	Dome	0	0	0	0	0	0	0	0
	Right side	0	0	0	0	2	0	0	2
	Left side	0	0	0	0	0	4	0	4
	Bladder neck	0	0	0	0	0	0	0	0
Total		39	0	3	1	6	4	2	55

cut-off value for blood cell count in urine to refer the patient to a cystoscopy procedure was detected to be 15 with 60% sensitivity and 50% specificity.

Discussion

Hematuria is a prevalent symptom and it may be an occult sign of genitourinary abnormality. This finding sometimes presents as a symptom but it can also be detected incidentally. It is necessary to find the underlying cause. Hematuria is described as the presence of RBCs that are visible in the urine (macroscopic hematuria) or directly detected by microscopy (microscopic hematuria) (8). Hematuria can be defined as ≥3 RBCs per (hpf2) and ≥5 RBCs/hpf3 in urine sample (3,8). Hematuria can be classified as nephrological (glomerular disease) or urological (tumors, urinary tract infection, stone disease, benign prostatic enlargement, urethral caruncle, meatal ulcers, trauma) in origin (3,4,5,8). Sometimes microscopic hematuria can also occur with an excessive exercise when there is no underlying cause (9). Based on biochemical and radiological studies, we decided that the case in our study was hematuria of urological origin. Since the risk of urinary system malignancy is relatively low in young people, the prevalence of an important underlying pathology for hematuria is low and it ranges between 0 and 7.2% (10). In this age group, hematuria related to nephrologic causes is more common than that of urological origin. Along with advancing age, the risks for important diseases also increase (8). Risk factors for significant diseases in patients with microscopic hematuria include male gender, age over 35 years, smoking history, analgesic abuse, exposure to chemicals (benzenes or aromatic amines), history of gross hematuria, history of urological disease, history of urinary tract infection, and history of pelvic irradiation (3,5,8). Macroscopic hematuria is more closely related to the underlying serious urological diseases (8). In our study, we performed cystoscopy for all patients with macroscopic hematuria. On the other hand, we performed cystoscopy by questioning of the risk factors for microscopic hematuria. All these patients had risk factors for microscopic hematuria.

Different radiological diagnostic methods are used to detect this abnormality such as KUB X-ray, intravenous pyelography, USG, computed tomography, computed tomographic urography and magnetic resonance imaging (3,5). The important thing is to find the underlying cause of hematuria with some of these imaging methods, not all of them. Although cystoscopy is an invasive procedure, it is an endoscopic method that allows direct observation of the urethra, prostate, and the bladder (11). The procedure can be performed using rigid or flexible cystoscopy, but rigid cystoscopy is more traumatic (11). Tissue biopsy may be done during cystoscopy. Cystoscopy is recommended in patients with a risk of malignancy in the urinary system (6). Radiological methods should be accompanied by cystoscopy in the evaluation of hematuria because in most cases, it has been determined that the lower urinary tract pathologies were the cause of bleeding (12). There is no radiologic method which shows the cause of the hematuria in the lower urinary tract as good as cystoscopy (12). Therefore, cystoscopy was performed after sonographic evaluation in all patients who presented with hematuria in our study. In some patients, a mass in the bladder was detected only by cystoscopy. In a study published in 2008, it has been reported that the sensitivity and specifity of USG were 50% and 95%, respectively (13). In a study published in 2002, the sensitivity and specifity of of USG in detecting bladder masses in patients who were admitted with hematuria were reported to be 63% 99%, respectively (14). In our study, we found that the sensitivity and specificity of USG in detecting bladder cancer were 50% and 94.9%, respectively. These results are compatible with the literature data.

Anticoagulant medication use at the therapeutic doses does not cause hematuria, thus, urologic problems should be investigated for hematuria etiology in these patients (12,15). We questioned the use of anticoagulant medication before the diagnostic methods in patients who presented with hematuria. We found that the international normalized ratio was within the normal limits. We did not consider the use of anticoagulant medication as the cause of hematuria.

When the literature is examined, there is no study that examines the relationship between the number of RBCs in urinalysis and the requirement of cystoscopy procedure. It was determined that the number of RBCs in urinalysis was 15 RBCs/hpf2 for the requirement of cystoscopy.

Study Limitations

The small number of patients may be the main limitation of the study. Further studies with a larger sample size would provide more reliable results.

Conclusion

With low sensitivity, USG could not offer enough knowledge about bladder masses as sufficiently as cystoscopy.

Ethics

Ethics Committee Approval: This study was approved by the Gülhane Training and Research Hospital Ethical Committee (approval number: 18/88, date: 05 April 2018).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.T., T.E., M.G., Concept: T.E., E.K., M.G., Design: S.Y., A.E.Ç., S.B., Data Collection or Processing: B.T., T.E., Analysis or Interpretation: M.G., S.B., Literature Search: B.T., S.Y., Writing: B.T., T.E.

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Does Ozone Administration Have a Protective Effect Against Cisplatin-induced Histological Changes in Rat Testis?

Cisplatine Bağlı Rat Testisinde Meydana Gelen Histolojik Değişikliklere Karşı Ozon Tedavisinin Koruyucu Bir Etkisi Var mıdır?

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What's known on the subject? and What does the study add?

There is currently no study of the protective effect of ozone treatment against cisplatin-induced testicular damages.

Abstract

Objective: We investigated the protective and therapeutic effects of ozone therapy (OT) on cisplatin (CP)-induced testicular damage.
Materials and Methods: Thirty healthy adult male Wistar rats were divided into five groups consisting of 6 animals each: 1) control, 2) CP, 3) OT, 4) OT + CP and 5) CP + OT groups. Histopathological findings, Johnsen scores, thiobarbituric acid-reactive substances (TBARS), glutathione (GSH), superoxide dismutase (SOD), catalase, and GSH peroxidase (GPx) levels were evaluated.
Results: CP caused a significant decrease in testicular weight and Johnsen score compared to the control group. In addition, TBARS level was significantly higher, whereas GSH, SOD, catalase and GPx levels were significantly lower in the CP group when compared to the control group. Pre- and post-CP OT significantly increased GSH, SOD, catalase and GPx levels and decreased TBARS level. Also, testicular weight and Johnsen score were increased with OT.
Conclusion: The present study showed that OT is protective against CP-induced testicular damage. OT may be beneficial to patients who underwent CP chemotherapy.
Keywords: Ozone therapy, Cisplatin, Chemotherapy, Testicular histopathology, Testis

Öz

Amaç: Bu çalışmada, ozon tedavisinin (OT) cisplatin tedavisine (CT) bağlı gelişen testis hasarını önleyici ya da tedavi edici etkisini araştırdık.
Gereç ve Yöntem: Wistar cinsi 30 sağlıklı yetişkin erkek rat, her biri 6 rattan oluşan 5 gruba ayrıldı: 1) Kontrol, 2) CT, 3) OT, 4) OT + CT ve 5) CT + OT grubu. Histopatolojik bulgular, Johnsen skorları, tiyobarbitürik asit reaktif maddeler (TBARM), glutatyon (G), süperoksit dismutaz (SOD), katalaz, G peroksidaz (GP) düzeyleri değerlendirildi.
Bulgular: CP grubu, kontrol grubuna kıyasla testis ağırlığında ve Johnsen skorunda belirgin bir düşüşe neden oldu. Ayrıca, TBARM düzeyi anlamlı derecede yüksek iken; G, SOD, katalaz ve GP düzeyleri CP grubunda kontrol grubuna göre anlamlı derecede düşük bulundu. CP + OT öncesi ve sonrası GSH, SOD, katalaz ve GP düzeylerini önemli ölçüde artırdı ve TBARM seviyesini düşürdü. Testikül ağırlığı ve Johnsen skoru OT ile arttı.

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Sonuç: Bu çalışma, OT'un cisplatine bağlı gelişen testis hasarını önleyici etkisi olduğunu göstermiştir. OT, cisplatin uygulanan hastalarda testis hasarını önlemede yararlı olabilir.

Anahtar Kelimeler: Ozon tedavisi, Cisplatin, Kemoterapi, Testiküler histopatoloji, Testis

Introduction

One of the most effective chemotherapeutic drugs in the treatment of reproductive organs (ovary, testis), bladder, lung, head and neck cancers is cisplatin (CP) (1,2). The curative effect is well known when CP is used alone or in combination with other drugs (3). On the other hand, CP has quite a lot of adverse effects, especially testicular toxicity that affects spermatogenesis, chromosomal abnormalities in spermatozoa and fertility. Due to these unwanted effects, clinical use of CP is limited most of the time (4). In many previous studies, it has been confirmed that CP that induces testicular oxidative stress had both short-term and long-term effects (5). Oxidative stress is usually held responsible for the pathogenesis of testicular damage after CP exposure (6). Therefore, anti-oxidants are widely recognized to guard rapidly dividing testicular cells against damage by CP (3,7).

Antioxidants are the natural defense mechanism against reactive O_2 species (ROS) in most of the organs including the testicle. Oxidative damage occurs when there is a shift in the balance between production of ROS and the antioxidant defense mechanism in favor of ROS (8,9). Ozone is an inorganic molecular colorless gas composed of three O_2 atoms with a significant pungent odor at room temperature (9,10,11). After ozone therapy (OT) administration, it dissolves in biological water and instantly reacts with antioxidant mechanisms. During these fast reactions, ozone is neutralized by activation of antioxidant mechanisms, which are superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase (GPx) (11). The stimulation of endogenous antioxidants prepares the host defense against ROS (9,10,11). The other important effects of ozone are immune modulation, neoangiogenesis and increased tissue oxygenation (11).

In the English literature, there is no previous study on the protective effect of ozone against CP-induced testicular injury. In this study, it was aimed to evaluate the effect of OT on testis histopathology before and after CP treatment in an experimental rat model.

Materials and Methods

The compatibility with ethical standards was provided using the experimental protocols for which the approval was officially taken from the local ethics committee on animal trials under the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. The approval was taken from Bezmialem Vakıf University Ethics Committee (number: 24.11.2015/237).

Animals

Thirty healthy adult male Wistar rats weighing between 245 and 310 g were used. The rats were kept in well-ventilated plastic cages at a room temperature of 25±3 °C and 12-hour light/dark cycle environment. Ad libitum feeding was applied with appropriate chow to laboratory conditions and potable water. The setting was acclimatized at one-week intervals.

Experimental Design

Thirty rats were randomly divided into 5 groups consisting of 6 animals each:

Group control: the rats received intraperitoneal O_2,

Group OT: the rats were administered intraperitoneal OT to determine the effect of OT on testicular histopathology,

Group CP: the rats received a single dose of 7 mg/kg of CP intraperitoneally to determine the effect of CP on testicular histopathology as described by Beytur et al. (12),

Group CP + OT (CP after OT): the administration of a single dose of 7 mg/kg of CP was followed by intraperitoneal OT in order to determine the effect of OT on the histopathology of testicles of the rats undergoing CP chemotherapy,

Group OT + CP (OT after CP): the rats received intraperitoneal OT and then were administrated a single dose of 7 mg/kg of CP intraperitoneally to determine the effect of pre-CP chemotherapy OT on testicular histopathology.

All experimental procedures were performed under anesthesia by administering intraperitoneal 5 mg/kg xylazine hydrochloride and 50 mg/kg ketamine hydrochloride to the rats, then, the rats were immobilized by fixing them on the 4 corners of a tray.

Ozone Therapy

The ozone-oxygen mixture was produced by an ozone generator (Medozon Compact-Hab Herrmann Apparatebau, GmbH, Germany). The measured level for ozone concentration was found to be 254 nm on an ultraviolet spectrophotometer. The mixture included the ozone concentration measured at 50 µg/mL. Three-day administration of 0.2 mg/kg/day was made for the subjects to receive 10 µg/mL ozone.

Histopathological Examination

Four days after the end of the experimental procedures, the rats were sacrificed by cervical dislocation, and bilateral orchiectomy was performed. The tunica albuginea was used to individually weigh testes. As described in a previous study, the left testis samples were examined by biochemical analysis and the right testis samples were examined histopathologically (10). Briefly, the samples were fixed in Bouin's solution and dehydrated in alcohol for 24 hours. After routine tissue processing, the samples were embedded in paraffin. Tissue sections (3-µm thick each) from the upper, lower and middle testicular regions were mounted for microscope slides. Staining cross-sections were provided using periodic acid-Schiff and hematoxylin-eosin under the standard protocols. The observation of the tissue slides was made through the standard light microscope by a pathologist, who was uninformed of the results, to apply experimental procedures. Calculation of the Johnsen scores was performed for each one. At least 50 tubules per tissue slide were examined and scored from 1 to 10 for each tissue slide according to spermatogenesis level (Table 1) (13).

Biochemical Analysis

A 10% homogenate of testicular tissue was prepared in 0.1 mol KCl buffer (pH 7.4) with Teflon-glass homogeniser. Following homogenization of the tissues, centrifugation was conducted at 18.000 g at 4 °C for 30 min. To establish a lipid peroxidation index, Yagi's (14) method was effective to identify the levels of thiobarbituric acid-reactive substances (TBARS). The spectrophotometrical measurement was 532 nm for the absorbance level. The results for the tissues were in nmol g^{-1} tissue. The Sedlak and Lindsay (15) method was applied to obtain the GSH levels. Absorbance occurred at 412 nm as displayed by spectrophotometer, and the records were presented in nmol mL^{-1} tissue. The technique introduced by Sun et al. (16) provided with identifying the levels of SOD activity.

Table 1. The Johnsen score (13)

Score	Level of spermatogenesis
1	No seminiferous epithelial cells, tubular sclerosis
2	No germ cells, Sertoli cells only
3	Spermatogonia only
4	Few spermatocytes, arrest of spermatogenesis at the primary spermatocyte stage
5	Many spermatocytes
6	Few early spermatids, arrest of spermatogenesis at the spermatid stage
7	No late spermatids, many early spermatids
8	Less than five spermatozoa per tubule
9	Slightly impaired spermatogenesis
10	Full spermatogenesis

In this method, inhibition of O_2-induced nitroblue tetrazolium reduction, produced by the xanthine/xanthine oxidase system, is decisive. For one unit of SOD activity, the quantity of enzyme was used, which is necessary to result in the half-inhibition of nitroblue tetrazolium reduction rate at 560 nm. The results in the study were expressed as IU mg^{-1} protein. Catalase activity was determined using the Aebi method (17). This method is based on the concept that catalase present in the sample converts H_2O_2 to H_2O and O_2. The spectrophotometrical measurement of H_2O_2 has decreased from 240 nm. The results were displayed in k mg^{-1} protein. The observations of the GPx activity levels were attained, thanks to the Paglia and Valentine's (18) method. This technique was established to match GPx activity and nicotinamide adenine dinucleotide phosphate oxidation using GSH reductase. The latter was spectrophotometrically measured at 340 nm. The results were showed in IU mg^{-1} protein.

Statistical Analysis

The statistics were exhibited in the format of mean ± standard deviation. The Kolmogorov-Smirnov test was used for normal distribution compatibility, and non-parametric tests of the Kruskal-Wallis and Mann-Whitney U for between-groups analysis. Significance level was defined as $p<0.05$. Statistical analyses were conducted by SPSS package (version 19.0 for Windows; IBM, NY, USA).

Results

None of the rats in the study, performed on a total of 30 rats, died during the experiment. Histopathological examination and biochemical analysis were performed on the rats.

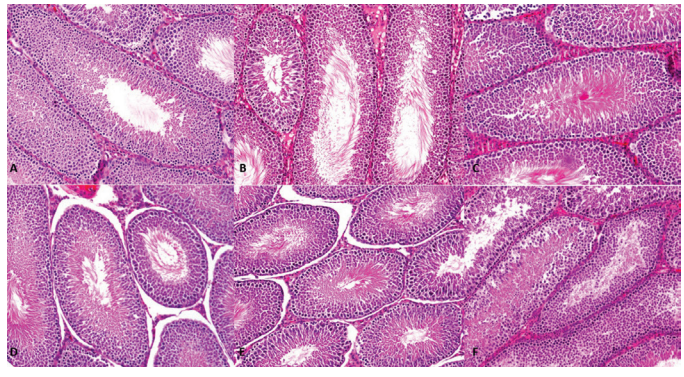

Figure 1. A) Normal testis histology (control group, hematoxylin and eozin, 100x), B) full spermatogenesis and normal testis histology (ozone therapy group, hematoxylin and eozin, 100x), C) necrosis of testicular tubules, impaired spermatogenesis (cisplatin group, hematoxylin and eozin, 40x), D) multinucleated giant cells in distributed testicular tubules (cisplatin group, hematoxylin and eozin, 40x), E) full spermatogenesis and normal testis histology (ozone theraphy + cisplatin group, hematoxylin and eozin, 100x, F) many early spermatids and disorganized epithelium (cisplatin + ozone theraphy group, hematoxylin and eozin, 100x)

We observed significant testicular damage in the CP group (Table 2). The weight of both the right and left testicles in the CP group was significantly lower than in controls. But pre- and post-CP OT was significantly prevented this decreases caused by CP. In the control group, the rat testes showed normal morphology and spermatogenesis, healthy seminiferous tubules containing plenty of spermatids and sperm in the lumen (Figure 1). High Johnsen scores (9.71±0.3) were detected in the control group. In the OT group, the rat testes showed mostly the same morphological characteristics as in the control group, but a few seminiferous tubules showed slightly impaired spermatogenesis. There was no significant difference in Johnsen score between OT and control groups (9.64±0.2 vs 9.71±0.3, p=0.833). In the CP group, the rat testes showed testicular interstitial fluid and interstitial edema, germ cell desquamation and irregular spaces in the epithelium, decreased spermatogenic cells and seminiferous tubules containing Sertoli cells and germ cell necrosis. The Johnsen scores were significantly decreased in the CP group compared to that in the control (8.16±0.8 vs 9.71±0.3, p<0.001) and OT (8.16±0.8 vs 9.64±0.2, p<0.001) groups. In the pre- and post-CP OT groups, the rat testes showed mild interstitial edema and tubules with incomplete maturation arrest. Spermatogenesis was maintained in the majority of the seminiferous tubules. The Johnsen scores were significantly increased in the CP + OT and OT + CP groups compared to that in the CP group (9.54±0.3 vs 8.16±0.8, p<0.001; 9.57±0.2 vs 8.16±0.8, p<0.001, respectively). Meanwhile, no significant difference was found in Johnsen score between CP + OT and control groups (p=0.381), OT + CP and control groups (p=0.377), and CP + OT and OT + CP groups (p=0.891).

Levels of TBARS, GSH, SOD, catalase and GPx in rat testis tissue are presented in Table 3. When the control group and CP group were compared in the testis tissues of the rat, the levels of TBARS were significantly higher in the CP group, whereas the GSH, SOD, catalase and GPx levels were significantly lower. On the other hand, pre- and post-CP OT caused a significant decrease in the TBARS level and an increase in GSH, SOD, catalase and GPx levels when compared to the CP group.

Discussion

It is well known that human testis is sensitive to CP. This study showed that CP chemotherapy induced significant damage in the testes of rats. Besides, pre- and post-CP OT was protective against spermatogenic cell damage.

CP is a highly effective anti-tumor drug used in the treatment of many different types of tumors, including testicular, ovarian, endometrium, cervical, bladder, lung and head and neck cancers. However, its usage is limited by its toxic effects on the reproductive system (4,19,20). The main unwanted effects of CP are ototoxicity, nephrotoxicity, peripheral neuropathy, azoospermia, sperm morphology, and motility modifications (19,21). As a result, prevention of side effects of CP is very important in terms of treatment protocol, benefits in quality of life and extending the limits of dose (4). CP targets testicular cell types such as Leydig cells, Sertoli cells and germ cells thus leading to male reproductive toxicity (22). In this research, testicular destruction induced simply by CP medication was seen as significant raises in lipid peroxidation, reduced antioxidant status and changed testicular histopathology in rats.

Oxidative stress plays a significant role in male reproductive dysfunction (23). Oxidative stress is an abnormal condition where the balance between the production of ROS and their adequate

Table 2. Comparison of testes weight and the Johnsen score among the five groups

	Control	OT	CP	CP + OT	OT + CP
Right testis weight (g)	1.321±0.05	1.317±0.04	0.868±0.03*	1.282±0.03$^{\gamma}$	1.291±0.02$^{\gamma}$
Left testis weight (g)	1.310±0.04	1.308±0.03	0.845±0.05*	1.289±0.03$^{\gamma}$	1.287±0.03$^{\gamma}$
Johnsen score	9.71±0.3	9.64±0.2	8.16±0.8*	9.54±0.3$^{\gamma}$	9.57±0.2$^{\gamma}$

OT: Ozone therapy, CP: Cisplatin, *significantly different from the control group, $^{\gamma}$significantly different from the cisplatin group, data expressed as mean ± standard deviation

Table 3. Comparison of thiobarbituric acid-reactive substances, glutathione, superoxide dismutase, catalase and glutathione peroxidase levels among the five groups

	Control	OT	CP	CP + OT	OT + CP
TBARS (nmol g^{-1} tissue)	23.51±1.23	24.86±3.12	49.82±3.95*	25.63±3.88$^{\gamma}$	24.90±4.13$^{\gamma}$
GSH (nmol mL^{-1})	192.74±3.81	194.41±4.22	103.13±8.74*	187.04±4.15$^{\gamma}$	190.07±5.99$^{\gamma}$
SOD (U mg^{-1} protein)	0.82±0.04	0.80±0.04	0.60±0.03*	0.79±0.03$^{\gamma}$	0.78±0.04$^{\gamma}$
Catalase (k mg^{-1} protein)	2.43±0.81	2.41±0.94	1.23±0.45*	2.36±0.66$^{\gamma}$	2.34±0.91$^{\gamma}$
GPx (U mg^{-1} protein)	220.11±26.52	215.63±28.68	151.18±28.40*	209.39±12.63$^{\gamma}$	211.55±16.27$^{\gamma}$

OT: Ozone therapy, CP: Cisplatin, TBARS: Thiobarbituric acid-reactive substances, GSH: Glutathione, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, *significantly different from the control group, $^{\gamma}$significantly different from the cisplatin group, data were expressed as mean ± standard deviation

elimination by antioxidant systems available in the body is severely disturbed (4,19). Within pathological circumstances, ROS could be produced not merely by macrophages and neutrophils but likewise spermatozoa and various other cell types (20,24,25).

O_2 free radical formation is associated with impaired GSH metabolism, changes in the antioxidant enzymes, and lipid peroxidation (4,20). Antioxidants are inactivating ROS and they maintain normal cell function (8,9). The enzymes such as GPx, SOD and catalase are endogenous defense mechanisms that remove the activation of superoxide, hydrogen peroxide and hydroxyl radicals (3,4,19,20). SOD changes superoxide anion in to water and O_2, whilst catalase changes peroxide radicals in to water and O_2. The reason for the decrease in enzymatic antioxidants is increased ROS production (8). TBARS are also a by-product of the damage that results from oxidative stress. TBARS produced from peroxidation of fatty acids by ROS are considered to be an indicator of lipid peroxidation (19). When there is a shift in the balance between the production of ROS and the antioxidant defense mechanism in favor of ROS, ROS interacts with proteins, lipids and nucleotides in the cell structure. These pathways induce an apoptotic process (8,9). Testis is a main organ for oxidative stress as a consequence of its large content material of polyunsaturated membrane lipids (12,20). Thus, sensitivity of testis to oxidative agents such as CP is high. Therefore, use of antioxidants can prevent CP-induced male infertility. In this study, we found that CP treatment caused increased oxidative stress and decreased antioxidant enzymes.

The antioxidant mechanism of ozone remains unknown. Once therapeutic ozone is administrated, ozone dissolves in the plasma and responds with polyunsaturated fatty acids and sulfhydryl groups. These reactions lead to the production of lipid hydroperoxides and hydrogen peroxides at low concentrations. Low-dose OT may act as cellular signal molecules and activates the cytoprotective pathways which increase the GSH synthesis and antioxidant capacity (11). Another antioxidant pathway of OT is inhibitory formation of xanthine oxidase thereby reducing the adenosine triphosphate depletion. Preserved adenosine induces vasodilation in the smooth muscle. It also inhibits the nuclear transcription factor kappa B, which is responsible for ozone, tissue damage, and inflammatory responses (26). Thus, ozone regulates inflammation and limits tissue injury. Ozone also has effects such as increasing blood flow to the tissues, activation of hypoxia-inducible factor-1a, vascular endothelial growth factor, activation of erythropoietin and glycolytic enzymes and increased O_2 delivery (11,26).

Molecular mechanism of radio protective substances is essential for drug approval. To our knowledge, no study investigating the molecular mechanism of ozone in recovery or protection against CP-induced testicular damage has been published.

Study Limitations

In our study, inadequate evaluation of tissue damage parameters and ROS is a limitation.

Conclusion

The current investigation demonstrated the fact that OT is shielding in CP-induced testicular destruction. OT might be effective in patients who go through CP chemotherapy. Further studies are needed to confirm our results and transition from experimental animal studies to clinical trials.

Ethics

Ethics Committee Approval: The approval was obtained from Bezmialem Vakıf University Ethics Committee (number: 24.11.2015/237).

Informed Consent: Experimental study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.A., P.Y., Concept: İ.A., Y.Ö.İ., R.G.E., Design: İ.A., Y.Ö.İ., Data Collection or Processing: İ.A., R.G.E., S.L.M., A.Ç., Y.E.A., H.K., Analysis or Interpretation: İ.A., R.G.E., Y.E.A., M.B.S., A.Ç., S.L.M., H.K., Literature Search: İ.A., Y.Ö.İ., Y.E.A., A.Ç., S.L.M., M.B.S., H.K., Writing: İ.A., Y.Ö.İ., R.G.E., M.B.S.

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The Incidence of Methemoglobinemia Due to Prilocaine Use in Circumcision

Prilokain ile Yapılan Sünnetlerde Methemoglobinemi İnsidansı

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What's known on the subject? and What does the study add?

Prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Abstract

Objective: Local anesthesia with prilocaine is widely used in circumcision procedures. However, the incidence of methemoglobinemia due to prilocaine use during these procedures remains unknown. Therefore, this retrospective study was planned to determine the possibility of development of prilocaine-associated methemoglobinemia during circumcision.

Materials and Methods: Medical records of 2.431 patients who were circumcised between 2008 and 2015 in University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Turkiye, were evaluated. Prior to all circumcision procedures, 1.5 mg/kg of local anesthetic was subcutaneously administered to the penis root at 4-5 points from a 20 mL vial containing 400 mg (20 mg/mL) of prilocaine (2%).

Results: Of the 2.431 patients included in the study, two (0.008%) developed methemoglobinemia requiring treatment. According to the medical records, five patients (0.021%) developed mild bruising on the hands, feet and sides of the lips.

Conclusion: Prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Keywords: Prilocaine, Circumcision, Methemoglobinemia, Local anesthesia, Complications

Öz

Amaç: Sirkümsizyon işleminde prilokain ile lokal anestezi uygulaması yaygın olarak kullanılmaktadır. Sirkümsizyon esnasında prilokain kullanımına bağlı methemoglobinemi insidansı bilinmemektedir. Bu retrospektif çalışma sirkümsizyon sırasında kullanılan prilokaine bağlı methemoglobinemi gelişme olasılığını ortaya koymak amacıyla planlanmıştır.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi, İzmir Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Üroloji Kliniği'ne 2008-2015 arasında gelen 2431 hastanın dosyaları incelendi. Tüm sirkümsizyon işlemlerinden önce, 20 mL'lik her flakonda 400 mg (20 mg/mL) prilokain (%2) içeren lokal anestezik 1,5 mg/kg olarak penis köküne 4-5 noktadan deri altına uygulandı.

Bulgular: Sağlık Bilimleri Üniversitesi, İzmir Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Üroloji Kliniği'ne 2008-2015 arasında gelen 2431 hastanın dosyaları incelendi. Çalışmaya dahil edilen 2431 hastadan iki hastada (%0,008) tedavi gerektiren methemoglobinemi gelişti. Beş hastada (%0,021) ise el, ayak ve dudak kenarlarında hafif düzeyde morarma olduğu anamnezde tespit edildi.

Sonuç: Yenidoğan ve çocuklarda edinsel methemoglobinemi olgularının erişkine oranla görece sık methemoglobinemi sebeplerinden biri olarak karşımıza çıkmıştır. Methemoglobinemiye neden olan faktörün saptanması, erken ve etkin şekilde askorbik asit veya metilen mavisi uygulanması yaşam kurtarıcı olmaktadır.

Anahtar Kelimeler: Prilokain, Sirkümsizyon, Methemoglobinemi, Lokal anestezi, Komplikasyon

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Introduction

Circumcision is one of the most widespread procedures in the world undertaken for religious reasons among Muslims and Jews and for hygienic or pathological phimosis-related medical conditions in males. Although circumcision can be performed with patients under general anesthesia, some surgeons prefer local anesthesia. In both cases, local anesthesia is applied around the penis to reduce pain during or after circumcision. With its short-acting profile in infiltration anesthesia, prilocaine is one of the most commonly used amide-type local anesthetics. Allergic reactions, such as edema, urticaria, dermatitis, and pallor are among the predominant side effects from low-dose prilocaine infiltration (1). One of the less frequently seen side effects is methemoglobinemia. Hemoglobin (Hb) is a molecule found in the erythrocytes that transport O_2 to tissues. For this process, the iron in the structure of Hb must be in the Fe^{+2} form. Methemoglobinemia occurs when this iron becomes Fe^{+3}, resulting in various oxidative stresses. Methemoglobin (MetHb) cannot carry O_2 and shifts the Hb-O_2 dissociation curve to the left, making it more difficult for O_2 to be delivered to the tissues. However, its concentration is reduced to less than 1% by the cytochrome-b5 reductase enzyme system; namely, the intracellular MetHb reductive system. Infants are more susceptible to oxidation since their cytochrome-b5 reductase enzyme levels are 50% lower than in adults (2). When the blood MetHb level is about 10-15%, cyanosis develops, and if it exceeds 35%, systemic symptoms including fatigue due to tissue hypoxia, tachycardia, respiratory distress, nausea, and vomiting occur. In cases where the blood MetHb level is 55% or above, lethargy, stupor and syncope develop, and if it is over 70% and treatment action is not taken, then it usually results in death (3).

Methemoglobinemia can be congenital or acquired. There are four types of congenital methemoglobinemia, all of which result from inherited autosomal recessive disorders in various enzyme systems. To date, many chemicals and drugs have been reported to cause acquired methemoglobinemia, including nitrotoluenes, phenacetin, chloroquine, dapsone, phenytoin, sulfonamides, and local anesthetics. Methemoglobinemia due to the treatment dose of prilocaine as a local anesthetic is very rare (4).

The exact incidence of methemoglobinemia is not known. Our clinic is one of the centers in which circumcision has been widely practiced for many years. This retrospective study was planned to determine the incidence of methemoglobinemia due to prilocaine in our patients.

Materials and Methods

Ethics approval by the institutional review board of our hospitals had been obtained for data collection and analysis (number: 21/02/2018/1771). Before POP surgery, all patients were requested to sign an informed consent approved by the Institutional Review Board of University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital. Medical records of 2.431 patients circumcised between 2008 and 2015 in University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Turkiye were evaluated retrospectively. The mean age of the patients was 7.2 years (ranging from 14 days to 13 years). None of the patients had any additional disease. Furthermore, no pathology had been detected during prenatal follow-ups or delivery. Prior to all circumcision procedures, 1.5 mg/kg of local anesthetic was subcutaneously administered to the penis root at 4-5 points from a 20 mL vial containing 400 mg (20 mg/mL) of prilocaine (2%). All surgeries were performed under local anesthesia.

Results

Of the 2.431 patients included in the study, two (0.008%) developed methemoglobinemia requiring treatment. According to the medical records, five patients (0.021%) developed mild bruising on the hands, feet and sides of the lips. However, no medical interventions were undertaken for these five patients since there was no problem in their general condition.

Case 1 was a 105-day-old infant who was hospitalized for the treatment of methemoglobinemia that developed after circumcision. He had been delivered via spontaneous vaginal route and had a birth weight of 3.100 g. Early circumcision was planned due to phimosis, but he had no other health problems in the previous 105 days. Two hours after circumcision, the parents brought the infant to the emergency department with the complaint that the whole body of the infant was bruised. On arrival, the child's blood pressure was 85/55 mmHg, respiratory rate was 33/min, and heart rate was 130/min. SO_2 was measured as 70% using a pulse oximeter. Arterial blood gas pH was 7.43, HCO_3 was 20 mEq/L, PCO_2 was 36 mmHg, and PO_2 was 94 mmHg. The MetHb level was 41.5%. According to the complete blood count analysis, the Hb level was 11.2 g/dL, hematocrit was 34.6%, and thrombocyte was 245000/mm^3. Based on these findings, methemoglobinemia was considered, and 100 mg/day of ascorbic acid and methylene blue was administered to the patient via 1 cc/kg/dose intravenous infusion from a 1% solution. Thirty minutes after the administration of methylene blue, pH was measured as 7.36, HCO_3 as 22 mEq/L, PCO_2 as 34.3 mmHg, PO_2 as 98 mmHg, and MetHb as 5.4%. At this stage, the patient's cyanosis completely resolved, and he had a normal

glucose-6-phosphate dehydrogenase (G6PD) level. The patient was monitored for 24 hours and discharged without cyanosis and with all vital signs stabilized.

Case 2 was a 35-day-old infant delivered through vaginal route weighing 2.950 g. Circumcision had been planned in the early period due to the development of pathological phimosis with no other health problems occurring in the first 35 days. Approximately one hour after circumcision, he was admitted to the emergency department due to his entire body being bruised. Upon admission, his blood pressure was 90/55 mmHg, respiratory rate was 34/min, and heart rate was 126/min. SO_2 was found to be 72% using a pulse oximeter. Arterial blood gas pH was 7.37, HCO_3 was 20 mEq/L, PCO_2 was 36 mmHg, and PO_2 was 95 mmHg. The MetHb level was measured as 42%. Complete blood count assessment showed that the Hb level was 11.0 g/dL, hematocrit was 33.2%, and thrombocyte was 215000/mm^3. These findings indicated methemoglobinemia; thus, 100 mg/day of ascorbic acid and methylene blue was administered to the patient via intravenous infusion as 1 cc/kg/dose of a 1% solution. Thirty minutes after methylene blue was administered, pH was found to be 7.36, HCO_3 21 mEq/L, PCO_2 35.4 mmHg, PO_2 97 mmHg, and MetHb level 5.6%. At this time, the patient's cyanosis had completely resolved. The patient also had a normal G6PD level. After being observed for a further 24 hours, the patient was discharged without cyanosis and with all vital signs stable.

Five other patients aged 14 days, 43 days, 63 days, 82 days and 1.5 years were found to have mild bruising only in hands and feet, and, thus, were diagnosed with methemoglobinemia. All these patients were discharged without any medical intervention after close observation in which no complication was identified.

Discussion

Methemoglobinemia can be seen in two forms, congenital or acquired. The diagnosis of congenital methemoglobinemia is based on the level of the intracellular cytochrome b5 reductase enzyme. A large number of agents are known to cause the development of acquired methemoglobinemia with most implicated examples being sulfonamides, local anesthetic drugs, and nitrate-containing vegetables (5). Circumcision is a commonly performed religious practice in Turkiye, and prior to this procedure, prilocaine is generally used to manage pain.

Four types of local anesthetics have been reported to cause methemoglobinemia; prilocaine, benzocaine, lidocaine, and tetracaine. It is well known that ortho-toluidine, a metabolite of prilocaine, leads to Hb oxidation (6,7). In clinical practice, the injectable form of prilocaine (Citanest®) and prilocaine-lidocaine (EMLA®) cream are the two most commonly used commercial preparations. At therapeutic doses (1-2 mg/kg/dose), prilocaine causes MetHb formation at levels that are usually too low to induce cyanosis, however, the risk of methemoglobinemia increases with the increased dose (8,9).

The main reasons why children are more susceptible to methemoglobinemia include inadequate soluble form of the nicotinamide adenine dinucleotide (NADH)-cytochrome b5 reductase enzyme, which deoxidizes MetHb and facilitates oxygen transport, fetal Hb being more sensitive to oxidation, and intestinal colonization with nitrate-producing bacteria. The risk of developing methemoglobinemia is higher particularly in newborns and infants since their MetHb reductase enzyme activity is low (10,11). However, in the literature, the development of methemoglobinemia has also been reported after topical use of local anesthetics at therapeutic doses, as in our patients (12,13).

Methemoglobinemia associated with local anesthetics can lead to life-threatening conditions (e.g., coma, seizures, respiratory depression, and shock) and permanent damage (e.g., hypoxic encephalopathy and myocardial infarction), and even death (14). Congenital heart diseases, pulmonary diseases, anemia and serious infections should be considered in the differential diagnosis of cases presenting with cyanosis suspected of having methemoglobinemia. In the absence of heart and lung diseases, cyanosis that does not respond to high-flow O_2 should be considered as an indication of methemoglobinemia. MetHb is normally formed in small quantities and is rapidly destroyed by the NADH-MetHb reductase (cytochrome b5 reductase) enzyme in the erythrocytes, however, congenital methemoglobinemia patients have a deficiency of this enzyme. "NADPH-MetHb reductase" is another MetHb reductase enzyme system that uses NADPH as a cofactor. This system is physiologically inactive but it becomes active in the presence of redox components. The mechanism of action of methylene blue in the treatment of methemoglobinemia is through the NADPH-MetHb reductase system. NADPH required for an effective treatment is derived from the hexose monophosphate pathway, therefore, the G6PD level should be normal (15,16). Thus, in individuals with G6PD deficiency, methylene blue does not have a role in the treatment of methemoglobinemia.

Since the G6PD level seen in our patients was normal, the methylene blue treatment was beneficial. In the treatment, the main objective is to terminate the application of the agent, which is primarily responsible for the condition. If the level of MetHb is less than 20%, recovery can be achieved by stopping the causative drug, but newborns and infants may still require treatment. If the MetHb level is greater than 70%, hyperbaric O_2 therapy and exchange transfusion can be undertaken (17,18). Since case 1 was an infant with a MetHb value of 41.5% and his cyanosis did not improve after the application of methylene blue, we administered 100 mg/day ascorbic acid. Since cyanosis continued to be observed, without waiting for an ascorbic acid

response, 1% methylene blue was applied by slow infusion under monitoring. Approximately half an hour after the administration of methylene blue, cyanosis was reduced and the MetHb level decreased to 5.4%. It should also be noted that ascorbic acid can be safely used in the treatment of methemoglobinemia when methylene blue is not available.

Conclusion

As a local anesthetic, prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Ethics

Ethics Committee Approval: The approval was obtained from University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital (number: 21/02/2018/1771).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A., G.Y., Concept: D.A., Design: D.A., M.O.Ş., Data Collection or Processing: D.A., G.Y., M.O.Ş., Analysis or Interpretation: D.A., M.O.Ş., Literature Search: D.A., M.O.Ş., Writing: D.A., G.Y., M.O.Ş.

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Is Anti-platelet Treatment Necessary for Penile Mondor's Disease?

Penil Mondor Hastalığında Anti-platelet Tedavi Gerekli midir?

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What's known on the subject? and What does the study add?

Literature regading treatment of penile Mondor's disease (thrombophlebitis of dorsal penile vein) is heterogeneous. Therefore, treatment is not standardized. With this study, we showed there is no need for anti-platelet treatment for penile Mondor's disease as thrombus resolution rates did not differ in antibiotic vs antibiotic + anti-platelet groups.

Abstract

Objective: The aim of this study was to determine if anti-platelet treatment would have any effect on the rate and duration of resolution in penile Mondor's disease.

Materials and Methods: A retrospective review of patients diagnosed with Mondor's disease between 2014 and 2018 was conducted. The patients were divided into two groups with regard to anti-platelet treatment. Age, initial symptom, medications [short-term fluoroquinolone antibiotics (Ab) ± low-dose acetyl salicylic acid (ASA)], and erectile function scores were evaluated. Moreover, ultrasonographic findings (location and length of thrombus) were noted.

Results: A total of 14 patients were diagnosed with penile Mondor's disease. The mean age of the patients was 36 years (range: 18-66). The initial symptom was penile induration in all patients. Thrombus was located distally in 3, mid penile in 5 and proximally in 6. The median length of thrombus was 20 mm (range: 10-50 mm). In 13 patients (92.8%), thrombus resolved and patients became symptom-free. The median time to resolution was 3 weeks (range: 2-7). Eight patients received Ab + ASA while 5 received Ab only. There was no statistically significant difference between the groups in terms of the rate and duration of resolution (p=1.00 and 0.55, respectively).

Conclusion: Our results showed that anti-platelet treatment may be unnecessary for the treatment of penile Mondor's disease.

Keywords: Penile, Mondor's disease, Anti-platelet, Treatment

Öz

Amaç: Çalışmamızın amacı anti-platelet tedavinin penil Mondor hastalığında rezolüsyon oranına ve rezolüsyon süresine olan etkisini araştırmaktır.

Gereç ve Yöntem: Kliniğimizde 2014-2018 yılları arasında penil Mondor hastalığı tanısı almış hastaların dosyaları geriye dönük olarak tarandı. Hastalar anti-platelet tedavi alıp almamalarına göre iki gruba ayrıldı. Yaş, başvuru şikayeti, verilen tedavi [kısa süreli florokinolon antibiyotikler (Ab) ± düşük doz asetil salisilik asit (ASA)] ve erektil fonksiyon skorlarına ait bilgiler kaydedildi. Ek olarak, ultrasonografi bulguları (trombüs uzunluğu ve yerleşimi) not edildi.

Bulgular: Toplamda penil Mondor hastalığı tanısı almış 14 hasta çalışmaya dahil edildi. Hastaların ortalama yaşları 36 (18-66 aralığında) olarak bulundu. Tüm hastalarda başvuru şikayeti peniste şişlik olarak saptandı. Trombüs, 3 hastada distalde, 5 hastada mid penil ve 6 hastada proksimal yerleşimdeydi. Medyan trombüs boyutu 20 mm (10-50 mm aralığında) idi. Trombüs toplamda 13 hastada (%92,8) rezolüsyona uğradı ve hastaların şikayetleri tamamen geriledi. Medyan rezolüsyon süresi 3 hafta (2-7 hafta arası) olarak bulundu. Çalışmamızda, 8 hasta Ab + ASA tedavisi almış iken 5 hastanın yalnızca Ab tedavisi almış olduğu saptandı. İki grup arasında rezolüsyon oranı ve rezolüsyon süresi arasında istatistiksel anlamlı fark bulunmadı (sırasıyla, p=1,00 ve 0,55).

Sonuç: Çalışmamızın sonuçlarına göre penil Mondor hastalığının tedavisinde anti-platelet tedavi gereksiz olabilir.

Anahtar Kelimeler: Penis, Mondor hastalığı, Anti-platelet, Tedavi

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Introduction

Named after French surgeon Henri Mondor, Mondor's disease (MD) has been described in late 1930s as thrombophlebitis of the superficial veins of the chest wall (1). However, thrombophlebitis of any location of the body can be called as MD. On the other hand, penile MD, described two decades later, is the thrombophlebitis of the superficial dorsal penile veins (2). It is relatively rare, benign, and usually self-limiting with possible spontaneous resolution. Literature regarding penile MD is limited due to a huge number of case reports but no larger scale series.

Although the exact cause is unknown, some conditions that might lead to MD have been postulated. These include a hypercoagulative state, vasculitis, cancer and sexually-transmitted diseases (3). Additionally, lymphangitis as the underlying pathology has also been reported (4). The common etiologic factor for penile MD has been proposed to be trauma (vigorous/prolonged sexual intercourse, masturbation, etc.) (5). The main complaint of the patients with penile MD is induration on the back of the penis with or without pain (6).

As penile MD is usually self-limiting and tends to resolve spontaneously, the treatment for the disease has been conservative in cases when there is no underlying cause. However, non-steroidal anti-inflammatory medication, anticoagulant ointment and antibiotic (Ab) prescription may be suitable for those with prominent inflammation (3). Eventually, data regarding any drugs that would change the course of the disease is scarce. The aim of this study was to evaluate if anti-platelet treatment would have any effect on the rate and duration of resolution in penile MD.

Materials and Methods

After obtaining approval from the local ethics committee (Konya Training and Research Hospital, number: 06.09.2018:17-02), a retrospective review of patients diagnosed with MD between 2015 and 2018 was conducted. Due to retrospective nature of the study informed consents were not obtained. Age, initial symptom, medications, and erectile function scores (IIEF-5) were evaluated. The patients received either a short course treatment with fluoroquinolone Ab (500 mg twice daily for 5 days) alone or with a combination of Ab and low-dose anti-platelet [acetyl salicylic acid (ASA) 1x100 mg daily] until resolution of thrombus. The patients were divided into two groups with regard to anti-platelet treatment status. All patients underwent Doppler ultrasonography (US) for confirmation of the diagnosis. Moreover, ultrasonographic findings (location and length of thrombus) were noted. The patients were followed up weekly and those with no sign of induration during the follow-up were regarded as having complete resolution. Time to resolution (weeks) and resolution rates were determined.

Statistical Analysis

The GraphPad Prism software was used for statistical analysis. Continuous variables were analyzed using Student's t-test where categorical variables were analyzed using Fischer's exact test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 14 patients were diagnosed with penile MD. The mean age of the patients was 36 years (range: 18-66). The initial symptom was penile induration in all patients. Doppler US results showed that thrombus was located in the distal penile shaft in 3, in the mid-shaft in 5 and, in the proximal shaft in 6. The median length of thrombus was 20 mm (range: 10-50 mm). In 13 patients (92.8%), thrombus resolved and patients became symptom-free. A 66-year-old patient in Ab + ASA group did not show resolution after 9 weeks and has been lost to follow-up. The median time to resolution was 3 weeks (range: 2-7 weeks). In our study, nine patients received Ab + ASA while 5 received Ab only. There was no statistically significant difference between the groups in terms of the rate and duration of resolution (p=1.00 and p=0.55, respectively). Median IIEF-5 scores of both groups were comparable (23.5 vs 24, p=0.45). There were two patients with co-morbidities in the Ab + ASA and none in Ab only groups. One of them had asthma and the other had hypertension that was controlled by a single calcium channel blocker. None of the patients had a history of thrombophilia. Table 1 summarizes data of the patients.

Discussion

Penile MD is actually not an infrequent disease with a prevalence of 1.4% (7). The main complaints of the patients are penile induration and pain (8). However, it is a relatively under-diagnosed problem, possibly due to a self-limiting and benign course as well as lack of severe symptoms. Therefore, there are no large-scale studies on penile MD and its treatment. Although it has a high resolution rate, patients' anxiety is an important aspect of the disease that drives physicians to prescribe medications. As penile MD is a thrombophlebitis, the main goal of the treatment is to reduce inflammation and resolve thrombosis. Physicians tend to prescribe different types of medications such as antibiotics, anti-platelet agents, non-steroidal anti-inflammatory drugs, and topical heparinoid ointments (3). It has been reported that antibiotic use might be beneficial especially in patients with acute cellulitis (9). Second generation cephalosporins and Abs have been suggested, possibly due to their Gram-negative bacteria coverage (3). All

Table 1. Overview of patients

Patient number	Age	Location of thrombus	Length of thrombus (mm)	Co-morbidity	Treatment	Time to resolution (weeks)
#1	18	Proximal	20	None	Ab	3
#2	31	Proximal	20	None	Ab	3
#3	58	Proximal	20	None	Ab	4
#4	29	Mid penile	15	None	Ab	3
#5	35	Proximal	15	None	Ab	3
#6	33	Mid penile	25	None	Ab + ASA	4
#7	23	Mid penile	30	None	Ab + ASA	7
#8	29	Distal	10	None	Ab + ASA	2
#9	30	Proximal	25	Asthma	Ab + ASA	4
#10	66	Proximal	50	None	Ab + ASA	-
#11	53	Distal	20	HT	Ab + ASA	3
#12	38	Distal	20	None	Ab + ASA	4
#13	32	Mid penile	15	None	Ab + ASA	2
#14	20	Mid penile	10	None	Ab + ASA	2

Ab: Antibiotic, ASA: Acetyl salicylic acid, HT: Hypertension

patients were admitted in the acute phase of the disease and thus, a 5-day Ab regimen was used. There is no study to date that evaluates and/or compares treatment options in penile MD.

In our study, we compared two groups of patients with regard to medical treatment. One group of patients received short-course Ab only and the other received Ab and low-dose ASA. There were no statistically significant differences between the groups in terms of rate of resolution and time to resolution. Even though the sample size was small and the side effects of low-dose ASA is scarce, our findings may contribute to reducing overtreatment of penile MD.

The most common etiology is trauma (prolonged sexual intercourse). On the other hand, infections, inflammatory processes, recent surgery for adjacent tissues and cancer may lead to penile MD (10). It is necessary to determine the etiology and treat the patient accordingly. There were no cases in our cohort that were secondary to previously stated conditions, so our data most likely represents a population of patients developing penile MD due to trauma to the penis.

Penile Doppler US is also found to be a good tool to evaluate these patients (11). Magnetic resonance angiography has been also shown to help diagnose penile MD (12), however, in our study, all patients were easily diagnosed using Doppler US in addition to physical examination. Doppler US is also important to make a differential diagnosis between sclerosing lymphangitis of the penis and Peyronie's disease (7).

In their study, Ozkan et al. (3) showed that MD was not associated with erectile dysfunction or permanent deformation of the penis. Our study was not designed to address this issue, but our findings include a normal IIEF-5 score in both groups before treatment. As most of our patients showed resolution of the thrombus and symptoms, it would not be naive to expect them to have no erectile dysfunction afterwards.

Study Limitations

Limitations of our study include retrospective design, lack of a control group, and small sample size. On the other hand, it is one of the few studies comparing two different treatments.

Conclusion

Our results showed that anti-platelet treatment may be unnecessary for the treatment of penile MD.

Ethics

Ethics Committee Approval: The approval was taken from the local ethics committee (Konya Training and Research Hospital, number: 06.09.2018:17-02).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.M.B., M.İ.D., Design: A.M.B., M.İ.D., Data Collection or Processing: A.M.B., M.İ.D., Analysis or Interpretation: A.M.B., M.İ.D., Literature Search: A.M.B., M.İ.D., Writing: A.M.B., M.İ.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Lower Urinary Tract Functions in Diabetic Patients

Diyabetik Hastalarda Alt Üriner Sistem Fonksiyonlarının Değerlendirilmesi

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What's known on the subject? and What does the study add?

Diabetes mellitus is a debilitating and costly disease with multiple serious complications. Lower urinary tract complications are among the most common complications of diabetes mellitus. Although these complications such as diabetic cystopathy and diabetic bladder dysfunction are very common, there is a lack of diabetes treatment guidelines about routine evaluation of lower urinary tract functions in this patient population. Our results indicates that the subgroups of diabetic patients with emphasized risk factors require a more detailed evaluation of lower urinary tract functions and the guidelines should pay more attention on this issue.

Abstract

Objective: In this study, we aimed to investigate the effect of diabetes-related metabolic changes and chronic complications on lower urinary tract (LUT) functions.

Materials and Methods: The study included 286 adult patients with type 1 and type 2 diabetes mellitus (DM). All patients' demographic data, diabetes-specific history, laboratory and physical examination findings were recorded. All the data were compared with uroflowmetric parameters and the scores of questionnaires used for evaluation of LUT symptoms and functions.

Results: In the presence of diabetic peripheral neuropathy (DPN), average urinary flow rate (Q_{ave}), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) score and the Overactive Bladder-questionnaire Short Form (OAB-q SF) score were significantly affected. In the presence of stage 3 or over diabetic nephropathy (DN), ICIQ-SF score was significantly higher. Also, in elderly group, Q_{ave} and OAB-q SF score were significantly affected. The Q_{ave} was lower both in patients who underwent any surgery due to diabetic complications and in patients with DM-related diseases. Q_{ave} and OAB-q SF score were significantly lower in males. Type 2 DM was associated with postvoid residual (PVR) increase and Q_{ave} decrease. Poor glycemic control was associated with lower OAB-q SF score. Finally, vitamin D deficiency was found to be associated with an increase in PVR volume.

Conclusion: The present study showed that DPN, stage 3 or over DN, aging, DM-related diseases and surgeries, male gender, type 2 DM, poor glycemic control and vitamin D deficiency cause a tendency to develop any kind of LUT dysfunction.

Keywords: Diabetes mellitus, Diabetic neuropathies, Lower urinary tract symptoms, Quality of life

Öz

Amaç: Bu çalışmanın amacı diyabete bağlı metabolik değişikliklerin ve kronik komplikasyonların alt üriner sistem (AÜS) fonksiyonları üzerine olan etkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya tip 1 ve tip 2 diabetes mellitus (DM) tanılı 286 erişkin hasta alındı. Tüm hastalara ait veriler retrospektif olarak tarandı. Tüm hastaların demografik bilgileri, diyabete özgü hastalık öyküleri, laboratuvar ve fizik muayene bulguları kaydedildi. Hastalara ait tüm veriler üroflovmetrik ölçüm sonuçları ve AÜS semptomu sorgu formlarından elde edilen skorlarla karşılaştırıldı.

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Presented in: The study has previously been presented in International Continence Society 47th Annual Meeting, Florence at 12-15 September 2017 as a e-poster presentation.

Bulgular: Diyabetik periferal nöropati (DPN) varlığında ortalama idrar akım hızının (Q_{ave}), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) skoru ve Overactive Bladder-questionnaire Short Form (OAB-q SF) skorunun anlamlı olarak etkilendiği saptandı. Evre 3 ve üzeri diyabetik nefropati (DN) varlığında ICIQ-SF skoru anlamlı olarak yüksek saptandı. Ayrıca yaşlı hasta grubunda Q_{ave} ve OAB-q SF skorunun anlamlı olarak azaldığı saptandı. Diyabetik komplikasyonlar nedeniyle cerrahi geçirenlerde ve DM ile ilişkili komorbid hastalığı olanlarda Q_{ave} anlamlı olarak düşük saptandı. Erkek hastalarda Q_{ave} ve OAB-q SF skoru anlamlı olarak düşük saptandı. Tip 2 DM'nin postvoid residual (PVR) volümde artış ve Q_{ave}'da azalma ile ilişkili olduğu saptandı. Kötü glisemik kontrolün OAB-q SF skorunda düşüş ile ilişkili olduğu gösterildi. Son olarak D vitamini eksikliğinin PVR volümde artış ile ilişkili olduğu saptandı.

Sonuç: Çalışmamızda DPN, evre 3 ve üzeri DN, ileri yaş, diyabetik komplikasyonlar nedeniyle geçirilmiş cerrahiler, DM ile ilişkili komorbid hastalıklar, erkek cinsiyet, tip 2 DM, kötü glisemik kontrol ve D vitamini eksikliği faktörlerinin diyabetik hastalarda AÜS disfonksiyonu gelişimine yatkınlık oluşturduğu saptanmıştır.

Anahtar Kelimeler: Diabetes mellitus, Diyabetik nöropati, Alt üriner sistem semptomları, Hayat kalitesi

Introduction

Diabetes mellitus (DM), which has an increased prevalence and common complications, is a serious health problem all over the world. It has many unfavourable effects on the lower urinary tract (LUT) due to being a systemic disease. It results in a wide spectrum of LUT symptoms (LUTS) with several pathophysiological mechanisms. The frequent symptoms are overactive bladder syndrome and detrusor dysfunction. It is believed that alterations in the severity and frequency of these symptoms are related to DM and its chronic complications (1,2,3,4,5,6). The aim of this study was to investigate the relationship between physio-pathological changes related to DM and LUT dysfunction.

Materials and Methods

A total of 286 patients with the diagnosis of type 1 and type 2 DM, who had been followed between January 2013 and January 2016 in the department of endocrinology at Ege University Faculty of Medicine, were enrolled in our study. One hundred and eighty six patients with the diagnosis of urethral stricture, bladder stone, benign prostatic hyperplasia (BPH), genitourinary infection or inflammation, previous genitourinary surgery, genitourinary radiation, urinary diversion, genitourinary malignancy or a neurologic condition were excluded. Data of 100 patients were analysed retrospectively. Age, sex and body mass index (BMI) were recorded as demographic parameters (Table 1). Type of DM, duration of DM, presence of DM-related diseases, previous surgery related to diabetic complications, presence of diabetic peripheral neuropathy (DPN), presence of diabetic nephropathy (DN), and presence of diabetic retinopathy (DR) were recorded as clinical parameters (Table 2). Fasting plasma glucose (FPG), serum glycosylated hemoglobin (HbA1c), serum vitamin D levels and calculated glomerular filtration rate (GFR) from serum creatinine were recorded as laboratory parameters (Table 3). Voided volume, average flow rate (Q_{ave}) and postvoid residual (PVR) volume were recorded as uroflowmetric parameters. International Prostate Symptom Score (IPSS), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and Overactive Bladder-questionnaire Short Form (OAB-q SF) scores were recorded as query form scores.

The voiding pattern, Q_{ave}, the voided volume and the PVR volume were taken into account when assessing the voiding functions of the patients. A PVR volume of less than 50 mL with appropriate flow rate was considered normal. Patients having a PVR volume of greater than 100 mL were considered to have diabetic bladder dysfunction (DBD). A cut-off value of a PVR volume greater than 50 mL but less than 100 mL and a bladder voiding efficiency (BVE) of less than 75% was used to identify patients with DBD (7). Using the voided volume and PVR volume, the BVE was calculated as follows: BVE=100% voided volume/(voided volume + PVR) (8). The conditions of the patients in terms of LUTS were evaluated using the Turkish version of the IPSS (9,10,11,12). The IPSS was used for quantification of the symptoms in diabetic patients, although it was developed to quantify LUTS in patients with BPH. However, it is well known that IPSS is not BPH-specific, and it is not unreasonable to use the IPSS for quantification of LUTS in diabetic patients (13). Patients with a IPSS score of ≥8 were considered to have clinically significant LUTS (14). The ICIQ-SF and OAB-q SF questionnaires were used for evaluation of overactive bladder

Table 1. Demographic data of participants

Parameter		Values, n (%)	Mean ± SD
Age (years)	18-54	52 (52)	50.5±16.6
	55-85	48 (48)	
Gender	Male	38 (38)	-
	Female	62 (62)	
BMI (kg/m²)	<25	38 (38)	28.5±8.3
	25-29.9	28 (28)	
	≥30	34 (34)	

BMI: Body mass index, SD: Standard deviation

syndrome and urinary incontinence (UI). The patients were divided into two groups according to age. The threshold age was set to 55 years (15). The threshold for long-term DM and short-term DM was set to 15 years (16). BMI was calculated by dividing weight in kilograms by height in meters squared for each participant [BMI=weight (kg)/height (m^2)]. Patients with a BMI of <25 kg/m^2 were considered normal, those with a BMI between 25-29.9 kg/m^2 were considered overweight and those with a BMI of ≥30 kg/m^2 were considered obese (17). Patients with a FPG of ≤130 mg/dL and/or a HbA1c value of ≤7% have achieved the glycaemic control goals, thus they were considered well-controlled diabetic patients (18). The incidence of diabetic complications is significantly increased in patients with a GFR of <60 mL/min/1.73 m^2 (stage 3 or over DN) (18). Therefore, in our study, our patients were divided into two groups: those with a GFR <60 mL/min/1.73m^2 and GFR ≥60 mL/min/1.73m^2. GFR was calculated using the Cockroft-Gault formula (calculated creatinine clearance=[(140-age) x 1.23 x body weight (kg)/ serum creatinine (mg/dL)] x 0.85 if female) (19). The presence of DPN was determined by 10-g monofilament test. Sensory evaluation was made by pressing on the three points of the sole of both feet (the thumb and the first and the fifth metatarsals) until the monofilament becomes "C" shaped. Detection of sensation loss at one or more points was considered loss of protective sensation (18). Presence of DR was determined by indirect ophthalmoscopy and all patients with pre-proliferative DR, proliferative DR and macular edema were considered to have any kind of DR (18). Patients with a vitamin D level of >20 ng/mL were considered normal, those with a level 10-20 ng/mL were considered with vitamin D insufficiency and those with a level of <10 ng/mL were considered with vitamin D deficiency (20,21,22). Macrovascular diseases, such as coronary artery disease, peripheral artery disease and carotid artery disease, were considered as having DM-related diseases. Major surgeries, such as coronary artery by-pass grafting and amputation, were considered surgeries that may be associated with diabetic complications.

The statistical analysis was performed by comparing all the recorded data of the patients having uroflowmetry measurement values, PVR volume, IPSS scores, ICIQ-SF scores and OAB-q SF scores.

Statistical Analysis

First of all, the frequency tables were prepared and then the numbers and the percentages belonging to all variables were put in tables. The descriptive statistical data were calculated for continuous variables. The cross-tabulation and the chi-square analysis were used for the analysis of the categorical variables. It was understood that variables that were smaller than the p value of 0.05 were not normally distributed in the Shapiro-Wilk normality test. For this reason, the Spearman's correlation coefficient was used in the analysis of the correlation for the continuous variables. The Mann-Whitney U test was used in order to compare two independent groups. The Kruskal-Wallis test was used for normal non-scattering variables and ANOVA for normal scattering variables. The significance level of all the hypothesis tests was 0.05. For the statistical analysis, IBM SPSS statistical package program version 21.0 was used.

Results

The age distribution was as follows: 52% of the patients were in the 18-54 age group, while 48% were in the 55-85 age group. The mean age of the whole group was 50.5±16.6 years. 62% of the patients were female and 38% were male. When the patients were grouped according to BMI, 38% of the patients were within the normal weight range, 28% were overweight and 34% were obese. The mean BMI of all patients was 28.5±8.3 kg/m^2 (Table 1). 27% of the patients were in type 1 DM group while 73% were in type 2 DM group. According to the duration of DM, 71% of the patients were in the group of short-term DM while 29% were in the group of long-term DM. The mean duration of DM was 13.2±9.2 years. According to the presence of additional DM-related diseases, there was at least one DM-related disease in 69% of the patients in whom 31% had no comorbidity. 52% of the patients did not undergo any surgical intervention owing to a diabetic complication; on the other hand, 48% of them had at least one surgical intervention due to a diabetic complication. With respect to the neurological examination, 59% of the patients were found to be normal and 41% of them had DPN. With respect to the GFR value, it was

Table 2. Clinical parameters of participants

Parameter		Values, n (%)	Mean ± SD
Type of DM	Type 1 DM	27 (27)	-
	Type 2 DM	73 (73)	
Duration of DM (years)	1-15	71 (71)	13.2±9.2
	>15	29 (29)	
DM-related diseases,	No	31 (31)	-
	Yes	69 (69)	
DM-related surgeries	No	52 (52)	-
	Yes	48 (48)	
Presence of DPN	No	59 (59)	-
	Yes	41 (41)	
Presence of DN (≥ stage 3)	No	87 (87)	-
	Yes	13 (13)	
Presence of DR	No	62 (62)	-
	Yes	38 (38)	

DM: Diabetes mellitus, DPN: Diabetic peripheral neuropathy, DN: Diabetic nephropahy, DR: Diabetic retinopathy, SD: Standard deviation

found that 13% of the patients had stage 3 or over DN (GFR <60 mL/min/1.73 m²) and 87% of them had stage 1 or 2 DN (GFR ≥60 mL/min/1.73 m²). Ophthalmologic evaluation showed that 62% of the patients were normal and 38% of them had DR (Table 2). According to FPG, 34% of the patients were found to have well-controlled DM (FPG 80-130 mg/dL) and 66% were found to have poorly-controlled DM (FPG ≥130 mg/dL). According to HbA1c value, 27% of the patients had achieved glycaemic control goal (HbA1c ≤7%) and 73% of the patients were in poor glycaemic control (HbA1c >7%) group. 67% of the patients had vitamin D deficiency, 17% had vitamin D insufficiency and 16% had normal vitamin D levels (Table 3).

The PVR measurement results showed that 65% of the patients had a PVR volume <50 mL, 19% had PVR volume between 50 mL and 100 mL and 16% had a PVR volume >100 mL. According to the DBD status, 79% of the patients did not have voiding dysfunction and 21% had DBD. According to the IPSS score, 55% of the patients had clinically significant LUTS while 45% had no clinically significant LUTS (Table 4). The mean ICIQ-SF score was 3.4±5.2. The mean ICIQ-SF quality of life (QoL) score was 1.4±2.7. The mean OAB-q SF symptom severity score was 27.5±21.0% and the mean OAB-q SF QoL score was 81.6±18.8%.

Table 3. Laboratory parameters of participants

Parameter		Values, n (%)	Mean ± SD
FPG (mg/dL)	80-130	34 (34)	172.3±73.9
	>130	66 (66)	
HbA1c (%)	≤7	27 (27)	8.8±2.4
	>7	73 (73)	
Vitamin D (ng/mL)	<10	67 (67)	25.4±26.4
	10-20	17 (17)	
	>20	16 (16)	
GFR (mL/min/1.73 m²)	<60	13 (13)	110.5±43.2
	≥60	87 (87)	

FPG: Fasting plasma glucose, HbA1c: Serum glycosylated hemoglobin, GFR: Glomerular filtration rate, SD: Standard deviation

Table 4. Postvoid residual, diabetic bladder dysfunction status and International Prostate Symptom Scores of participants

Parameter		Values, n (%)	Mean ± SD
PVR (mL)	<50	65 (65)	
	50-100	19 (19)	60.9±101.0
	>100	16 (16)	
DBD	No	79 (79)	-
	Yes	21 (21)	
IPSS	0-7	45 (45)	
	8-19	42 (42)	9.6±7.2
	20-35	13 (13)	

PVR: Postvoid residual, DBD: Diabetic bladder dysfunction, IPSS: International Prostate Symptom Score, SD: Standard deviation

When the presence of DPN was evaluated, Q_{ave} in the DPN presence was found to be 34% lower ($p<0.05$). Again, in the presence of DPN, the ICIQ-SF total score was found to be 2.1 times higher than in the non-DPN group (p=0.015). ICIQ-SF QoL score was significantly higher in DPN group (p=0.038). In the presence of DPN, the OAB-q SF symptom severity score was 1.4 times higher than in the non-DPN group (p=0.022). In addition, in the presence of DPN, the OAB-q SF QoL score was 12% lower than in the non-DPN group (p=0.003).

When the GFR-related data were analysed, the ICIQ-SF total score was significantly higher in the group with low GFR (p=0.020). Also, the ICIQ-SF QoL score was significantly higher in the group with low GFR, thus, the QoL was significantly worse (p=0.011).

When the age-related parameters were examined, Q_{ave} was found to be 24% lower in the elderly group than in the younger group (p=0.008). In addition, the OAB-q SF symptom severity score was significantly increased (p=0.007) and the OAB-q SF QoL score was significantly decreased (p=0.002) in the elderly group.

When the history of surgeries related to diabetic complications was assessed, Q_{ave} was 24% lower in patients who underwent surgery due to diabetic complications (p=0.010). In addition, DBD was found to be 4.7 times more frequent in the group with a history of surgery (p=0.006). Also, Q_{ave} was found to be 26% lower in patients with additional DM-related disease (p=0.010).

When the gender-related parameters were examined, it was found that Q_{ave} in male patients was 34% lower than that in females ($p<0.05$). In addition, the OAB-q SF QoL score in male patients was found to be significantly lower than in females (p=0.035).

In terms of type of DM, it was found that type 2 DM was significantly associated with PVR increase (p=0.047). Q_{ave} was also 26% lower in the patients with type 2 DM (p=0.003).

According to the results of HbA1c analysis, the OAB-q SF QoL score was found to be 10% lower in the high HbA1c group (p=0.026). According to the results of analysis on vitamin D, PVR was significantly higher in the group with vitamin D deficiency (p=0.006) (Table 5).

Discussion

The main goal of our study was to investigate the relationship between DM and LUT functions which has been investigated by many authors (3,4,6,23). The generally accepted view in this regard is that pathologies caused by DM at the microvascular level, as well as DM-related metabolic changes, affect LUT functions in a certain way. DM causes changes in the mass,

Table 5. Parameters associated with lower urinary tract functions

DPN				
		No	Yes	p value
Q_{ave} (mL/s)		11.6±0.7	7.6±0.7	0.0002
ICIQ-SF total score		2.4±0.5	5.0±0.9	0.015
ICIQ-SF QoL score		1.0±0.3	1.9±0.4	0.038
OAB-Q SF symptom severity score (%)		23.6±2.5	33.1±3.4	0.022
OAB-Q SF QoL score (%)		86.1±1.9	75.1±3.4	0.003
DN				
		No	Yes	
ICIQ-SF total score		3.0±0.5	6.1±1.4	0.02
ICIQ-SF QoL score		1.2±0.2	3.0±0.9	0.011
Age (years)				
		18-54	55-85	-
OAB-Q SF symptom severity score (%)		22.6±2.7	32.9±3.1	0.007
OAB-Q SF QoL score (%)		85.7±2.3	77.2±2.8	0.002
History of surgery				
		No	Yes	
Q_{ave} (mL/s)		11.3±0.7	8.5±0.7	0.01
Voiding dysfunction	**No**	47	32	0.006
	Yes	5	16	
DM-related comorbid disorders				
		No	Yes	
Q_{ave} (mL/s)		12.2±1.1	9.0±0.6	0.01
Gender				
		Male	Female	
OAB-Q SF QoL score (%)		75.4±3.8	85.4±1.8	0.035
Type of DM				
		Type 1 DM	Type 2 DM	
Q_{ave} (mL/s)		12.3±0.9	9.1±0.6	0.003
HbA1c (%)				
		≤7	>7	
OAB-Q SF QoL score (%)		88.0±2.6	79.2±2.3	0.026

DPN: Diabetic peripheral neuropathy, Q_{ave}: Average urinary flow rate, ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form, QoL: Quality of life, OAB-Q SF: Overactive Bladder-quastionnaire Short Form, DN: Diabetic nephropathy, DM: Diabetes mellitus, HbA1c: Serum glycosylated hemoglobin

compliance and parenchyma composition of bladder tissue (24). The main pathologies that have been most searched and associated with DM are OAB syndrome, detrusor hyporeflexia, detrusor areflexia, urge incontinence and stress UI. These pathologies can be put under the diabetic cystopathy (DC) framework.

In diabetic patients, LUTS is insidious and often patients with DC do not notice this. Most of these patients show delayed clinical presentation after decompensation has developed (25). However, in diabetic patients, LUT dysfunction may also occur without LUTS, and LUTS alone may not be used to predict diabetic LUT dysfunction (13). Liu and Daneshgari (24) have detected that more than 50% of diabetic patients had LUT dysfunction although they were asymptomatic. DC is a condition that must be detected before it becomes symptomatic because it has an insidious onset and it causes many permanent anatomical and functional disorders until it becomes symptomatic (26).

It is well known that one of the most important factors in the etiopathogenesis of DC is DPN. DM is a disease that causes peripheric and autonomic neuropathy over time and eventually it ends up with deterioration of LUT functions. In a study by Bansal et al. (1) published in 2011, a significant relationship between electrophysiologically proven DPN and urodynamically proven DC was reported. In our study, the pathology which had

the strongest relationship with LUT dysfunction was found to be DPN. Our statistical analysis showed that Q_{ave} was 34% lower in the DPN presence ($p<0.05$). Again, in the presence of DPN, the ICIQ-SF total score was found to be 2.1 times higher than in non-DPN group (p=0.015) and ICIQ-SF QoL score was significantly higher in the DPN group (p=0.038). Also, our study showed that in the presence of DPN, the OAB-q SF symptom severity score was 1.4 times higher than in the non-DPN group (p=0.022). In addition, in the presence of DPN, the OAB-q SF QoL score was 12% lower than in the non-DPN group (p=0.003). According to these results, very strong evidence has been obtained by showing the relationship between DPN and LUT dysfunction.

The relationship between DN and LUTS is another issue being investigated in the literature. In patients with DM-related complications, such as retinopathy or nephropathy, the incidence of LUTS has been reported to be 20% higher than in patients without complications (27). In our study, when GFR-related data were analysed, the ICIQ-SF total score was significantly higher in the group with low GFR (p=0.020). Also, ICIQ-SF QoL score was significantly higher in the group with low GFR, indicating that the QoL was significantly worse (p=0.011). According to these findings, it can be said that stage 3 or over DN creates a tendency to UI in these patients and severely impairs QoL.

Age is one of the demographic parameters that may be closely associated with LUT functions in diabetic patients. In our study Q_{ave} was found to be 24% lower in the elderly group than in the younger group (p=0.008). In addition, the OAB-q SF symptom severity score was significantly increased (p=0.007) and the OAB-q SF QoL score was significantly decreased (p=0.002) in the elderly group. Liu et al. (28) showed that the prevalence of OAB was 2.4-4.2 times higher in type 2 DM patients who were older than 50 years. Also, Bani-issa et al. (2) showed that age, duration of DM and obesity were the most significant risk factors for all types of UI.

DM-related diseases and surgical interventions related to diabetic complications are the signs of the poorly controlled DM. In our study Q_{ave} was found to be 26% lower in patients with additional DM-related diseases (p=0.010). Also, Q_{ave} was 24% lower in patients who underwent surgery due to diabetic complications (p=0.010). In addition, DBD was found to be 4.7 times more frequent in the group with surgical history (p=0.006). Based on our findings, it can be assumed that surgical interventions due to a diabetic complication and the presence of DM-related diseases may be significant predictors of LUT dysfunction.

The prevalence of vitamin D deficiency in diabetic patients was evaluated by Al-Timimi and Ali (32) in a study conducted in 2013. They found that low vitamin D levels were found in 2/3 of patients with poor glycaemic control and prolonged type 2 DM. Similarly, Isaia et al. (33) reported that vitamin D deficiency was more common in diabetic patients. Our results showed that 67% of the patients had vitamin D deficiency, 17% of them had vitamin D insufficiency and 16% of them had normal vitamin D levels. PVR was significantly higher in the group with vitamin D deficiency (p=0.006). It is known that high PVR is an important cause of LUTS and it is the result of many LUT dysfunctions. According to our findings, it can be said that vitamin D deficiency has a significant effect on LUT functions.

The duration of DM is an important predictive factor for microvascular and macrovascular complications of DM (18). Several reports showed a relationship between duration of DM and LUTS. Bani-issa et al. (2) showed that longer duration of DM was associated with UI in type 2 diabetic women. Yu et al. (34) showed that a duration of DM ≥20 years was associated with voiding difficulty in female patients. Also Beylot et al. (35) showed that the duration of DM increased the risk of UI. Although our results did not show a significant association between the duration of DM and any kind of LUTS, there is strong evidence in the literature on this issue. The reason for the insignificant finding regarding the association between the duration of DM and any kind of LUTS in our study may be the limited number of patients involved.

Study Limitations

The limiting factors in our study can be put forward as the retrospective design and relatively limited number of patients.

Conclusion

The results obtained from our study showed that presence of DPN and a DN higher than stage 2, age ≥55, previous surgery history related to diabetic complications, presence of DM-related diseases, male gender, diagnosis of type 2 DM, poor glycaemic control and presence of vitamin D deficiency were the predisposing factors for developing any kind of LUT dysfunction in diabetic patients. Finally, we recommend that evaluation of LUT should be done as a routine part of evaluation for diabetic patients considering the risk factors even if they are asymptomatic. The guidelines on DM management should pay more attention on this issue.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Due to retrospective nature of the study, no written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ş., I.Y.Ş., C.Ö., Design: A.Ş., I.Y.Ş., Data Collection or Processing: Ü.E., I.Y.Ş., Analysis or Interpretation: Ü.E., F.K., Literature Search: Ü.E., A.Ş., Writing: Ü.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
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Enterovesical Herniation: A Rare Complication After Transurethral Resection of Bladder Tumor

Enterovezikal Herniasyon: Mesane Tümörü Transüretral Rezeksiyonu Sonrası Nadir Görülen Bir Komplikasyon

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Abstract

Enterovesical herniation through an acquired bladder wall defect after transurethral resection is an exceedingly rare complication. Small bladder perforations may go unrecognized after transurethral resection as adherent bowel loops seal the defect. We present a very rare case of internal herniation of both small bowel and sigmoid colon into the urinary bladder following transurethral resection of a bladder tumor. Magnetic resonance imaging revealed herniation of bowel loops into the lumen of the urinary bladder through a defect in the dome. On exploratory laparotomy, internal herniation of the ileum and sigmoid colon through a defect in the superior wall of the urinary bladder was found.
Keywords: Bladder tumor, Transurethral resection, Internal hernia

Öz

Transüretral rezeksiyon sonrası gelişen mesane duvar defekti ile ilişkili enterovezikal herniasyon, son derece nadir görülen bir komplikasyondur. Transüretral rezeksiyon sonrası küçük mesane perforasyonları, yapışık barsak anslarının defekti kapatması nedeniyle tanınamayabilir. Bu çalışmada, bir mesane tümörünün transüretral rezeksiyonunu takiben mesane içine hem ince barsak hem de sigmoid kolonun internal herniasyonuna dair çok nadir bir olgu sunulmuştur. Kubbedeki bir defekt üzerinden barsak anslarının mesane lümenine doğru herniasyonu manyetik rezonans görüntüleme ile görüntülendi. Laparotomi araştırmasında, mesane üst duvarındaki bir defektten ileum ve sigmoid kolonun internal herniasyonu saptandı.
Anahtar Kelimeler: Mesane tümörü, Transüretral rezeksiyon, İnternal herni

Introduction

Transurethral resection of bladder tumor (TURBT) is the initial and most commonly performed surgery for bladder tumor (1). Although this endourological procedure is typically safe and well-tolerated, the surgeon should be vigilant during surgery to avoid complications such as bladder perforation. Internal herniation of the bowel through an unrecognized iatrogenic rent in the bladder wall is a rare but recognized complication. Only 7 cases of enterovesical herniation have been reported previously in the literature making it one of the most uncommon causes of internal hernia (2). We present a very rare case of internal herniation of the small bowel along with Richter's herniation of the sigmoid colon into the urinary bladder following TURBT.

Case Presentation

A 36-year-old man presented with urinary symptoms of enterovesical fistula, such as fecaluria and pneumaturia, 3 weeks after TUR of bladder tumor. It was associated with burning micturition and dysuria. Abdominal examination revealed an approximately 6 cm x 6 cm globular lump in the suprapubic region that was persistent after per-urethral catheterization. There were no signs of generalized peritonitis or intestinal obstruction. Digital rectal examination was performed and rectal mucosa was found to be normal. Past history revealed that he had undergone TUR of a 2.28 cm x 1.19 cm bladder tumor involving the posterior wall of bladder 3 weeks ago. No iatrogenic bladder perforation was documented during the

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procedure. Enterovesical fistula was suspected and magnetic resonance imaging (MRI) of the pelvis was performed instead of contrast-enhanced computed tomography (CT) to delineate the fistula tract as the serum creatinine was marginally above baseline. MRI showed herniation of bowel loops into the lumen of the urinary bladder through a defect in the dome with conglomerated gut loops in the supra-vesical region as a possible sequel of intraperitoneal bladder perforation (Figure 1). Cystoscopy demonstrated herniated wall of the bowel through a defect in the antero-superior aspect of the bladder with overlying debris; mucosa over the trigone and posterior wall was normal. A loop transverse colostomy was performed initially at presentation for temporary diversion of the enterovesical fistula. Exploratory laparotomy was performed 6 weeks later when faecaluria had subsided and urine was sterile. Internal herniation of a loop of the ileum anteriorly along with Richter's hernia of the sigmoid colon posteriorly through the same defect in the superior wall of the urinary bladder was found (Figure 2). The gut loops were incarcerated into the bladder with severe surrounding inflammation. A portion of irreducible herniating loop of the small bowel and sigmoid colon was resected along with excision of a part of the bladder wall surrounding the hernia defect. The bladder was closed in two layers and a suprapubic cystostomy was done. The patient had urinary leakage from the site of bladder repair which manifested as high output of clear fluid having raised creatinine content in the pelvic drain during the second postoperative week. The urinary leak and drain output diminished with prolonged per urethral catheterization for 6 weeks. The catheter was removed after documenting no extravasation in the cystography performed 6 weeks after surgery.

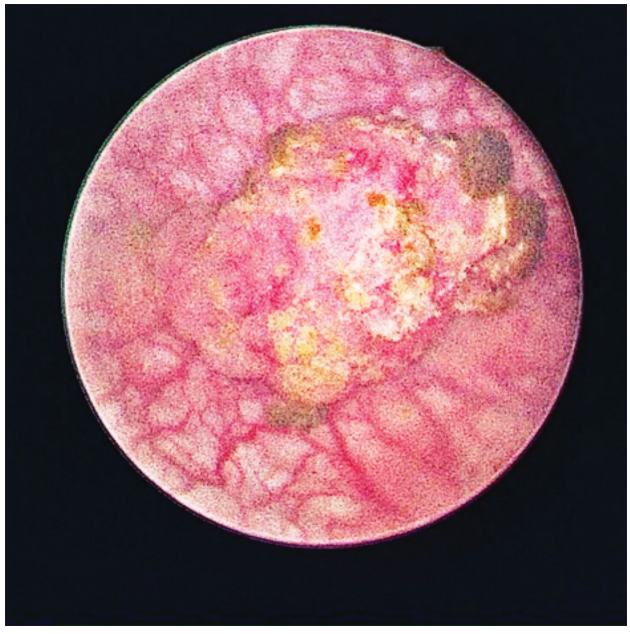

Figure 1. Cystoscopic view of the bladder tumor

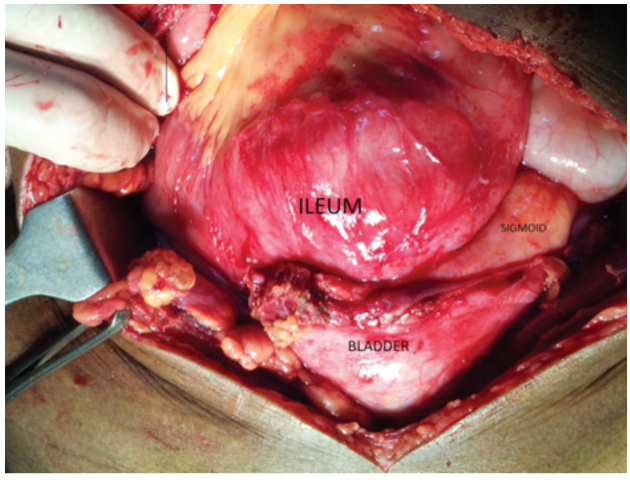

Figure 2. Intraoperative picture showing internal herniation ileum and antemesentric wall of sigmoid colon (posteriorly) into the urinary bladder

Written informed consent form was obtained from the patient.

Discussion

The goal of TUR is to achieve visibly complete resection along with ensuring adequate depth of resection. Small perforations might occur in the event of adequate resection of advanced tumors (3). Most of them are extraperitoneal and managed adequately with bladder drainage through urethral catheter. Intraperitoneal bladder perforation after TURBT is a dreaded complication that may lead to various sequels such as hemorrhage, peritonitis, urinoma, infection tumor spillage, TUR syndrome and even death. When diagnosed intraoperatively, it usually requires open surgical repair. It has an incidence of 0.36% in tumors involving the anterior wall, dome and high posterior wall with deep infiltration (4).

Internal hernias are defined by the protrusion of a viscus through a natural or acquired peritoneal or mesenteric aperture within the confines of the peritoneal cavity (5). The internal hernia orifice can be postsurgical, traumatic, or congenitally acquired. Only 7 cases of herniation of gut loops into the urinary bladder have been reported in the literature. Spontaneous rupture, alcohol-related bladder injury, total abdominal hysterectomy and TURBT were the etiologies in the reported cases (2,6,7,8,9). Internal herniation through an acquired bladder wall defect after TUR is an exceedingly rare complication, previously reported in only one patient (2). The patients have presented with symptoms of haematuria or inability to void. Cases reported by Yalla et al. (6) and Twemlow et al. (9) had additional features of bowel obstruction and strangulation. Our patient presented with urinary symptoms of passage of fecal matter and air in urine with no symptoms suggestive of bowel obstruction or strangulation. Internal hernia of a portion of the

ileum along with antimesentric wall of the sigmoid colon had occurred through an unrecognized perforation in the dome of the urinary bladder following TURBT. Ischemic injury to the wall of the sigmoid protruding into the bladder probably resulted in ischemic necrosis and perforation of the antimesenteric wall, which resulted in fistula formation.

Although CT is the modality of choice in the evaluation of colovesical fistula, MRI has excellent intrinsic soft tissue resolution that allows accurate delineation of the fistula tract with a sensitivity and specificity reaching up to 100% (10,11,12). MRI was performed in our patient, which accurately identified the bowel loops herniating into the urinary bladder. Surgical exploration with reduction and repair of enterovesical herniation is recommended. It eliminates the risk of future bowel obstruction, strangulation, urinary extravasation, peritonitis, and possible enterovesical fistula formation.

Enterovesical herniation is an unusual but known complication after bladder perforation. Small bladder perforations may go unrecognized after TUR as adherent bowel loops seal the defect. Delayed presentation of gut herniation may be in the form of fecaluria due to formation of enterovesical fistula or with signs of intestinal obstruction. MRI of the pelvis is an excellent diagnostic tool and should be performed when clinical suspicion is high. Delayed surgical intervention after fecal diversion appears to be the definitive treatment for intravesical hernia with enterovescical fistula formation.

Ethics

Informed Consent: Written informed consent form was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.S., Concept: K.S., Design: K.S., S.C., Data Collection or Processing: K.S., S.C., Analysis or Interpretation: K.S., P.K.S., D.K., Literature Search: K.S., P.K.S., Writing: K.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Endourology

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Ureteral Jet Flow Dynamics Can Provide Information About the Mechanism of Stone Formation

Üreteral Jet Akım Dinamikleri Taş Oluşum Mekanizması Hakkında Bilgi Verebilir

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Abstract

Ureteral jet dynamics, which have been shown in recent studies to indicate stone formation mechanism in adults and children, provide information about ureteral peristaltism. The dynamics were measured with Doppler ultrasonography and included ureteral jet flows and ureteral jet patterns. In this paper, we present radiographic images of a non-obstructive lower pole stone in the right kidney and a non-obstructive upper pole stone in the left kidney measuring <1 cm and ureteral jet dynamics in a 26-year-old male patient. Our opinion is that the dynamics can provide information about stone formation mechanism.

Keywords: Ureteral jet flow, Continuous jet pattern, Mechanism of stone formation, Jet dynamics, Ureteral peristaltism

Öz

Son çalışmalarda yetişkinlerde ve çocuklarda taş oluşum mekanizmasını aydınlatan üreteral jet dinamikleri üreteral peristaltizm hakkında bilgiler vermektedir. Üreteral jet akım hızlarını ve paternlerini içeren bu jet dinamikleri Doppler ultrasonografi ile ölçülmektedir. Bu yazıda, sağ böbrekte <1 cm non-obstrüktif alt pol taşı ve sol böbrekte <1 cm non-obstrüktif üst pol taşı olan bir hastanın görüntülemelerinin üreteral jet dinamikleri eşliğinde sunulması amaçlandı. Bizim düşüncemiz üreteral jet dinamikleri taş oluşum mekanizması hakkında bilgiler verebilmektedir.

Anahtar Kelimeler: Üreteral jet akım, Kontinu jet patern, Taş oluşum mekanizması, Jet dinamikleri, Üreteral peristaltizm

Introduction

Ureteral jet dynamics, which have been shown to indicate stone formation mechanism in adults and children in recent studies, provide information about ureteral peristaltism (1,2).

Case Presentation

We prospectively evaluated a 26-year-old male patient with a non-obstructive lower pole stone in the right kidney and a non-obstructive upper pole stone in the left kidney measuring

<1 cm who underwent non-contrast computed tomography due to intermittent flank pain (Figure 1). Metabolic evaluation of 24 h-urine collection test, urinalysis and blood-creatinine level were found to be within the normal ranges. A radiologist performed Doppler ultrasonography (D-US) for the assessment of ureteral jet dynamics. D-US was performed with the patient in the supine position with full bladder after hydration with water, using a 3-5 MHz convex probe with angle correction (Philips HDI 5000; Bothell, WA). A sample volume with an axial length of 2 mm was used and the wall filter was between 50 and 100 Hz for D-US measurements.

Parameters were average and maximum jet-flow rate (JETave and JETmax), duration of jet-flow (JETtime) and jet-flow pattern (JETpattern), the latter described by Leung et al. (3,4). The images are given in Figure 1.

Written informed consent was taken from the patient before the procedure.

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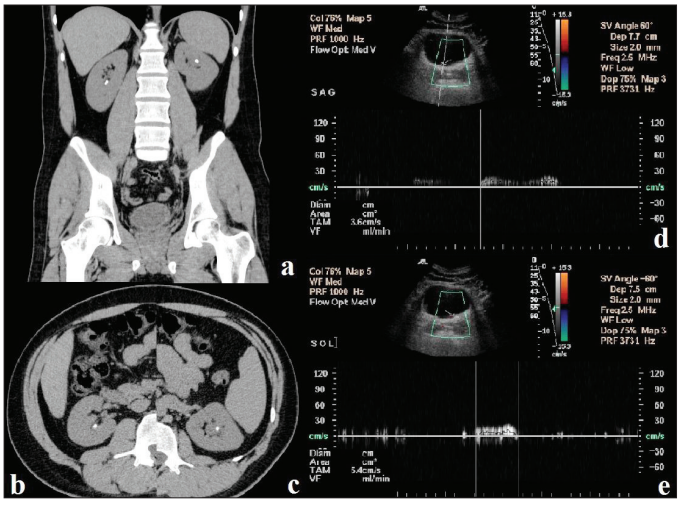

Figure 1. a) Bilateral kidney stones; b) <1 cm non-obstructive lower pole stone in right kidney and; c) <1 cm non-obstructive upper pole stone in left kidney stone of the patient on non-contrast computed tomography images; d) the ureteral jet flow of right ureter in the patient; JETave (3.6 cm/sec), JETtime (1.6 sec) and continuous JETpattern; e) the ureteral jet flow of left ureter in the patient; JETave (5.4 cm/s), JETtime (1 sec) and continuous JETpattern

Discussion

In recent studies, the association between non-obstructive kidney stones and ureteral jet dynamics was evaluated in adult and pediatric stone formers and JETave was found to be significantly lower in affected renal units and continuous JETpattern rate was found to be higher in affected renal units when compared with healthy renal units (1,2). Also, in a renal units with a JETave of <9.5 cm/sec for children and <9 cm/sec for adults were 5.6 and 19.3 times more likely to have a kidney stone, respectively. In the current patient, the JETave was found to be <9 cm/sec and the JETpattern was continuous for bilateral ureters. Low JETave and continuous JETpattern of bilateral renal units were similar to that in the above mentioned studies. Therefore, ureteral jet dynamics may also be included to the evaluation of stone formers.

In conclusion, decreased peristaltism measured with D-US included <9 cm/sec JETave and continuous Jetpattern, which may be an explanation for stone formation mechanism in adults.

Ethics

Informed Consent: Written informed consent was taken from the patient before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç., C.A., Design: S.Ç., C.A., Data Collection or Processing: S.Ç., C.A., G.U., Analysis or Interpretation: S.Ç., O.B., Ö.D., M.S., Literature Search: S.Ç., C.A., O.B., Writing: S.Ç.

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CASE REPORT
Endourology

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Nephrocutaneous Fistula: An Unusual Nephrectomy Indication in Percutaneous Nephrolithotomy

Nefrokutanöz Fistül: Perkütan Nefrolitotomide Ender Bir Nefrektomi Nedeni

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Abstract

Percutaneous nephrolithotomy (PNL) is recognized as the gold standard treatment method for stones larger than 2 cm due to its high success and acceptably low complication rates. The complications of PNL are well defined. Prolonged urinary leakage is one of them. In this study, a case of post-PNL urine leakage that was eventually treated with nephrectomy is discussed.
Keywords: Prolonged urinary leakage, Nephrocutaneous fistula, Percutaneous nephrolithotomy

Öz

Perkütan nefrolitotomi (PNL) yüksek başarı ve kabul edilebilir komplikasyon oranlarından dolayı 2 cm'den büyük taşlar için altın standart tedavi yöntemi olarak kabul edilmektedir. PNL'nin komplikasyonları iyi tanımlanmıştır. Uzamış idrar kaçağı bunlardan biridir. Bu çalışmada PNL sonrası idrar kaçağı devam eden ve sonrasında nefrektomi ile tedavi edilen bir olgu tartışılmıştır.
Anahtar Kelimeler: Uzamış idrar kaçağı, Nefrokutanöz fistül, Perkütan nefrolitotomi

Introduction

Percutaneous nephrolithotomy (PNL) is recognized as the gold standard treatment method for stones larger than 2 cm due to its high success and acceptably low complication rates (1). The complications of PNL are well defined. Prolonged urinary leakage is one of them. Urinary leakage after nephrostomy tube removal is considered normal up to a certain extent and until the tract heals, except for cases of ureteral obstruction where the leakage continues and requires intervention (2). In this study, a case of post-PNL urine leakage that was eventually treated with nephrectomy is discussed.

Case Presentation

A 20-year-old woman was admitted to our clinic with the complaints of left-sided pain persisting for 1 year. Her medical and family history was unexceptional. Her physical examination was normal and the blood test results were within the normal limits. Her urine culture yielded 105 CFU/mL *Escherichia coli*. Non-contrast computed tomography (CT) of the abdomen showed a staghorn stone in the left kidney (Figure 1). Renal scintigraphy displayed 41% contribution of the left kidney to total renal function as well as tubular dysfunction in addition to parenchymal and cortical hypoactive large deformation areas. PNL was planned when no bacterial growth was detected in the urine culture following antibiotic therapy. PNL was performed through 3 different accesses in the upper, middle and lower calyces. One nephrostomy tube was placed at the end of the operation and the other access sites were closed primarily. There were no intraoperative complications. Two units of erythrocyte transfusion were given due to postoperative haemodynamic instability. Hemodynamic stability was achieved and the patient was discharged without any problems on the postoperative third day.

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The patient was admitted again on the postoperative seventh day with the complaint of continuing urinary leakage from the incision site. Non-contrast CT of the abdomen revealed residual stones of 18x10 and 25x12 mm in the posterior middle and lower calyces of the left kidney. A double J stent (DJS) was inserted. Urinary leakage disappeared and the patient was discharged and scheduled to be followed up after 1 month. In the control visit, the DJS was removed. After the procedure, the patient was admitted once again with the complaint of leakage from the wound site. She was hospitalized and antibiotherapy was initiated upon positive urine culture. Again, a DJS was inserted. She was discharged and a follow-up for urine culture was planned but the patient did not attend the follow-up visit. Four months after the last control, she presented with purulent discharge from the wound site despite the DJS. Antibiotherapy was initiated and non-contrast CT of the abdomen was taken (Figure 2). CT revealed parenchymal thinning; hence, renal cortical scintigraphy was repeated. Since the left kidney was observed to get smaller in size than the right one, and due extensive parenchymal dysfunction and 9% contribution of the left kidney to total kidney function, the patient underwent nephrectomy.

Written informed consent was taken for publication of the case report.

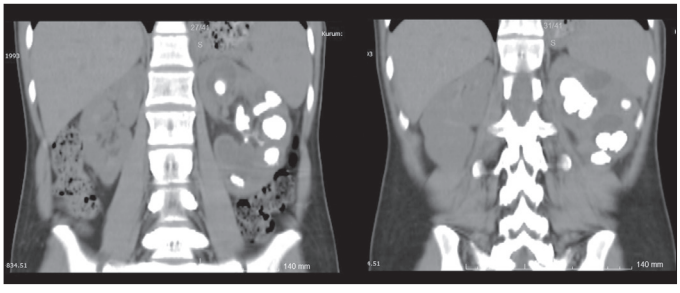

Figure 1. Preoperative multipl stones in the left kidney on computed tomography

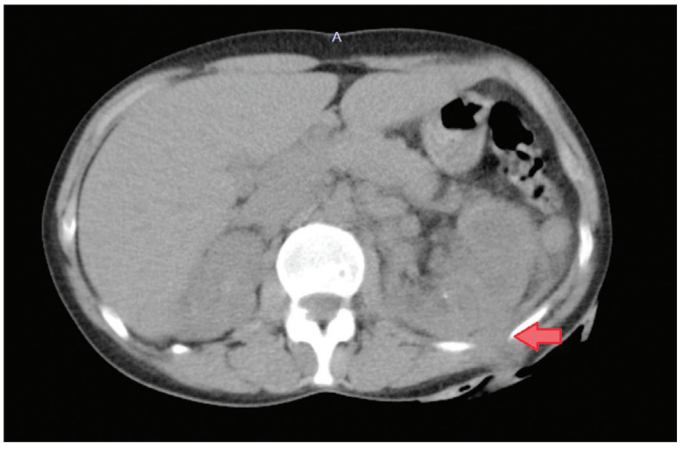

Figure 2. Tract of nephrocutaneous fistula in the left kidney on computed tomography

Discussion

After the publication of the first PNL series by Wickham and Kellet (3) in 1981, the method of open stone surgery has been almost abandoned. In a study conducted with 12.000 patients, the rate of PNL complications was reported to be 10.8% for fever, 7% for transfusion, 1.5% for thoracic complication, 0.5% for sepsis, 0.4% for organ injury and 0.4% for embolization (4). Prolonged urinary leakage is one of them. Urinary leakage after the removal of nephrostomy tube is considered normal up to a certain extent and until the tract heals. The most common complication requiring reoperation with a frequency rate of 4% is prolonged urinary leakage from the tract, exceeding 24 hours (5). Urinary leakage occurs due to peripheral obstruction because of a stone or a clot. It is usually treated with DJS insertion (2). In a study, it has been reported that it was only the presence of preoperative hydronephrosis that was increasing prolonged urinary leakage and its duration, while the size of the stone, the number of accesses, and the shape of the used sheath had no influence (6). There was no preoperative hydronephrosis to predict prolonged urinary leakage in our case.

Spontaneous nephrocutaneous fistulas usually occur in non-functioning or weakly functioning kidneys. Lewi and Scott (7) pointed out three correlations between nephrocutaneous fistula and renal stones: 1) presentation with perinephric abscess, 2) presence of staghorn stone in the non-functioning kidney, 3) presence of peripherically located stones in radiography. Unlike the study by Lewi and Scott (7), nephrocutaneous fistula after PNL is discussed in our case, however, renal deformation, presence of staghorn type peripheral stones, and recurrent urinary infections in the postoperative period are similar findings.

There are very few data available in the literature on the treatment of post-PNL nephrocutaneous fistulas. Treatment modality for the fistulas continuing after elimination of the obstructive causes is not clear. Resection of the fistula tract is the standard treatment for urinary fistulas (8), but several studies reported positive results with fibrin glue injection for nephrocutaneous fistula treatment (9). Resection of the fistula tract and fibrin glue injection were not considered in our case because of purulent discharge from the kidney and dysfunction of the kidney over time, and, thus, nephrectomy was planned.

In conclusion, DJS can be attempted primarily in uncomplicated nephrocutaneous fistula treatment. As a remedy in case of failure, blocking the tract with fibrin glue and surgical excision of the tract may be considered as an option in the treatment. Factors affecting systemic healing, such as therapy-resistant urinary infection, may increase the risks such as developing nephrocutaneous fistula and failure in closing by conservative

method as well as the consequences leading to organ loss, as we encountered in our case.

Ethics

Informed Consent: Written informed consent was taken for publication of the case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Y.Y., Design: T.S., M.Y.Y., Data Collection or Processing: T.Ç., M.H.Ö., Analysis or Interpretation: Y.Ö.İ., G.K., Literature Search: M.K., B.E., Writing: M.Y.Y., T.S., C.S.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support

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CASE REPORT
Pediatric Urology

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Journal of Urological Surgery, 2019;6(1):62-64

Nephrogenic Adenoma of the Urinary Tract in Pediatric Patients: A Report of 2 Cases

Pediatrik Hastalarda Üriner Sistemin Nefrojenik Adenomu: 2 Olgu Raporu

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Abstract

Nephrogenic adenoma (NA) is a rare, benign proliferation of glands of the urinary tract, usually occurring as a result of chronic inflammation, trauma or other similar chronic injuries to the urothelial mucosa. We aimed to share two pediatric cases diagnosed with NA in our hospital between the years 2010 and 2016. The first case was polypoid type NA of the bladder and the second case was fibromyxoid NA of the urethra.
Keywords: Nephrogenic adenoma, Genitourinary tract, Pediatric urology, Bladder, Urethra

Öz

Nefrojenik adenom (NA) üriner sistemin nadir görülen, glandüler yapılarının benign proliferasyonudur ve genellikle kronik enflamasyon, travma veya ürotelyal mukozanın benzer şekilde kronik hasarlanmasının sonucunda görülür. Biz de kliniğimizde 2010 ve 2016 yılları arasında tanı koyulan iki adet NA olgusunu paylaşmayı amaçladık. İlk olgu mesanede görülen polipoid tip NA iken, ikinci olgu üretrada görülen fibromiksoid tip NA idi.
Anahtar Kelimeler: Nefrojenik adenom, Genitoüriner sistem, Pediatrik üroloji, Mesane, Üretra

Introduction

Nephrogenic adenoma (NA) is a rare benign proliferation in the urinary tract, usually occurring as a result of chronic inflammation, trauma or other similar chronic injuries to the urothelial mucosa. NA was first reported by Davis (1) in 1949 as a hamartoma of the bladder and came to be named NA after the resemblance to renal tubules was recognized. It is reported in all urothelial lined sites from the renal pelvis to urethra with the highest frequency in the urinary bladder (2). NAs rarely occur in pediatric population and are not still well studied despite the reported recurrence rate of 80% with a latency period of 4 years (3). We aimed to share two pediatric cases diagnosed with NA of the lower urinary tract in our hospital between the years 2010 and 2016.

Case Presentations

Case 1

The first patient is 2-year-old boy, who was referred from abroad with recurrent urinary tract infections (UTIs) and bilateral hydroureteronephrosis. He was operated due to pyloric stenosis on the fifth postnatal day and was followed up for epidermolysis bullosa and corneal damage. His history revealed recurrent UTIs and cloudy urine. Further investigation in another institution noted for a right duplex system and cystoscopy was uninformative. He was once hospitalized for acute renal failure. Finally, the patient was referred to our institution for recurrent UTIs, hematuria and bilateral hydronephrosis. He had intravenous pyelogram and voiding cystourethrography showing bilateral hydroureteronephrosis and absence of vesicoureteral reflux (Figures 1a, b). Remarkably, polypoid mass

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lesions were seen at the base of the bladder (Figure 1a). Thus, to exclude tumor, cystourethroscopy was performed and fibrin surfaced polypoid lesions covering the trigone of the bladder and including bilateral ureteral orifices were seen. The lesions were resected with meticulous coagulation to preserve ureteric orifices. Histopathological evaluation of the lesions confirmed the diagnosis of NA with staining with PAX-2 at both superficial and tubular regions (Figure 1c). After resection, in the early postoperative period, there was a marked improvement with decrease in hydroureteronephrosis and symptoms. Follow-up after 3 months with cystoscopy was planned but the patient was lost to follow-up due to being abroad.

Case 2

The second urethral NA case is a 4-year-old boy referred for distressful dysuria and macroscopic hematuria. This was most remarkable for a urethral pathology including urethral trauma (not present in the history at all) thus, the radiologic examination consisted of an abdominal ultrasonography and a plain abdominal X-ray including the penis to exclude stone disease. Laboratory tests (only hematuria, no infection) and radiological examinations (completely normal urinary tract) failed to confirm a specific diagnosis, thus, we carried out cystoscopy to examine the urethra and the bladder. There was mild urethral stenosis but required meatoplasty for cystoscopy. At urethroscopy, a 3-4 mm small polypoid lesion was seen in the bulbar urethra. The appearance and location were accepted as unusual that at that time thought to be related with a trauma or probable previous urethral catheterization (there was no history for both however). The lesion was completely removed by cold cut biopsy forceps and the base and circumference area were fulgurated using holmium laser meticulously to prevent damage to the urethra. The bladder mucosa was normal except mild trabeculation. Histological examination of the polyp confirmed the diagnosis of fibromyxoid NA because of pseudovascular tubular structures that were immunostained with ceratine 7, panceratine, PAX-2 and PAX-8 (Figure 2). After treatment, there was marked regression of the symptoms, mainly hematuria. Confident with the diagnosis, we preferred to follow-up the patient deferring diagnostic cystoscopy as late as possible to avoid further trauma to the urethra considering the casual effect on the lesion for a period of 2 years.

Informed consent was obtained from both patients.

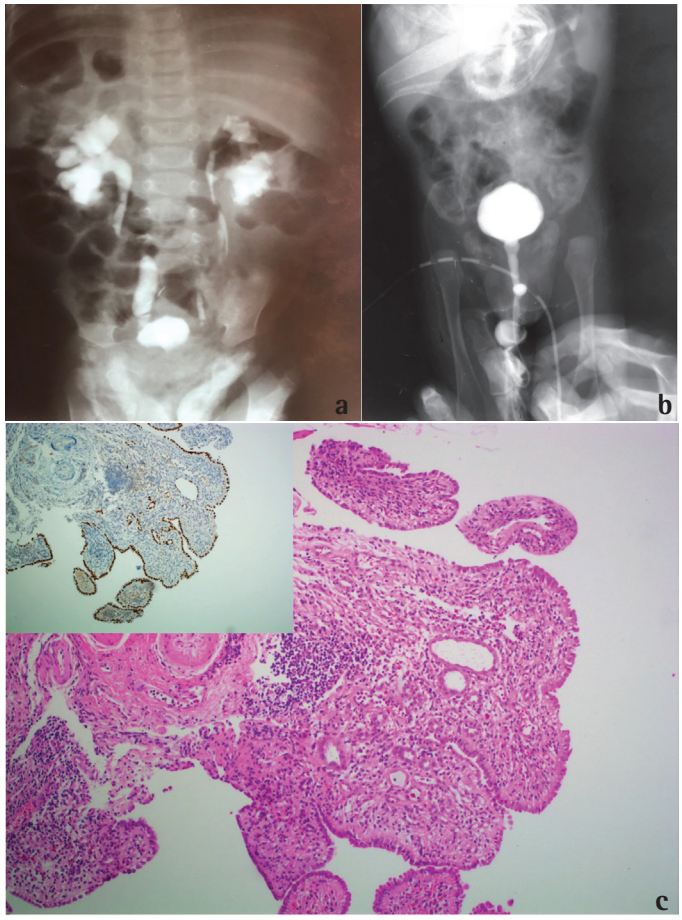

Figure 1. a) Intravenous pyelogram showing bilateral hydroureteronephrosis and polypoid mass lesions at the base of the bladder, b) voiding cystourethrography showing absence of reflux, c) polypoid type nephrogenic adenoma characterized by urothelial lining with PAX-8 (+) (inset) cuboidal cells (inset: Tubules easily recognized by PAX-8 immunohistochemistry)

Discussion

NA is a rare entity in adults and children. While it is 3 times more frequent in males than in females, the ratio is thought to be reversed in children. It is more frequently observed in the bladder than in the urethra with the occurrence rate of 15% (4).

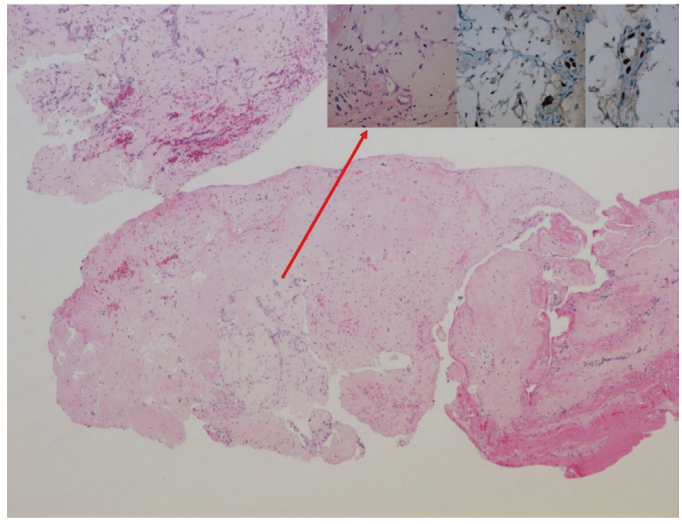

Figure 2. PAX-8 (+) (inset) spindle cells and rare tubular structures embedded in an abundant fibromyxoid stroma in fibromyxoid type nephrogenic adenoma (hematoxylin and eozin, 40x; inset: Tubules easily recognized by PAX-8 immunohistochemistry)

There are numerous diseases that could result in macroscopic hematuria in children and the majority is related to nephrologic causes, namely immunoglobulin A nephropathy. The common causes for non-glomerular gross hematuria could be hypercalciuria (stones), urethrorrhagia (trauma) and hemorrhagic cystitis (infection). Neoplastic lesions are relatively uncommon, but must be excluded.

Accordingly, our second NA case represents a very rare cause of gross hematuria. Similarly, physical examination and radiological evaluation rarely yield informative evidence for diagnosis. Kumar et al. (5) have also reported that children with gross hematuria with normal radiographic results required cystoscopy. Accordingly, we undertook cystoscopy in our cases to diagnose and also made profit of treatment. In fact, NA has a non-specific endoscopic appearance and may mimic tumors, thus, histopathological examination of resected or biopsy specimens is essential for the diagnosis.

The most common histological description of NA is presence of tubular structures resembling mesonephric tubules (6). Papillary projections may also be seen. The small tubules are often surrounded by a thickened hyalinised basement membrane without a desmoplastic stromal response (2,3,7). The main differential diagnoses include prostatic adenocarcinoma and clear cell adenocarcinoma of the urethra in adults and rhabdomyosarcoma and transitional cell carcinoma in children (1,4,7). Certain immunohistological markers, such as PAX-2 or PAX-8, may help to differentiate NA from urothelial carcinomas or prostatic adenocarcinoma but expression of PAX-2 and PAX-8 is also seen in clear cell adenocarcinoma and may be hard to discriminate from NA (7). An experienced pathologist can make decision with the help of histological key features. Positive reaction with panceratine antibody, vimentin antibody and cytoceratine indicates the mesonephrogenic origin (8). Our both cases were tubular structured and the bladder case was PAX-2-positive and urethral case was immune-stained additionally with PAX-8, ceratine 7 and panceratine. In addition, urethral NA was a rare type that can mimic mucinous adenocarcinoma (9).

The lesion is usually solitary but can be multifocal (4); in our urethral case, it was an example of a solitary lesion and in the bladder case, it was a multifocal lesion. History of UTI, inflammation, trauma or recent surgery, calculi or catheterization in most cases or immunosuppression after transplantation are possible causes of NA. Our bladder case had a history of recurrent UTI and recent repetitive cystoscopy but, on the other hand, urethral case did not provide the condition of chronic injuries to the urothelial mucosa. By this way, every gross hematuria in a child, not associated with a diagnosis, requires cystoscopy.

There is a consensus that NA is a benign lesion. The main treatment is transurethral resection and fulguration of the tumor base. However, the recurrence rate has been reported to be as high as 37% (8). Because of this predisposition, a follow-up with cystoscopy is recommended (4). Also repeating surgeries are known to be a reason of trauma to the urothelial mucosa and we think about not to perform cystoscopy while the patient is asymptomatic to avoid urethral injury.

Ethics

Informed Consent: Informed consent was obtained from both patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.T., M.Ö.T., Design: E.T., M.Ö.T., Data Collection or Processing: E.T., M.Ö.T., İ.I.G., Analysis or Interpretation: S.G., İ.I.G., Literature Search: E.T., Writing: E.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Endourology

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Zinner's Syndrome: Case Report of a Rare Maldevelopment in the Male Genitourinary Tract

Zinner Sendromu: Erkek Ürogenital Sistemde Nadir Görülen Bir Gelişim Bozukluğu Olgusu

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Abstract

Zinner's syndrome is a rare embryologic anomaly of the distal portion of the mesonephric duct comprising a triad of ipsilateral renal agenesis, seminal vesicle cyst and ejaculatory duct obstruction. We report ultrasound and magnetic resonance imaging findings of this rare developmental anomaly involving the mesonephric duct, in an asymptomatic 17-year-old boy who would probably remain undiagnosed until later age. The patient presented with no specific symptoms and was incidentally diagnosed on imaging exams.
Keywords: Zinner's syndrome, Seminal vesicles, Ejaculatory duct, Renal agenesis

Öz

Zinner sendromu; ipsilateral renal agenezi, seminal vezikül kisti ve ejakülatör kanal obstrüksiyon triadını içeren, mezonefrik kanalın distal kısmında nadir görülen, embriyolojik bir anomalidir. Muhtemelen daha sonraki yaşlara kadar tanı konulmadan kalacak olan 17 yaşındaki asemptomatik bir erkek çocukta, mezonefrik kanalı tutan bu nadir gelişimsel anomalinin ultrason ve manyetik rezonans görüntüleme bulgularını sunuyoruz. Spesifik bir semptomu bulunmayan hastaya, görüntülenme muayenelerinde tesadüfen tanı konulmuştur.
Anahtar Kelimeler: Zinner sendromu, Seminal vezikül, Ejakülatör kanal, Renal agenezi

Introduction

Zinner's syndrome is a rare embryologic anomaly of the distal portion of the mesonephric duct, responsible for the emergence of the ureteric bud, vas deferens, ejaculatory duct, seminal vesicle, hemitrigone, epididymis and paradidymis, during the 4th and the 13th gestational week. The common origin of the mesonephric duct and the ureteric bud, which will form the definitive adult kidney, is responsible for the associated maldevelopment of the genital and urinary tracts, including atresia of the ejaculatory duct, obstruction of the seminal vesicles with formation of cysts and ipsilateral renal agenesis or dysplasia (1,2,3,4). More rarely, the ureteric bud can arise in a more cranial position of the mesonephric duct, leading to a distal ureteric bud with anomalous drainage, for example into the vas deferens, seminal vesicle, ejaculatory duct, bladder neck and urethra.

This syndrome is considered to be the male version of Mayer-Rokitansky-Kuster-Hauser syndrome (5). The diagnosis is usually made between the 2nd and the 5th decades of life, concomitant with the period of maximum sexual activity, when cysts start to become more apparent (1). Patients usually present with multiple and unspecific symptoms, and the diagnosis is often made by imaging studies. The clinical manifestations include voiding symptoms (dysuria, frequency, urgency), haematuria, perineal or scrotal pain, recurrent urinary tract infection, epididymitis, prostatitis, painful ejaculation, haematospermia, and infertility. Small cysts in the seminal vesicles, less than 5 cm in size, are usually asymptomatic and often detected incidentally (4,5,6,7). We report ultrasound (US) and magnetic resonance imaging

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(MRI) findings of this extremely rare developmental anomaly involving the mesonephric duct in a 17-year-old boy who would probably remain undiagnosed until later age. The patient presented with no symptoms related to this anomaly and was incidentally diagnosed on imaging exams.

Case Presentation

A 17-year-old boy with a medical history of Fabry disease and right renal agenesis was sent to our department for routine US evaluation. He was asymptomatic, with no abdominal or genitourinary complaints. External genitalia were normally developed and the vas deferens was palpable bilaterally. Blood analysis, renal function and urinalysis were also normal.

We performed US that revealed the presence of a multilocular cystic mass located in the right side of the pelvis inferolateral to the urinary bladder. The mass had internal low level echoes, probably due to hemorrhage or increased concentration of proteinaceous content. US also showed absence of kidney in the right renal fossa (Figure 1). With the US findings, the diagnosis of Zinner's syndrome was considered.

Pelvic MRI was subsequently performed to confirm that the cystic mass was arising from the seminal vesicle. MRI showed a multilocular cystic lesion replacing the right seminal vesicle and measuring 74x56 mm. The multiloculated seminal vesicle cyst presented hypersignal on T2 and T1-weighted images, which reflects hemorrhage or increased proteinaceous content. T1 post-contrast and subtraction images showed lack of contrast enhancement. Additionally, a tubular structure with a superior blind-ending was also apparent, coursing along the right iliac vessels and draining into the right seminal vesicle, consistent with ectopic atretic ureter (Figure 2). On imaging findings, no clearly dilation of the vas deferens was found along its path.

We found no association in the literature between Zinner's syndrome and Fabry disease.

At present, the patient remains asymptomatic, on conservative management and with periodic clinical follow-up.

Oral informed patient consent for publication has been obtained.

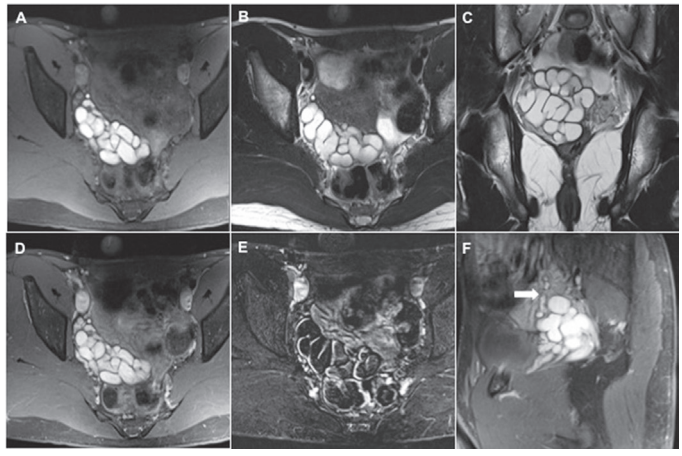

Figure 2. A) Axial T1W shows a hyperintense multiloculated right seminal vesicle cyst, reflecting probably increased concentration of proteinaceous fluid or eventually haemorrhage, B) axial and, C) coronal T2W magnetic resonance imaging demonstrate multiple cystic intercommunicating hyperintense structures. The lesion measures 74x56 mm, D) axial T1W magnetic resonance imaging post-contrast and, E) subtraction images show lack of contrast enhancement, F) parasagittal T1W magnetic resonance imaging showing the tubular remnant ureter (arrow) communicating with the right seminal vesicle cyst

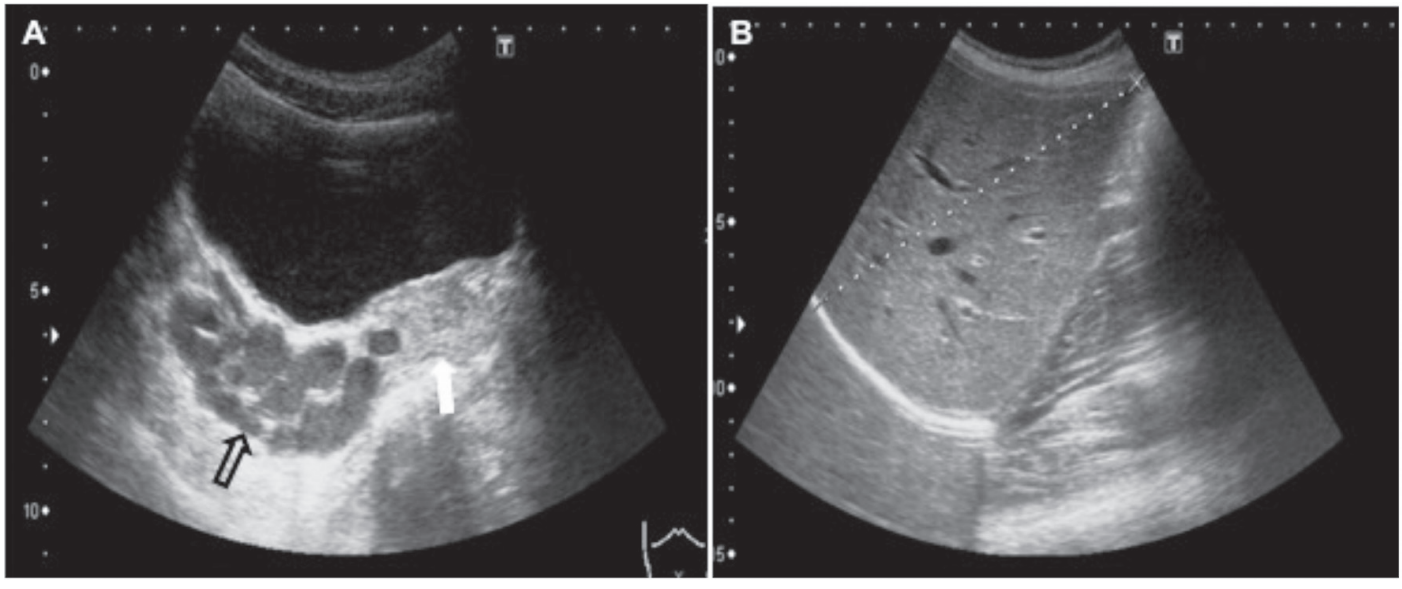

Figure 1. A) Pelvic ultrasound shows a multiloculated cystic structure (open arrow) in the right side of the pelvis inferolateral to the urinary bladder and adjacent to the prostate (white arrow). The mass has low level internal echoes, resulting from haemorrhage or increased proteinaceous content; B) absent right kidney in the renal fossa

Discussion

Zinner's syndrome is a rare malformation affecting the seminal vesicle and the upper urinary tract simultaneously. The diagnosis is usually made between the 2nd and the 5th decades of life due to enlargement of the seminal vesicle cysts (at least 5 cm to induce symptoms) (1,2,3,4). Most commonly, patients present with genitourinary symptoms and perineal pain that was not our case probably due to early diagnosis.

In the evaluation of patients with suspected mesonephric duct development failure, US can be very useful for the diagnosis, detecting an anechoic cystic mass in the pelvic fossa, but it can be more limited to study the rest of the pelvic smaller anatomic structures and their relationships. MRI offers anatomic details of the different pelvic structures, leading to a definitive diagnosis and is also of utmost importance for surgical planning. On MRI, seminal vesicle cysts are in a characteristic periprostatic and paramedian location, with bright signal on T2-weighted images, variable signal intensity on T1-weighted images, depending on the amount of protein or blood content, and no contrast enhancement. MRI may also reveal an ectopic ureter draining into the seminal vesicle, which is often difficult to identify with other imaging techniques.

Differential diagnosis involves several cystic diseases of other pelvic organs, including prostatic utricle cysts, ejaculatory duct cysts, prostatic cysts, diverticula of ampulla of vas deferens, ureteroceles, and abscess. Cyst location and other developmental abnormalities (renal agenesis or anomalies of the external genitalia) help to make the differential diagnosis (4,8).

Treatment of the seminal vesicle cysts is determined according to symptom existence. Symptomatic seminal vesicle cysts may require interventional treatment, which may be by minimally invasive surgery, or an approach through natural orifices (transrectal aspiration and transurethral resection), or open surgery. Minimally invasive approach with laparoscopic surgery and most recently with robotic-assisted approach has gained substantial acceptance and is the preferential method in most cases. Transrectal and transurethral approaches portend the risk of recurrence and open surgery is only reserved for recurrent or complex cases (9).

In conclusion, congenital anomalies of the male urogenital tract may not be considered by clinicians, especially when patients present with no precise symptoms. Familiarity with the imagiological findings of this anomaly is essential to make a prompt diagnosis, with MRI proving the best soft tissue contrast. In this case, concomitant follow-up and screening, as well as genetic counseling during adolescence and adult life are also advisable.

Ethics

Informed Consent: Oral informed patient consent for publication has been obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Pathology

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Isolated Bladder Condyloma in an Immunocompetent Female: Case Report and Literature Review

İmmünokompetan Bir Kadında İzole Mesane Kondilomları: Olgu Sunumu ve Literatür İncelemesi

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Abstract

Condyloma acuminata (CA), lesions caused by strains of the human papilloma virus, are usually limited to anogenital and mucocutaneous regions. Though uncommon, isolated urinary CA lesions have been seen in some immunocompromised patients. We report a rare case of an immunocompetent 37-year-old female with innumerable bladder condylomas.
Keywords: Condyloma acuminata, Bladder, Human papilloma virus, Immunocompetent

Öz

İnsan papilloma virüsü suşlarının neden olduğu kondiloma aküminata (CA) lezyonları, genellikle anogenital ve mukokutanöz bölgelerle sınırlıdır. Bağışıklık sistemi baskılanmış bazı hastalarda nadir de olsa izole üriner CA lezyonları görülmüştür. Bu çalışmada, sayısız mesane kondilomlu ve immünokompetan olan 37 yaşında bir kadına ait nadir bir olgu sunulmuştur.
Anahtar Kelimeler: Kondiloma akuminata, Mesane, İnsan papilloma virüsü, İmmünokompetan

Introduction

There are over 200 strains in the human papilloma virus (HPV) family, but there are four predominant infectious strains associated with symptoms and carcinomas: HPV 6 and HPV 11 cause approximately 90% of all genital warts, HPV 16 and HPV 18 are associated with anogenital carcinomas (1). Condyloma acuminata (CA), the warty lesions caused by HPV, are generally present on external genitalia and mucocutaneous junctions and can spread locally. There are rare reports of CA found in the urinary tract, but these are generally seen in patients who are immunocompromised and who have had a history of genital CA (2). While genital condylomas have been associated with increased risk of cervical, anogenital, penile, and head and neck cancers, their role in urothelial carcinoma has been very inconclusive, (3) with some reports suggesting an increased risk for progression to squamous cell carcinoma and need for close monitoring (4). We report a rare case of isolated bladder CA found in an immunocompetent female without a history of genital CA.

Case Presentation

The patient is a 37-year-old female with a history of kidney stones who presented with left flank pain and gross hematuria. Computed tomography scan of the abdomen and pelvis showed multiple small stones in her left kidney. Given the small size and location, she was managed conservatively. However, she continued to have flank pain on follow-up and decided to pursue elective ureteroscopy and laser lithotripsy for stone treatment.

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Standard cystoscopy was performed at the start of the case which revealed numerous bladder lesions that appeared papillary along with some lesions of abnormal mucosa concerning for carcinoma *in situ*. The largest lesion measured approximately 1x2 cm in the right posterior wall, but smaller lesions were seen throughout the bladder including the dome, lateral walls and trigone.

Given this finding and concern for urothelial carcinoma, we determined that it was in the patient's best interest to proceed with transurethral resection of bladder tumor with cold cup biopsies and to abort the ureteroscopy so as not to expose the upper tracts to possible carcinoma. The patient was informed of the findings after the procedure.

The bladder biopsy pathology came back as fibrovascular cores consistent with underlying papillary growth but no carcinoma. Immunohistochemical staining was positive for p40 and elevated ki-67 but negative for GATA3, p16 and CK20. The differential diagnosis was for condyloma acuminatum versus urothelial hyperplasia and the pathology was sent to Stanford University for consultation read. A review of the patient's previous surgical pathology showed that she had a similar bladder mass resected in 2012, which was read as urothelial hyperplasia. This specimen was also sent along to for re-analysis.

The Stanford pathology read determined that both the 2012 and current bladder tissue samples were consistent with condyloma acuminatum. The haemotoxylin and eosin staining showed nonkeratinizing squamous mucosa with koilocytic and papillomatous changes consistent with CA (Figure 1). Both tissue samples were then sent to the Mayo Clinic Laboratories in Rochester for HPV typing. Commercial typing is available for six strains: HPV 8, 11, 16, 18, 33 and 51, and both samples were negative for all six.

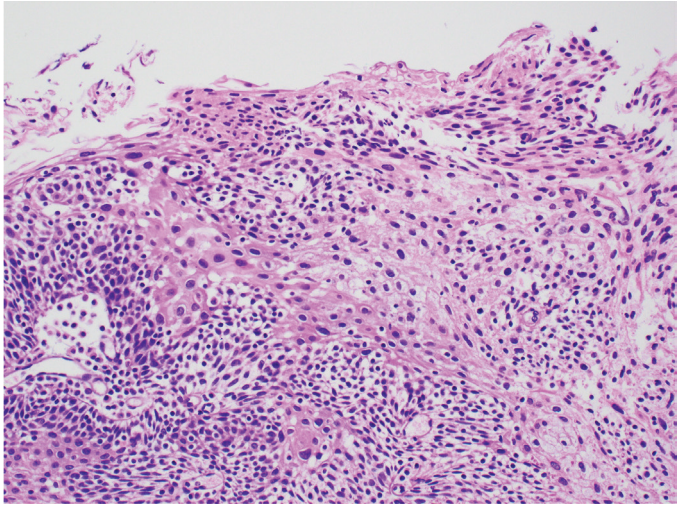

Figure 1. Biopsy histology at 200x magnification showing well-developed koilocytic change characteristic of human papilloma virus-effect with enlarged, hyperchromatic nuclei and perinuclear clearing

On her post-operative visit, the patient was evaluated for any signs of immunocompromise. She denied any history of HPV, sexually transmitted infections or genital condylomas. She had not had any abnormal pap smears or irregularities reported on gynecologic exam. Labs for hepatitis B, hepatitis C, gonorrhea, chlamydia and human immunodeficiency virus (HIV) were all negative. The patient was then seen back in the clinic 3 months after the procedure for follow-up cystoscopy, which was negative for any signs of recurrence.

Written informed consent was obtained from the patient.

Discussion

A review of current English literature conducted through PubMed yielded 44 articles with a total of 52 cases of CA reported in the bladder. Of these cases, 16 (31%) had a history of or concurrent anogenital condylomas, 14 (27%) had concurrent urethral and ureter involvement, 19 (36%) had isolated bladder condylomas and 3 (6%) studies had only abbreviated abstracts available. The male-to-female ratio in our review was 1:1.6, which is consistent with the literature.

Urinary involvement is theorized to be secondary to local invasion, which may explain the higher rate of incidence in women given their shorter urethral length (5). However, in patients without a history of genital CA and are otherwise asymptomatic, it has been suggested that isolated bladder or ureteral involvement may be due to iatrogenic urogenital inoculation with urethral procedures and catheterization (6).

Isolated involvement of the bladder continues to be very rare with only 19 cases reported in the English literature. The majority of these patients had some form of immunocompromise including a recent history of renal transplant (7,8,9,10), HIV-positive status (11,12) chronic lymphocytic leukemia (13) and multiple sclerosis (14). Indeed, immunodeficiency has been cited as a risk factor for the development of symptomatic HPV infection in general, as studies of HPV cervical infections show that the large majority of female patients with appropriate T-cell immune responses are able to clear the infection, even when they are infected with high-risk strains (15). Of the 19 cases of isolated bladder lesions, only 7 cases (13%) occurred in immunocompetent patients.

Of these cases, only 8 cases had positive identification of the HPV strain involved: HPV 6/11 was identified in 5 cases (6,13,16), HPV 16/18 in one case (4), and two cases simply reported immunohistochemistry-positive for HPV without specifying the strain (8,12). Several cases reported negative results of HPV testing, similar to our case, which is likely a reflection of testing limitations as there are over 40 transmissible strains of HPV and commercial testing is limit to the most common HPV strains.

HPV is a well-known risk factor for the development and progression of certain types of cervical, anal, anogenital, and nasopharyngeal cancers, especially in immunocompromised states. However, our study and a review of the literature show that even immunocompetent patients are at risk of developing isolated urinary CA. Although the relationship between HPV and urothelial carcinomas is controversial, close monitoring with routine cystoscopy is strongly recommended for these patients.

Acknowledgments

We would like to acknowledge the work and contributions of the Stanford Pathology Department as well as the Mayo Clinic Medical Laboratories in Rochester. The authors do not have any conflicts of interest to disclose.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.W., M.D., J.R., Concept: J.R., Design: N.W., J.R., Data Collection or Processing: N.W., M.D., J.R., Analysis or Interpretation: N.W., M.D., J.R., Literature Search: N.W., Writing: N.W.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Reconstructive Urology

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Recurrent Urethral Diverticulum: A Case Report

Rekürren Üretral Divertikül: Bir Olgu Sunumu

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Abstract

Recurrence of urethral diverticulum after surgical repair is common and well established in the literature. However, data on the rates of multiple recurrences in the same patient is lacking. Here, we present the case of a 42-year-old female patient with a history of multiple urethral diverticula, who presented with a urethral diverticulum containing a large calculus. Our aim was to review the risk factors and management of patients who present with recurrent urethral diverticula.
Keywords: Urethral diverticulum, Stress urinary incontinence, Pelvic surgery

Öz

Cerrahi onarım sonrası üretral divertikül rekürrensi yaygındır ve literatürde iyi bilinmektedir. Bununla birlikte, aynı hastada çoklu rekürrens oranları hakkındaki veriler yetersizdir. Burada, üretral divertikülde büyük bir taş ile başvuran ve çoklu üretral divertikül öyküsü olan 42 yaşındaki bir kadın olgu sunulmuştur. Bu çalışmada, tekrarlayan üretral divertikül ile başvuran hastaların risk faktörlerinin ve yönetiminin gözden geçirilmesi amaçlanmıştır.
Anahtar Kelimeler: Üretral divertikül, Stres üriner inkontinans, Pelvik cerrahisi

Introduction

Female urethral diverticulum (UD) is relatively common, as it affects 1%-6% of women. Diagnosis can be significantly prolonged by non-specific symptoms which include dysuria, recurrent urinary tract infection (UTI), incontinence and dyspareunia. Management is guided by the patient's symptoms, and ranges from observation to surgical intervention. Recurrence of UD after surgery is also common, occurring at a rate between 8% and 20%. Thus, UD should be suspected in patients with a surgical history of urethral diverticulectomy who present with non-specific urinary symptoms.

Case Presentation

A 42-year-old (G4P3013) woman with an extensive genitourinary and pelvic surgical history presented with symptoms of recurrent UTI, stress urinary incontinence (SUI) and a feeling of vaginal fullness. Her past medical history included a history of uterine prolapse and recurrent UD, requiring prior surgical interventions as described below.

At age 29, the patient presented with urinary incontinence and was found to have a UD at an outside hospital. There, she underwent a diverticulectomy, which was complicated the following year by urethrovaginal (UV) fistula and subsequently repaired via a vaginal approach.

At age 34, the patient presented with stage 3 pelvic organ prolapse, SUI and a recurrence of UD. She subsequently underwent a supracervical hysterectomy with abdominal sacrocolpopexy, rectus fascial sling, and urethral diverticulectomy. Intraoperatively, a recurrent UV fistula was encountered and repaired, with placement of a Martius flap to augment the repair. SUI recurred six months after surgery, and the patient was lost to follow-up.

At age 42, the patient again presented with symptoms of recurrent UTI, SUI and a feeling of vaginal fullness. She had a history of eight UTIs in the past year and two episodes of pyelonephritis.

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Before outpatient work up could be completed, she presented to the emergency room (ER) with the complaints of severe left-sided back pain, nausea and vomiting. A non-contrast computed tomography scan at the time of ER presentation revealed two large calculi-one partially obstructing the proximal left ureter and one peri-urethral stone measuring 1 cm in diameter within a posterior proximal UD. After successful treatment of her renal stone, she underwent pelvic magnetic resonance imaging, which revealed a bi-lobed diverticulum with a wide mouthed orifice coming off of the posterior mid urethra (Figure 1A). Each lobe measured 1 cm in diameter, with the inferior lobe containing a 1.0 cm calculus (Figure 1B).

The patient subsequently underwent urethral diverticulectomy. An ostium containing a stone in the posterior proximal urethra to the left of midline just distal to the urethrovesical junction was visualized via cystoscopy (Figure 1C). At the mid urethra, there was a transverse band thought to be the previous rectus fascial sling. Next, an inverted U-incision was made on the anterior vaginal wall. The vaginal epithelium was dissected off of the underlying fibromuscular connective tissue to create a U-flap. The previously placed fascial sling was identified, dissected off from the surrounding fibromuscular connective tissue, and divided at the midline. A vertical incision was made over the proximal urethra and the diverticulum sac containing the stone was entered (Figure 1D). The wall of the diverticulum was completely mobilized and transected near the urethral ostium, and the calculus was removed (Figure 1E). The urethrotomy was closed with interrupted sutures of 4-0 Vicryl, with care to include the urothelium on each side. Backfill of the urethra with a Trattner catheter with methylene blue solution demonstrated a watertight closure after a single layer. The rectus fascial sling was re-approximated with two mattress sutures of Vicryl in an overlapping fashion to re-establish support to the urethra. The vaginal incision was closed with horizontal mattress sutures of 2-0 Vicryl.

At 6 months postoperatively, her repair has healed without complication or recurrence, and she is being treated for urge predominant mixed urinary incontinence, without signs of SUI on exam.

Written informed consent was obtained from the patient.

Discussion

The exact pathogenesis of urethral diverticula remains unknown. The leading theory holds that an obstructed peri-urethral gland becomes infected and forms an abscess which subsequently ruptures into the urethral lumen, creating an ostium (1). Other theories include trauma, mid-urethral sling, peri-urethral bulking agents, and obstetrical complication (1). In many cases, however, the exact cause of UD is unclear, as is the case with this patient. Definitive treatment of UD is surgical intervention with techniques including marsupialization, endoscopic un-roofing, fulguration and most commonly, complete excision with reconstruction (2). Failure to treat UD can result in inflammation and neoplastic degeneration (3), though the exact natural course of untreated UD remains unknown.

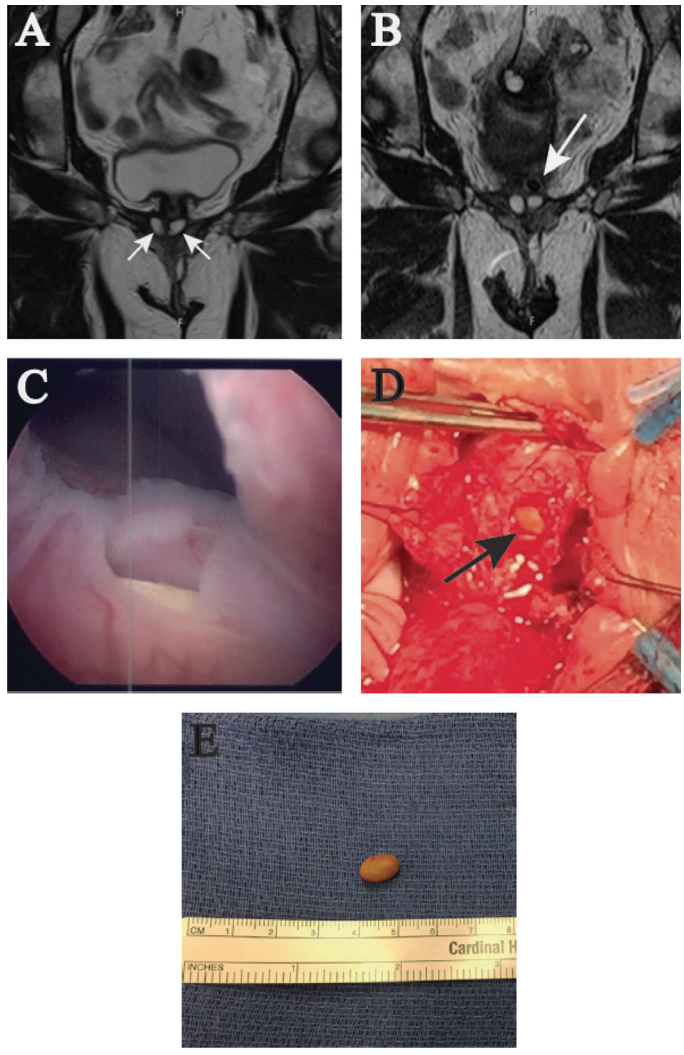

Figure 1. A) T2 weighted magnetic resonance imaging showing bilobed diverticulum (arrows), B) T2 weighted magnetic resonance imaging showing a calculus within the left lobe of the diverticulum (arrow), C) cystoscopy revealing ostium of diverticulum containing a calculus in close proximity to the bladder neck, D) vertical incision and entry into diverticulum sac, E) calculus excised from left lobe of diverticulum

This case demonstrates an example of complex UD recurrence. Varying rates of UD recurrence have been reported in the literature and range from 8% to 17% (4,5,6), with one group reporting a 5-year recurrence rate of more than 20% (7). Major risk factors for recurrence have been identified and include history of female pelvic surgery, proximal UD, and prior attempted surgical repair of UD (6). Of note, the patient in this case had all three of these major risk factors.

SUI is a frequent symptom at presentation in many UD patients, and it can also develop de novo after repair of UD. Whether stress incontinence should be treated at the time of the diverticulectomy or in a delayed procedure is an interesting question, as SUI can be due to the UD and/or be a complication of the UD repair itself. Interestingly, the patient had a history of UV fistula, which is also a potential complication of UD repair (8). The risks of the procedure must be carefully weighed against the patient's symptoms and current quality of life. It was our decision to proceed with the complex repeat UD repair and concomitantly treat the patient's SUI by re-approximating the previously placed rectus fascial sling.

In conclusion, UD is relatively common and presents with symptoms of dysuria, UTI, incontinence and dyspareunia. Recurrent UD occurs in a significant subset of patients, with risk factors including history of female pelvic surgery, proximal UD, and prior attempted repair of UD. Guidelines on management of patients with recurrent UD in the context of multiple surgical repairs are lacking. These patients may need to be more closely followed postoperatively.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: L.A.R., M.L., Design: L.A.R., M.L., Data Collection or Processing: L.A.R., M.L., Analysis or Interpretation: L.A.R., M.L., Literature Search: L.A.R., M.L., Writing: L.A.R., M.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
General Urology

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Spontaneous Rupture of Proximal Ureter: A Case Report

Spontane Proksimal Üreter Rüptürü: Olgu Sunumu

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Abstract

Spontaneous non-traumatic urinary collecting system ruptures without distal obstructive causes are rare and uncommon. They should be considered in the differential diagnosis of renal colic or acute abdomen. Here, we present a case of spontaneous rupture of the left proximal ureter with perirenal fluid extravasation without an identified cause. The patient was treated conservatively and in the first week, symptom improvement was shown by control imaging methods. Ureteral stent placement or percutaneous nephrostomy, even open surgery are options for the management of spontaneous rupture of the urinary collecting system, however, conservative management may be an option for selected patients.

Keywords: Rupture, Ureter, Collecting system, Spontaneous

Öz

Distal obstrüktif nedenlere bağlı olmayan, spontane, travmatik olmayan üriner toplayıcı sistem rüptürleri nadir görülmektedir. Ayırıcı tanıda akut abdomen ve renal kolik nedenler göz önünde bulundurulmalıdır. Burada, nedeni bilinmeyen perirenal sıvı kaçağıyla gözlenen sol proksimal üreter spontan rüptürü olgusunu sunmaktayız. Hastaya konservatif tedavi verilerek tedavisinin ilk haftasında semptomlarında iyileşme gözlendi. Üriner toplayıcı sistem rüptürlerinde tedavi olarak üreteral J stent yerleştirilmesi, perkütan nefrostomi uygulanması, hatta cerrahi bir seçenek iken; konservatif tedavi de seçilmiş hastalarda bir tedavi yöntemi olabilir.

Anahtar Kelimeler: Rüptür, Üreter, Toplayıcı sistem, Spontane

Introduction

Urinary collecting system ruptures are uncommon and are often due to distal obstructive conditions such as urinary stones or external mass pressure to the ureter. However, in the literature, spontaneous non-traumatic urinary collecting system ruptures with perinephric fluid extravasation without distal obstructive causes have been reported (1,2). Here, we present a case of spontaneous rupture of the left proximal ureter without an identified cause.

Case Presentation

A 65-year-old female patient was admitted to the emergency room due to severe left flank pain, which aroused her from sleep. There was no history of trauma affecting the left lumbar region. She never had urinary stone disease. In addition, no history of operation or comorbidity was noted. Her physical examination was normal except left costovertebral angle tenderness. The mere pathological laboratory findings were leukocytosis (12960/uL) and an increase in erythrocyte sedimentation rate (22; N: 0-20 mm/hour). Contrast-enhanced computed tomography (CT) of the abdomen showed a perfusion reduction in the left renal parenchyma, with a collection of fluid causing perirenal reticular density suggesting urinoma. CT urography showed contrast agent extravasation from the left proximal ureter and contrast material accumulation around the perirenal area. There was no sign of obstruction. A consent form had been taken when she was hospitalized, and followed up conservatively. In the first week, control abdominal imaging methods showed disappearance of perirenal reticular density. Eventually, she did not need any surgical intervention.

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Discussion

Spontaneous rupture of the urinary collecting system is a rare condition. Some hypothesis for the mechanisms of spontaneous urinary collecting system ruptures, such as urinary stone movement causing internal ureteral erosion for distal urinary stones, have been proposed (3). Besides, there are some reported cases of spontaneous ureteral rupture due to malignancies (4,5) and pregnancy (6).

The term "spontaneous" for urinary collecting system ruptures was defined in a study as being with no external trauma, no cystoscopic ureteral manipulation, no external compression or any urinary surgical intervention (7). As defined, there was no underlying cause for a ureteral rupture in our case.

There is no specific clinical manifestation for spontaneous rupture of the urinary collecting system. Sudden onset of flank pain, mimicking renal colic symptoms, or acute abdomen might be the main symptoms (8).

Despite the rupture level in the urinary system may vary, the most commonly described site is the renal fornix (9). The rupture level of ureteropelvic junction or proximal ureter level is rare. The cause of rupture is the increase of intraluminal pressure by external or internal obstruction of the ureter. Urinary system ultrasonography may show hydronephrosis and perinephric fluid. Contrast-enhanced CT and CT urography may be the best diagnostic imaging methods for urinary collecting system ruptures (10).

Spontaneous urinary collecting system ruptures may cause major consequences, such as urinoma, perirenal abscess formation, and urosepsis. Ureteral JJ stent placement, percutaneous nephrostomy, or even surgical repair such as urinary diversion may be required for treatment. However, in selected cases, observation and conservative management may be an option. Akpinar et al. (11) reported four patients with the complaint of sudden onset abdominal and flank pain. All patients had urinary extravasation on their CT scans. One patient underwent ureteral stent placement, and the rest of them were followed conservatively. Perirenal fluid resolution was seen on CT images within three days. The patients were followed for a mean period of 17 months without any problems (11). Al-mujalhem et al. (12) declared that conservative management was a valid option for non-complicated spontaneous renal forniceal rupture.

Spontaneous urinary collecting system rupture should be considered in emergency rooms in the differential diagnosis of renal colic or acute abdomen. There is no evidence yet for the best treatment option, however, conservative management may be an option for selected cases besides other invasive treatment methods. All cases should be reported in order to expand the patient pool and further literature data is needed to determine the most appropriate treatment modality.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.O.K., A.S.T., F.Ç., R.Ö., Concept: İ.O.K., A.S.T., R.Ö., Design: İ.O.K., A.S.T., R.Ö., Data Collection or Processing: İ.O.K., A.S.T., Analysis or Interpretation: İ.O.K., A.S.T., F.Ç., R.Ö., Literature Search: İ.O.K., A.S.T., F.Ç., R.Ö., Writing: İ.O.K., A.S.T., F.Ç., R.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Endourology

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Two Cases of Bladder Adenocarcinoma After Augmentation Cystoplasty

İki Olguda Augmentasyon Sistoplasti Sonrası Mesanede Adenokarsinom

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Abstract

To draw attention to the disregarded malignancy risk after ileocystoplasty, we present two cases of adenocarcinoma. The first case was metastatic at initial diagnosis. Despite chemotherapy, the condition progressed and the patient died at the 9th month. The second patient has received cystectomy followed by chemotherapy and radiotherapy. Although the second patient was an immunosuppressed renal transplant, she was disease-free at the 27th month. As the malignancy risk after bladder augmentation is a proven fact, until the discovery of a proper diagnostic method, we recommend doing routine annual cystoscopic biopsy starting after the 10th year of ileocystoplasty.
Keywords: Augmentation, Ileocystoplasty, Adenocarcinoma, Bladder, Malignancy

Öz

Augmentasyon ileosistoplasti sonrası yeterince önemsenmeyen kanser riskine dikkat çekmek için, adenokarsinom tanısı almış iki olguyu sunuyoruz. İlk hasta tanı anında metastatik hastalığa sahipti. Kemoterapiye rağmen ilk olguda hastalık ilerlemiş ve hasta tanı sonrası 9. ayda kaybedilmiştir. İkinci hasta sistektomiyi takiben radyoterapi ve kemoterapi almıştır. İkinci hasta böbrek nakli sebebiyle immünitesi baskılanmış olmasına rağmen, tanı sonrası 27. ayda hastalıksız ve sağdır. Augmentasyon sonrası mesane kanseri gelişme riski kanıtlanmış bir gerçektir. Tanı için uygun bir yöntem keşfedilene kadar augmentasyon iliosistoplasti sonrası 10. yıldan sonra hastalara rutin yıllık sistoskopik biyopsilerin yapılmasını öneriyoruz.
Anahtar Kelimeler: Augmentasyon, İliosistoplasti, Adenokarsinom, Mesane, Malignite

Introduction

Augmentation cystoplasty (AC) is the most definite procedure providing good renal function and continence to patients. The development of malignancy after AC is a known fact but the necessity of routine surveillance is still controversial. As to draw attention to malignancy risk after AC, we present our two patients who suffered from bladder adenocarcinoma.

Case Presentations

Case 1

The first patient was a 31-year-old male under follow-up after AC. Medical history included AC-Mitrofanoff procedure-psoas hitch in 1995 and left simple nephrectomy in 2012. His serum creatinine level was 1.49 mg/dL at that time. He presented with dysuria and debilitation in August 2015. His serum creatinine level was 3.11 mg/dL. Abdominopelvic computed tomography (CT) revealed a mass lesion originating from the basis-left bladder wall and liver lesions in addition to multiple conglomerated lymphadenopathies (Figure 1). Cystoscopy demonstrated a tumor originating from the native bladder, where the ileal segment was preserved. Transurethral resection and punch biopsy sampling were performed. Pathological examination showed high-grade mucinous adenocarcinoma in the native bladder and chronic inflammatory changes in the ileal part. Because of hydroureteronephrosis, a percutaneous nephrostomy tube was placed. The patient was given 4 cycles of capecitabin

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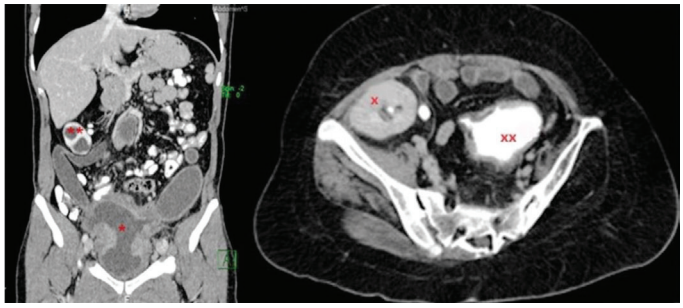

Figure 1. *Mass lesion in the bladder, **right kidney with hydroureteronephrosis (Case 1); ˣtransplanted kidney, ˣˣbladder-confined tumor with diffuse wall thickening (Case 2)

plus oxaliplatin. Re-evaluation revealed progressive disease with new nodules in the right lung basis, multiple metastases emerging in the liver, peritoneal carcinomatosis, and severe right hydroureteronephrosis, despite stable lymphadenopathies and the tumor in the bladder. The second line chemotherapy with 7 cycles of bevacizumab plus irinotecan, fluorouracil, and leucovorin were administered. However, CT showed additional liver metastases, enlarging lymphadenopathies and growing peritoneal carcinomatosis. He was admitted to the hospital with ileus and acute kidney failure (creatinine: 3.56 mg/dL). Abdominal CT revealed partial intestinal obstruction, thus, nasogastric decompression and palliative care were applied. The patient deteriorated rapidly and died during the 10th day of palliative support, 9 months after diagnosis.

Case 2

The second case was a 30-year-old female with a history of meningomyelocele operation in 1985 and ileocystoplasty in 1992. The bladder as well as the ileal segment and junction were tumor-free according to the biopsy sampling done in 2008. She ended up with renal failure and had renal transplantation in 2013. Despite negative conventional urine cytologies, surveillance cystoscopy in August 2015 showed a tumor originating from the native bladder reaching to the junction. Transurethral bladder resection was performed. Pathological evaluation of the tumor showed mucinous adenocarcinoma with muscularis propria invasion in the bladder with chronic inflammatory changes in the ileal segment (Figure 2). Further evaluation by CT demonstrated a tumor confined to the bladder (Figure 1). She received 2 courses of oxaloplatin. Radical cystectomy, hysterectomy and ureterocutaneostomy of the transplanted ureter were performed. Pathological examination showed that the tumor invaded the perivesical fat and parametrium. The ileal segment and uterus/cervix were spared but urethral and radial surgical margins were positive for tumor cells. Three cycles of irinotecan-folinic acid-fluorouracil were planned. Repeat thoracoabdominal CT detected no metastatic disease. After the 4th cycle, she developed toxic hepatitis thus, the chemotherapy was ceased and a 28 day-180 cGy radiotherapy was given.

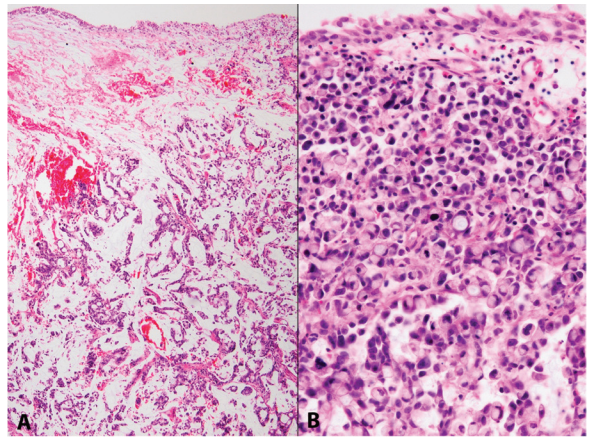

Figure 2. Mucinous adenocarcinoma similar to the first case, having focal signet ring cell morphology (as seen in panel B) with malignant cells containing large intracytoplasmic mucin vacuoles (A: hematoxylin and eosin, 40x; B: hematoxylin and eosin, 200x) (Case 2)

Twenty seven months after the initial diagnosis, the patient was disease-free with a serum creatinine level of 0.6 mg/dL.

Informed consents of patients are obtained for this study.

Discussion

The incidence of malignancy after AC has been reported to vary from 1.2% to 5.5% (1,2). In a recent study, Husmann (3) reported that 2.5% of non-augmented controls developed a bladder tumor, suggesting that augmentation was not primarily responsible for the tumor development. The malignancy risk is increased mostly after 10 years following augmentation (4,5). Malignancy involving the bowel segment, native bladder, anastomosis line or all parts have been reported (5). Stone et al. (6) demonstrated malignancy at the ileovesical junction in three patients 7.22 and 24 years after augmentation ileocystoplasty. Kimura et al. (7) reported adenocarcinoma at anastomosis line and ileum. Our cases had tumors originating from the vesical region and showing adenocarcinoma histology similar to that reported by Ueda et al. (8).

Cases of adenocarcinoma, urothelial carcinoma, squamous cell carcinoma, various sarcomas and small cell neuroendocrine tumors developing after augmentation have been reported (5). El Otmany et al. (9) reported squamous cell carcinoma at the ileal segment. A case of urothelial carcinoma at the ileal segment occurring 43 years after ureteroileocystoplasty has been reported by Nakata et al. (10) in 2005. Sato et al. (11) reported adenocarcinoma of the ileum and transitional cell carcinoma of the native bladder in a patient who had undergone left nephrectomy and augmentation ileocystoplasty 40 years previously. Takasaki et al. (12) reported a case of signet ring cell adenocarcinoma at the ileum 20 years after ileocystoplasty. Both of our patients had mucinous adenocarcinoma, one with signet

ring morphology. Although the signet ring cell morphology is known to have worse prognosis, our second case is disease-free in the 27th month with multimodal treatment.

Some authors suggest routine surveillance with urine cytology, cystoscopy and/or radiologic evaluations in this patient population beginning 5-10 years following AC (2,13). Shokeir et al. (4) recommended routine urine cytology at least annually beginning 10 years after surgery. Moudouni et al. (14) recommended surveillance to be started between the 5th and 10th postoperative years after augmentation.

Despite the numerous cases worldwide, the need for malignancy surveillance after AC has not yet gained universal acceptance. Hamid et al. (1) retrospectively analyzed 92 consecutive patients who underwent regular control cystoscopy 10 years after AC. As the only malignant case in their series was symptomatic, they did not recommend routine cystoscopy yearly at least in the first 15 years (1). Higuchi et al. (15) proposed not to do routine endoscopy and cytology after AC due to low malignant transformation and high cost. It is postulated that after enteric augmentations during a 10-year time span, more than 990 cystoscopies would be performed to find one cancer (13). These studies generate the main controversy on this topic that the authors could not reach a consensus.

We were not able to perform surgery in our first case because of his poor medical condition. He died of rapidly progressive disease. Despite her immunosuppressed condition, our second case is still alive with no evidence of disease after extensive surgery, chemotherapy and radiotherapy. This limited experience has shown us the value of multimodal approach with debulking surgery and adjuvant therapies in patients with mucinous adenocarcinoma.

As the malignancy risk after bladder augmentation is a proven fact, the need for a more cost-effective and useful surveillance tool is clear. We believe that a method less invasive than endoscopic biopsy and more sensitive than urine cytology should be used in daily practice. Until the discovery of a proper diagnostic method, we recommend doing routine annual cystoscopic biopsy for patients starting after the 10th year of augmentation ileocystoplasty.

Ethics

Informed Consent: Informed consents of patients are obtained for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.C., A.E., B.A., D.E.B., S.T., Concept: E.C., H.S.D., A.E., S.T., Design: E.C., H.S.D., S.T., Data Collection or Processing: E.C., H.S.D., A.E., D.E.B., Analysis or Interpretation: E.C., A.C.B., K.K., Ke.K., Literature Search: E.C., Writing: E.C., H.S.D., D.E.B., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Transplant Survey

Doi: 10.4274/jus.2019.06.001

Re: Fosfomycin Trometamol in the Prophylaxis of Post-kidney Transplant Urinary Tract Infection: A Controlled, Randomized Clinical Trial

Arreola-Guerra JM[1], Rosado-Canto R[1], Alberú J[2], Maravilla E[3], Torres-González P[3], Criollo E[4], Pérez M[5], Mancilla E[5], Arvizu M[6], Morales-Buenrostro LE[6], Vilatobá-Chapa M[2], Sifuentes-Osornio J[1]

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Transpl Infect Dis 2018;20:e12980. doi: 10.1111/tid.12980. Epub 2018 Sep 10.

EDITORIAL COMMENT

This is a well designed randomized, controlled, double-blind clinical trial evaluating whether the addition of fosfomycin trometamol (FOS) to trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis following renal transplantation diminishes the risk of urinary tract infection (UTI) during the first 6 months following renal transplantation in adult patients. The intervention group (group 1, n=32) received FOS every 10 days and TMP-SMX three times per week; the control group (group 2, n=35) received TMP-SMX daily. The authors found no difference in the time to first infection or the incidence of infections with the addition of FOS, and the study was halted at the time of intermediate analysis, as there was no possibility of benefit. A higher incidence of bacteriuria was reported than in previous years, with high levels of fosfomycin-resistant Klebsiella. Although interventions performed by the authors, such as catheter and stent placement, were quite standard, it is possible that these results may not be generalized to other settings with different patterns of infection and resistance like in patients undergoing urological procedures and in females with recurrent UTI in whom FOS has been superior.

Yarkın Kamil Yakupoğlu, MD

Transplant Survey

Doi: 10.4274/jus.2019.06.002

Re: Hand-assisted Laparoscopic Retroperitoneal Donor Nephrectomy: A Single-institution Experience of Over 500 Cases-operative Technique and Clinical Outcomes

Kumar S, Witt RG, Tullius SG, Malek SK

Brigham and Women's Hospital, Clinic of Surgery, Boston, MA, USA

Clin Transplant 2018;32:e13261. doi: 10.1111/ctr.13261. Epub 2018 May 12.

EDITORIAL COMMENT

Laparoscopic living donor nephrectomy is the gold standard for performing live donor nephrectomies, however, there is no consensus as to the best variation of the technique. In this single center retrospective study, the authors have described their hand-assisted laparoscopic retroperitoneal donor nephrectomy technique and outcomes in 507 consecutive donors over a 14-year period. The authors have completed their procedures with low morbidity and short operative times, and with safe removal of either the right (33.7%) or left kidney (66.7%), regardless of vascular anatomy with minimal warm ischemia time, without the need for conversion to open procedure. Lack of venous thrombosis in right donor nephrectomies and only one incisional hernia development are of importance in contradiction to previously reported series. However, the retrospective nonrandomized nature of the study prevents making rigid conclusions.

Yarkın Kamil Yakupoğlu, MD

Basic Research

Doi: 10.4274/jus.2019.06.003

Re: A Literature Review of Proton Beam Therapy for Prostate Cancer in Japan

Hoshina RM[1], Matsuura T[2,3,4], Umegaki K[2,3,4], Shimizu S[2,3,5]

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J Clin Med 2019;8. pii: E48. doi: 10.3390/jcm8010048.

EDITORIAL COMMENT

Prostate cancer (PCa) is one of the most common urological malignancies in men. The PCa incidence increases with age in addition to other comorbidities. Therefore, individualized therapy is the most suitable treatment modality. There is a variety of management options for PCa such as surgery, radiotherapy, hormone therapy, ablative therapy, active surveillance, as well as multimodal therapies. One of the standard treatments for localized PCa is radiation therapy, but it has considerable acute and late adverse effects on the gastrointestinal and genitourinary tract. Over the years, new radiotherapy techniques, such as image-guided radiotherapy, 3-dimensional conformal radiation therapy and intensity-modulated radiotherapy have decreased the risk of organ toxicity. On the other hand, the use of proton beams in radiation therapy further more reduces this probability. The two proton beam delivery techniques- passively scattered and intensity-modulated proton therapy-have been described in which irradiation affects only a localized area with reduced risk of damage to the adjacent tissues. Disadvantages of proton beam therapy (PBT) are the size of the device, cost, PBT facilities, and insurance. There have been various studies regarding the efficacy and adverse effects of PBT in patients with localized PCa. However, very few developed countries have this overly expensive treatment modality. In this review, Japanese authors have reported their results about this topic. PBT can be a suitable treatment option for localized PCa as a monotherapy or multimodal therapy for prognosis and quality of life of patients. In the near future, with further researches, development of engineering methods and achieving cost effectiveness, the role of PBT in the treatment of PCa may be clarified.

Fehmi Narter, MD, PhD

Basic Research

Doi: 10.4274/jus.2019.06.004

Re: Genomic Markers in Prostate Cancer Decision Making

Cucchiara V[1], Cooperberg MR[2], Dall'Era M[1], Lin DW[3], Montorsi F[4], Schalken JA[5], Evans CP[1]

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Eur Urol 2018;73:572-582. doi: 10.1016/j.eururo.2017.10.036. Epub 2017 Nov 10.

EDITORIAL COMMENT

Prostate cancer (PCa) is the most common urological cancer in men and prostate-specific antigen remains one of the most useful biomarkers for the diagnosis and treatment of this disease. However, it has limited specificity and there is a need for more sensitive and specific biomarkers. In this context, after the extraordinary development in molecular and genomic techniques, new biomarkers have been described. These assays have been classified as the urine-based, blood-based and tissue-based methods. SelectMDx, Mi-Prostate Score, and ExoDx can be useful in identification of patients who may benefit from prostate biopsy. PCA3 and ConfirmMDx predict the outcome of subsequent biopsy in men with previous negative pathological findings. Decipher, Oncotype DX, and Prolaris are commercially available tools and can be used for PCa risk stratification and identifying men at the highest risk of adverse outcome. Furthermore, some markers, such as androgen receptor splice variant 7 (AR-V7) expression and mutations in DNA mismatch repair genes, may help select treatment in castration-resistant PCa. AR-V7 expression predicts resistance to abiraterone/enzalutamide, while poly polymerase-1 inhibitor and platinum-based chemotherapy could be indicated in metastatic patients who are carriers of mutations in DNA mismatch repair genes. Introduction genomic biomarkers have improved the detection, prognosis, and risk evaluation of PCa. In the near future, we may use many biomarkers for diagnosis, follow-up and treatment of PCa.

Fehmi Narter, MD, PhD

Andrology

Doi: 10.4274/jus.2019.06.005

Re: Five Things I Wish I Would Have Known Earlier in My Career: Lessons Learned in Peyronie's Disease Surgery

Lue TF, Shindel AW

University of California-San Francisco Faculty of Medicine, Department of Urology, San Francisco, CA, USA

J Sex Med 2018;15:1070-1072. doi: 10.1016/j.jsxm.2018.04.645. Epub 2018 May 31.

EDITORIAL COMMENT

In this invited commentary, World's famous expert in Peyronie's disease (PD) surgery, Tom Lue et al. shared their decades of experiences on use of saphenous vein for plaque incision and grafting, management of large calcified or ossified plaques, circumcising vs longitudinal incisions, management of hourglass deformity and circumferential narrowing, and management of residual curvature after penile prosthesis implantation. The authors suggest no treatment in patients for whom penile deformity poses no or minimal bother. They stated that surgery was indicated for large ossified plaques, severe hourglass deformities or indentations with marked hinging, curvatures greater than 90°, and failure of collagenase. They recommended collagenase injections as a safe and effective first-line therapy for bothersome PD.

Emre Bakırcıoğlu, MD

Andrology

Doi: 10.4274/jus.2019.06.006

Re: Collagenase Clostridium Histolyticum for the Treatment of Peyronie's Disease: A Prospective Italian Multicentric Study

Capece M[1], Cocci A[2], Russo G[3], Cito G[2], Giubilei G[4], Cacciamani G[5], Garaffa G[6], Falcone M[7], Timpano M[7], Tasso G[2], Sessa F[2], Campi R[2], Di Maida F[2], Cai T[8], Morelli G[9], Giammusso B[3], Verze P[1], Palmieri A[1], Ralph D[6], Mirone V[1], Mondaini N[10]

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Andrology 2018;6:564-567. doi: 10.1111/andr.12497. Epub 2018 May 7.

EDITORIAL COMMENT

Collagenase clostridium histolyticum (CCH) is the first licensed drug for the treatment of Peyronie's diease and is indicated in patients with palpable plaque and a curvature deformity of ≥30°. This multicentiric study focused on the results of CCH injections performed in five centers in Italy. A total of 135 patients have completed the treatment with three injections of CCH (0.9 mg) given at 4-week intervals in combination with home modeling activities including stretching and vacuum device use on a daily basis. An improvement in the angle of curvature was recorded in 94.8% of the patients by a mean of 19° (0-40°) or 42.9% (0-67%) from baseline ($p<0.001$). There was a statistically significant improvement in all international index of erectile function and physician data query questionnaires subdomains. This prospective multicentric study confirms that the three-injection protocol is effective enough to achieve a good result and to minimize the cost of the treatment.

Emre Bakırcıoğlu, MD