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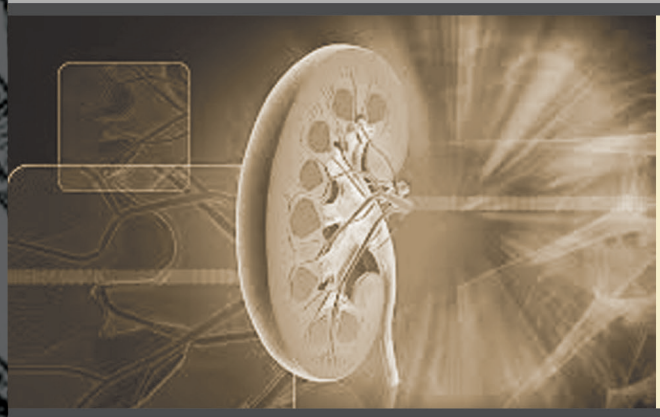

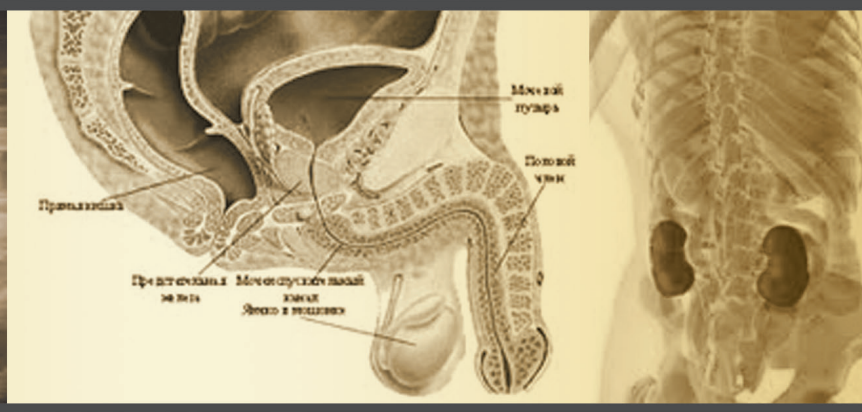

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3. Complete Book

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).

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

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REVIEW

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Current Approaches to Surgical Antimicrobial Prophylaxis and Use of Antimicrobial Prophylaxis in Urological Procedures

Cerrahi Öncesi Profilakside Güncel Yaklaşımlar Işığında Ürolojik Preoperatif Antibiyotik Uygulamaları

Pınar Şen, Tuna Demirdal

İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Department of Infectious Disease and Clinical Microbiology, İzmir, Turkiye

Abstract

Surgical site infections (SSIs) are the most common and preventable type of healthcare-associated infections in low and middle-income countries and affect one-third of patients that have undergone surgical procedures. As the number of surgical procedures performed increases, the prevention of SSIs becomes more important. It is considered that, it is possible to prevent approximately half of all SSI cases. However, due to the contribution of many factors to the development of SSIs, it may be difficult to effectively prevent these infections, and there is a need to take various preventive measures before, during and after surgery. This review presents the current recommendations on the use of prophylactic antimicrobial agents for the prevention of SSIs and recommendations about antimicrobial prophylaxis in urological procedures.
Keywords: Surgical site infections, antibiotics, prophylaxis

Öz

Cerrahi alan enfeksiyonları (CAE) en sık görülen sağlık bakımıyla ilişkili enfeksiyonlar olup önlenebilir olması nedeniyle önem arz etmektedir. CAE önlenmesi için uygulama çeşitleri gittikçe artmakta ve buna bağlı olarak kanıta dayalı müdahale talepleri gün geçtikçe artmaktadır. Bu nedenle önceden yayınlanan kılavuzlara ek güncelleme ihtiyacı doğmaktadır. Yeni ve güncellenmiş öneriler sadece sağlık mensupları için değil, aynı zamanda profesyonel dernek ve kuruluşlar için de bir kaynak olabilme özelliğini taşımaktadır. Bu derlemede CAE önlemeye yönelik profilaktik antimikrobiyal ajan kullanımıyla ilgili güncel önerileri sunmak amaçlanmıştır.
Anahtar Kelimeler: Cerrahi alan enfeksiyonları, antibiyotik, profilaksi

Introduction

Healthcare-associated infections are the most important adverse events that affect patient safety across the globe (1). The World Health Organization (WHO) has reported that surgical site infections (SSIs) are the most common and preventable type of healthcare-associated infections in low- and middle-income countries and affect one-third of patients that have undergone surgical procedures (1,2). According to the Ministry of Health in Turkey, SSIs are the third most common healthcare infections in the country, accounting for approximately 20% of all infections (2). In Turkey, the incidence of SSIs after surgery has been reported to be 1% by the National Hospital Infection Control Unit whereas it is 1.9% in the United States (1,3,4,5).

As the number of surgical procedures performed increases, the prevention of SSIs becomes more important (6). It is considered that by using evidence-based strategies, it is possible to prevent approximately half of all SSI cases (7). However, due to the contribution of many factors to the development of SSIs (8), it may be difficult to effectively prevent these infections, and there is a need to take various preventive measures before,

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during and after surgery. Improving surgical techniques and ventilation in the operating room, sterilization, barrier precautions, and antibiotic prophylaxis are among the main measures for preventing SSI-related morbidity and mortality (8,9). Thus, surgeons, infectious disease specialists and healthcare workers play a major role in protecting patients from SSIs (2). This review presents the current recommendations on the use of prophylactic antimicrobial agents for the prevention of SSIs, provided by various guidelines [WHO, Centers for Disease Control and Prevention (CDC), American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, the Society for Healthcare Epidemiology of America and the European Association of Urology (EAU)].

Definition of Surgical Site Infections

Different definitions have been made in relation to SSIs, however, all sources agree that there is no single objective gold standard test for these infections (10). According to the definition provided by CDC, SSI is a post-operative infection that occurs at the site of incision, in the organ or at the surgical site (10). Based on this definition, SSIs are divided into the following three classes; superficial incisional, deep incisional, and organ/space (11). Superficial and deep incisional SSIs are further classified as primary or secondary according to the infection being identified in the first incisional line or second incisional line in the presence of multiple incisions, respectively (8,11). Taking the day of surgery as the first day, superficial incisional SSIs are defined as the presence of infections in the skin and subcutaneous tissue that develop within the first 30 days of procedures performed with an incision (8,11). Deep incisional SSIs are infections that develop in the deep tissue incision, such as the muscle or fascia within 30 or 90 days of surgery, and lastly, organ/space SSIs are those that involve any body region deeper than the muscle/fascia layer and develop within 30 or 90 days of surgical intervention (11). Table 1 shows the types of surgery in which 30-day and 90-day surveillance for SSIs are undertaken.

The degree of wound contamination is one of the most important factors in the development of SSIs (12). Surgical wounds are divided into the four classes of clean, clean-contaminated, contaminated, and dirty-infected (2). According to the US National Nosocomial Infections Surveillance (NNIS) system, the rate of infection is 1-3% in clean wounds, 3-10% in clean-contaminated wounds, 5-15% in contaminated wounds, and 7% in dirty-infected wounds (12).

Causative Microorganisms

The main source of SSI-causative microorganisms is endogenous fluoride from the mucous membranes, skin and intestinal system (9). The most determinative factor in determining the agents to be used in antibiotic prophylaxis is the identification of microorganisms and resistance patterns that are most often the agents of SSIs. The presence of more comorbid diseases in surgical patients in recent years and the emergence of pathogens resistant to antimicrobial agents lead to additional cost and

Table 1. Surveillance periods according to surgical procedure (11)

30-day surveillance	90-day surveillance
- Abdominal aortic aneurysm repair	- Open reduction of fracture
- Shunt for dialysis	- Herniorrhaphy
- Neck surgery	- Breast surgery
- Kidney surgery	- Cardiac surgery
- Exploratory laparotomy	- Coronary artery bypass graft (with both chest and donor site incisions or chest incision only)
- Limb amputation	- Hip/knee prosthesis
- Vaginal/abdominal hysterectomy	- Craniotomy
- Cesarean section	- Peripheral vascular bypass surgery
- Appendix/small colon/colon/rectal surgery	- Pacemaker surgery
- Carotid endarterectomy	- Spinal fusion
- Laminectomy	- Ventricular shunt
- Gastric surgery	
- Ovarian surgery	
- Prostate surgery	
- Bile duct, liver or pancreatic surgery	
- Spleen surgery	
- Thyroid and/or parathyroid surgery	
- Thoracic surgery	
- Liver/kidney/heart transplant	

difficulties in the treatment of SSIs (13,14). Therefore, it is important to determine the most frequent bacterial agents. The most common pathogens reported in one or more SSIs by 1029 health institutions include; *Staphylococcus aureus* (30.4%), coagulase-negative *staphylococci* (11.7%), *Escherichia coli* (9.4%), *Enterococcus faecalis* (5.9%), *Pseudomonas aeruginosa* (5.5%), *Enterobacter* spp. (4%), and *Klebsiella* spp. (4%) (15). Endogenous and exogenous fungi, such as *Candida albicans* rarely present as the cause of SSIs (15).

Surgical Site Infection Risk Factors

There are many factors that affect surgical wound healing and the possibility of infection (16), including patient-related (endogenous) and procedure-related (exogenous) variables (1). Some factors, such as patient age and gender are fixed but other potential variables, e.g., nutritional status, smoking, rational antibiotic use, compliance with asepsis-antisepsis techniques, technical conditions of the operating room, and intraoperative techniques, can be improved to provide positive surgical outcomes (1,16). A systematic review of 57 studies conducted in various countries showed that a high body mass index, severe wound class, diabetes, and a high NNIS risk index were associated with increased SSIs (17). The NNIS index is a classification developed by the CDC to identify risk of SSIs after surgery and compare the infection rates between surgical patients (18). This scoring system is based on different variables, such as the physical status score in the scale developed by the American Society of Anesthesiologists and the duration of operation (18). Other risk factors include increased prevalence of resistant microorganisms, increased number of patients with comorbidities and immunosuppression due to the prolonged life span, and the increasing number of surgical interventions undertaken for these patients (e.g., prosthetic applications and organ transplantation) (8), as well as non-compliance with surgical asepsis and inappropriate use of antibiotics (8,19).

Recommendation Categories

Recommendations regarding the prevention of SSIs have been grouped into the following categories based on a standard system reflecting the level of supporting evidence and regulations (20):

- **Category IA:** A strong recommendation supported by high to moderate quality evidence suggesting net clinical benefits or harms.
- **Category IB:** A strong recommendation supported by low quality evidence suggesting net clinical benefits or harms or an accepted practice (e.g., aseptic technique) supported by low to very low-quality evidence.
- **Category IC:** A strong recommendation required by state or federal regulation.
- **Category II:** A weak recommendation supported by any quality evidence suggesting a trade-off between clinical benefits and harms.
- **No recommendation/unresolved issue:** An issue for which there is low to very low-quality evidence with uncertain trade-offs between the benefits and harms or no published evidence on outcomes deemed critical to weighing the risks and benefits of a given intervention.

Current Recommendations

- **Parenteral Antimicrobial Prophylaxis**

Preoperative antimicrobial agents should only be administered in the presence of indications based on published clinical practice guidelines and in cases where sufficient bactericidal concentrations of serum and tissue are achieved with incision (category IB) (Table 2) (20,21,22). The 1999 CDC guidelines and other clinical practice guidelines for the prevention of SSIs recommend a single intravenous dose of prophylactic antibiotic only when it is indicated as appropriate (16). For most prophylactic agents, the 1999 CDC guidelines recommend the administration of antimicrobial prophylaxis 60 minutes before incision, but for vancomycin and fluoroquinolones, this should be administered 60 to 120 minutes before incision (1,16,21). However, there is no clear data concerning the need for complete or partial infusion of the parenteral antibiotic dose prior to surgical incision (20).

Preoperative antimicrobial agents should not be administered based on clinical outcomes (in cases of no recommendation/unresolved issue) (20).

In all cesarean procedures, an appropriate parenteral prophylactic antimicrobial agent should be administered before skin incision (category IA) (20). Clinical practice guidelines suggest using prophylactic antibiotics 60 minutes prior to skin incision in both elective and emergency cesarean sections (21,22,23). Antimicrobial prophylaxis is no longer recommended after cord clamping (16).

In clean and clean-contaminated procedures, no additional prophylactic antimicrobial agents should be administered after the closure of surgical incision even in the presence of a drain (category IA) (20).

A review of the literature shows the lack of randomized controlled trials evaluating the benefits and ill effects of weight-adjusted parenteral antimicrobial prophylaxis and their impact on SSI risk (no recommendation/unresolved issue) (20). However, recommendations have been made based on observational and pharmacokinetic data (20). Clinical practice guidelines suggest increasing the dose of single-dose prophylactic antimicrobial

agent to be used in obese and morbidly obese patients (21,22,23,24). For example, for cefazolin, >2 g is recommended for patients weighing 60-80 kg and 3 g for patients >120 kg (21,23,25). The appropriate dose for aminoglycosides should be calculated by adding 40% of the difference between the actual and ideal body weights of patients to their ideal body weight (21,24,26). For vancomycin, the recommended dose is 15 mg/kg (25).

There are only a limited number of randomized controlled trials that have investigated the benefits and ill effects of a repeated intraoperative dose of parenteral prophylactic antibiotics to prevent SSI (no recommendation/unresolved issue) (20). However, suggestions have been made based on observational and pharmacokinetic data (20). Clinical practice guidelines indicate that prophylactic antimicrobial agents should be repeated in cases of prolonged treatment (when the duration of the surgical procedure exceeds the prophylactic half-life of the antibiotic or is longer than 3-4 hours), blood loss of more than 1500 mL, and widespread burns (21,24,25,27).

A wide-scale meta-analysis of the efficacy and optimal application duration of postoperative antimicrobial prophylaxis demonstrated high quality evidence that there was no benefit in continuing antimicrobial prophylaxis after the closure of surgical incisions (28,29,30). A meta-analysis of three randomized controlled trials in cardiovascular surgery showed moderate quality evidence that the continuation of antimicrobial prophylaxis did not provide any additional benefits after intraoperative closure of surgical incision (28,31,32).

Table 2. Suggested empiric antibiotics by surgical procedure (21,22)

Surgery	Suggested antibiotics	ß-lactam allergy
Cardiac/vascular/thoracic surgery	Cefazolin	Vancomycin[1]
Cardiac surgery with prosthetic material	Cefazolin + vancomycin	Vancomycin[1]
Cardiac device insertion (pacemaker implantation)	Cefazolin	Vancomycin[1]
Gastroduodenal surgery	Cefazolin	Vancomycin[1] + gentamicin
Biliary tract surgery	Cefazolin	Metronidazole + levofloxacin
Colorectal surgery, appendectomy	Cefazolin + metronidazole	Metronidazole + levofloxacin
Other general surgery (hernia repair, breast)	Cefazolin	Vancomycin[1]
Gynecological (hysterectomy), cesarean delivery	Cefazolin	Clindamycin[1] + gentamicin
Head and neck surgery	Clean: Cefazolin Clean-contamined: • Ear/sinonasal procedure: Cefazolin • Oral mucosal procedure: Cefazolin + metronidazole Contamined: Cefazolin + metronidazole	Clindamycin
Neurosurgery	Cefazolin	Vancomycin[1]
Orthopedic surgery	Cefazolin	Vancomycin[1]
Plastic surgery	Cefazolin	Vancomycin[1]
Urological surgery[2]	Cefazolin	Clindamycin[2a] + gentamicin[2b]
		Open/laparoscopic surgery: (clean) (skin incision, does not involve genitourinary tract) Clindamycin[2a]
	Open/laparoscopic surgery involving intestine: (clean-contamined) (radical cystectomy + ileal conduit) Cefoxitin	Open/laparoscopic surgery involving intestine: (clean-contamined) (radical cystektomy + ileal conduit) Metronidazole + levofloxacin
	If prosthetic material involved in urologic procedures, should add one-time dose of gentamicin	If prosthetic material involved in urologic procedures, should add one-time dose of gentamicin if not already given

[1]Clindamycin can be used as an alternative to vancomycin. Clindamycin and vancomycin are recommended alternative agents to cefazolin for patients with beta-lactam allergies, [2]Urology notes, [2a]If significant concern for methicillin-resistant ***Staphylococcus aureus***, vancomycin should be considered as an alternative to clindamycin, [2b]Ciprofloxacin is a reasonable alternative. However, according to the 2015 SHC antibiogram, more ***Escherichia coli*** isolates were susceptible to aminoglycosides than fluoroquinolones (http://lane.stanford.edu/biomed-resources/antibiograms-shc.html)

- **Non-parenteral Antimicrobial Prophylaxis**

The existing randomized controlled trials present contradictory data concerning the benefits and ill effects of intraoperative antimicrobial irrigation (e.g., intra-abdominal, deep or subcutaneous tissues) in preventing SSIs (no recommendation/unresolved issue) (20). Two clinical practice guidelines based on reviewing evidence suggest using antimicrobial wound irrigation or intracavity lavage to reduce the risk of SSI (1,27).

There is no randomized controlled study that evaluated soaking prosthetic devices in antimicrobial solutions before implantation for the prevention of SSIs (no recommendation/unresolved issue) (20).

Antimicrobial agents (e.g., ointments, solutions or powders) should not be applied to surgical incision to prevent SSIs (category IB) (20). However, clinical practice guidelines have different approaches concerning the recommendation of the application of non-parenteral antimicrobials to surgical incision in the absence of SSIs (27,33).

Autologous platelet-rich plasma transfusion (spray or gel) is not considered necessary for the prevention of SSIs (category II) (20).

The use of triclosan-coated sutures should be considered for preventing SSIs (category II) (20).

In randomized controlled trials in the literature, it has been suggested that there was uncertainty regarding the benefits and ill effects associated with antimicrobial dressings applied to surgical incisions following primary closure in the operating room (no recommendation/unresolved issue) (20).

Current Recommendations on Prophylaxis in Urological Surgery

EAU Panel of Urological Infection Guidelines consists of a group of urologists with expertise in this field and in infectious diseases. These Urological Infection Guidelines, first published in 2001 and revised in 2017, state that the infection risk varies according to the type of intervention, and there are no clear instructions concerning antimicrobial prophylaxis due to the wide variety of the intervention types and the recent developments in minimally invasive surgery; thus, these guidelines propose evaluating the requirements of each case individually to make a decision about prophylaxis (34). Furthermore, according to the EAU guidelines, when selecting antimicrobial agents, the role of local pathogen profiles, pathogen susceptibility and virulence, procedure-specific risk factors, contamination load, target organ and local inflammation should be taken into consideration (34). Table 3 presents the recommendations on antimicrobial prophylaxis according to surgical procedure. In cases where antimicrobial prophylaxis is indicated, fluoroquinolones, trimethoprim ± sulfamethoxazole, aminopenicillin/beta-lactamase inhibitor, second- or third-generation cephalosporin, or even piperacillin/tazobactam are among the recommended agents.

Prophylaxis in Diagnosis

- **Cystoscopy**

The frequency of infectious complications reported after cystoscopy, standard urodynamic investigation and ureteroscopy is very low if the urine is sterile in the preoperative period (35). Routine antimicrobial prophylaxis is not recommended due to the frequency of diagnostic cystoscopy, low risk of infection, and developing bacterial resistance (34). However, bacteriuria, permanent catheterization, neurogenic lower urinary tract disease, and urogenital infection history are among the risk factors that should be considered (36).

- **Transrectal Prostate Biopsy**

It has been found that administration of antimicrobial prophylaxis in transrectal prostate biopsy significantly reduces the risk of infection after the procedure (37); therefore, antimicrobial prophylaxis is recommended after transrectal biopsy (34). Although fluoroquinolones are the most frequently used agents in prophylaxis, the duration of prophylaxis and the choice of antibiotics should be discussed first (34). It has also been reported that the use of fosfomycin trometamol or prophylactic antimicrobial based on rectal swab is currently being investigated as an alternative to antimicrobial prophylactic agents, meta-analyses are being undertaken, and new recommendations on prophylaxis will be included in guidelines to be published in the following years (38,39,40).

Prophylaxis in Endourological Treatment Procedures (Urinary Tract Entered)

- **Transurethral Resection of the Bladder**

There is limited evidence of the benefit of antimicrobial prophylaxis before transurethral resection of the bladder (34). In studies on the benefits of prophylaxis, no distinction has been made concerning simple fulguration, large or multiple tumors, or presence of necrotic material. Therefore, the present guidelines recommend the selection of appropriate prophylaxis depending on the tumor differentiation.

- **Transurethral Resection of the Prostate**

According to the results of a considerable number of studies undertaken on this procedure, antimicrobial prophylaxis

Table 3. Recommendations for propylactic agent in urological surgery (33)

Surgical procedure	Antimicrobial prophylaxis
Diagnostic procedures	
Cystoscopy	-
Urodynamic study	-
Transrectal core biopsy of prostate	Fluoroquinolones Trimethoprim ± sulphamethoxazole
Diagnostic ureteroscopy	Optional
Endourological/endoscopic therapeutic procedures	
Fulguration of small baldder tumours	Optional
Transurethral resection of the bladder	Trimethoprim ± sulphamethoxazole
Transurethral resection of the prostate	Aminopenicillin / beta-lactamase inhibitor
Shock-wave lithotripsy	Cephalosporin (2 or 3. group)
Ureteroscopy for stone management	
Percutaneous and retrograde intrarenal stone management	
Open and/or laparoscopic surgery	
Nephrectomy ± ureterectomy	Optional
Adrenalectomy	
Radical prostatectomy	
Planned scrotal surgery, vasectomy, varicocele surgery	-
Prosthetic implants	Aminopenicillin/beta-lactamase inhibitor
Artificial sphincter	Piperacillin/tazobactam
Ureteropelvic junction repair	Optional
Partial bladder resection	Optional
Cystectomy with urine deviation	Cefuroxim Aminopenicillin/beta-lactamase inhibitor + metronidazole

significantly reduces bacteriuria and septicemia, and prophylactic agents before transurethral resection of the prostate is recommended (35).

- **Ureteroscopy**

There are no prospective controlled studies evaluating the use of prophylactic agents in ureteroscopy (34). The current guidelines state that a differentiation should be made between diagnoses in healthy individuals pertaining to low-risk procedures, such as treatment of distal ureteral stones and high-risk procedures; e.g., treatment of obstructing proximal stones. Therefore, it is advisable to take the decision concerning prophylactics based on patient-related risk factors (41).

- **Percutaneous Nephrolithotripsy**

It has been shown that the infection risk is high in percutaneous nephrolithotripsy and retrograde intrarenal stone treatment, and prophylactic antibiotics significantly reduce the risk of infectious complications (41,42). It has been noted that in these cases, a single dose of prophylactic antibiotics is sufficient (43).

- **Extracorporeal Shock Wave Lithotripsy**

Antimicrobial prophylaxis is not recommended as a standard application in extracorporeal shock wave lithotripsy (35). However, it is indicated to use prophylaxis for the control of bacteriuria and in elevated bacterial load, such as permanent catheter, nephrostomy tube, or presence of infective stones (44).

- **Laparoscopic Surgery**

Although there are not an adequate number of studies on antimicrobial prophylaxis in laparoscopic surgery, it seems reasonable to follow the recommendations provided for open surgical interventions (34).

- **Nephrectomy, Adrenalectomy**

Although antimicrobial prophylaxis is not recommended as standard, it has been reported that in some cases, its use can be assessed at the discretion of the surgeon (45).

- **Prostatectomy**

Antimicrobial prophylaxis is recommended in open enucleation of prostate adenoma due to the high risk of postoperative

infection (46). It has been reported that since there is no clear data concerning antimicrobial prophylaxis in radical prostatectomy, this application should be undertaken at the discretion of the surgeon (34).

- **Cystectomy + Ileal Conduit**

The evidence obtained is mostly based on colorectal surgery, and there is only limited data on surgical interventions in urology (19,47). It is recommended to use prophylactic antibiotics as a single dose or for the first 12 hours, however, antimicrobial therapy may be continued up to 72 hours in the presence of factors, such as prolonged surgery or comorbid risk status (34). Antibiotic agents selective to aerobic and anaerobic pathogens should be used.

- **Prosthetic Implantation: Testis, Penile Prosthesis and Artificial Sphincter**

Infectious complications in implant surgery are usually problematic and cause the removal of the prosthesis (48); thus, antimicrobial prophylaxis is recommended (34).

Conclusion

Since SSIs are healthcare-related infections, it is important to effectively prevent patients from contracting them. The number of applications for the protection against SSIs is increasing, which in turn raises the demand for interventions based on evidence. Therefore, there is a need to revise the previously published guidelines. New and updated recommendations will be a guide for not only healthcare professionals, but also for professional associations and organizations. These revisions can also be used to develop more detailed implementation guidelines based on previous documents and identify future research priorities. The unresolved issues mentioned in the revised guidelines refer to important points that need to be investigated in the future. For this reason, there is a need for further well-designed studies.

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Outcomes of Percutaneous Nephrolithotomy in Patients with Anomalous Kidney

Anomalili Böbreği Olan Hastalarda Perkütan Nefrolitotomi Sonuçlarımız

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

There are limited studies related to percutaneous nephrolithotomy in the anomalous kidney. So we decided to share our results by scanning our patient data retrospectively.

Abstract

Objective: To evaluate the success and complication rate of percutaneous nephrolithotomy (PNL) performed in patients with congenital anomalies such as horseshoe kidneys, crossed renal ectopia and renal malrotation.
Materials and Methods: Data of 1472 patients who underwent PNL operation in our clinic between January 2007 and January 2015 were analyzed retrospectively. PNL was performed in 28 renal units of 26 patients with congenital renal anomalies. Demographic data of the patients, type of congenital renal anomalies, success rate of PNL and complications were evaluated.
Results: Out of 28 PNL-performed renal units, 14 were found out to be with fusion and 14 with rotation anomalies. The average age of the patients was 53 (±1.97) years, 19 were male and 7 were female with an average stone size of 515 (±87.4) mm^2. The average operating time was 109 (±11.0) minutes and fluoroscopy time was 191 (±48.4) seconds. The stone-free rate detected postoperatively by computed tomography was 55%. Complications included postoperative fever in 3 patients, postoperative arteriovenous fistula in 1 patient, and intraoperative colon injury in 1 patient.
Conclusion: PNL is a safe and effective method in the treatment of stones in kidneys with congenital anomalies.
Keywords: Anomalous kidneys, complication, percutaneous nephrolithotomy

Öz

Amaç: Atnalı böbrek, crossed renal ektopi ve böbrek malrotasyonu gibi anomalili böbreği olan hastalarda yapılan perkütan nefrolitotomi (PNL) sonuçlarını ve komplikasyonlarını değerlendirmek amaçlandı.
Gereç ve Yöntem: Ocak 2007 ve Şubat 2015 yılları arasında kliniğimizde PNL yapılan 1472 hastanın verileri retrospektif olarak incelendi. Böbrek anomalisi olan 26 hasta ve toplamda 28 renal üniteye PNL yapıldı. Hastaların demografik verileri, konjenital anomalinin tipi, PNL başarısı ve komplikasyonlar değerlendirildi.
Bulgular: Opere edilen 28 renal ünitenin 14 tanesinde füzyon, 14 tanesinde ise rotasyon anomalisi vardı. Hastaların ortalama yaşı 53 (±1,97) yıldı. Hastaların 19 tanesi erkek, 7 tanesi kadındı ve ortalama taş boyutu 515 (±87,4) mm^2 olarak hesaplandı. Ortalama operasyon zamanı 109 (±11,0) dakika ve floroskopi süresi ise 191 (±48,4) saniyeydi. Postoperatif istenen bilgisayarlı tomografide %55 taşsızlık saptandı. Komplikasyon olarak ise 1 hastada intraoperatif kolon yaralanması, 3 hastada ateş yüksekliği ve 1 hastada arteriyovenöz fistül gözlendi.
Sonuç: Konjenital anomalili böbrek taşı tedavisinde PNL güvenli ve başarılı bir yöntemdir.
Anahtar Kelimeler: Anomalili böbrek, komplikasyon, perkütan nefrolitotomi

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Introduction

Clinical approach to kidney stones in abnormal kidneys is regarded as a specific and difficult case in urology practice. Percutaneous nephrolithotomy (PNL) is the gold standard treatment method for kidney stones larger than 2 cm (1). However, it is not established yet for stones that occur in rare cases such as horseshoe kidney, renal malrotation, crossed renal ectopia, and pelvic kidneys.

As for patients with a kidney anomaly, the goal of the treatment for kidney stones is to render the patient free of stone with highest treatment performance and lowest complication rates, as it is for kidneys with normal anatomy. In this study, we evaluated the success rates and complications of PNL that we performed in patients with renal anomalies.

Materials and Methods

A total of 1472 patients, who underwent PNL in our clinic between January 2007 and January 2015, were retrospectively analysed. A total of 26 patients with renal abnormalities (28 renal units) whose data were appropriate and complete were included in the study. Of these, PNL was performed in 14 renal units with fusion anomaly (13 horseshoe kidney, 1 crossed renal ectopia with fusion) and in 14 renal units with rotation anomaly.

All patients were evaluated with non-contrast abdominal computed tomography (CT) preoperatively and informed consent was obtained from patients before the surgery.

Surgical Procedure

Complete blood count, biochemical tests, coagulation tests and urine culture were performed in all patients preoperatively. Appropriate antibiotic treatment was given to patients with positive urinary cultures and they were operated when they had sterile urine cultures. The patient was placed in the prone position after a 6 Fr open-ended catheter was inserted through the urethra via cystoscopy while in the lithotomy position. The procedure was performed under general anesthesia. Following the injection of a contrast agent via the urethral catheter, an access needle was introduced into the renal collecting system through the appropriate calyx under fluoroscopic guidance. After placement of the guiding catheter, the Amplatz dilator set was used in order to create the tract, first with a 6 Fr dilator followed by a 28-30 Fr dilator, using the single step method. If necessary, a second access was created with the same method. The stones were removed by using a 24 Fr nephroscope and an ultrasonic lithotripter. A 14 Fr re-entry Malecot catheter was routinely inserted after the operation was terminated. The stone-free status of the patients was evaluated 1 month after surgery with non-contrast abdominal CT.

Results

The average age of the patients was 53 (±1.97) years; 19 were male and 7 were female. Of patients with horseshoe kidney anomaly, 5 had stones in the right kidney, 3 in the left kidney, and 4 in both kidneys. Among 4 patients with bilateral kidney stones, PNL operation was performed only in one patient in different sessions. Of patients with rotational kidney anomaly, 7 had stones in the left kidney, 6 in the right kidney, and 1 in both kidneys. For patient with rotation anomaly and bilateral kidney stones, PNL was performed in the left kidney and extracorporeal shock wave lithotripsy in the right kidney. The average stone size in 2 dimensional measurements was 812.5 mm^2 in kidneys with horseshoe abnormalities while it was 600 mm^2 in kidneys with rotational abnormalities and 300 mm^2 in crossed renal ectopia (Table 1).

Access was achieved to the stones in anomalous kidneys by a single access in 21 of 28 renal units and by double access in 7 renal units, out of which 3 had horseshoe anomaly and 4 had rotational anomaly. Out of 10 kidneys with horseshoe anomaly, 5 single intercostal accesses were performed in the upper calyx group of the kidney. In one patient with crossed fused renal ectopia, single subcostal access to mid-calyx group was performed. Single access was performed to 10 out of 14 kidneys with rotation anomaly; namely 5 subcostal accesses to mid-calyx group, 4 subcostal accesses to upper calyx group and 1 intercostal access to upper calyx group (Table 2).

Table 1. Characteristics of the patients

Renal anomaly	Horseshoe kidney	Crossed renal ectopia	Rotational anomaly	Total
Renal units (n)	13	1	14	28
Age	53.5	55	50.5	53 (±1.97)
Gender (n)				
Female			8	7
Male	13	1	6	19
Side of stone (n)				
Left	3	1	7	11
Right	5		6	11
Bilateral	5		1	6
Average size of the stone (mm^2)	812.5	300	600	515 (±87.4)
Localization of the stone				
Pelvis	5		5	10
Calyces		1	4	5
Pelvis and calyces	8		5	13

The mean operation and fluoroscopy time and length of hospital stay are noted in Table 3. CT scans taken at postoperative 1st month showed residual stones in 6 of 13 (53% success) horseshoe kidneys. Residual stone was detected in the patient with crossed renal ectopia and in 5 of 14 renal units with rotational anomalies (64% success). 1.55 gr/dL decrease of hemoglobin (Hb) was determined in patients with horseshoe kidney, 5.2 gr/dL in the patient with crossed renal ectopia and 0.9 gr/dL in those with rotational renal anomalies. After discharge, 3 patients were hospitalized again; one with horseshoe kidney due to fever, one with crossed renal ectopia due to fever and recurrent hematuria, and one with rotational anomaly due to fever. The patient with recurrent hematuria was diagnosed with arteriovenous (AV) fistula and treated with superselective embolization. Colon injury was developed in a patient with rotational anomaly and the patient was treated conservatively. None of the patients developed sepsis and required any post-operative intensive care (Table 3).

Table 2. Access details

Renal anomaly	Horseshoe kidney	Crossed renal ectopia	Rotational anomaly	Total
Number of access				
Single	10	1	10	21
Double	3		4	7
Access place				
Upper calyx	13		6	19
Mid-calyx	3	1	9	13
Lower calyx			3	3
Access type				
Intercostal	5		2	7
Subcostal	11	1	16	28

Table 3. Peroperative data and complications

Renal anomaly	Horseshoe kidney	Crossed renal ectopia	Rotational anomaly	Total
Mean operation time (min.)	120	65	120	109 (±11.0)
Mean scopy time (sec.)	120	65	93	191 (±48.4)
Length of hospital stay (day)	2	11	2	3
Success rate	7 (53%)	0 (0%)	9 (64%)	16 (57%)
Postoperative hemoglobin decrease gr/dL	1.55	5.2	0.9	1.77
Complication rates				
Fever	1	1	1	3
AV fistula		1		1
Colon injury			1	1

AV: Arteriovenous

Discussion

Anomalies of fusion are the most common type among renal anomalies and horseshoe kidney is the most common type of fusion anomalies. It occurs in about 1/400 live births in the general population (2).

The final position of the adult kidney in the renal fossa is defined as the positioning of the kidney with an orientation of the renal calyces to outwards (the lateral) and the renal pelvis to inwards (the medial). When this positioning is not complete, then it is called malrotation. One autopsy series reported 1 in 939 cases (2,3).

Crossed fused renal ectopia refers to an anomaly that the kidney is located on the opposite side where its ureter inserts into the bladder. This type is divided into two groups as fused or unfused and also into sub-grubs among themselves according to the form of the anomaly. Its incidence is generally estimated to be 1 in 1.000 live births (2,4).

In patients with renal abnormalities, urinary stasis and infection due to abnormal localization of the renal pelvis and ureter as well as abnormal vascularization lead to stone formation (2).

Technically, PNL operation in a kidney with anomaly is a surgical application that creates concern for urologists. The main factors of difficulty include selecting the appropriate calyx and a suitable angulation for the access and operation within an unusual pelvicalyceal system. Its abnormal relationship with the surrounding organs and its abnormal vascularization, yet requiring abnormal angulation in accessing an abnormal pelvicalyceal, may increase the risk of injury in the surrounding organs and major veins. Most of the horseshoe kidneys reside lower in the abdomen than normal kidneys and intercostal accesses to reach upper- or mid-calyces are needed less than in normal kidneys. For the most reliable access to a horseshoe kidney, the upper calyx group, particularly far posterior and medial calyces should be preferred. Lower pole access is not recommended because the lower calyx group is located medially and anteriorly and in close proximity to the main vessels (5). In our cases, 5 of 16 accesses were intercostal and complications such as pneumothorax and hidrotorax and any pulmonary complications were not seen in any of our patients (6). Abnormal anatomic relationships of the abnormal kidney with the surrounding organs should always be kept in mind by the surgeon. Additionally, in our cases with rotation anomaly, the incidence of injuries to the adjacent organs such as the colon was relatively higher than in normal kidneys. This occurs as a result of incomplete development of the lateroconal fascia of the retrorenal colon and failure of the kidney to attain the

place where it should be and its replacement by colon instead (7). Radio-anatomical evaluation by noncontrast abdominal CT imaging is recommended for all patients in order to prevent possible injury to the adjacent organs (8). The management in a possible colon injury includes withdrawing the nephrostomy slightly to provide it to serve as a drain for the injured region, placing a ureteral stent, and initiating parenteral antibiotherapy as a conservative approach (7). In the group with rotation anomaly, one patient had a colon injury and was treated conservatively. Another handicap originates from abnormal placement of renal vessels, which can result in injury to major vessels, AV fistula and pseudoaneurysms. Only one of our patients experienced vascular injury and this resulted in an AV fistula and treated successfully with superselective embolisation.

In a study of 52 renal anomalies including 31 horseshoes kidneys, 4 crossed ectopia, 7 rotation anomalies and 4 ectopic kidneys, Gupta et al. (9) reported that the mean hospital stay was 3.2 days and the average decrease in Hb was 1.4 g/dL. Mosavi-Bahar et al. (10) reported their own PNL series performed in 7 horseshoes, 5 rotation anomalies, 3 ectopic kidneys and noted length of hospital stay of 3 days and 1.7 g/dL decrease of Hb. The average hospital stay was 3 days and average decrease of Hb was 1.7 g/dL in our study, which is similar to the literature.

Gupta et al. (9) reported a success rate of 86% in the first attempt. The success rate was evaluated by using spot graphics in their study. The success rate in our study was 57%. Stone-free status was assessed by abdominopelvic CT in our study so this may explain the difference between success rates.

Study Limitations

The main limitations of the study include its retrospective design, the fact that surgeries were not performed by the same surgeon, and the relatively low number of patients.

Conclusion

Patients with renal malformation can be treated with PNL safely and effectively.

Ethics

Ethics Committee Approval: Retrospective study.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Which Factors Affect the Hospital Re-admission After Treatment Approaches to Urethral Strictures?

Üretra Darlıklarında Tedavi Yaklaşımlarına Göre Hastaneye Tekrar Başvuruyu Etkileyen Faktörler

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

According to this study because re-admission to the hospital in younger patients with fewer comorbidities can be expected, it may be advisable to discharge this patient group after detailed examination.

Abstract

Objective: To investigate patient- and procedure-related factors associated with hospital re-admission following urethral manipulations for the treatment of urethral strictures.

Materials and Methods: Data of patients who underwent dilation or internal urethrotomy for urethral strictures between 2011 and 2016 were retrospectively analyzed. Patients who were admitted to our institute for any reason within one month after hospital discharge were evaluated. The patient- and procedure-related factors affecting the readmission rates were revealed by multiple binary logistic regression using stepwise backward elinimination.

Results: The average age of 76 male patients was 61.7±14.4 years. The mean maximal flow rate at preoperative uroflowmetry was 6.01±4.3 and the median American Society of Anesthesiologists score was 2.38. The process was the first for 45 (59.2%) patients, the second for 16 (21.1%) patients, the third for 9 (11.8%) patients, and the fourth for 6 (7.9%) patients. Amplatz dilators, cold knife and Ho:YAG laser were used in 50%, 27.6% and 22.4% of patients, respectively. The mean length of hospital stay was 0.89±0.31 days, and the complication rate was 19.7% (15/76). The mean urethral catheter dwell time was 8.9±14.2 day. Overall, the procedure was successful in 61 (80.3%) patients and failed (Q_{max} <15 mL/sec) in 19.7% of the cases. Fifteen (19.7%) patients were re-admitted, while 2 (2.6%) patients among them were re-hospitalized for further treatment. Comorbidity and age were independent predictors of re-admission.

Conclusion: We found that younger age and lower comorbidities predicted hospital re-admission following procedures for urethral strictures.

Keywords: Urethral strictures, re-admission, risk factor

Öz

Amaç: Üretral darlıklara müdahale edildikten sonra hastaneye tekrar başvuru nedenleri ile ilişkili hasta ve prosedüre bağlı faktörleri araştırmaktır.

Gereç ve Yöntem: 2011 ile 2016 yılları arasında üretra darlığı nedeni ile dilatasyon veya internal üretrotomi uygulanan hastaların tıbbi kayıtları retrospektif olarak incelendi. Hastaneden taburcu olduktan sonraki 30 gün içinde hastaneye herhangi bir sebeple yeniden başvuran hastalar değerlendirildi. Tekrar başvuru oranlarını etkileyen hasta ve prosedüre bağlı faktörler, geriye doğru kademeli çoklu ikili lojistik regresyon analizi kullanılarak ortaya çıkarıldı.

Bulgular: Yetmiş altı erkek hastanın yaş ortalaması 61,7±14,4 yıldı. Preoperatif üroflowmetride ortalama maksimal akım hızı 6,01±4,3, ortalama Amerikan Anesteziyologları Derneği skoru 2,38 idi. Kırk beş (%59,2) hastada birinci, 16 (%21,1) hastada ikinci, 9 (%11,8) hastada üçüncü, 6 (%7,9) hastada dördüncü kez işlem yapıldı. Amplatz dilatörleri, soğuk bıçak ve Ho:YAG lazeri sırasıyla %50, %27,6 ve %22,4 hastalarda kullanıldı. Ortalama yatış süresi 0,89±0,31 gün, komplikasyon oranı %19,7 (15/76) idi. Ortalama uretral kateterin kalma süresi 8,9±14,2 gündü. Toplam 61 (%80,3) hastada başarı elde edildi. Olguların %19,7'sinde işlem başarısız oldu (Q_{maks} <15 mL/sn). On beş (%19,7) hasta hastaneye tekrar başvurdu; 2 (%2,6) hasta daha ileri tedavi için hastaneye yatırıldı. Komorbidite ve yaş, hastaneye tekrar başvurunun bağımsız öngörü faktörüdür.

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Sonuç: Genç yaş ve düşük komorbiditenin üretra darlıkları için yapılan müdahaleler sonrasında hastaneye tekrar başvuruyu öngörebileceğini tespit ettik.
Anahtar Kelimeler: Üretral darlıklar, tekrar başvuru, risk faktörü

Introduction

It is necessary to learn more about the causes of hospital readmission following a pathology or an operation to improve the medical care of a patient and medical costs for such a case.

This study investigated the factors that are related to patient and procedure that increase the risk of hospital re-admission following urethral manipulations for the treatment of urethral strictures. As far as we know, this is the first study analyzing the factors affecting these rates.

Materials and Methods

After approval of the Ethics Committee (Institutional Review Board) of the Bülent Ecevit University Faculty of Medicine (date: 08/03/2017, meeting number: 2017/05, protocol number: 2017-34-08/03), the medical records of patients who underwent dilation or internal urethrotomy for urethral strictures in our clinic from 2011 to 2016 were analyzed retrospectively. Patients, who were admitted to our institute for any reason related with the procedure within one month after hospital discharge, were evaluated. The written approval of all patients was obtained. The exclusion criteria were requirement of additional intervention e.g. transurethral prostate resection, transurethral bladder resection, treatment for more than one urethral stricture, any manipulation in the bladder, female gender, and age under 18 years. In this study, demographic data including patient age, American Society of Anesthesiologists (ASA) Physical Status Classification scores, Age-adjusted Charlson Comorbidity Index (ACCI) scores, type of anesthesia used, the location and length of the stricture, stricture etiology, preoperative uroflowmetry and parameters of the procedure, such as duration of the operation, method used in the surgery, the number of operation, properties of the urethral catheter used, length of hospital stay and urethral catheter withdrawal time were all evaluated. All patients were called for control at 1 month postoperatively and follow-up uroflowmetry was performed. If there were patients readmitted within the one month period until the first check-up, the duration, the reasons for re-admission and the type of treatment administered were all assessed.

Surgical Procedure

After giving a second-generation cephalosporin for prophylaxis, all patients were placed in the lithotomy position. With appropriate anesthesia, a standard cystourethroscopy (20 Fr, Storz) was performed to exclude any urethral pathology. When a stricture was measured on a fluoroscopic image or seen on cystoscopy, a 0.035-inch safety wire was pushed forward to the bladder with the patient in the lithotomy position under fluoroscopic control (Figure 1a). Subsequently, a single 12 o'clock incision was made until the full thickness of the fibrous scar was divided with a standard Sachse urethrotomy knife with 21 Fr urethrotome or Holmium laser probe (Stone Light, Mountain View, CA; Quanta System, Group, Italy) with cystoscope (20 Fr, Storz) (Figure 1b) or dilated more than 2 Fr of the planned urethral catheter diameter with amplats dilators after coaxial placement via the guide and under fluoroscopy to minimize the traumatic process (Figure 1c). A complete success

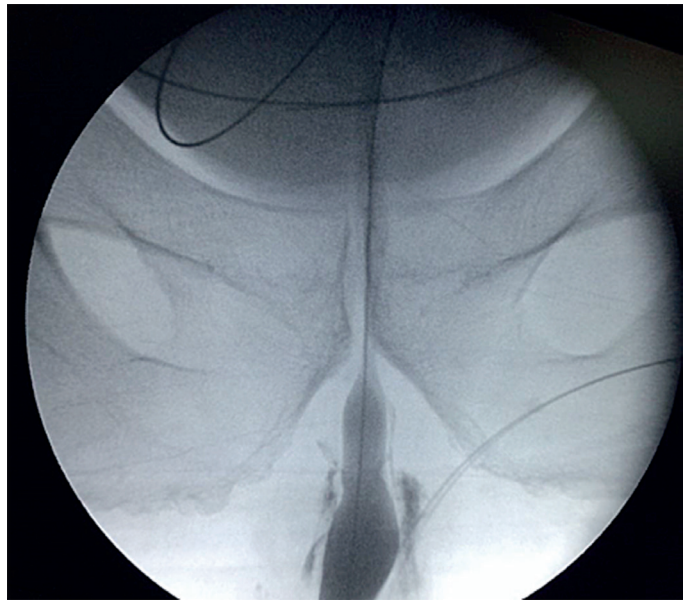

Figure 1a. Advanced guidewire to the bladder under fluoroscopic control

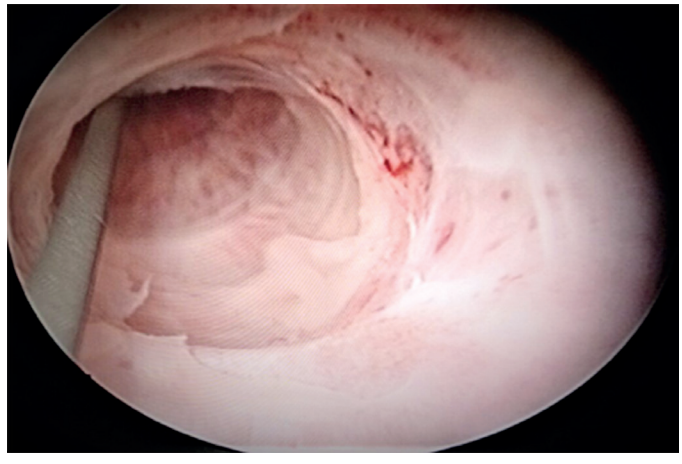

Figure 1b. After incision with a standard urethrotomy knife or Holmium laser

was considered once the 21 F urethrotome sheath or 20 Fr cystoscope was freely inserted into the bladder. After the process a 16 Fr or 18 Fr silicone Foley catheter, occasionally, in recurrent strictures, a wider catheter existing in the operation room, was placed according to the decision of the physician. The patients were discharged with an indwelling catheter in the appropriate postoperative period. Oral second-generation cephalosporin was given until the catheter was removed. Urethral catheters remained in place for up to 90 days.

Statistical Analysis

This study was performed with SPSS 19.0. In the data set, descriptive statistics of the continuous variables were shown as mean and standard deviation and descriptive statistics of the categorical variables were shown as frequency and percent. The chi-square and Mann-Whitney U tests were used for comparison of the categorical variables. The factors influencing the hospital re-admission rates were revealed by multiple binary logistic regression using stepwise backward elimination. A p value of less than 0.05 was considered statistically significant.

Results

The average age of a total of 76 male patients included in the study was 61.7±14.4 (range: 22-82) years. The mean ACCI score was 4.2±2.6 (range: 0-12). The mean maximum flow rate at preoperative uroflowmetry was 6.01±4.3 (0-14). The mean ASA score was 2.38. According to the ASA physical status classification, the patients were categorized as ASA 1 (n=11; 14.5%), ASA 2 (n=28; 36.8%), or ASA 3 (n=34; 44.7 %), or ASA 4 (n=3; 3.9%). The process was the first for 45 (59.2%) patients, the second for 16 (21.1%) patients, the third for 9 (11.8%) patients and the fourth for 6 (7.9%) patients. The data about the strictures is given in Table 1.

Amplatz dilators were used in 38 (50%) patients, cold knife in 21 (27.6%) and holmium laser in 17 (22.4%) patients. The mean duration of the operation was 11.7±2.9 (range: 7-21) minutes. After the operation, in 57.9% of patients, 16 Fr urethral catheter, in 34.2% - 18 Fr urethral catheter, in 3.9% - 20 Fr urethral catheter and in 3.9% of the patients, 22 Fr urethral catheter, all silicon in nature, were inserted.

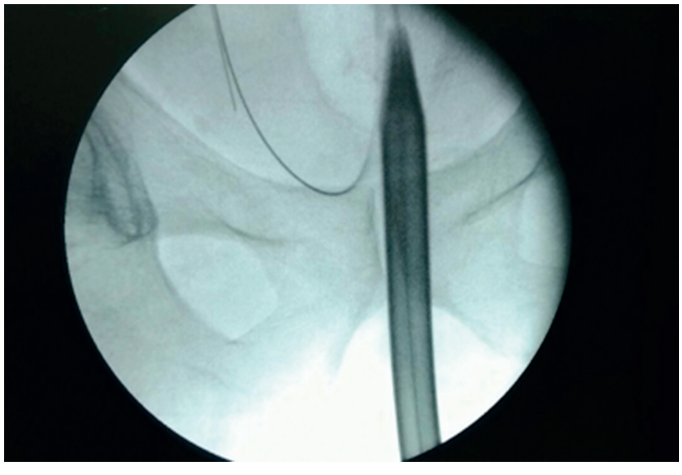

Figure 1c. Amplats dilation via the guidewire under fluoroscopy

The average length of hospital stay was 0.89±0.31 (range: 0-1) days, and the complication rate was 19.7% (15/76). The mean urethral catheter dwell time was 8.9±14.2 days. Overall, the procedure was successful in 61 (80.3%) patients. The procedure failed (Q_{max} <15 mL/sec) in 19.7% of cases. After discharge from the hospital, among 15 (19.7%) patients who were re-admitted, 2 (13.3%) were re-hospitalized for further treatment. The most common causes for re-admission were urinary retention (46.6 %), incontinence (13.3%), and tenesmus (13.3%). One patient (6.6%) with urinary retention and one patient (6.6%) with pulmonary edema were hospitalized again. Overall, 1 (6.6%) patient had grade 1 (hematuria), 6 (40%) had grade 2 (epididimitis; n=1, incontinence; n=2, tenesmus; n=2, dysuria; n=1), 6 (40%) had grade 3a (urinary retention), 1 (6.6%) had grade 3b (urinary retention), and 1 (6.6%) patient had grade 4 (pulmonary edema) complication according to the Clavien-Dindo classification of surgical complications (Table 2).

In Table 3, the therapies administered to overcome the causes of re-admission are summarized.

Table 1. The data about the stricure

Etiology of stricture	**n**	**%**
Primary	6	7.9
RRP	12	15.8
Cystourethroscopy	7	9.2
Urethral catheter insertion	12	15.8
Traffic accident	4	5.3
TUR-P	22	28.9
TUR-B	12	15.8
Urethroplasty	1	1.3
Stricture location	**n**	**%**
Bulbous	17	22.4
Memrenous urethra	39	51.3
Bladder neck	8	10.5
Penile urethra	12	15.8
Sricture length (mm)	**n**	**%**
5	3	3.9
10	61	80.3
20	10	13.2
20<	2	2.6

RRP: Radical retropubic prostatectomy, TUR-P: Transurethral resection of the prostate, TUR-B: Transurethral resection of the bladder

Table 2. Common diagnoses at re-admission

Reason for re-admission	n	%
Pulmonary edema (contrast nephropathy)	1	1.3
Dysuria	1	1.3
Epididymitis	1	1.3
Difficulty in urination	6	7.8
Incontinence	2	2.6
Retention	1	1.3
Tenesmus	2	2.6
Ureterorrhagia	1	1.3

Table 3. The therapies applied to overcome the couses of re-admission

Applied therapy	n	%
Amplatz dilatation	1	1.3
Medical	7	9.2
CIC dilatation	5	6.6
Follow-up	1	1.3
Internal urethrotomy	1	1.3

CIC: Clean intermittent catheter

Table 4. The association of re-admission rate with Age-adjusted Charlson Comorbidity Index scores and patients age

	Age			p
Re-admission	**n**	**Mean**	**(Min-Max)**	
No	61	63.79±13.9	22-82	**0.005**
Yes	15	53.20±13.8	28-80	
		ACCI		
Re-admission	**n**	**Mean**	**(Min-Max)**	
No	61	4.68±2.5	0-12	**0.007**
Yes	15	2.66±2.2	0-8	

p<0.05: The level of significance
ACCI: Age-adjusted Charlson Comorbidity Index, Min: Minimum, Max: Maximum

In univariate analysis, the re-admission rate was significantly associated with lower ACCI scores and patient age (Table 4, 5). In multivariate analysis, ACCI was an independent predictor of re-admission, while the other preoperative factors had not any predictive effect on re-admission.

Discussion

Male urethral strictures, a major challenge for urologists, are one of the urological diseases (1,2). In parallel with the improvements in endoscopic procedures, treatment for urethral strictures has also improved. Cold knife incision, laser ablation or dilation methods can be used for stricture treatment. To make cold knife incision for urethral strictures, internal optical urethrotomy (IOU) was first introduced by Sachse (3) in 1974. IOU and urethral dilation together are generally considered to be the first choice for the treatment of most urethral strictures (2). Whichever method is preferred, a permanent urethral catheter in various sizes is inserted when the procedure is completed.

Table 5. The association of re-admission rate with sricture and operative data

	Re-admission		p
Stricture location	**No**	**Yes**	
Bulbous	14 (23%)	3 (20%)	
Memrenous urethra	33 (54%)	6 (40%)	0.188
Bladder neck	4 (6.6%)	4 (26.7%)	
Penile urethra	10 (16.4%)	2 (13.3%)	
Sricture length (mm)	**No**	**Yes**	
5	3 (4.9%)	0 (0%)	
10	49 (80.3%)	12 (80%)	0.591
20	8 (13.1%)	2 (13.3%)	
20<	1 (1.6%)	1 (6.7%)	
Etiology of stricture	**No**	**Yes**	
Primary	3 (4.9%)	3 (20.0%)	
RRP	8 (13.1%)	4 (26.7%)	
Cystourethroscopy	5 (8.2%)	2 (13.3%)	
Urethral catheter insertion	11 (18%)	1 (6.7%)	0.008
Traffic accident	2 (3.3%)	2 (13.3%)	
TUR-P	20 (32.8%)	2 (13.3%)	
TUR-B	12 (19.7%)	0 (0%)	
Urethroplasty	0 (0%)	1 (6.7%)	
Operation method	**No**	**Yes**	
Dilatation	30 (49.2%)	8 (53.3%)	1.000
Internal urethrotomy	31 (50.8%)	7 (46.7%)	
Instrument used	**No**	**Yes**	
Amplatz	30 (49.2%)	8 (53.3%)	0.805
Laser	13 (21.3%)	4 (26.7%)	
Cold knife	18 (29.5%)	3 (20.0%)	
The number of processes	**No**	**Yes**	
1	36 (59%)	9 (60%)	
2	13 (21.3%)	3 (20%)	1.000
3	7 (11.5%)	2 (13.3%)	
4	5 (8.2%)	1 (6.7%)	
Urethral catheter diameter (Fr)	**No**	**Yes**	
16 Fr silicon	32 (52.5%)	12 (80%)	
18 Fr silicon	24 (39.3%)	2 (13.3%)	0.134
20 Fr foley	3 (4.9%)	0 (0%)	
22 Fr silicon	2 (3.3%)	1 (6.7%)	
Hospital stay (day)	**No**	**Yes**	
0	6 (9.8%)	2 (13.3%)	0.653
1	55 (90.2%)	13 (86.7%)	

p<0.05: The level of significance
RRP: Radical retropubic prostatectomy, TUR-P: Transurethral resection of the prostate, TUR-B: Transurethral resection of the bladder

The patient may be re-admitted after surgery due to various reasons. Many studies in the literature have investigated the reasons for re-admissions and the financial impact of re-admissions (4,5). The evaluation of these factors in the prediction and prevention of re-admissions can undoubtedly make a significant contribution. There are studies in the literature that review re-admissions after urolithiasis treatment and most have used national healthcare data instead of clinical or operative data (4,6,7,8).

Transurethral bladder tumor and prostate resection, transurethral laser prostatectomy, hydroentanglement, and suspension procedures were investigated by Rambachan et al. (5), and the median re-admission rates were found to be 4.97, 4.24, 4.27, 1.92, and 0.85% (total median rate 3.7%), respectively. Gender, patient age, anesthesia risk scores and history of malignancy and coagulation disorders were found to be risk factors for hospital re-admission. In this study, 30.9% of re-admitted patients had medical complications and the commonest complication was urinary tract infection (20.6%). Complications associated with surgical procedure were seen in 4.1% of patients, of which 21.3% had infection at the surgical field. Re-operation was required in 21.3% of re-admitted patients (5).

In a study by Scales et al. (4), re-admission rates after shock wave lithotripsy, ureterorenoscopy (URS), and percutaneous nephrolithotripsy (PCNL) were generally 12%, but only 15% was after PCNL and URS. The re-admission rates rose in high-volume hospitals and were even higher in cases with a Charlson Comorbidity Index score of ≥2 (4). In another study, unplanned hospital re-admission occurred in approximately one in every 10 patients, with elective re-admission rate of 13.6%. In other studies, the rate of re-admission following stone treatment was around 5% to 15%. Readmitted patients had relatively longer initial hospital stays (8).

In this study, we investigated the related factors that increase the risk of re-admission in patients following IOU for urethral strictures. To our knowledge, this is the first such work. Similarly, this study included all post-operative re-admissions within 30 days after hospital discharge like studies of other procedures. The effects of factors such as preoperative comorbidities, operative data, length of hospital stay, and complications after operation were all revealed by this study. The average re-admission rate in our study was 19.7% which was a little higher than in the literature.

The role of etiology as the predictor of the outcome of IOU has long been investigated (9,10). Kumar et al. (9) reported higher success rates with iatrogenic strictures when compared with posttraumatic and post-inflammatory etiology. However, Desmond et al. (10) could not find any association between the etiology of the stricture and the outcome of urethrotomy. In our study, although the re-admission rates due to the etiology of the stricture seems to be statistically significant, we could not make any conclusion about the relationship of the etiology of the stricture with re-admission rates and outcomes of the procedure.

Data on the effects of the diameter of the catheter placed after urethral stricture surgery are still insufficient. However, it is known that ischemia is involved in the process of recurrence of urethral stricture in most cases (11). Due to the pressure they exert on the urethral wall, larger diameter catheters may interfere with re-epithelialisation, which would result in urethral healing (12,13). In a study of Yürük et al. (14), urethral stricture recurrence was found to be more common in patients with prolonged (≥5 days) catheterization and with large (22 Fr) catheters. Despite this information, according to our findings, we could not find any significant relationship of re-admission rates with the catheter diameter and catheter dwell time.

In a study, age was found to act as a prognostic factor that means patients younger than 13 and older than 60 years of age were found to be more exposed to postoperative complications. Odd ratio (OR) for this category was 3.4 (95% confidence interval 1.86.6, $p<0.001$); thus, the probability to suffer a complication during postoperative period was nearly 3.5 times higher for patients under 13 and over 60 years compared with patients aged between 13 and 59 years (15). In our study, age and ACCI were found to be a factor related with re-admission. In multivariate analysis, OR for ACCI was 0.69 which means that an increase in the score of ACCI reduces the re-admission rate nearly by 50%.

Ambulatory urological surgery is highly safe when evaluated for postoperative complications. Surgical procedures performed under general anesthesia, except for factors that cannot be changed, such as age, sex, surgical type, and the complexity of surgery, are independent risk factors for complications after operation and re-admission (15). Similarly, complicated procedures increase the risk of complications (15). In our study, an increase in preoperative comorbidities decreases the rate of hospital re-admission; likewise older age also reduces the hospital re-admission rate. We think that this may be related to the operator being more careful in the elderly and comorbid patient groups.

Study Limitations

This study has some weaknesses: the accuracy of our analysis may be debatable because of its retrospective nature. Furthermore, since the data on outpatient visits are limited, postoperative complications may be underestimated. Other limitations are small sample sizes for urethral stricture surgery. In addition, a large number of different data have been classified so that a detailed analysis of the process has become impossible. In the current conditions, with larger series of patients, it is likely to make further comments.

Conclusion

Operation for urethral stricture, which is among the ambulatory urological surgical procedures, is generally a safe procedure, but it may cause more irritation to a patient group that will be re-admitted to the hospital. When the cost is taken into account, identification of this group of patients is important. According to this study, because hospital re-admission in younger patients

with fewer comorbidities can be expected, it may be advisable to discharge, this patient group after detailed examination.

Ethics

Ethics Committee Approval: The study was approved by Bülent Ecevit University Local Ethics Committee (date: 08/03/2017, meeting number: 2017/05, protocol number: 2017-34-08/03).

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

Peer-review: Externally peer-reviewed.

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Are There Any Differences in the Neural and Extracellular Matrix Proteins Density Between Children and Adults with Intrinsic Ureteropelvic Junction Obstruction?

Çocuk ve Erişkin Üreteropelvik Bileşke Darlığında Nöral ve Ekstraselüler Matriks Proteinleri Arasında Farklılık Var mı?

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

There are lots of studies on the histology of the obstructed segment of UPO patients. Although there are some conflicting results, most of the studies performed to date state that while muscle and neural tissue decrease in UPO, connective tissue and extracellular matrix proteins increase. All these studies have been conducted whether on children or adults. This is the first study that compared the specimens from adult and child population. Our study will help us better understand the progression of ureteropelvic junction obstruction throughout life and create a better understanding on the timing and need of surgery.

Abstract

Objective: To compare changes in connective, neural and muscle tissues, and extracellular matrix in child and adult patients so that we can create a more objective view on the timing of surgery.

Materials and Methods: Twenty-six patients, who were operated for ureteropelvic junction (UPJ) obstruction in our clinic between September 2014 and May 2016, were included in the study. For the evaluation of connective tissue, Masson's trichrome staining was used. Muscle, extracellular matrix elements and neural tissue were evaluated with immunohistochemistry using alpha-smooth muscle actin (α-SMA), Tenascin C and S100, respectively. Microscopically, the tissues were scored according to their staining density (0: No staining; 1: Minor; 2: Moderate, 3: Dense).

Results: There were 12 children and 14 adults in the study groups. The initial evaluation showed no statistically significant difference between studied tissue types with respect to staining density for all parameters (Masson: p=0.414, α-SMA: p=0.204, Tenascin-C: p=0.264, S100: p=0.534). There was no statistically significant correlation between staining density and renal function percentage of the affected kidney (Masson: r=0.454, p=0.051 - α-SMA: r=-0.323, p=0.177 - Tenascin-C: r=0.290, p=0.229 - S100: r=-0.080, p=0.744).

Conclusion: Our preliminary study showed some structural changes between adult and child patients but there is no statistically significant difference between the groups with respect to staining density scores. These results state that although UPJ obstruction is an ongoing process, there is no correlation between the histological deterioration degree of the UPJ segment and the loss on renal function for both children and adults.

Keywords: Extracellular matrix, immunohistochemistry, muscle tissue, connective tissue, neural tissue, ureteropelvic junction

Öz

Amaç: Cerrahi zamanlaması üzerine daha objektif bir görüş oluşturabilmek için çocuk ve erişkin hastaların bağ, sinir, kas dokuları ve ekstraselüler matriks proteinlerindeki değişiklikleri karşılaştırmaktır.

Gereç ve Yöntem: Kliniğimizde Eylül 2014-Mayıs 2016 tarihleri arasında üreteropelvik bileşke (UPB) darlığı nedeniyle opere edilen 26 hasta çalışmaya dahil edildi. Bağ dokusu değerlendirmesi için Masson trikrom boyama kullanıldı. Kas, ekstraselüler matriks elemanları ve sinir dokusu

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sırasıyla alfa smooth-muscle aktin (α-SMA), Tenascin C ve S100 kullanılarak immünhistokimyasal olarak değerlendirildi. Mikroskopik dokular boyama yoğunluğuna göre skorlandı (0: Boyanma yok, 1: Minör, 2: Orta, 3: Yoğun).
Bulgular: Çalışma grubunda 12 çocuk ve 14 yetişkin vardı. İlk değerlendirme, incelenen doku tiplerinde, tüm parametreler için boyama yoğunluğuna göre istatistiksel olarak anlamlı bir fark olmadığını gösterdi (Masson: p=0,414, α-SMA: p=0,204, Tenascin-C: p=0,264, S100: p=0,534). Etkilenen böbreklerin boyanma yoğunluğu ile renal fonksiyon yüzdesi arasında istatistiksel olarak anlamlı bir korelasyon yoktu (Tenascin-C: r=0,290, p=0,229 - S100: r=-0,080, p=0,744).
Sonuç: Çalışmamız yetişkin ve çocuk hastalar arasında bazı yapısal değişiklikler olduğunu göstermiş ancak boyama yoğunluğu puanlarında gruplar arasında istatistiksel olarak anlamlı bir fark bulunamamıştır. Bu sonuçlar, UPB darlığının devam eden bir süreç olduğunu göstermekle birlikte, UPB segmentinin histolojik bozulma derecesi ile hem çocuklarda hem de erişkinlerde böbrek fonksiyonlarındaki kayıp arasında bir korelasyon olmadığını ortaya koymaktadır.
Anahtar Kelimeler: Ekstraselüler matriks, immünhistokimya, kas dokusu, bağ dokusu, sinir dokusu, üreteropelvik bileşke

Introduction

Ureteropelvic junction (UPJ) obstruction (UPJO), which is defined as impairment in the urine passage from the renal pelvis to ureters, is the leading underlying pathological condition in antenatal hydronephrosis (1). Although UPJO can be diagnosed at any age, developments on fetal screening studies such as ultrasound led to diagnosis of this condition as early as antenatal life.

The underlying pathophysiological mechanisms of UPJO have been investigated in many studies. Anomalies in muscle tissue of the renal pelvis and ureter are the most commonly suggested factors playing a role in the development of UPJO (2). Some studies also show that abnormal neural stimulation and structural defects in collagen can also have a role in the development of the disease. There are conflicting results in studies on the effect of the distribution of neural tissue and extracellular matrix (ECM) in UPJO. In a recent study, it has been showed that in children with intrinsic UPJO, there was increased expression of collagen fibers and ECM; whereas a marked decrease in the density of muscle and neural tissues were observed (3).

In recent years, the increased number of early-diagnosed UPJO cases has led to the question about timing of surgery. Current approach to UPJO is based on functional studies. Our lack of knowledge on the developmental process of the disease makes it impossible to establish treatment strategies based on pathophysiology. Although most cases of UPJO are followed without any interventions up to adult life, there are limited data on the course and long-term histological changes of the disease.

This preliminary study aims to investigate changes in UPJ with respect to muscle, connective tissue, ECM and neural tissues between pediatric and adult patients. To our knowledge, our study is the first study assessing histological changes in children and adult populations. Our results may help obtain a clearer picture about pathophysiological development of UPJO and help us develop more objective treatment strategies based on pathophysiology.

Materials and Methods

Thirty patients who were operated for UPJO in our clinic between September 2014 and May 2016 were selected for the study. Four cases whose UPJO was caused by extrinsic etiologies like crossing vessels were excluded and final analysis was conducted on the remaining 26 intrinsic UPJO patients. The patients were grouped as adults and children with respect to their age; patients younger than 18 years of age were defined as children.

Exclusion Criteria

In all UPJO cases, the diagnosis was confirmed with radiologic and scintigraphic methods before the surgery. Ureteropelvic obstruction cases with renal stone in the affected side or with vesicoureteral reflux were not included in the study. In case of uncertainty in the diagnosis, cases were evaluated with retrograde pyelography to confirm UPJO. In two patients, laparoscopic simple nephrectomy was performed for recurrent febrile urinary tract infections. The remaining patients underwent Anderson-Hynes pyeloplasty. All pyeloplasty cases were planned as laparoscopic surgery.

Surgical Selection

Patients, whose renal function was recorded to be less than 40% on the affected side at the time of diagnosis, who had a decline in renal function for more than 10% in consecutive scans, who had a completely obstructed UPJ even after diuretic admission in nuclear renogram, and patients whose affected kidney showed an increase in anterior-posterior pelvis diameter in consecutive scan, were recommended for pyeloplasty according to the European Association of Urology Guidelines.

Immunohistochemistry

After the UPJ segments excised during the pyeloplasty were fixated in 4% formaldehyde with neutral buffering, they were

embedded in paraffin blocks for preservation until histological evaluation. These paraffin blocks were cut with microtome blade into 5-micrometer sections and after complete removal of paraffin from the samples, 4 types of staining were chosen to evaluate the samples.

All staining procedures were conducted in histology and embryology laboratory in our institute. For the evaluation of connective tissue, Masson's trichrome staining (Sigma Aldrich HT15-1KT) was performed. Muscle density, neural structure and ECM elements were evaluated immunohistochemically. For these purposes, alpha-smooth muscle actin (α-SMA), Tenascin C (TNC) and S-100 were chosen as markers.

Expose Mouse and Rabbit Specific HRP/DAB Detection IHC kit (Abcam, ab804436) was used according to the instructions provided by the manufacturer on all slides. After passing through alcohol series, the slides were blocked with hydrogen peroxide for 10 minutes. Then, the slides were washed with phosphate buffer solution (PBS) (Biomatik, A3602) twice. For α-SMA, no antigen exposure was performed. Citrate buffer (Bio-Optica, 15-M103) was used for antigen exposure in TNC and S-100 staining procedures and the slides were washed with PBS three times. In order to block non-specific background staining, protein block was performed in room temperature for 10 minutes. After protein block, monoclonal antibodies which were α-SMA (Abcam, 7817,1:400, 1 hour incubation in room temperature), TNC (Santa Cruz, SC25328, 1:50, 1 night incubation in +4 °C) and S-100 (Santa Cruz, SC53438, 1:50, 1 hour incubation in room temperature) were used. The slides were washed with PBS three more times. After this, HRP conjugate was dropped for 15 minutes in room temperature and the slides were washed with PBS 4 times. Next, DAB solution was dropped and the slides washed with PBS four more times. Staining of nucleus was performed with Mayer's hematoxylin.

Evaluation and Scoring

All slides were observed with light microscope (Olympus BX51i Tokyo, Japan) by two independent observers and for each staining, a semi-quantitative scoring was performed. With respect to staining densities, the slides were scored between 0 and 3 (0: No staining, 1: Mild, 2: Moderate, 3: Dense). For determination of staining density of S-100 protein, 5 random areas with resemblance were chosen and with respect to staining density, 0 was scored in case of 1-3 positive staining, 1 was scored in case of 4-8 positive staining and 3 was scored in case of 9 or more positive staining.

Statistical Analysis

Statistical analyses were performed using the original SPSS software, version 22.0 (IBM Corp, NY, USA), with significance set at $p<0.05$. Baseline variables were described using means and standard deviations, or medians and 25th and 75th percentile values as appropriate. The Mann-Whitney U test was used to evaluate the difference between quantitative measurements that does not have normal distribution. Chi-square test was applied to evaluate categorical data and the two-sided p value was used in inference. Correlation between two quantitative variables was evaluated with Spearman's correlation coefficient. Confidence intervals were set at 95% before performing all tests.

This study was approved by the Ethics Committee of Marmara University Faculty of Medicine (approval number: 09.2015.070) and conducted with the guidance of the declaration of Helsinki. Informed consents were taken from all the participating patients. The financial support for this study was provided by Marmara University Scientific Research Projects Commission.

Results

Of 26 patients included in the study, 12 were in pediatric age group and 14 were in adult age group. Median patient age for all groups was 19.5 (5-30) years. Median age was 63.5 (13-127) months in children and 26.5 (22-39) years in adults. There was no statistically significant difference between groups with respect to gender distribution and laterality of the disease (Table 1).

All patients who underwent laparoscopic pyeloplasty were evaluated either with mercaptoacetyltriglycine or diethylenetriaminepentaacetate scintigraphy. All renograms showed obstructive pattern in all patients with no response to diuretic admission. The median calculated split renal functions were 44.5 (37.0-51.0) and 47.35 (43.5-50.0) in children and adults, respectively. There was no statistically significant difference between the groups with respect to measured renal function percentage (p=0.436).

In tissue slides with Masson's trichrome staining, the collagen fibers were observed as blue stained and muscle tissue elements were seen as pink-red stained. Histologically; in the slides of adult patients, it has been observed that connective tissue was increased in submucosal area, muscular and adventitia layers, whereas muscular tissue was observed to be decreased in these

Table 1. Comparison of descriptive variables among patient groups

		Patient group		
	Children (n=12)	**Adults (n=12)**		**p**
Gender	Male (n=18)	9 (50%)	9 (50%)	0.555[1]
	Female (n=8)	3 (37.3%)	5 (62.5%)	
Laterality	Right (n=10)	5 (50%)	5 (50%)	0.756[1]
	Left (n=16)	7 (43.8%)	9 (56.3%)	

[1]Chi-square test

areas. On the contrary, on the slides of children, decreased connective tissue and increased muscle tissue elements were observed microscopically. Although histologically structural changes were observed, there were no statistically significant difference with respect to staining density scores between the groups (p=0.414).

On slides evaluated with immunohistochemistry; positive stained antibodies of α-SMA, TNC and S-100 were observed as brown areas whereas other tissue elements were seen in light blue color (Figure 1, 2).

Although it was microscopically observed that muscle tissue on adult slides seemed to be decreased and thinned, there was no statistically significant difference between adult and children tissues with respect to α-SMA staining density scores (p=0.204). When the two groups were compared with respect to TNC staining density scores, 25.0% of adult patient slides were scored as dense stained whereas only 8.3% of child slides were scored as dense. Although this difference was also observed under the microscope, the difference was not statistically significant (p=0.264). Comparison of neural tissue with the use of S-100 showed no difference between groups both microscopically and with respect to staining density scores. The rate of dense stained slides was 16.7% in children and 8.3% in adults in S-100 staining (p=0.534).

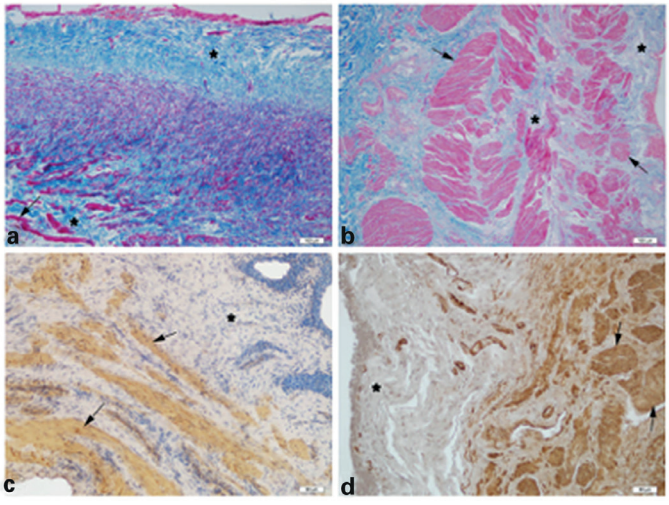

Figure 1. Trichrome staining of masson in an adult (a) and child (b) & alpha smooth muscle actin immunohystochemical staining in an adult (c) and child (d)

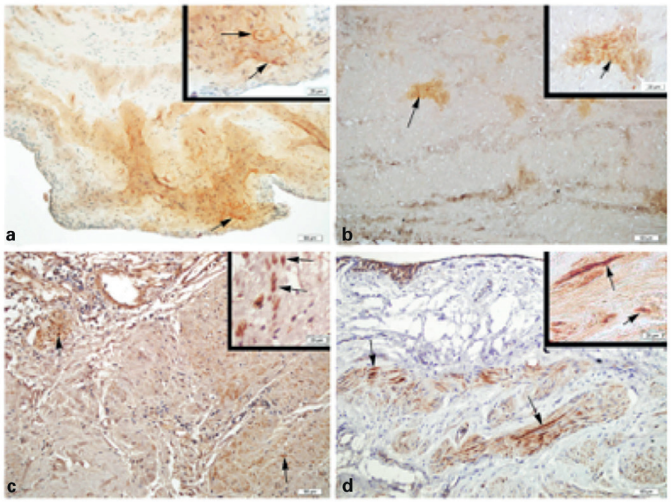

Figure 2. Tenascin C immunohistochemical staining in an adult (a) and child (b) & S-100 immunohistochemical staining in an adult (c) and child (d)

There was no statistically significant correlation between all the 4 staining scores and anterior-posterior renal pelvis diameter of patients measured preoperatively. The measured renal function percentage was as also not correlated with staining density for all the 4 tissues (Table 2).

There was also a strong correlation between the staining densities of α-SMA and S-100 proteins in pediatric patient group (r_s=0.889 - p<0.001). This correlation could not be observed in adult patient group (r_s=0.149 – p=0.612). Other staining parameters were not correlated in all patient groups.

Table 2. Correlation between staining densities and radiologic parameters

	Masson	α-SMA	TNC	S-100
APPD	r_s=0.250, p=0.333	r_s=-0.107, p=0.684	r_s=0.168, p=0.518	r_s=0.127, p=0.628
Renal function (%)	r_s=0.454, p=0.0.51	r_s=0.323, p=0.177	r_s=0.290, p=0.229	r_s=0.080, p=0.744

α-SMA: Alpha smooth muscle actin, TNC: Tenascin C, APPD: Anterior posterior pelvis diameter, r_s=Spearmen correlation coefficient

Discussion

Studies on the pathophysiology of UPJO usually concentrate on the muscle tissue changes, ECM elements, connective tissue and neural structures of the obstructed segment. Kaya et al. (3) showed that in children with UPJO, smooth muscle elements and neural tissue decreased in UPJ segment whereas ECM and connective tissue increased. To our knowledge, this is the first study comparing child and adult UPJ tissues.

There are other studies demonstrating the effect of abnormal neural structures in UPJO. In their study, Wang et al. (4) demonstrated decreased nerve growth factor mRNA in UPJO tissue. The close relationship of apoptosis in the muscle tissue as a result of impairments in the neural stimulus is also shown in the same study. The correlation between decrease in neural tissue and increase in apoptosis index of muscle tissue is also demonstrated in another study (5). Although the correlation between neural and muscle tissues is well demonstrated, it is still unclear whether the decrease in neural stimulus causes muscle atrophy or muscle atrophy itself causes neural denervation. This relationship was also observed in our study in pediatric patient group. In our study, histologically, the

structures of neural elements showed similar characteristics in children and adult patient groups, and given that there was no statistically significant difference between the groups with respect to staining density scores, it can be presumed that in the pathophysiological process of UPJO, neural tissue disorders remain in a stable course. On the other hand, in the analysis of α-SMA, the average score of the pediatric patient group was higher than that of the adult group and the microscopic images of the two groups showed that the muscle fibers observed in the pediatric patient group were more regular and thicker. This suggests that the pathology due to UPJO may be in an advancing fashion for the muscle tissue.

Tenascins are a family of glycoproteins that have four different types affecting the structure of ECM and the physiology of ECM-associated cells. TNC is mostly involved in smooth muscle (6). This glycoprotein is effective particularly during organogenesis. In organs that completed their development; it can either be in very small amounts or not be found. However, in pathological conditions such as infection, inflammatory conditions or tumor growth, the efficacy and quantity of the TNC increase in the tissue. In fully developed organs, TNC plays a role in the development of fibrosis, ECM secretion and cell proliferation (7). In a study conducted in pediatric patient group, it has been shown that an increase in TNC may have an important role in deterioration of muscle tissue in ureterovesical junction of patients with vesicoureteral reflux (8). Similarly, an increase in TNC levels has been reported in children with UPJO compared to that in controls (3). In our study, even if not statistically significant, increased TNC concentration in the adult patient group, especially in muscle and connective tissues, demonstrates that UPJO is not a static process with regard to structure and turn-over of ECM products.

In a study comparing the results of preoperative renal nuclear scintigraphy with histological changes in kidney biopsy taken during the operation, it was observed that in 25% of pediatric patients with UPJO, there was inconsistency between renal biopsy and renal scintigraphic results (9). Also Zhang et al. (10) showed that the samples taken from the UPJ segment in pyeloplasty only correlated with renal function percentage if there was severe fibrosis in the UPJ. Consistent with these results, our study demonstrated that there was no correlation between deterioration of UPJ segment and scintigraphic renal function percentage. With these results, it can be interpreted that the radiologic and nuclear imaging modalities lack to demonstrate molecular changes in the course of UPJO.

In recent years, with the use of prenatal screening tests; UPJO has started to be diagnosed earlier. This situation complicated the decision of the surgeon with regard to the timing of treatment. A study in which patients with grade 3 hydronephrosis according to the Society of Fetal Urology criteria were randomized to follow-up and surgical treatment arms in the antenatal period; 25% of patients in the follow-up arm developed surgical need within 3 years after randomization (11). Likewise there are other studies which shows better recovery in renal functions after early repair of UPJO (12,13). Nevertheless, in a study which evaluated kidney function after pyeloplasty in pediatric patient group, functional improvement was reported after treatment regardless of age (14). Contrary to these results, there are other studies questioning the benefit of early repair in UPJO (15,16).

Study Limitations

Our study has some limitations such as lack of a control group for comparison. This is mainly due to the fact that the aim of this study was to compare adult and children patient populations. The changes in children are well documented by previous studies but difference between children and adults have not been reported. On the other hand, although most of the studies on UPJO were conducted with almost the same number of patients with our study, it is clear that with greater number of patients the difference between groups could reach to a statistically significant level. Studies with larger sample would help us differentiate the pathophysiological changes between children and adults.

Conclusion

The timing of surgery is still a matter of debate with the conflicting evidence in the literature. Understanding the pathophysiology and progress of the disease has an utmost importance in decision-making for treatment. Given the results in our study, it can be said that although some structures like muscle seem to deteriorate over time, there is no statistically significant difference between child and adult UPJ segments with respect to staining densities of connective, muscle, neural tissues and ECM components. Although this may indicate that patients would not get any additional benefit from treatment with early surgery instead of waiting until a functional impairment; it is clear that imaging studies do not always demonstrate the actual damage. In the future studies on the markers that may have potential to show early renal damage will be of utmost importance for decision making for the timing of UPJ surgery.

Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of Marmara University Faculty of Medicine (approval number: 09.2015.070).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.K., C.A., Y.T., Ç.A.Ş., Concept: B.Ş., C.K., F.Ş., Design: B.Ş., C.K., F.T., Data Collection or Processing: B.Ş., Y.T., Ç.A.Ş., Analysis or Interpretation: B.Ş., F.E., E.K.D., Literature Search: B.Ş., Writing: B.Ş., C.K.

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Effects of Obesity on the Perioperative Results and Continence Status in Laparoscopic Radical Prostatectomy

Obezitenin Laparoskopik Radikal Prostatektomide Peroperatif Sonuçlara ve Kontinansa Olan Etkisi

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

In this study, we reviewed the outcomes of initial 300 surgeries. The results showed the obese patients can operated even at the early stages of the learning. The urinary continence rate in obese patients were lower than the others at 6th month. However, these rates were similar at one year follow-up. There is more information regarding obesity and robot assisted prostatectomy according to laparoscopic radical prostatectomy. The series regarding laparoscopic radical prostatectomy and obesity have large number of patients or long ago studied. Therefore, the current study will provide additional information to the literature and will guide to the surgeons who are willing to perform laparoscopic radical prostatectomy.

Abstract

Objective: To assess the effects of obesity on the surgical success and perioperative results and continence status in laparoscopic radical prostatectomy (LRP).

Materials and Methods: The results of 300 consecutive patients undergoing LRP between April 2004 and January 2014 were analyzed retrospectively. Twenty patients were excluded from the study, thus, 280 patients remained. The patients were separated into 3 groups according to their body mass index. Based on this classification, group 1 (<25 kg/m^2) was normal, group 2 (25–30 kg/m^2) was overweight, and group 3 (>30 kg/m^2) was obese. The demographic data, intraoperative results, pathological results, and states of continence were compared among the groups.

Results: There were 81 patients in group 1, 152 patients in group 2, and 47 patients in group 3. There were no significant differences when the groups were compared according to age and prostate specific antigen values. The intraoperative blood loss was high in group 3 only. Moreover, the estimated blood loss, transfusion, operative time, bilateral nerve-sparing rate, hospitalization days, and complication rate were similar between the groups. There were no significant differences when the pathological results were compared according to the positive surgical margins and Gleason scores. Although the continence rates in group 3 were significantly low 6 months after the operation ($p<0.05$), the results were similar at 1 year ($p=0.738$).

Conclusion: LRP can be applied confidently in obese patients as well as normal and overweight patients.

Keywords: Body mass index, laparoscopic surgery, obesity, prostatectomy

Öz

Amaç: Laparoskopik radikal prostatektomi (LRP) cerrahisinde obezitenin cerrahi başarı, perioperatif sonuçlara ve kontinansa olan etkisinin araştırılmasıdır.

Gereç ve Yöntem: Nisan 2004-Ocak 2014 tarihleri arasındaki 300 LRP uygulanan hastanın sonuçları retrospektif olarak incelendi. Yirmi hasta çalışma dışı bırakıldıktan sonra kalan 280 hasta çalışmaya alındı. Hastalar vücut kitle indeksine göre 3 gruba ayrıldılar. Grup 1: <25 kg/m^2 olanlar

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normal, 25-30 kg/m^2 olanlar kilolu ve >30 kg/m^2 olanlar obez olarak sınıflandırıldı. Gruplar demografik veriler, intraoperatif sonuçlar, patoloji sonucu ve kontinans durumuna göre karşılaştırıldı.

Bulgular: Grup 1'de 81 hasta, grup 2'de 152 hasta, grup 3'te 47 hasta mevcuttu. Yaş ve prostat spesifik antijen sonuçlarına göre karşılaştırıldıklarında anlamlı fark bulunmadı. İntraoperatif hemogram kaybı anlamlı olarak obez grupta yüksek izlendi. Bununla birlikte tahmini kan kaybı, transfüzyon ihtiyacı, operasyon süresi, bilateral sinir koruyucu oranları ve hastanede yatış süresine göre karşılaştırıldığında sonuçları gruplar arası benzerdi. Gruplar komplikasyonlar açısından, Satava ve modifiye Clavien skorları ile karşılaştırıldığında, anlamlı fark görülmedi. Patoloji sonuçları, pozitif cerrahi sınır ve gleason skoruna göre karşılaştırıldığında anlamlı fark izlenmedi. Ameliyattan sonra 6. ayda obez grupta anlamlı olarak düşük izlenmesine rağmen, 1. yılda kontinans oranlarındaki sonuçlar benzerdi.

Sonuç: LRP normal kilolu ve aşırı kilolu hastalarla karşılaştırıldığında, obez hastalara da güvenle uygulanabilir.

Anahtar Kelimeler: Vücut kitle indeksi, laparoskopik cerrahi, obezite, prostatektomi

Introduction

Obesity is an important public health problem affecting a considerable part of Turkey's population. Over the last 20 years, the adult obesity prevalence in Turkey has increased significantly; while 18.8% of the adult population was obese in 1990 (women 28.5%, men 9%), the prevalence increased to 36% in 2010 (women 44%, men 27%). In the future, this prevalence is expected to increase even more (1). In cases of obesity, not only the fat mass, but also the amount of the serum testosterone, estrogen, insulin, and insulin-like growth hormone-1 related to prostate cancer increase (2). In addition, obesity increases the mortality risk and the advanced disease risk in prostate cancer (3). Numerous studies are available regarding the effects of obesity on robot-assisted laparoscopic prostatectomy (RALP) and laparoscopic radical prostatectomy (LRP) surgeries. In some case series, the operation time, blood loss, and disease stage in obese patient groups were reported to increase (4,5). However, in other studies, no effects on the intraoperative and early oncological periods were seen (6).

In this study, we evaluated the effects of obesity on the perioperative, intraoperative, oncologic, and continence results in patients undergoing extraperitoneal LRP.

Materials and Methods

After receiving approval from the Uludağ University Ethics Committee (approval number: 52588837-000/464), the results of 300 consecutive patients undergoing LRP between 2004 and 2014 were analyzed from the prospective radical prostatectomy database, retrospectively. Patients with concomitant bladder tumors (n=1), unrecorded body mass index (BMI) (n=5), those receiving adjuvant hormonal therapy (n=10), shorter one year follow ups and followed up for less than 1 year (n=4) were excluded from this study. Therefore, the 1-year follow-up results in 280 patients were analyzed. The BMI was scaled according to the World Health Organization recommendations, and the patients were separated into 3 groups according to their BMI. Group 1 was classified as having a normal weight (BMI <25 kg/m^2), group 2 was overweight (BMI =25–30 kg/m^2), and group 3 was obese (BMI >30 kg/m^2). Overall, 81 patients in group 1, 152 patients in group 2, and 47 patients in group 3 were included in this study. Age and prostate specific antigen (PSA) level were recorded as the preoperative findings, while hemogram results, estimated blood loss, transfusion need, operative time, bilateral nerve-sparing status, and pathological results, including the surgical margins, tumor grade end pathological stages, and complications, were recorded as the intraoperative findings. The Satava classification was used for intraoperative complications (7), and postoperative complications were analyzed with the modified Clavien classification (8). PSA values were obtained every 3 months, and continence status was evaluated every 6 months. The continence status of the patients was determined and registered to the database by an urologist who was not involved in primary surgical care of the patients. The patients were evaluated with detailed history, total urine examination, and post voiding residual volume for evaluation of incontinence. The total number of pads used in each day was questioned and the patients who were free of pad or using only one pad per day were considered as having social continence.

With regard to the surgical technique, a retroperitoneal space was created in the Trendelenburg position, and 5 ports were used in the procedure. Next, the retropubic space was created, the endopelvic fascia was incised, and the puboprostatic ligament was cut. The dorsal vein complex was ligated using a radiofrequency vessel-sealing device; then, the bladder neck was cut and a Benique bougie was used to apply traction to the prostate. The posterior seminal vesicle and vas deferens were dissected and cut. The Denonvilliers' fascia between the rectum and prostate was cut and dissected towards the apex of the prostate, and the neurovascular bundle in the laterals was controlled with a Weck clip, without cauterization. Neuron sparing was implemented according to the touch and biopsy results of the patient and the localization of the mass. The apex of the prostate and the urethra were dissected, the retrourethral muscles were cut and put into a specimen bag, and a urethrovesical anastomosis was created using the van Velthoven technique (9). Patients with a PSA >10 and Gleason

score >6 underwent pelvic lymph node dissections. One week later, the catheter was removed. The pelvic floor exercises were instructed to all of the patients postoperatively for achievement of an early continent state.

Statistical Analysis

The statistical analysis was performed using SPSS version 23 software (SPSS Inc., Chicago, Illinois, USA). The Shapiro-Wilk's test was used to assess the normality of the continuous variables. Continuous variables that were not normally distributed were compared by using the Kruskal-Wallis One-Way ANOVA, while the normally distributed continuous variables were compared using an ANOVA. The nominal variables were compared with a chi-square test, and a p value of lower than 0.05 was accepted as statistically significant.

Results

The average age of the patients was 63.9±5.6 years, and there were no statistically significant differences among the groups (p=0.33). In addition, there were no statistically differences in PSA level, bilateral nerve sparing rate, operative time, and hospitalization days between the groups (Tables 1, 2). Moreover, the estimated blood loss and blood transfusion rate were similar among the groups, however, the intraoperative hemoglobin losses were -1.9 (-6.5/-0.5) in group 1, -1.9 (-9.2/-0.1) in group 2, and -2.6 (-5.3/-0.5) in group 3 (p=0.035).

As an intraoperative complication, 1 patient in the overweight group underwent a laparoscopic repair during the same session due to a rectal injury. One patient from the normal weight group and 1 patient from the overweight group underwent open surgery due to postoperative rectal injuries. One patient from the overweight group was followed up in the intensive care unit on the 3rd day because of sepsis and was discharged after reaching general wellness. All patients with postoperative complications classified as grade 1 according to the modified Clavien classification had wound site infections. Grade 2 patients, with the exception of 2 patients under treatment because of high fever in the overweight group, required transfusion because of bleeding. Overall, there were no differences in intraoperative and postoperative complications between the groups (Table 2).

The pathological results and postoperative continence states are indicated in Table 2. According to the pathological results, there were 54 (66.7%) patients with organ-confined diseases pT2 in the normal group, 91 in the overweight group (59.9%), and 24 (51.1%) in the obese group. Locally advanced disease pT3 was observed in 27 patients (33.3%) in the normal group, 61 patients (40.1%) in the overweight group and 23 patients (48.9%) in the obese group. Although more locally advanced disease patients were seen in the obese group, this was not statistically significant (p=0.082). There were no statistically significant difference among the groups in terms of bilateral neuroprotective rate and positive surgical margins (p=0.353 and p=0.813, respectively). In addition, there was no statistically significant difference in Gleason score between the groups (p=0.917).

The incontinence rate was higher in the overweight and obese groups when compared to the normal group at the 6th month of follow-up (p=0.04), but the rates were similar at the end of the 1st year (p=0.738). However, the continence rates were similar among the first 140 patients and the remaining 140 patients

Table 1. Comparisons of the demographic data and intraoperative results

		Group 1 (normal) (n=81)	Group 2 (overweight) (n=152)	Group 3 (obese) (n=47)	p
Age		63.9±5.6	62.6±6.1	63.4±5.9	0.33
Prostate-specific antigen (ng/mL)		7.95 (1–45)	7.8 (1–38)	9.5 (1–27)	0.232
Hemoglobin level difference (g/dL)		-1.9 (-6.5/-0.5)	-1.9 (-9.2/-0.1)	-2.6 (-5.3/-0.5)	0.035
Estimated blood loss (mL)		100 (20/600)	100 (20/500)	100 (20/1000)	0.866
Transfusion		4 (4.9%)	13 (8.6%)	4 (8.5%)	0.385
Operative time (minutes)		140 (70–570)	135 (60–480)	148 (80–540)	0.272
Hospitalization days		3 (1/42)	2 (1/23)	2 (1/11)	0.119
Satava	2	0	1 (rectal injury: laparoscopic repair in the same session)	0	0.651
	3	1 (rectal injury: required open surgery)	2 (rectal injury: required open surgery)	0	
Clavien	1	3 (3.7%)	6 (3.9%)	1 (2.1%)	0.484
	2	4 (4.9%)	12 (7.9%)	4 (8.5%)	
	3	0	0	0	
	4	0	1 (0.7%) urosepsis	0	

Hemoglobin level difference = preoperative hemoglobin level - postoperative hemoglobin level

Table 2. The tumor-node-metastasis classification of the pathological results after the laparoscopic radical prostatectomies, Gleason scores, and continence states

		Group 1 (normal weight) (n=81)	Group 2 (overweight) (n=152)	Group 3 (obese) (n=47)	p
Stage	pT2	54 (66.7%)	91 (59.9%)	24 (51.1%)	0.082
	pT3	27 (33.3%)	61 (40.1%)	23 (48.9%)	
	≤6	49 (60.5%)	95 (62.5%)	30 (63.5%)	
Gleason score	7	30 (37.0%)	47 (30.9%)	14 (29.8%)	0.917
	>7	2 (2.5%)	10 (6.6%)	3 (6.4%)	
Surgical margin +		25 (30.8%)	42 (27.6%)	15 (31.9%)	0.813
Bilateral nerve sparing +		31 (38.3%)	72 (47.3%)	20 (42.6%)	0.353
Incontinence rate after 6 months		10 (12.3%)	42 (27.6%)	15 (31.9%)	0.04
Incontinence rate after 1 year		3 (3.7%)	9 (5.92%)	3 (6.38%)	0.738

when compared regarding their weight status at the 6th month of follow-up.

Discussion

In this study, the effects of obesity on LRP were investigated. In a study evaluating the effect of BMI on pathological and functional outcomes following open radical prostatectomy, an increase in the complication rates and disruptions in function and continence was observed, especially in groups of obese and overweight patients (10). As opposed to open surgery, clinical studies about the effects of obesity on LRP have reported that obesity extends the operative time and increases blood loss. However, in contrast with open radical prostatectomy, the complication and function rates were similar to those of normal weight patients (4,5).

Brown et al. (11) stated that the operative time was longer in obese patients because of the long dissection, anastomosis, and port implantation times. In addition, there could be a longer extraperitoneal space preparation time and more difficulty in conveying the medical instruments to the depth of the pelvis (4). In previous RALP studies, the operative time was longer in obese patients and similar to that of laparoscopic surgery (12,13,14). In a robotic surgery, wider spaces are required to be able to move the robot's arms in a more comfortable way; thus, these processes are conducted intraperitoneally. The time is also longer in a robotic surgery because the space is limited, since obese patients have more fat in the pelvic area (15). In our study, we found that the average operative time in obese patients was not statistically significant, but was 8-13 minutes longer. We believe that the preparation of the extraperitoneal space and difficulty in conveying the laparoscopic hand tools to the depth of the pelvis extended the time.

In one study comparing the complications between obese and normal and overweight patients undergoing LRP, there were similar complication rates according to the Clavien classification (5). In our study, when the groups were compared according to the modified Clavien classification, one patient had urosepsis, however, there were no differences between the groups. Sundi et al. (6) compared LRP and RALP in 193 prostate cancer cases, and they determined that the operative time in the LRP group was longer, but the complication rates were similar. In another study, it was observed that the complication rate in the RALP group was higher (12).

Many studies have shown that the average blood loss, which is another parameter affected by obesity, was higher in obese patients than in those of normal weight (4,5,10). Eden et al. (16) especially indicated that obesity and blood loss were interrelated, which may be due to lack of experience. In contrast with LRP surgeries, the average blood loss in patients having normal weights was similar to that in obese patients undergoing RALP surgery (6,17). In our study, the average blood loss and transfusion needs in normal weight, overweight, and obese patients were similar. However, the hemoglobin reduction was higher in obese patients, which could be the reason for the hemodilution related to the intravenous fluid injection during the postoperative period (15). Brown et al. (11) monitored postoperative hemoglobin loss in obese and non-obese groups and indicated no statistically significant difference.

Amling et al. (18) stated that obese patients developed prostate cancer at younger ages and in advanced stages, however, another series showed that the average ages and PSA levels were not statistically different (4,5). In our study, there was no statistically significant difference in PSA levels between normal and obese patients. According to a study by Mitchell et al. (19), obesity increased the risk of advanced disease, but PSA can not be used as a foresight criterion for showing the tumor burden in patients having high BMI.

It has been reported that the aggressive disease encountered in many of the studies was seen more often in obese patients (18,20,21). Chronic inflammation, hypoxia induced by obesity,

and defects in the immune functions are the presumed reasons for this situation (22). Especially, pT3 disease and Gleason scores over 7 were statistically high (5,6,23,24). Lower PSA levels due to the greater body areas in obese patients and late diagnoses have been suggested to be reasons for a more aggressive and advanced stage disease (21). In our study, when considering the pathological results, the advanced-level disease pT3 rate was high, but the results were statistically similar to those in the other groups. The possibility of local recurrence was observed to increase up to 50% over five years with a Gleason score over 7, pT3 disease, and positive surgical margins. Therefore, positivity of the surgical margins constitutes a considerable part of the surgery (25). Freedland et al. (3) reported 30% surgical margin positivity for the normal weight patients and 45% for the obese patients in a 1.106-case series. In addition, Campeggi et al. (4) observed 27% surgical margin positivity for their obese patients. They stated that although aggressive disease was observed in obese patients, the reasons for the surgical margin positivity were iatrogenic. Gözen et al. (5) attributed the high level of surgical margin positivity in obese patients to aggressive disease. In our study, the surgical margins among the three groups were similar.

Patients with a BMI of >25 exhibited a higher rate of incontinence after RALP and open radical prostatectomy procedures (10,26). According to one meta-analysis, in terms of the criteria determining urinary incontinence after an RALP, a high BMI was one of the most important criteria in determining incontinence (27). In addition, obese patients were reported to have weaker urinary function, with the inefficacy of the neuroprotective surgery and sutures being reported as the reason. Gu et al. (15) observed that there were no differences between obese group and the other groups according to the analysis they conducted at the 3rd and 12th months after RALP. Moreover, Eden et al. (16) determined that there were no differences in continence between obese and normal weight patients after LRP. According to a study by Wiltz et al. (28), the continence rates in obese patients in their 1st and 2nd years in an RALP series were low. In our study, we observed that the significantly high incontinence levels in the overweight and obese patients during the first 6 months of follow-up were similar to those in the other groups at the end of the 1st year. We believe that this depends on the sphincter tonus recovery over time.

Study Limitations

The limitation of this study was its retrospective design. However, the data were collected prospectively with a standard data sheet, which could have minimized the potential bias.

Conclusion

During our 1-year follow-up, the complications, oncological results, and continence in normal, overweight, and obese patients undergoing LRP surgery were similar. However, the incontinence rate was higher in overweight and obese patients during the first 6 months. Despite its difficulty when compared with normal weight patients, LRP surgery can be implemented with confidence in obese patients.

Ethics

Ethics Committee Approval: The study was approved by the Uludağ University Local Ethics Committee (approval number: 52588837-000/464).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.V., H.V., Y.K., İ.Y., Concept: O.K., Ç.G.Ö., Y.K., H.V., Design: O.K., Ç.G.Ö., Data Collection or Processing: O.K., Ç.G.Ö., B.C., K.Ö.G., Analysis or Interpretation: O.K., Literature Search: O.K., Ç.G.Ö., B.C., Writing: O.K., Ç.G.Ö.

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Efficacy of Low Density Linear Shockwave Treatment in Severe Arteriogenic Erectile Dysfunction Patients

Ağır Arteriyojenik Erektil Disfonksiyonlu Hastalarda Düşük Dansiteli Linear Şok Dalga Tedavisinin Etkinliği

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

There are studies showing that low-intensity linear shockwave treatment (LI-ESWT) was effective and successful in erectile dysfunction (ED) due to vascular disorders, especially in arteriogenic ED. It has been claimed that LI-ESWT caused neovascularization by stimulating angiogenesis and increased endothelial cell proliferation. The efficacy of LI-ESWT + phosphodiesterase type 5 inhibitors (PDE5i) was compared with PDE5i treatment only in patients with severe ED who were diagnosed with penile arteriogenic ED based on penile Doppler ultrasonography.

Abstract

Objective: The aim of this study was to evaluate the efficacy of low-intensity linear shockwave treatment (LI-ESWT) in patients with severe arteriogenic erectile dysfunction (ED) by comparing LI-ESWT combined with daily use of phosphodiesterase type 5 inhibitors (PDE5i) with the daily use of PDE5i alone.

Materials and Methods: A total of 23 patients were included in the study. The patients were separated into two groups: LI-ESWT + tadalafil 5 mg (n=10) group and tadalafil 5 mg only group (n=13). LI-ESWT was applied once a week for four weeks. Oral tadalafil 5 mg once a day was started and continued for three months in both groups. The patients were evaluated with the International Erectile Function Index Questionnaire Erectile Function Domain (IIEF-EF), Erection Hardness Score (EHS) and Sexual Encounter Profile (SEP) 2 and 3 before treatment and the 1 and 3 months after treatment.

Results: No statistically significant difference was detected among IIEF-EF scores measured before and 1 and 3 months after treatment (p=0.091, p=0.198). At the end of the third month, IIEF score increased 4 points in LI-ESWT + tadalafil 5 mg group and 3.2 points in tadalafil 5 mg only group. No statistically significant difference was detected in EHS, and the rate of positive responses to SEP2 and SEP3 questions at the 1st and 3rd months between the groups.

Conclusion: LI-ESWT is easily applicable without any significant side effects and it has positive effects on the outcomes, however, it is not an effective treatment method in patients with severe arteriogenic ED.

Keywords: Low-intensity linear shockwave treatment, phospodiesterase type 5 inhibitors, erectile dysfunction

Öz

Amaç: Bu çalışmanın amacı, şiddetli arteriyojenik erektil disfonksiyona (ED) sahip hastalarda, fosfodiesteraz tip 5 (PDESİ) inhibitörünün (Tadalafil 5 mg) günlük kullanımı ile kombine edilen düşük dansiteli lineer şok dalga tedavisini (LI-ESWT), sadece PDESİ'nin günlük kullanımı ile kıyaslayarak LI-ESWT'nin etkinliğini değerlendirmektir.

Gereç ve Yöntem: Toplam 23 hasta çalışmaya dahil edildi. Bu hastalar LI-ESWT + tadalafil 5 mg tedavisi (n=10) uygulanan, sadece tadalafil 5 mg tedavisi uygulanan (n=13) hastalar şeklinde iki gruba ayrıldı. LI-ESWT, 4 hafta boyunca haftada bir kez uygulandı. Her iki gruptaki hastalara da

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günde bir defa tadalafil 5 mg tedavisi oral olarak başlandı ve tedaviye her iki grupta 3 ay devam edildi. Tedavi öncesi ve sonrası 1. ay ve 3. ayda hastalar Uluslararası Erektil Fonksiyon İndeks Formu-Erektil Fonksiyon Alanı Skoru (IIEF-EF) ve Ereksiyon Sertlik Derecesi Skoru (ESDS) seviyeleri ve Seksüel İlişki Profili (SEP) 2 ve 3 ile değerlendirildi.

Bulgular: Tedavi öncesi ve tedavi sonrası 1. ve 3. ayda ölçülen IIEF-EF skorları arasında istatiksel anlamlı fark saptanmadı (p=0,091; p=0,198). Üçüncü ay sonunda LI-ESWT + tadalafil 5 mg grubunda IIEF-EF skoru 4 puan, Tadalafil 5 mg grubunda 3,2 puan artış gösterdi. İki grup arasında 1. ve 3. ayda ölçülen ESDS, SEP2 ve SEP3 pozitif hasta oranları arasında istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: LI-ESWT, ED tedavisinde kolay uygulanabilir, belirgin yan etkisi olamayan ve sonuçlar üzerinde pozitif etkisi olan bir uygulamadır. Fakat ağır arteriyojenik ED mevcut hastalarda etkin bir tedavi yöntemi değildir.

Anahtar Kelimeler: Düşük dansiteli linear şok dalga tedavisi, fosfodiesteraz tip 5 inhibitörleri, erektil disfonksiyon

Introduction

Erectile dysfunction (ED) is the inability to maintain an erection sufficient for satisfactory sexual function (1). The prevalence in males over forty years of age has been reported to be 52% in United States and 69.2% in Turkey (2). A prevalence of nearly 322 million people in 2025 is predicted (3). Penile erection occurs due to a complex interaction of psychological, neural, vascular and endocrine factors. ED is related to these multifactorial problems and its prevalence increases with age. Factors associated with vascular disorders play an important role in ED etiology. These causes are divided into three categories as arteriogenic ED, venogenic ED and mixed vasculogenic. Among vasculogenic ED causes, arteriogenic factors play an important role (1,4).

Even though phosphodiesterase type 5 inhibitors (PDE5i) are actively used as the primary option in ED treatment, the demanded response is not achieved in 40-50% of patients. Although application of vasoactive agents and penile prosthesis implantation are recommended as secondary and tertiary treatment options in irresponsive patients, patients are generally not interested in these treatments (5). Thus, treatment methods which may be tolerated easily by non-invasive patients are required.

There are studies showing that low-intensity linear shockwave treatment (LI-ESWT) is effective and successful in patients with ED due to vascular disorders, especially in those with arteriogenic ED (6,7,8). It is claimed that LI-ESWT causes neovascularization by stimulating angiogenesis and increases endothelial cell proliferation (7,9).

The aim of this study was to evaluate the efficacy of LI-ESWT in patients with severe arteriogenic ED by comparing LI-ESWT combined with the daily use of PDE5i (tadalafil 5 mg) with the daily use of PDE5i.

Materials and Methods

Patients presenting with the complaint of ED between October 2014 and December 2015 were evaluated.

A careful and detailed anamnesis was taken to eliminate psychogenic and neurological factors. Genital examination and neurological examination, including perianal sensation, anal sphincter tonus and bulbocavernosus reflex, were made. International Erectile Function Index Questionnaire - Erectile Function Domain Scores (IIEF-EF) were calculated and ED degree was determined. The patients were also evaluated with Erection Hardness Score (EHS) and sexual encounter profile (SEP) 2 and 3 before the treatment. IIEF-EF score, EHS evaluation and SEP2 and SEP3 questions are present in Table 1.

Hormone tests and other laboratory tests, including follicle-stimulating hormone, luteinizing hormone, testosterone, prolactin, and blood glucose tests, urinalysis, kidney and liver function tests, lipid profile and complete blood count of the patients were evaluated.

Penile Doppler ultrasonography (PDU) was performed in all patients with suspected vasculogenic ED.

Table 1. Scores for erectile dysfunction evaluation parameters

IIEF-EF score
≤5: No attempts at intercourse
6-10: Severe ED
11-16: Moderate ED
17-21: Mild to moderate ED
22-25: Mild ED
≥26: "Normal" erectile function
EHS
Grade 1: Tumescence but no rigidity
Grade 2: Tumescence with minimal rigidity
Grade 3: Rigidity sufficient for sexual intercourse
Grade 4: Fully rigid erection
SEP2
In the past 4 weeks, were you able to penetrate your partner?
Yes/No
SEP3
Have you had an erection long enough for you to have successful intercourse?
Yes/No

IIEF-EF: The International Erectile Function Index Questionnaire - Erectile Function Domain Score, EHS: Erection Hardness Score, SEP2: Sexual Encounter Profile 2, SEP3: Sexual Encounter Profile 3, ED: Erictile dysfunction

Before the PDU, 60 mg papaverine HCl was intracavernosally injected using a 26-gauge 2 mL injector from the proximal 1/3 part of the penis. Then, at the 5th, 10th, 15th and 20th minutes, arterial and venous penis flows were evaluated. Acuson S2000, 9 MHz linear probe (Siemens Medical, Erlangen, Germany) was used for measurements. In patients with a peak systolic blood flow velocity below 30 cm/second, arterial insufficiency (arteriogenic ED), in patients with end-diastolic flow velocity, venous insufficiency (venogenic ED) and in patients with both of these problems, the diagnosis of mixed ED was established.

A total of 23 patients in severe ED group with an IIEF-EF score of 10 and below and having arteriogenic ED based on PDU result were included in the study. These patients were separated into two groups: LI-ESWT + tadalafil 5 mg treatment (n=10) group and tadalafil 5 mg only (n=13) group. LI-ESWT (RENOVA, Direx Medical Systems, Israel) was applied once a week for four weeks in four different anatomic areas: the right and left corpus cavernosum and the right and left penile crura. The treatment was performed as follows: 5000 waves of 0.09 mJ/mm^2, 300 intensity waves/min (5 Hz), 40 mm deep, in four areas (cavernosum right, left waves on each side 900, and left and right crus waves 1600 on each side); each session lasting 20 min with a one-week interval between each session (7,8). 5 mg tadalafil treatment was orally started once a day in both groups and the treatment was continued for three months. In the first and third months after treatment, the patients were re-evaluated with IIEF-EF score, EHS, SEP 2 and 3.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Necmettin Erbakan University Local Ethics Committee (approval number: 2017-822). Consent according to Helsinki Declaration was taken from the patients.

Inclusion Criteria

Patients over 20 years of age who were followed up for at least three months and had ED lasting more than three months, had a IIEF-EF score of ≤10, penile arterial deficiency based on PDU, EHS ≤2, no neurological, hematological, oncological or psychiatric disorder or penile anatomic anomaly and not using antiandrogen and not receiving radiotherapy were included in the study. All individuals who participated in the study were informed about the study and their written consents were obtained.

Statistical Analysis

LI-ESWT + tadalafil and tadalafil only groups were statistically compared. The chi-square (χ^2) test was used for analysis of the relationship between categorical variables. For comparisons between two groups, Student's t test and Mann-Whitney U test were used as appropriate. Two-Way ANOVA was used to assess the changes in pre-treatment and post-treatment variables. A p value of less than 0.05 was considered statistically significant. Statistical evaluation of data was made using SPSS 15 for Windows.

Results

The mean age of the patients in LI-ESWT + tadalafil and tadalafil groups was 52.7 (44-64) years and 54.2 (38-67) years, respectively (p=0.32).

No statistically significant differences were detected in the details of patient characteristics in two groups. Details of patient characteristics in the groups are shown in Table 2.

Table 2. Details of patient characteristics in the groups

	LI-ESWT + tadalafil 5 mg	Tadalafil 5 mg	p
Number (%)	10 (41.6)	13 (58.3)	
Mean age	52.7 (44-64)	54.2 (38-67)	0.32
Hypertension (%)	7 (70)	8 (61.5)	0.26
Diabetes mellitus (%)	6 (60)	7 (53.8)	0.34
Heart disease (%)	4 (40)	5 (38.4)	0.22
Dyslipidemia	3 (30)	4 (30.7)	0.42
Body mass index >30 (%)	4 (40)	4 (30.7)	0.17
ED duration >3 years (%)	8 (80)	10 (76.9)	0.59

ED: Erectile dysfunction, LI-ESWT: Low density linear shockwave treatment

In LI-ESWT + tadalafil 5 mg and tadalafil 5 mg only groups, the median IEEF-EF scores were as follows: before treatment: 7.1 (5-10), 7.6 (6-10) (p=0.26), 1 month after treatment: 10.6 (7-14), 9.35 (6-13) (p=0.1), and 3 months after treatment: 11.1 (7-14), 10.8 (7-13) (p=0.21), respectively. No statistically significant difference was detected in IIEF-EF scores measured before treatment and 1 and 3 months after treatment. At the end of the third month, the mean IIEF-EF score increased 4 points in LI-ESWT + tadalafil 5 mg group and 3.2 points in tadalafil 5 mg only group (p=0.33). In both evaluations made in 1 and 3 months after treatment, there were two (20%) patients with an EHS score of >2 in LI-ESWT + tadalafil 5 mg group and three patients in tadalafil 5 mg only group. No statistically significant difference was detected in EHS score in 1 and 3 months after treatment between the groups (p=0.16 and p=0.16, respectively). No statistically significant difference was detected in the rate of patients reporting positive responses to SEP2 and SEP3 in 1 and 3 months after treatment between the groups (p=0.25 and p=0.25, respectively). Pre- and after-treatment IIEF-EF

scores and EHSs, and the rate of patients who reported positive responses to SEP2 and SEP3 are given in Table 3. None of the patients reported a significant side effect or discomfort due to LI-ESWT treatment.

Table 3. International Erectile Function Index Questionnaire – Erectile Function Domain Score, Erection Hardness Score and Sexual Encounter Profile 2, Sexual Encounter Profile 3 positive patient ratios before and after treatment

	LI-ESWT + tadalafil 5 mg	Tadalafil 5 mg	p
Basal IIEF-EF score (median)	7.1 (5-10)	7.6 (6-10)	0.26
1st month IIEF-EF score (median)	10.6 (7-14)	9.35 (6-13)	0.1
3rd month IIEF-EF score (median)	11.1 (7-14)	10.8 (7-13)	0.21
Basal EHS >2 number of patients (%)	0 (0)	0 (0)	
1st month EHS >2 number of patients (%)	2 (20)	3 (23)	0.16
3rd month EHS >2 number of patients (%)	2 (20)	3 (23)	0.16
Basal SEP2 (+) number of patients (%)	1 (10)	1 (7.6)	0.25
1st month SEP2 (+) number of patients (%)	2 (20)	3 (23)	0.16
3rd month SEP2 (+) number of patients (%)	2 (20)	3 (23)	0.16
Basal SEP3 (+) number of patients (%)	0 (0)	0 (0)	
1st month SEP3 (+) number of patients (%)	1 (10)	1 (7.6)	0.25
3rd month SEP3 (+) number of patients (%)	1 (10)	1 (7.6)	0.25

IIEF-EF score: The International Erectile Function Index Questionnaire - Erectile Function Domain Score, LI-ESWT: Low density linear shockwave treatment, EHS: Erection Hardness Score, SEP2: Sexual Encounter Profile 2, SEP3: Sexual Encounter Profile 3

Discussion

ED treatment options have quite increased in time. PDE5i, intracavernosal injections and penile prostheses are used for treatment in general. Though these treatments are effective and safe, they are "optional" therapies. Although these treatments aim to improve sexual function and erection quality, their improving effects on erection mechanism are generally not permanent or natural. Search for a better treatment for spontaneously re-providing sexual activity in males is the next step in ED management. No significant progress has been achieved although researches on stem cell treatment or gene therapy are being continued (10).

Organic and psychological factors are the main underlying causes in ED etiology. Organic factors play a significant role in the etiology and vasculogenic factors primarily cause ED. Thus, diseases causing vascular pathologies are the main risk factors for vasculogenic ED and, ED risk increases nearly 1.5-4 times in the presence of these risk factors (11,12). Vasculogenic ED occurs with the relaxation problem in endothelium-dependent or endothelium-independent smooth muscle cells and atherosclerotic obstruction in cavernous arteries. As atherosclerosis affects the whole vascular system in the body, the earliest symptom is expected to occur in the artery with the smallest lumen diameter. Atherosclerosis-related symptoms in penile artery are observed in early period since the lumen of penile artery is also narrow (13,14).

Insufficient penile artery flow is responsible for 55% of EDs and severe penile arterial flow inadequacy in 90% of patients in whom a response to treatment cannot be achieved with PDE5i (15).

LI-ESWT has been used as a new therapy for ED in the last 10 years. Clinical studies and reports on this subject have increased especially in recent years. This means that LI-ESWT has gradually gained acceptance both by doctors and the patients (16).

Pelayo-Nieto et al. (8) applied LI-ESWT with 5000 shockwaves to 15 patients with mild-moderate ED once a week for four weeks and detected an increase of 5.46 (14.23-19.69) points in IIEF scores ($p<0.013$) and 33% recovery in patients with a EHS below 2 ($p<0.01$) in the evaluation they made at the end of the first month of treatment.

Vardi et al. (17) applied a total of six sessions of LI-ESWT (twice in three weeks) for nine weeks after administration of PDE5i treatment for a month in a sham-controlled study they made. According to the evaluation made one month after treatment, there was an increase of 6.7 points in IIEF score in the treatment group and 3 points in sham group ($p=0.0322$). Therate of patients with an EHS of 3 and above increased to 77.5% and the penile blood flow increase was also found to be significant in the treatment group. In the evaluation made in the third month, it was reported that IIEF score increased another two points.

Bechara et al. (7) applied LI-ESWT (four weeks, 5000 shockwaves once a week) in 20 patients irresponsive to PDE5i treatment. They reported a rate of response to treatment of 60% and an increase of 5.8 points in IIEF-5 score. The rate of patients reporting positive responses to SEP2 and SEP3 also increased at a statistically significant level. It was reported that only 20% of patients in this study (n=4) were in severe ED group and 3 out of 8 patients not responding to treatment (37.5%) were in severe ED group.

Chung and Cartmill (18) reported that IIEF score increased ≥5 points in 60% of patients in the evaluation made six weeks later on 30 patients who received LI-ESWT (3000 shockwaves, 6 weeks, once in two weeks).

In their placebo-controlled study, Olsen et al. (19) evaluated patients 5, 12 and 24 weeks after LI-ESWT (3000 shockwaves, 5 weeks) treatment lasting five weeks. Patients who had an EHS below 2 before the treatment were included in both groups. While the rate of patients with an EHS between 3 and 4 was 57% in the fifth week in LI-SWT group, it was measured as 54% in placebo group. These rates decreased in the 24th week to 19% and 23%, respectively. No significant difference was detected in IIEF scores between the two groups.

Srini et al. (20) applied LI-ESWT to patients responding to PDE5i and reported that 78% and 71% of patientshad a EHS between 3 and 4 in the first and fifth months, respectively.

Reisman et al. (21) reported that there was an increase of 8.5 points in IIEF-5 score in severe ED patients after LI-ESWT. It was reported that the rate of patients reporting positive responses to SEP3 increased from 25% to 60% in the first month.

Yee et al. (22) reported that there was no significant difference in IIEF and EHS scores between treatment and sham groups 13 weeks after LI-ESWT.

Although there been studies reporting that LI-ESWT provided a benefit in ED treatment, there are differences between the results. The reason for this may be the application of this treatment without separating ED patients into specific groups and application of different shockwaves for different durations with different protocols during the treatment. Moreover, in different studies, whether or not PDE5i was used before and during treatment may also have resulted in differences (7,17,18,19,20,21,22). Therefore, we tried to specify ED patients in our study and patients in severe ED group found to have arterial insufficiency based on penile Doppler ultrasonography results were included in the study group. We evaluated whether LI-ESWT treatment created a difference or not by giving PDE5i to both groups during the treatment. No significant LI-ESWT treatment-related side effect was observed in any of the previous studies, and in our study.

In a meta-analysis made quite recently, it was reported that IIEF of the patients in mild ED group increased significantly ($p<0.0001$) but a significant increase was not observed in IIEF in severe and moderate ED patients ($p=0.30$ and $p=0.49$, respectively). Additionally, in this study, it was reported that increased number of shockwaves and treatment periods less than 6 weeks cause a better therapeutic efficiency (23).

We applied 5000 shockwaves once a week for four weeks in our study. There was no difference between the two groups in diseases which could create vascular pathology. However, although we additionally gave tadalafil 5 mg/day to our LI-ESWT patient group, no significant difference was detected in IIEF score between them and the group given tadalafil 5 mg/day only. While IIEF-EF score increased 4 points in LI-ESWT + tadalafil group at the end of the third month, it increased 3.2 points in tadalafil group.

We assume that the main reason behind the significant difference found between the two groups after the treatment is the inclusion of severe arteriogenic ED patients in the study. Similarly, Bechara et al. (7) reported that 3 out of 4 patients in severe ED group were irresponsive to LI-ESWT. In addition, the form of LI-ESWT protocol and treatment duration are controversial in many studies (8,17,18,19). However it has been reported that treatment lasting longer than six weeks did not have a positive effect on the results (23). There is no study comparing the treatments lasting 4, 5 and 6 weeks. Thus, we have not found a difference between treatment responses since the LI-ESWT protocol we applied for four weeks was not satisfactory. A satisfactory recovery may not have occurred in the results since the rate of the presence of the diseases which could result in vascular pathologies was high in both groups.

These results showed that LI-ESWT + tadalafil treatment does not have any effect in patients with severe ED penile arterial insufficiency compared to tadalafil treatment only. Therefore, we assume that penile prosthesis treatment would be more appropriate in patients with severe ED, penile arterial insufficiency and in those not benefiting from medical treatment. LI-ESWT treatment is not reimbursed by the Ministry of Health of Turkiye and the cost of four-week treatment is nearly 4000 Turkish Liras (1072$) per patient. Its high cost makes the applicability of this treatment more difficult.

Study Limitations

Low number of patients, presence of diseases which may cause vascular pathologies in our patients (i.e. diabetes mellitus, hypertension and coronary heart disease) and the cost of the treatment can be counted among our limitations for applying the treatment only four weeks and for not increasing the number of LI-ESWT sessions.

Conclusion

LI-ESWT can be applied without any significant side effects and has positive effect on the results. However, it provides no advantage in patients with severe ED or penile arterial insufficiency. Studies separating larger number of participants into more specific ED groups are required to evaluate the treatment efficacy better.

Ethics

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Local Ethics Committee (approval number: 2017-822).

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

Peer-review: External and internal peer-reviewed.

Authorship Contributions

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

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Preventing Excessive Blood Loss During Percutaneous Nephrolithotomy by Using Tranexamic Acid: A Double Blinded Prospective Randomized Controlled Trial

Traneksamik Asidi Kullanarak Perkütan Nefrolitotomi Sırasında Aşırı Kan Kaybını Önleme: Çift Körü Körüne Prospektif Rastgele Kontrollü Deneme

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

Percutaneous nephrolithotomy is most frequently performed procedure for renal stones measuring 2 cm. Perioperative hemorrhage being most common complication, warrants as important predicting factor of adverse outcomes. Prevention with inexpensive safe drug like Tranexamic acid would ultimately turn out to be cornerstone for establishing future guidelines. Currently there is only one study published internationally highlighting this notion. Therefore this study will be beneficial for researchers in shaping the current practices.

Abstract

Objective: Percutaneous nephrolithotomy (PCNL) is most frequently performed procedure for renal stones 2 cm and larger. Perioperative hemorrhage being most common complication, warrants as important predicting factor of adverse outcomes. Prevention with inexpensive and safe drug like tranexamic acid (TA) would ultimately turn out to be cornerstone for establishing future guidelines. Aim of this study is to evaluate whether TA is efficacious in preventing blood loss during PCNL.

Materials and Methods: Ethical review board approval taken. Sample size calculation yielded 240 patients, comprising 120 in each group. Group A receiving TA and group B receiving placebo. Age, gender, body mass index (BMI), stone size, volume and location, preoperative blood count, creatinine, urine analysis, coagulation profile and necessary radiological investigations done. Randomization through lottery method. Both patient and investigator were blinded. Hemoglobin (Hb) and hematocrit (Hct) levels done at 24 hours postoperatively and fall in values recorded.

Results: Both groups were equal in characteristics like age, gender, BMI, stone size, volume and location ($p>0.05$). Operative variables like calyx punctured, position of puncture and operative time were also found to be similar in both groups. Median change in Hb in placebo group was 1.6 interquartile range (IQR) 4, while in TA group was 1.3 (IQR 7.8) ($p=0.001$). Similarly, median change in Hct level in placebo group was 3.6 (IQR 11.8) and in TA group was 2.4 (IQR 13) ($p<0.001$). Sixteen patients were transfused after surgery; 12 (75%) belonged to placebo group while 4 (25%) belonged to TA group ($p=0.038$). Hospital stay was not significantly different in both groups ($p=0.177$) with median of 4.0 and IQR of 0 in both groups.

Conclusion: TA during PCNL reduces blood loss and minimizes blood transfusion rate.

Keywords: Tranexamic acid, percutaneous nephrolithotomy, bleeding, blood transfusion

Öz

Amaç: Perkütan nefrolitotomi (PNL), 2 cm ve daha büyük böbrek taşları için en sık uygulanan prosedürdür. Perioperatif kanama en yaygın komplikasyon olup, istenmeyen sonuçların öngörülen önemli faktörüdür. Traneksamik asit (TA) gibi ucuz ve güvenli ilaçlarla önleme, nihayetinde gelecek kılavuz ilkeleri oluşturmak için temel taş haline dönüşebilir. Bu çalışmanın amacı, TA'nın PNL sırasında kan kaybını önlemede etkili olup olmadığını değerlendirmektir.

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Gereç ve Yöntem: Etik kurulun onayı alındı. Örneklem boyutu hesaplamasında, her bir grupta 120'den oluşan 240 hasta oluşturulmuştur. Grup A, TA ve grup B'yi alan plasebo. Yaş, cinsiyet, vücut kitle indeksi (VKİ), taş boyutu, hacim ve yer, preoperatif kan sayımı, kreatinin, idrar analizi, pıhtılaşma profili ve gerekli radyolojik tetkikler yapıldı. Piyango yöntemi ile rastgele oluşturma. Hem hasta hem de araştırmacı kör oldu. Postoperatif 24 saat yapılan hemoglobin (Hb) ve hematokrit (Hct) düzeyleri ve düşen değerler kaydedildi.
Bulgular: Her iki grup yaş, cinsiyet, VKİ, taş boyutu, hacim ve yer gibi özelliklerde eşitti (p>0,05). Her iki grupta da, kaliks ponksiyonu, ponksiyon yeri ve operasyon süresi gibi operatif değişkenlerin benzer olduğu bulundu. Plasebo grubunda Hb'de medyan değişim 1,6 [çeyrekler arası aralık (IQR) 4] iken, TA grubunda 1,3 (IQR 7,8) idi (p=0,001). Benzer şekilde, plasebo grubundaki Hct düzeyindeki medyan değişim 3,6 (IQR 11,8) ve TA grubunda 2,4 (IQR 13) idi (p<0,001). Ameliyat sonrası 16 hasta transfüze edildi; 12 (%75) plasebo grubuna, 4 (%25) TA grubuna (p=0,038) aitti. Her iki grupta da ortalama 4,0 ve IQR 0 olan hastanede kalış süresi iki grup arasında anlamlı farklılık göstermedi (p=0,177).
Sonuç: PNL sırasında TA kan kaybını azaltır ve kan transfüzyon hızını en aza indirir.
Anahtar Kelimeler: Traneksamik asit, perkütan nefrolitotomi, kanama, kan transfüzyonu

Introduction

Percutaneous nephrolithotomy (PCNL) is the standard of care for the management of large upper urinary tract calculi because of its higher stone clearance and cost-effectiveness when compared with other treatment alternatives such as extracorporeal shockwave lithotripsy and flexible ureteroscopy (1). Although the safety of PCNL has been established from various studies and resources (2), there is still compelling evidence that hemorrhage is one of the commonest complications of PCNL. The source of bleeding during or after PCNL is usually the segmental arteries, and is mostly controlled by conservative measures (3). Failure to identify a bleeding arterio-venous fistula or a pseudo aneurysm may result in catastrophe and may alter the disease outcome (4). Such cases may require angiographic embolization for the cessation of bleeding (5). Hemorrhages that require embolization are between 0.3% and 1.4% (4,6). This angiographic embolization can be selective or highly selective, depending on the level and degree of hemorrhage (7). Another dilemma about the outcome of hemorrhage after PCNL is that there is no fixed consensus about the management of hemorrhage post PCNL (5,8). The inference from different studies suggests that the blood transfusion rate for hemorrhage post PCNL ranges between 3 to 23% (4,6,9).

In urological surgeries, postoperative blood loss is thought to be associated with an increase in urinary fibrinolytic activity. Urine and urothelium contain high concentrations of plasminogen activators that facilitate the lysis of clots (10). Therefore, administration of antifibrinolytic agents might be beneficial in reducing the amount of postoperative blood loss resulting from these urological surgeries (11,12). Taking these facts in to consideration, there have been various measures undertaken to prevent or control hemorrhage during PCNL. One of these is the use of tranexamic acid (TA) which is a synthetic derivative of amino acid lysine and has an antifibrinolytic activity by reversibly binding to plasminogen (13). TA is ten times more potent in binding to plasminogen than aminocaproic acid which is a derivative and analogue of amino acid lysine and has been used historically for perioperative and postoperative bleeding control, but with conflicting results (14,15,16). TA accumulates in the extracellular space of tissues where it exerts its antifibrinolytic action. The consequent stabilization of the blood clots is not associated with laboratory signs of excessive fibrinolysis in the clots (17). Presence of dissoluble blood clots has not been reported in patients receiving TA in different urological surgeries, which would have hampered the vision of surgeon (18). Moreover, the safety of TA has been reported in several studies which clearly negates its thromboembolic outcomes (19,20,21).

Therefore preventing this complication with a safe and inexpensive drug like TA would ultimately turn out to be a cornerstone for establishing future guidelines for PCNL. Furthermore, lack of national and international data on use of TA in this particular urological surgery highlights the need for the above mentioned notion. There is only one study performed internationally by Kumar et al. (22). Other than that, there are 2 reviews by other authors pertaining to the same study. Fenner (23) in 2013, has commented on the study of Kumar et al. (22) and has re-emphasized the use of TA in selected group of patients in whom prolonged operative time is anticipated. Ritter and Michel (24) has also commented on the study of Kumar et al. (22) in 2013 with similar remarks but pointed out few pitfalls in the study like the confounding factors for perioperative and postoperative bleeding which were never discussed in the study and that type and technique of puncture which is a very important predictor of intraoperative hemorrhage, was also never discussed.

Materials and Methods

This double blind randomized controlled trial was conducted at the Kidney Centre Postgraduate Training Institute, Karachi, Pakistan from 7th October 2015 to 1st April 2016 (on completion of sample size). The Kidney Centre Ethical Review Committee approval was taken prior to the study (approval number: 20-URO-022015, date: February 2015). Using sample size calculator, PASS version 11, primary investigator applied 2-proportion formula with 95% confidence interval and 80% power of test to yield a sample size of 240, consisting of 2 equal groups of 120 subjects of group A (TA) and group B (placebo), taking in to account the efficacy of TA to prevent bleeding as 98%, and of placebo as 89%. The reference for variables was taken from a similar previous study (22) in which the TA group had 2% patients needing blood transfusion, in contrast to 11% of patients in control group. All patients aged 16–75 years of both genders, undergoing PCNL for renal stone size of more than 2 cm on ultrasound and X-ray kidney, ureter, and bladder (KUB) or 1 to 2 cm if stone refractory to lithotripsy, were considered for study after informed consent. Non-anemic patients with baseline hemoglobin (Hb) levels of above 12 gm/dL were enrolled. Patients excluded from the study were those with known bleeding disorder (e.g. hemophilia), deranged coagulation profile in preoperative lab workup, serum creatinine greater than 1.5 mg/dL, patients on aminosalicylic acid, clopidogrel or other blood thinning products and patients giving history of hypersensitivity to TA. Informed consent was taken from the patient by primary investigator. Age, gender, body mass index (BMI), stone size, stone volume and stone location were recorded in all patients. Preoperative complete blood count, creatinine, urine analysis, coagulation profile partial thromboplastin, activated partial thromboplastin time and necessary radiological investigations [X-ray KUB, ultrasound KUB, computed tomography (CT) pyelogram etc.] were done in all cases. The ampules of TA and placebo were similar in appearance but were differently coded by a person other than the primary investigator. Randomization for the allocation of subject patients into each group underwent through lottery method by the operating room holding bay staff, to which both the subject (patient) and the investigator (surgeon) were blinded (double blinding). Allocated patient were administered injection TA 1 gm or placebo by the recovery bay staff, before the patient was taken to the operating table. PCNL was performed and all necessary data (like renal calyx punctured and position of puncture) ware recorded. Surgery was carried out by consultant urologist with minimum experience of 10 years. Most frequent modality for positioning the patient for PCNL in our center is the prone position and all of the cases performed for this study were in the same position. The preferred puncture access was performed under fluoroscopic guidance and the technique was either "triangulation" (parallax) or the "bull's-eye" (eye of the needle), depending upon the preference of surgeon. Tract dilatation was performed in all cases with help of Alken's metallic telescoping dilators starting from 9 to 27 French in all patients. A 30 French Amplatz sheath then placed over Alken's dilators to gain access in to renal calyceal system. This was followed by introducing the nephroscope and fragmenting renal stone with pneumatic lithotripter. The fragmented stones were then removed using forceps. Stone clearance was checked on table using the fluoroscope, as well as on first postoperative day using X-ray KUB. Use of a drainage tube (nephrostomy tube) was dependent on duration of surgery, in order to avoid perinephric collection of irrigation fluid, and this nephrostomy tube was usually removed on the first or second postoperative day.

Hb and Hct levels were done at the end of 24 hours postoperatively and fall in values was recorded for calculating efficacy for bleeding control among both arms. The impact of stone size, duration of procedure and blood transfusion rate were also compared between patients of both arms.

Statistical Analysis

Decoding of ampules was performed at the end of all data collection by same assistant who performed coding of ampules in the beginning. Data analysis performed by IBM SPSS version 21. Descriptive analyses of variables presented in terms of frequencies and percentages. Mean and standard deviation computed for normal continuous variables while median with interquartile range (IQR) was used for skewed continuous variables. Normality of data checked by Shapiro-Wilk test. To observe difference between two groups, t-test was applied for normally distributed continuous variables, while Mann-Whitney test was used for asymmetric continuous variables. To detect association between two categorical variables, chi-square test was executed with level of significance as ≤0.05 (p value).

Results

The study incorporated total of 240 participants, 120 in each arms. Both placebo and TA groups were equal in their baseline characteristics (p>0.05) like age, gender, BMI, stone size, stone volume and stone location (Table 1).

Operative characteristics like renal calyx punctured, position of puncture and operative times were also compared between the two groups with no resultant significant difference (Table 1).

Table 1. Demographic, clinical and operative characteristics

Variables		Type of drug		p
		Placebo n=120	Tranexamic acid n=120	
Age (median with IQR)		40, 22	41, 22	0.80
Gender Male (n with %)		82 (68.3%)	72 (60%)	0.18
Female (n with %)		38 (31.7%)	48 (40%)	
BMI (kg/m^2) (median with IQR)		26.17, 8.25	25.73, 7.47	0.23
Stone size (cm) (median with IQR)		2.9, 1.60	2.55, 1.50	0.74
Stone volume (cm^3) (median with IQR)		3.18, 4.90	2.15, 4.53	0.74
Stone location	Multiple calyces (n)	14	15	0.98
	Upper calyx (n)	26	24	
	Pelvis (n)	31	30	
	Lower calyx (n)	49	51	
Operative parameters				
Renal calyx punctured	Upper calyx	57	59	0.44
	Lower calyx	63	61	
Position of puncture	Supracostal	57	54	0.39
	Infracostal	63	66	
Operative time in minutes (median with IQR)		90, 55	85, 30	0.24
Dilators size	20 Fr (<2 cm stones)	11	13	0.41
	30 Fr (>2 cm stones)	109	107	

IQR: Interquartile range, BMI: Body mass index, Fr: French

Table 2. Preoperative and postoperative laboratory parameters of patients receiving tranexamic acid and placebo

Clinical variables	Type of drug		p
	Placebo (n=120)	TA (n=120)	
Preoperative Hb (gm/dL) (median with IQR)	14, 7.7	13.35, 9.1	0.015
Postoperative Hb (gm/dL) (mean ± SD)	12±1.78	11.8±1.8	0.446
Change in Hb (median with IQR)	1.6, 4	1.3, 7.8	**0.001**
Preoperative Hct (%) (mean ± SD)	39.8±4.6	38.6±4.9	0.048
Postoperative Hct (%) (mean ± SD)	36±4.5	35.6±4.8	0.578
Change in Hct (median with IQR)	3.6, 11.8	2.4, 13	**<0.001**

TA: Tranexamic acid, Hb: Hemoglobin, Hct: Hematocrit, SD: Standard deviation, IQR: Interquartile range

Laboratory variables like pre-operative Hb and pre-operative Hct level were statistically different in both groups (p<0.05). Median pre-operative Hb in placebo group was 14 (IQR 7.7) while in TA receiving group was 13.35 (IQR 9.1). Similarly mean pre-operative Hct was also high in in placebo group (39.8±4.6) as compared to TA group (38.6±4.9). To overcome this problem we observed the changes in both Hb and Hct dropped differently in placebo and TA groups. Median of change in Hb levels in placebo group was 1.6 (IQR 4), while in TA group was 1.3 (IQR 7.8) (p=0.001). Similarly, median of change in Hct levels in placebo group was 3.6 (IQR 11.8) and in TA group was 2.4 (IQR 13) (p<0.001) (Table 2).

Total number of patients needing blood transfusion after surgery was 16, among whom 12 (75%) belonged to placebo group while only 4 (25%) belonged to TA group (p=0.038) (Table 3).

The hospital stay was not significantly different in both groups (p=0.177) with median of 4.0 and IQR of 0 in both groups (Table 3).

Table 3. Blood transfusion and hospital stay in both groups

		Type of drug		Total	p
		Placebo n=120	TA n=120		
Blood transfusion	No (n %)	108, 48.2	116, 51.8	224	0.038
	Yes (n %)	12, 75	4, 25	16	
Hospital stay in days (median, IQR)		4.0, 0	4.0, 0		0.177

TA: Tranexamic acid, IQR: Interquartile ratio

Discussion

The present study supports the hypothesis with expectant results and further asserts the need for considering alternative and simple means to minimize blood loss during PCNL. The study also emphasizes on technical aspects of PCNL to minimize confounders for blood loss in similar future studies. We hope to stimulate a notion in the minds of researchers to ponder upon possibilities of non-surgical and inexpensive means of controlling excessive hemorrhage during one of the commonest and traumatic surgical procedures in urology.

The notion of performing this study was based on few concrete observations from literature search which will be discussed sequentially in this section. Only one published international study was found during our study duration which was performed by Kumar et al. (22), which had a sample size of 200 patients (100 in each arm). In view of that, we took an ample sample size (240) which correlated with the frequency of PCNL cases in our center. Secondly, the study by Kumar et al. (22) inadequately mentioned some very important intraoperative details like stone location and volume, puncture technique, calyx punctured and position of puncture, type and size of dilators along with Amplatz size. We feel that these details hold utmost importance because these are vital confounders and affect the results of study.

Many urological surgeries have reaped their benefit of reduced intra and postoperative hemorrhage with the use of TA. Radical cystectomy is one of the bloodiest surgeries when vascular anatomy is taken in to perspective. Pelvic area is considered to be highly vascular and is very prone to bleeding. On top of that, malignancy causes increased angiogenesis which in turn increases the chances of intra and postoperative hemorrhage. A retrospective review stated that patients who underwent open radical cystectomy had less frequent need for perioperative blood transfusion when they were given intravenous TA (25).

A very recent study from North India by Bansal and Arora (26) proposes through randomized controlled trial that TA reduces blood loss during PCNL and also diminishes need for blood transfusion with additional benefits of shorter operative time and hospital stay. But in this study, TA was used in irrigation fluid rather than intravenous administration which resulted in fall in Hb and total blood loss in Tranexamic group to be significantly lower than placebo group (1.71 vs. 2.67 gm/dL, 154.55 vs. 212.61 mL, respectively ($p<0.0001$).

Similarly, use of TA in lowering blood loss and need for transfusion has been documented in various published studies pertaining to Obstetrics/Gynecology, Orthopedics, Head and Neck and Cardiac surgery (27,28,29,30).

Study Limitations

Few limitations in our study are worth mentioning for future researchers to take in to account. Some patients (24 out of 240) underwent tract dilatation up to 18 French and subsequent Amplatz size of 20 French. These were the cases where stone size was less than 2 cm. This was probably a limitation of the study but since both arms contained similar number of such patients (11 in placebo and 13 in TA group) ($p=0.41$), this limitation would not become a source of large and significant bias. Hounsfield unit calculation of stone on a CT scan which gives a good estimation of degree of hardness of a stone, could not be calculated in our study due to lack of necessary software in the CT scan console. This is yet another limitation of the study which could have effects on operative times and subsequent blood loss. Another limitation of the study is that the dose of TA was constant (1 gm) in all the patients, despite the weight of patient to whom it was administered. Food and drug administration approved drug dosage literature only suggests a single perioperative dose of 10 mg/kg in hemophilia patients undergoing tooth extraction, whereas no patient in in our study received a dose less than this suggested dosage.

Conclusion

It can be concluded with great confidence that an inexpensive and relatively safe drug like TA is highly efficacious in preventing excessive blood loss during a traumatic surgery like PCNL. We can also conclude that TA not only makes surgery easy and operative time short, but also minimizes the need for blood transfusions during PCNL. Despite that fact, further similar prospective trials are needed to strengthen the level of evidence for guidelines on the use of this drug and to evaluate the demographical variation in the results of its use.

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I am also gratified to put word of thanks for my parents and my beloved wife for their motivation, co-operation and affection in helping me tide over my difficulties and enabling me to do my postgraduate training and to complete this research work.

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Primary investigator, patients or helper nurses in holding bay didn't have any conflict of interest. Drug TA was provided free of cost by Hilton Pharma (PVT) Ltd. without demand of any favor in return.

Ethics

Ethics Committee Approval: This study was approved by the Kidney Centre Ethical Review Committee (approval number: 20-URO-022015, date: February 2015).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: Primary investigator, patients or helper nurses in holding bay didn't have any conflict of interest.

Financial Disclosure: Study drug tranexamic acid was provided free of cost by Hilton Pharma (PVT) Ltd. without demand of any favor in return.

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CASE REPORT
Andrology

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Necrotizing Fungal Infection Following Penile Prosthesis Implantation: A Case Report

Penil Protez İmplantasyonu Sonrası Nekrotizan Mantar Enfeksiyonu: Olgu Sunumu

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Abstract

Infection is one of the most devastating complications of penile prosthesis implantation. Although the infection prevalence have decreased owing to new technologies and growing surgical experience, it is still a troublesome situation. We present a 50-year-old male patient who had necrotizing fungal infection after penile prosthesis implantation caused by Trichosporon asahii.
Keywords: Fungi, infection, necrosis, penile prosthesis, Trichosporon asahii

Öz

Enfeksiyon, penil protez implantasyonunun en tahrip edici komplikasyonudur. Cerrahi deneyimin gelişmesi ve yeni teknolojiler sayesinde enfeksiyon prevalansı düşmekte olmasına rağmen, halen sıkıntılı bir durum olmaya devam etmektedir. Penil protez implantasyonu sonrası "Trichosporon asahii"nin sebep olduğu nekrotizan mantar enfeksiyonu gelişen 50 yaşında erkek olguyu sunmaktayız.
Anahtar Kelimeler: Mantar, enfeksiyon, nekroz, penil protez, Trichosporon asahii

Introduction

Penile prosthesis implantation is an important treatment option for severe erectile dysfunction (1). In spite of increased experience of surgeons and advances in implant technology, prosthesis-derived infection remains as a serious adverse event (2). We present a case of necrotizing fungal penile infection after penile prosthesis implantation that resulted in total penectomy.

Case Presentation

Written informed consent was obtained from the patient. A 50-years-old male patient was admitted with the complaint of erectile dysfunction for 4 years. He had type 2 diabetes mellitus for 10 years and had been under insulin treatment for the last three years. International Index of Erectile Function score was 0. He reported that previous treatments with phosphodiesterase type 5 inhibitors had been unsuccessful. His physical examination was normal.

The patient underwent malleable penile prosthesis implantation (Coloplast®, Minneapolis, USA) via penoscrotal approach under perioperative vancomycin and gentamycin prophylaxis. The patient was discharged on postoperative 1st day uneventfully.

At the postoperative 10th day, the patient applied to our outpatient clinic with severe penile pain and hyperaemia in the incision line. Oral cefuroxime axetil 500 mg twice daily and dexketoprofen 50 mg once a day were initiated. However, ecchymosis and severe oedema occurred in the next 48 hours even after the oral treatment (Figure 1). Considering prosthesis-related infection, the patient was hospitalized and the prosthesis was removed same day. Tissue and drainage samples were obtained for antimicrobial culture study. As a "Trichosporon asahii" fungus was isolated in the culture, systemic antifungal (fluconazole 100 mg, twice a day) treatment was added. As patchy necrotic areas were observed at the glans penis, hyperbaric oxygen therapy was administered, however, necrosis spread despite antimicrobial and hyperbaric oxygen

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treatment. In 72 hours, the ischemia and necrosis increased till the base dominantly on the dorsal skin of the penis. The patient underwent penile amputation surgery.

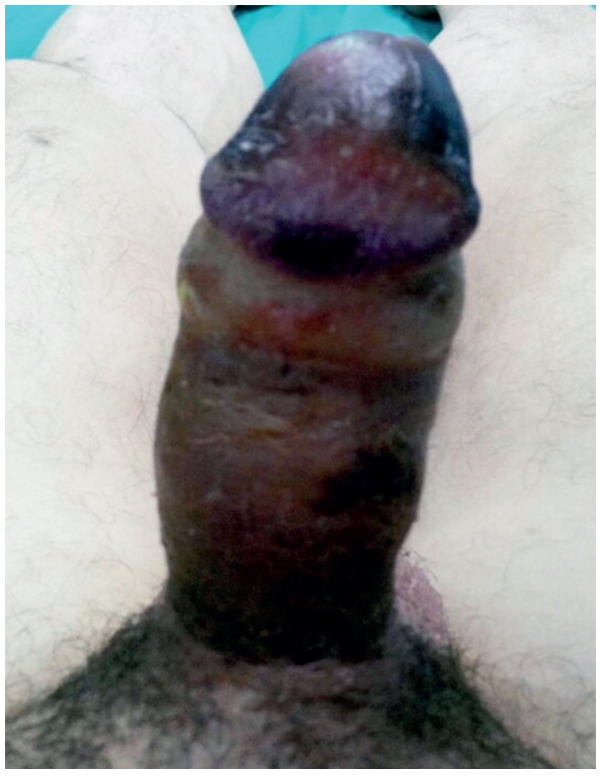

Figure 1. Necrotizing infection of the penis

Discussion

Penile prosthesis implantation is an effective and acceptable method for the management of organic erectile dysfunction (3). Infection is the most important complication of this procedure. Although the rates of infection have decreased in the past years; still, 1-3% of cases suffer from this complication (4). The cost of a penile prosthesis infection has been shown to be six fold the original operation (5). Mulcahy and Carson (6) evaluated the rate of infection associated with penile prosthesis implantation in diabetic and non-diabetic patients. They demonstrated a significantly higher rate of infection in diabetic patients (1.88% in diabetics vs. 1.53% in non-diabetics) (6).

Pathogens may contaminate implant via atmospheric exposure, unknown urinary tract infection or urethral injury during surgery, or via haematogenous or lymphogenous spread (7). The most common cause of infections is direct contact of the prosthesis with the skin flora during surgery. Coagulase-negative staphylococci are the most frequently isolated organisms from infected prostheses (5). The second most common infecting microorganism is *Enterobacter aerogenes.* Fungal infections have been described in approximately 5 percent of cases (5).

All humans are colonized as a commensal interaction with yeast and their virulence is related to the deterioration of host defense. The most common conditions for Candida proliferation include immunocompromised states, diabetes mellitus, antibiotic overuse, indwelling devices, and intravenous drug use (8,9).

Trichosporon asahii and other members of the genus Trichosporon are basidiomycetous yeasts defined by the structure of true hyphae and pseudohyphae, arthroconidia, and blastoconidia (10). They have been isolated from soil and other environmental sources and from enclosed surfaces. In addition, they may be a part of the normal flora of the human skin, gastrointestinal tract and respiratory system (11).

An ideal treatment for Trichosporonosis has not yet been clearly defined (12). It has been recommended that antifungal drug resistance and high mortality rates seen in severe Trichosporonosis may be accomplished by the combination of two classes of antifungals (amphotericin B and fluconazole) (10). However, even after prompt and forceful antimicrobial treatment, it may not be sufficient to avoid catastrophic situations like local tissue necrosis leading to amputation.

Although a significant decrease in infectious complications has been accomplished in penile prosthesis surgery, these complications may still cause catastrophic outcomes. Although fungal infections are rarely seen after penile prosthesis implantations, surgeons must consider antifungal therapy if post-surgical infection does not ameliorate with antibiotic treatments, especially in patients with the poor host defense mechanisms.

Ethics

Informed Consent: Written informed consent was obtained from the presented case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.G.Ç., Design: M.G.Ç., E.E., Data Collection or Processing: E.E., Analysis or Interpretation: M.K., E.E., Literature Search: U.Y., M.G.T., Writing: M.G.T., M.G.Ç.

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
General Urology

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Bilateral Primary Renal Lymphoma Presenting with Acute Renal Failure

Akut Böbrek Yetmezliği ile Prezente Olan Primer Bilateral Renal Lenfoma

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Abstract

Non-Hodgkin's lymphoma is a multisystem disease presenting with painless lymph node involvement in patients between 40 and 70 years of age. Kidney failure can be seen in about 10% of lymphoma patients due to different reasons. However, renal failure caused by lymphomatous parenchymal infiltration of the kidneys is very rare. In this study, we present a case of bilateral primary renal lymphoma presenting with acute renal failure.

Keywords: Lymphoma, acute renal failure, renal mass

Öz

Non-Hodgkin lenfoma 40-70 yaşları arasında ağrısız lenf nodu tutulumu ile giden multisistemik bir hastalıktır. Lenfomalı hastaların %10'unda farklı sebeplerden dolayı böbrek yetmezliği izlenebilir. Fakat böbrek parankiminin lenfomatöz infiltrasyonuna bağlı böbrek yetmezliği çok nadir görülen bir tablodur. Biz bu çalışmada akut böbrek yetmezliği ile prezente olan primer bilateral renal lenfoma olgusunu sunuyoruz.

Anahtar Kelimeler: Lenfoma, akut böbrek yetmezliği, renal kitle

Introduction

Non-Hodgkin's lymphoma is a multisystem disease presenting with painless lymph node involvement in patients between 40 and 70 years of age (1). Extranodal involvement of the kidney is common and this situation is usually asymptomatic (2). Autopsy studies have shown that about 50% of lymphoma cases have secondary involvement of the kidneys (3,4). Kidney failure can be seen in about 10% of lymphoma patients due to different reasons. However, renal failure caused by lymphomatous parenchymal infiltration of the kidneys is very rare (5). In this study, we present a case of bilateral primary renal lymphoma presenting with acute renal failure.

Case Presentation

Informed consent was obtained from the patient. A 64-year-old male patient presented to our clinic with the complaint of chronic fatigue. Vital signs were normal and no comorbidities were detected. Systemic examination was unremarkable. The patient had normal urinalysis values. Among the biochemical parameters, only the creatinine level was slightly above the normal levels (4.5 mg/dL).

Ultrasonography showed both kidneys larger than normal and increased echogenicity of the renal parenchyma.

Computed tomography scan detected bilateral solid masses with irregular borders infiltrating the parenchyma and collection system which extended towards the perirenal tissues. The mass

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on the left kidney was larger than that on the right kidney (Figure 1). Magnetic resonance imaging showed that both kidneys were larger than normal and both kidneys had irregularly bordered solid tumor infiltrations with heterogeneous intensity.

Since the patient had bilateral masses on both kidneys, biopsy was indicated. Two samples was obtained from the left kidney using a 18G Tru-cut biopsy needle by entering the parenchyma from the lower pole of the kidney.

Pathology reported "B-Cell lymphoma" after histopathological and immunohistochemical assessment of the samples (Figure 2).

The patient was diagnosed with primary renal lymphoma and was referred to the hematology department for chemotherapy.

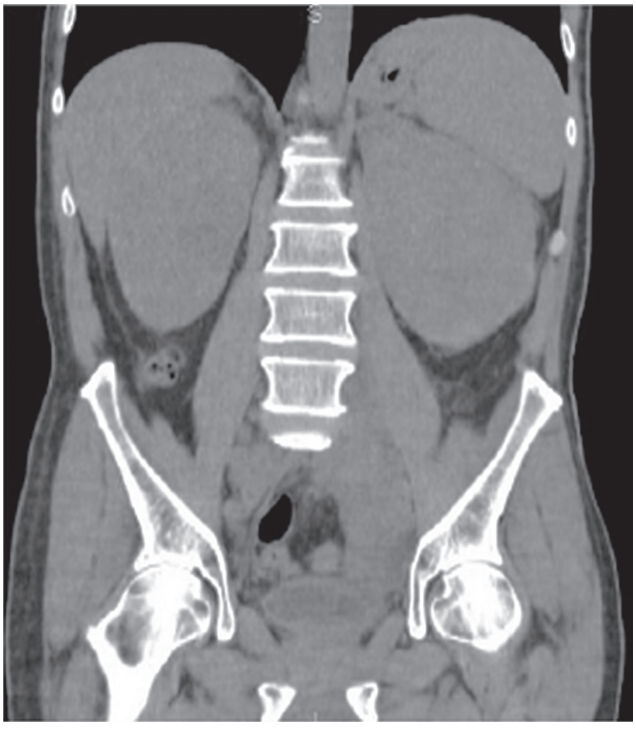

Figure 1. Irregularly bordered solid mass infiltrating parenchyma and collection system which extended towards perirenal tissues

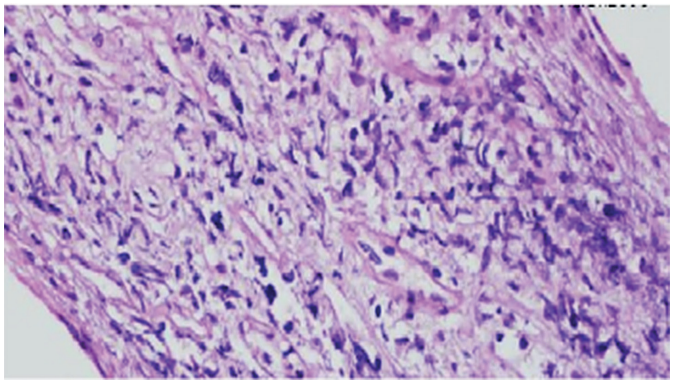

Figure 2. Histopathological and immunohistochemical assessment of the samples; B-cell lymphoma

Discusion

In the literature, the incidence of renal involvement in Non-Hodgkin's lymphoma has been reported to be 2.7-6% (6).

Primary renal lymphoma makes up about 0.7% of extranodal lymphomas in the USA and 0.1% in Japan. For primary renal lymphoma diagnosis, there should be no lymphoma involvement in any other area other than kidneys (7). The etiology of primary renal lymphoma is still debated since the kidneys do not contain any lymphoid tissue (8).

Glicklich et al. (9) speculated that tumor infiltration was due to pressure on tubular lumen which caused intrarenal obstruction and showed a flattening of both tubular and epithelium cells in histology results.

In their study, Li et al. (10) highlighted the importance of biopsy in proteinuria and renal failure patients with renal masses and diagnosed 18 out of 20 patients with non-Hodgkin's lymphoma, with 9 bilateral cases.

In cases with suspected renal lymphoma, the diagnosis should be confirmed by ultrasound-guided Tru-cut biopsy (11).

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer Review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ü., H.T., O.K., Concept: S.Ü., A.S.D., Design: S.Ü., O.K., Y.Y., Data Collection or Processing: A.O.Ç., O.K., H.T., Analysis or Interpretation: A.S.D., A.C.E., Literature Search: E.M.Y., S.Ü., Writing: S.Ü.

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
Urooncology

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An Extremely Rare Kidney Tumor: Primary Intraparenchymal Squamous Cell Carcinoma

Oldukça Nadir Bir Böbrek Tümörü: Primer İntraparankimal Skuamöz Hücreli Karsinom

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Abstract

Primary squamous cell carcinoma of the renal parenchyma is a rare entity and only 4 cases have been reported in the literature. A 73-year-old female patient presented to our clinic with the complaint of right flank pain. On radiologic evaluation, a 6x5x4 cm hypodense mass showing heterogeneous contrast enhancement was observed in the upper pole of the right kidney. An uneventful laparoscopic radical nephrectomy was performed. Final pathologic diagnosis was squamous cell carcinoma. No pathological involvement was observed on postoperative positron emission tomography/computed tomography. Our patient is still alive and she has not received any adjuvant treatment.
Keywords: Squamous cell carcinoma, kidney, cancer

Öz

Primer renal parankimal renal skuamöz hücreli karsinom oldukça nadir bir patoloji olup, bugüne değin literatürde sadece 4 olgu bildirilmiştir. Yetmiş üç yaşında kadın hasta kliniğimize sağ flank ağrısı şikayetiyle başvurdu. Radyolojik incelemede sağ böbrek üst polünde 6x5x4 cm boyutunda heterojen kontrastlanma gösteren hipodens kitle saptandı. Hastaya laparoskopik nefrektomi uygulandı ve patolojik incelemede tanının skuamoz hücreli karsinom olduğu görüldü. Hastaya metastaz araştırması için çekilen postoperatif pozitron emisyon tomografisi/bilgisayarlı tomografide herhangi bir patolojik tutulum görülmedi. Hastamız halen sağlıklıdır ve herhangi bir adjuvan tedavi almamıştır.
Anahtar Kelimeler: Skuamöz hücreli karsinom, böbrek, kanser

Introduction

Primary squamous cell carcinoma (SCC) of the renal pelvis is a quite rare type of cancer accounting for 0.5-15% of all urothelial cancers. It has a poor prognosis due to its rarity and ambiguous clinical and radiological features (1). Only few cases of primary SCC of the renal pelvis have been reported in the literature (2,3,4,5). In this paper, we present the case of primary SCC of the renal pelvis in a 73-year-old female patient.

Case Presentation

On March 2013, a 73-year-old female patient presented to our clinic with the complaint of right flank pain. She had no weight loss or hematuria. The patient had no history of renal calculus, urinary tract infection or pyonephrosis. On physical examination, right costovertebral angular sensitivity was noted. No palpable lymph node was observed. Routine blood examination revealed the followings: Hg: Hemoglobin 10.0 and Htc: Hematocrin 30.5. Serum urea and creatinine levels were normal. Ultrasound showed a hypoechoic mass in the upper pole of the right kidney. No hydronephrosis was observed on ultrasound. Contrast-enhanced computed tomography (CT) showed a 6x5x4 cm hypodense mass showing heterogeneous contrast enhancement in the upper pole of the right kidney (Figure 1).

Upon the suspicion of renal vein invasion, contrast enhanced

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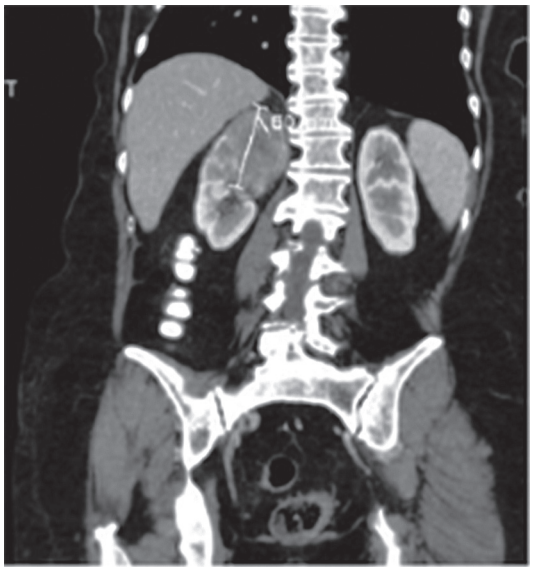

Figure 1. Computed tomography image of the tumor that is originated from the upper pole of the right kidney

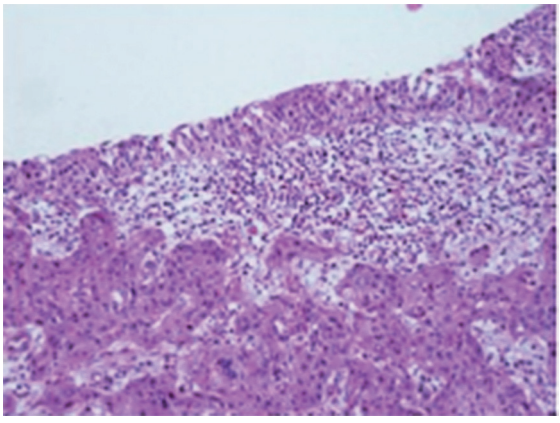

Figure 2. The relationship between the tumor and renal pelvis at 100x magnification

abdominal magnetic resonance imaging (MRI) was performed. No vascular invasion was observed on MRI and no distant metastasis was found on preoperative abdominopelvic CT and thorax CT. An uneventful laparoscopic radical nephrectomy was performed. When the pathology specimen was analyzed, no tumor or stone was observed macroscopically in the pelvicalyceal system. The mass was located in the upper and mid pole of the kidney.

In the histopathologic examination, it was found that the tumor was moderately differentiated and contained focal necrosis; there was common infiltration in the renal parenchyma and an infiltration to the renal pelvis. Angiolymphatic invasion was present. There was no invasion in the capsule, hilus, surrenal gland, perirenal or peripelvic fatty tissue. All the surgical margins were clear (pT3Nx according to AJCC 2011 TNM staging). Although SCC invasion was histopathologically observed in the renal pelvis, no squamous metaplasia or dysplasia was found in the urothelial mucosa (Figure 2).

When all these factors were combined, it was shown that the tumor was a SCC that was primarily derived from the renal parenchyma. After the pathology was determined as SCC, positron emission tomography/CT was performed to investigate any metastasis, however, no pathological involvement was observed.

Our patient is still alive and she has not received any adjuvant treatment. The patient is under follow-up for nine months and no pathology has been detected on control imaging.

Informed consent was filled out by the patient.

Discussion

Transitional cell carcinoma (TCC) is the most common cancer of the renal pelvis. When compared to TCC, renal SCC is a rarely seen tumor mostly affecting women aged between 50 and 70 years. Primary SCC of the renal pelvis is generally diagnosed at the advanced stage and when invaded to the adjacent tissues (6). Our case was a 73-year-old female who had primary SCC of the renal parenchyma with renal pelvis invasion but no distant metastasis. Urothelial SCC generally arises through a process of metaplasia, mostly keratinizing squamous metaplasia of the urothelium. Squamous metaplasia is the precursor of SCC, however, there are disagreements in the previous studies. Such disagreements may be engendered by the rare incidence of SSC of the upper urinary system (7). The histologic features of squamos carcinoma are keratotic cellular debris, pearl formation and intercellular bridges. However, if there is a keratinized squamous metaplasia on the adjacent urothelial surface, especially if dysplasia accompanies, these findings support the diagnosis of the tumor as primary renal pelvis SCC (8,9).

In our case, no squamous metaplasia/dysplasia or dysplastic urothelial component was observed in the urothelium.

Among the etiological factors; a staghorn stone that is present in the kidney for a long time, recurrent urinary tract infection, smoking, schistosomiasis, exogenous or endogenous chemicals, vitamin A deficiency, and hormonal imbalance can be specified (7). In our case, none of these predisposing factors was observed.

Since imaging properties of SCC are non specific, radiological diagnosis of SCC is not easy. The most common radiologic finding is a solid infiltrating mass with or without calcifications (10). The differential diagnosis of SCC include renal neoplasms and xanthogranulomatous pyelonephritis (XGP). Radiological feature of XGP on contrast-enhanced CT is low-attenuating areas surrounded by enhancing thinned renal parenchyma from chronic hydronephrosis (bear-paw sign) (11). However, this sign may not be seen frequently.

When a renal tumor is diagnosed as SCC, distinction between primary renal SCC and metastatic SCC should be done. In order to make this differentiation, the combination of clinical history, imaging and histopathological evaluation is needed (7). After metastatic SCC is excluded, differentiation between SCC of the renal pelvis and intraparenchymal SCC should also be done (10).

We did not observe paraneoplastic syndromes like hypercalcaemia, leucocytosis or thrombocytosis which could accompany SCC (12).

In the literature, there are limited number of reported cases of primary SCC of the renal parenchyma and these cases have shown poor prognosis. Our case was organ-confined and it was considered that the prognosis would be good.

Ethics

Informed Consent: Consent form was filled out by the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., A.Y., Concept: M.Y., A.Y., T.İ., Ö.İ., G.İ., Design: M.Y., A.Y., T.İ., Ö.İ., G.İ., Data Collection or Processing: M.Y., A.Y., T.İ., Ö.İ., G.İ., Analysis or Interpretation: M.Y., A.Y., T.İ., Ö.İ., G.İ., Literature Search: M.Y., A.Y., T.İ., Ö.İ., G.İ., Writing: M.Y., A.Y., T.İ., Ö.İ., G.İ.

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CASE REPORT
General Urology

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Journal of Urological Surgery, 2017;4(4):211-214

Cough-Induced Spontaneous Rupture of the Kidney Secondary to Anticoagulant Therapy: Wunderlich's Syndrome

Antikoagülan Tedaviye Sekonder Öksürüğün İndüklediği Spontan Böbrek Rüptürü: Wunderlich Sendromu

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Abstract

Spontaneous renal or other organ ruptures secondary to anticoagulants have rarely been reported. The clinical features of renal rupture include acute flank/abdominal pain, haematuria, hypotension and shock. It can occur due to increased intraabdominal pressure during coughing. Rupture is most commonly caused by renal tumors such as angiomyolipomas. In the literature, other known causes are long-term haemodialysis, arteriosclerosis or arteritis. Wunderlich's syndrome is an extremely dangerous complication that may cause death if not treated intensively. If the haemorrhage is self-limiting and the patient is responsive to fluid replacement, the patient can be managed conservatively. Selective angiographic embolization and emergency nephrectomy (partial or total) are the treatment options. In the literature, we found only one case that was presented as spontaneous non-traumatic renal rupture associated with coughing. In our case, total nephrectomy had to be performed, but it was not adequate.
Keywords: Spontaneous renal rupture, cough, anticoagulant, Wunderlich's syndrome

Öz

Spontan böbrek veya diğer organ rüptürleri antikoagülanlara sekonder çok nadir bildirilmiştir. Klinik tabloda akut flank/karın ağrısı, hematüri, hipotansiyon ve şok görülebilir. Öksürük esnasında karın içi basıncının artışına bağlı oluşabilir. Rüptürün en sık sebebi anjiomyolipomlar gibi böbrek tümörleridir. Diğer sebepler arasında uzun süreli diyaliz, arteritler ve ateroskleroz sayılabilir. Eğer agresif tedavi edilmezse hayatı tehdit eden bir durumdur. Hemoraji kendini sınırlarsa konservatif yaklaşılabilir. Anjiyografik selektif embolizasyon ve parsiyel/total nefrektomi diğer tedavi seçenekleridir. Literatürde buna benzer bir olgu bildirilmiştir. Bizim olgumuzda takip sonrası total nefrektomi yapılsa da, bu yeterli olmamıştır.
Anahtar Kelimeler: Spontan böbrek rüptürü, öksürük, antikoagülan, Wunderlich sendromu

Introduction

Wunderlich's syndrome is a spontaneous non-traumatic bleeding confined to the subcapsular and/or perinephric spaces in patients with no known underlying cause and constitutes an emergency medical condition (1,2). Various terms have been used including spontaneous perirenal haematoma, spontaneous subcapsular renal haemorrhage, nontraumatic perirenal haematoma and spontaneous perinephric haematoma. The etiology of spontaneous renal rupture has not been described yet. Possible causes include benign [e.g., angiomyolipomas (AML), tuberous sclerosis, renal cyst, adenoma, lipoma, and hamartoma] and malignant (e.g., oncocytoma, renal clear cell carcinoma, and Wilms' tumor) tumors or it can occur secondary to vasculitis (polyarteritis nodosa), nephritis, blood dyscrasias (anticoagulant agents, polycythaemia), renal stone disease, arteriovenous malformations and fistulas, venous thrombosis or rupture of renal artery/intraparenchymal aneurysm (3,4). Wunderlich's syndrome is clinically characterized by the "Lenk's triad" which includes acute flank pain, flank mass and hypovolemic shock. In this case report, we aimed to present and discuss a rare syndrome according to the literature.

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Case Presentation

This case is a 41-year-old male who was admitted to the emergency room (ER) with weakness, changes in urine color, nausea and mild abdominal pain after a coughing episode on going through the last few days. There was not any trauma history. His physical examination elicited a solid mass palpated on the left flank region. The patient had mild pallor, his pulse was normal, pulse rate was 88/min, blood pressure was 110/70 mmHg, respiratory rate was 22/min, and body temperature was 36.8 °C. However, on the examination there was not any tenderness in the abdomen. In his medical history, there were acute rheumatic fever, atrial and mitral valve regurgitation and cerebrovascular occlusive disease. Moreover, he had been using some medications, namely warfarin (1 mg 1x1/oral daily), and metoprolol succinate (25 mg 1x1/oral daily). In our case, he had hypertension in his medical history, and had not undergone any operation. Abnormal values in the first laboratory analysis were serum glucose 155 mg/dL, total bilirubin 1.98 mg/dL, direct bilirubin 0.62 mg/dL, albumin 3.3 g/dL, sodium^{++} 131 mmol/L, calcium^{++} 8.3 mg/dL, urea 46 mg/dL, whole blood analysis [white blood cell 12.1 103/uL, hemoglobin (Hgb) 11.3 g/dL, hematocrit (Htc) 34.1%, platelets 239 103/uL], and coagulation tests [prothrombin time (PT) 29.7 sec, activated partial thromboplastin time (APTT) 39.7 sec, PT% %27, international normalized ratio (INR) 2.9]. Macroscopic hematuria was seen in the urine sample and then microscopic urine examination confirmed that during the ER stay. After the initial evaluation, he was hospitalized in the urology department because of decrease in the blood test values (Hgb and Htc) and hematoma around the kidney. Informed consent was obtained from the patient. On the first contrast-enhanced computed tomography (CT) of the abdomen, there was grade IV renal injury and retroperitoneal hematoma on the left side (Figure 1). During the first 3 days, the patient was closely followed up conservatively. At this period, the oral anticoagulant agent was stopped. Daily whole blood count and coagulation tests were obtained. After being clinically stable for a two-day period, control abdominal CT revealed expanding retroperitoneal hematoma (Figure 2). Blood count and coagulation tests values reached the dangerous level (Htc 20.1% minimum -34% maximum, PT 24.5 sec. minimum -49.5 sec. maximum, APTT 35.6 sec. minimum -180 sec. maximum, PT (%) 15% minimum -35% maximum, INR 2.19 minimum -5.59 maximum) in this hemodynamically unstable period. Selective angioembolization was tried but it was not successful. Lastly, patients' clinical status had gone worse and emergency radical

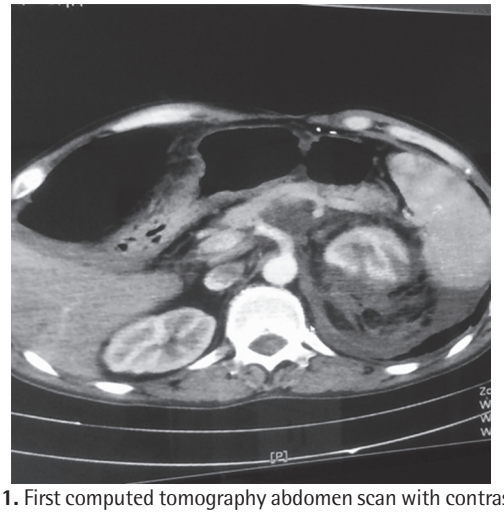

Figure 1. First computed tomography abdomen scan with contrast, there was grade 4 renal injury and retroperitoneal hematoma on the left side according to the American Association for the Surgery of Trauma classification

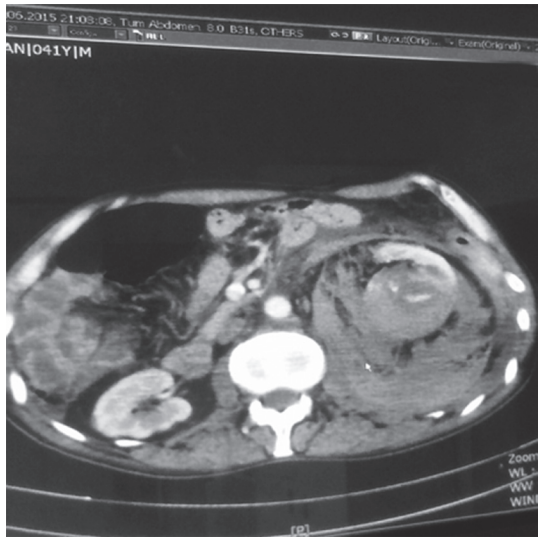

Figure 2. During the conservative approach, there was enlarged retroperitoneal hematoma on the preoperatively computed tomography abdomen scan with contrast

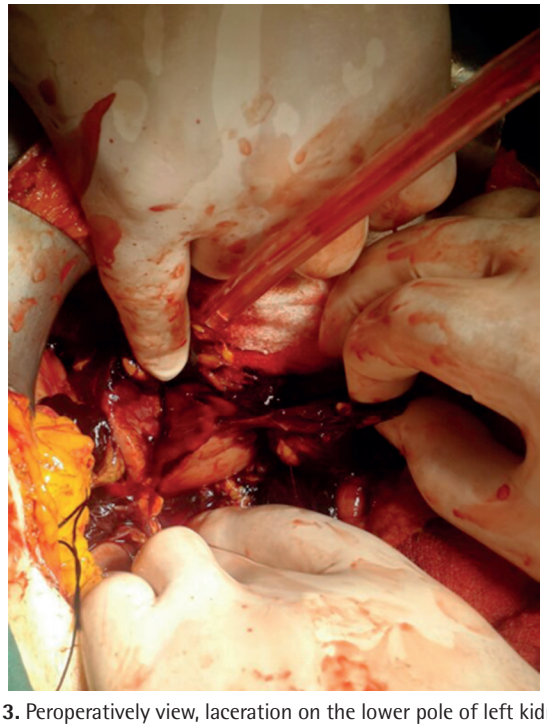

Figure 3. Peroperatively view, laceration on the lower pole of left kidney

nephrectomy operation was preferred at the fourth day for the protection of the vital findings. At the time of operation, a lower pole laceration was found on the left kidney and total nephrectomy was performed (Figure 3, 4). All along this period, 4 units of whole blood and 2 units of red cell transfusions were made. Postoperatively, the patient was transferred to the intensive care unit. During the two days in this unit, new clinical progressive mortal condition has evolved. Despite all the aggressive treatment attempts, the patient died. According to the pathology report, pathological material did not involve any tumor as an AML or other pathologies like aneurysm in the kidney specimen and the report declared only lower pole renal rupture on the left side.

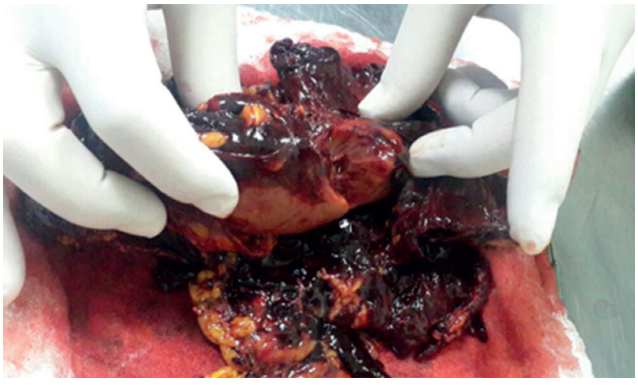

Figure 4. Postoperatively macroscopic view, about 3 cm laceration on the lower pole of left kidney

Discussion

Most of the urological surgeons may not be used to this terminology. In the literature, we could just find extremely rare case reports about this syndrome. On the other hand, Herlyn-Werner-Wunderlich syndrome is a different condition that is characterized by a triad of type 3 Müllerian duct anomaly, obstructed hemivagina and mesonephric duct anomalies (including congenital renal anomalies) (5). These two different terms can be easily confused.

Spontaneous organ or tissue ruptures secondary to anticoagulant therapy occurring in arteries, veins, spleen, pancreas, and kidneys have been reported in the literature (6,7,8,9,10), however, the etiopathogenesis is not clear yet. At the molecular level during the tissue-coagulation process many molecules like tissue factor are important. A reasonable mechanism has been suggested that an unrecognized minor trauma initiates hematuria, which continues due to depletion of the clotting factors. As we well know, bleeding is the most frequent adverse effect of anticoagulant therapy in somewhere. The incidence of major bleeding in patients under oral anticoagulant therapy is 0.5%–1.6% in per year. In addition, antiplatelet or fibrinolytic treatment increases the risk of bleeding (8). One of the most common locations for anticoagulant-related bleeding is the urinary tract (15%). The retroperitoneum is a rare location for spontaneous bleeding (1%) (8). However, retroperitoneal hemorrhage is a serious complication of anticoagulant therapy that may cause significant mortality.

The majority of patients with this syndrome are managed conservatively but very close follow-up is a necessity. If there is any suspicion about this unstable, hemodynamically serious condition, you may have to choose an aggressive emergency treatment modality. The patient is usually discharged with a transient mild hematuria caused by an intraparenchymal microaneurysm which may be easily misdiagnosed thus can be a life-threatening problem. Predisposing factors for spontaneous renal ruptures are congenital malformations of the kidney, smoking, hypertension, atherosclerosis, pregnancy, minor traumas (coughing episode), recent surgical operation, malignancy, renal angiomyolipoma, radiation, and/or anticoagulant therapy, and cyclophosphamide usage (6,7,8,9,10). Rupture is the most dangerous result and the risk depends on age, gender, histology, and size of the laceration. Diagnosis of the spontaneous renal rupture is not easy. Hematuria can be microscopic or gross and hemodynamic instability may occur in a rupture (6,7). A pioneer symptom that could help the diagnosis of a spontaneous renal rupture is the deterioration of the condition of patient with an increase in the intra-abdominal pressure (during defecation or coughing) as in our case. In patients who have non-traumatic acute flank or abdominal pain, it is important to determine whether the patient has been taking anticoagulation medication due to bleeding diathesis or not. If an emergency laparotomy is not necessary, we recommend that these cases should be treated surgically after clinical stabilization. Kidney ruptures are the main reason for haematomas and the patients need a proper balance between coagulation mechanisms and anticoagulation. Endovascular surgery (selective transcatheter arterial embolization) is considered to be an option for the management of this syndrome. In our case, the rupture caused a life-threatening hemorrhage and hypovolemic shock. Therefore, we performed a definitive diagnostic operation as open exploratory laparotomy, and subsequently, a radical nephrectomy was the only option but it was not adequate. Early laparotomy at the time of admission might be a good option for patients with macroscopic hematuria or grade 4 renal trauma (laceration to the lower pole of the kidney), however, close follow-up is also a preferred option nowadays. Especially, partial/total nephrectomy or kidney repair can be better than conservative management or endovascular treatment (selective angiographic embolization) for grade 4 renal trauma as for grade 5 cases.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.F.N., Concept: K.F.N., Design: K.S., Data Collection or Processing: Ö.K., Analysis or Interpretation: B.E., Literature Search: K.F.N., Writing: K.S.

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

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CASE REPORT
General Urology

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Giant Size Xanthogranulomatous Pyelonephritis: A Case Report

Dev Boyutlarda Ksantogranülomatöz Piyelonefrit Olgusu

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Abstract

According to the literature, differential diagnosis of xanthogranulomatous pyelonephritis (XGP) can mostly not be recognized preoperatively and is frequently confused with kidney tumor. A 46-year-old female patient was admitted to our urology department with the sole complaint of swelling of the left side of her abdomen and, following her examination and tests, her left kidney was found to turn into a giant size, painless, hydronephrotic mass with stones. However, since a giant solid mass was observed during the operation, it was thought that the mass could be XGP. I would like to report such a case, which may not pre-operatively be considered as XGP on the basis of the complaints, history, and physical examination and imaging findings.

Keywords: Giant size, xanthogranulomatous pyelonephritis, stone

Öz

Literatürde ksantogranülomatöz piyelonefritin (KGP), ameliyat öncesi ayırıcı tanısının çoğunlukla yapılamadığı ve sıklıkla böbrek tümörü ile karıştırıldığı vurgulanmaktadır. Sadece karnının sol yanında şişlik yakınması ile hastane üroloji polikliniğine başvuran 46 yaşındaki kadın hastanın, muayene ve tetkiklerinde, sol böbreğinin dev boyutlarda, ağrısız, taşlı, hidronefrotik bir kitle halini aldığı anlaşıldı. Ancak ameliyat sırasında dev boyutlarda solid bir kitle ile karşılaşılınca, bu kitlenin KGP olabileceği düşünüldü. Yakınmaları, öyküsü, fizik muayene ve görüntüleme bulguları ile ameliyat öncesi, KGP olabileceği düşünülmeyen böyle bir olguyu paylaşmak istedim.

Anahtar Kelimeler: Dev boyut, ksantogranülomatöz piyelonefrit, taş

Introduction

Xanthogranulomatous pyelonephritis (XGP) is a rare chronic bacterial infection of the kidney (1,2,3). The involved kidney almost all the time involves stones and is hydronephrotic. It is more prevalent among the female and the middle-age group. The disease is rarely focal but mostly the entire kidney is involved and the involved kidney is generally dysfunctional.

There is diffuse obstructive infection, accumulation of lipid-laden macrophages associated with impairment of local immunity and granulomatous infiltration (4,5). Such cases may be confused with neoplastic or inflammatory renal parenchymal diseases. Since pre-operative differential diagnosis is mostly not likely, definitive diagnosis is made based on histopathology (6,7).

Case Presentation

A 46-year-old female patient was admitted to our urology department with the sole complaint of painless swelling of the left side of her abdomen. She had abdominal swelling, which grew in the course of time, for the last 1.5 years, but did not previously consult a medical doctor as she had no any other complaint.

A cystic painless mass with a smooth surface, which was covering the left upper, middle and partly the lower quadrant of the abdomen, was detected during physical examination. The costovertebral angles were not tender. She reported not to pass any stone before, had fever or any urination complaints. There was nothing specific about her history or family history.

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During abdominal ultrasound, advanced left hydronephrosis, a 22 mm stone in the pelvis and a solid mass lesion measuring 67x48 mm which entirely covered the dilated calyx at the mid-segment of the kidney were detected and, thus, advanced imaging tests were suggested. There was nothing specific in her urine analysis and no culture growth as well. Her complete blood count results were as follows: White blood cell count: 12.200/mL, hemoglobin: 8.7 gr/dL and hematocrit: 28.9%. Biochemical test results were within the normal range. As a result of complete abdominal computed tomography (CT) and abdominal magnetic resonance imaging (MRI), an advanced enlargement in the size of the left kidney (extended to the pelvis), advanced stage hydronephrosis, advanced thinning of the parenchyma (Figures 1, 2), a 3 cm stone at the pelvis and a 2 cm stone at the lower pole and retraction through the adjacent structures were observed (Figure 3). Informed consent was obtained from the patient.

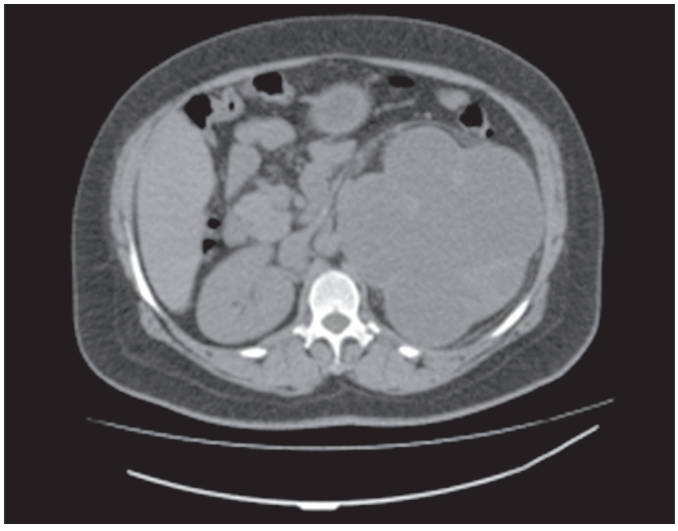

Figure 1. Abdominal computed tomography transverse section. The homogenously dense mass with smooth lobulated margins is covering left half of the abdomen

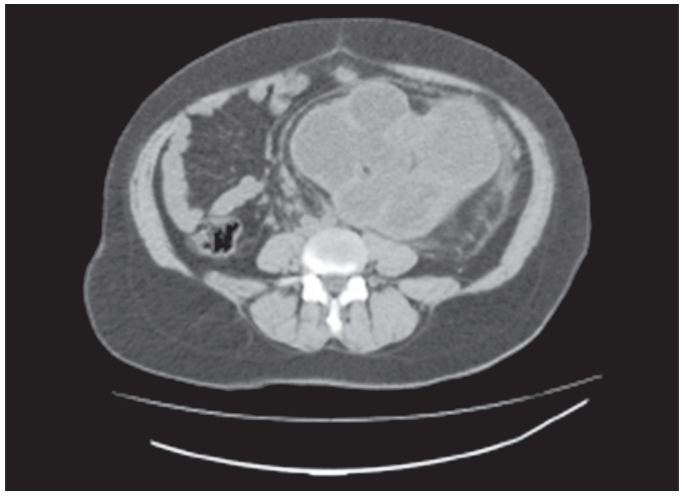

Figure 2. Homogeneously dense mass is extended to the right side of the abdomen

Surgical Intervention

The patient was operated under general anesthesia with the preliminary diagnosis of advanced stage left hydronephrosis and kidney stones. Left flank incision was performed. It was perioperatively observed that the kidney together with the Gerota's facia was adhered to the anterior and posterior abdominal walls, there were hydronephrotic areas (thinning of the parenchyma) only at the upper pole, the other areas had hard granulomatous tissue, and the kidney turned into a large well-circumscribed mass (extended to the pelvis). It was decided to remove the kidney. The purulent exudate at the hydronephrotic areas of the upper pole was discharged to mobilize the kidney. The left adrenal gland was spared and mobilized using blunt dissection. The pedicles were tied and the kidney mass in the size of 28x18x9 cm and weight of 3.045 kg was removed (Figure 4). Small peritoneal gaps at the anterior abdominal wall adjacent

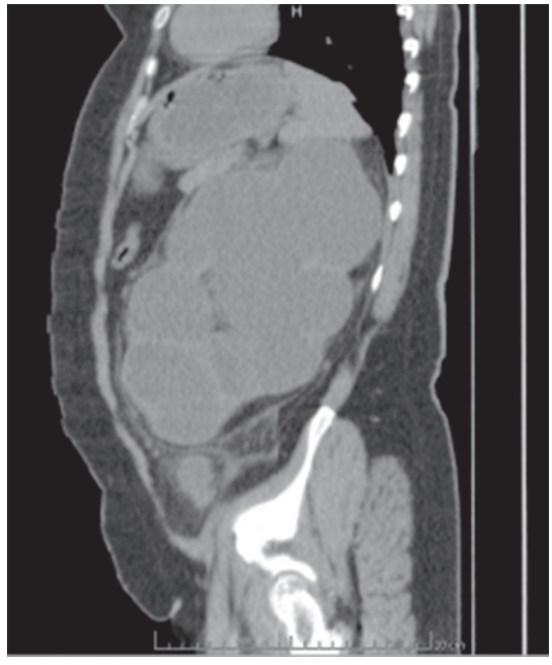

Figure 3. Homogeneously dense giant size mass at the vertical section of multi-slice abdominal computed tomography

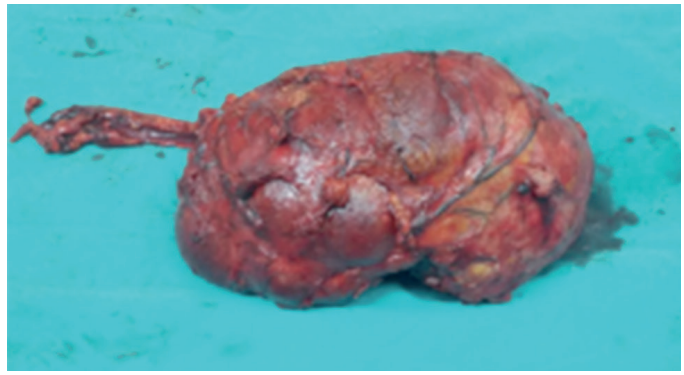

Figure 4. The kidney in the size of 28x18x9 cm and weight of 3.045 kg, as removed operatively

to the spleen were closed. Three units of erythrocyte suspension were perioperatively and postoperatively administered. The patient had no perioperative or postoperative complication and was discharged on day 3 with full recovery.

Histopathological diagnosis of the kidney was reported as "XGP + nephrolithiasis + pyonephrosis".

Discussion

XGP is a chronic suppurative infection in which lipid-laden macrophages replace the renal parenchyma. Although the involvement is mostly unilateral, some bilateral XGP cases have rarely been reported. The etiology of the disease is suggested to be urinary tract obstructions with or without stones, treatment of urosepsis, disorders of lipid metabolism, impaired immunity, chronic renal ischemia, and lymphatic obstructions (4,8,9). Our case had no immune deficiency or any other concomitant disease to impair immunity and had no history of urosepsis.

Kidney involvement in XGP can be local or extended. It is commonly the extended type, which has the tendency to involve the entire kidney and the perirenal tissue and it resembles renal tumors (7). It is difficult to make differential diagnosis preoperatively. The sole complaint of our 46-year-old patient was the swelling of the left side of her abdomen. There was no suspicion of XGP preoperatively since no flank pain, fever or urination complaints were reported and there were signs of stone and hydronephrosis during abdominal ultrasound and multi-slice abdominal CT.

The clinical course of XGP generally varies. Most common symptoms are intermittent flank pain, fever or chills. One or more of signs, such as weight loss, mass, high blood pressure or enlarged liver, may be present (10,11). Among these signs, our case only had a giant mass covering the left half of her abdomen.

Studies, which have assessed XGP from radiological point of view, reported that it was difficult to make diagnosis preoperatively but there still were certain radiological signs. These signs are extended and local enlargement in the kidneys, kidney or ureteral stones, enlarged kidney on ultrasound, pyonephrosis, multiple subcortical anechoic lesions, extended enlarged kidney on CT and multiple sites with abscess density at the parenchyma. Ultrasound findings of our case were advanced enlargement of the kidney, a 22 mm stone in the pelvis and advanced hydronephrosis. Multislice CT and abdominal MRI findings of our case were advanced enlargement in the size of the left kidney (extended to the pelvis), advanced stage hydronephrosis, advanced thinning of the parenchyma, a 3 cm stone at the pelvis and a 2 cm stone at the lower pole. There was slight enlargement of the liver.

Leukocytosis and anemia have been reported in laboratory tests in 83% and 61% of XGP patients (4,12). Leukocytosis and anemia results of the complete blood count in our case did not support these findings. The bacteria, which grow in the urine culture are mainly *Escherichia coli* and *Proteus mirabilis* and *Pseudomonas aeruginosa* to a lesser extent (4,13). Since the left kidney was dysfunctional in our patient, there were no leukocytes in urine and no culture growth as well.

XGP is a rare disease with a varying clinical course, which is difficult to diagnose and treatment of which results in organ loss (nephrectomy).

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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

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Transplant Survey

Doi: 10.4274/jus.2017.04.026

Re: Early Removal of Double-J Stents Decreases Urinary Tract Infections in Living Donor Renal Transplantation: A Prospective, Randomized Clinical Trial

Liu S[1], Luo G[1], Sun B[1], Lu J[1], Zu Q[1], Yang S[1], Zhang X[1], Dong J[2]

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Transplant Proc 2017;49:297-302. doi: 10.1016/j.transproceed.2016.12.007.

EDITORIAL COMMENT

Routine use and the duration of a double-J stent placement are controversial for renal transplant recipients. In this interim analysis of a double-blind, randomised controlled trial, differences in urological complications (e.g., urinary tract infections) between ureteral stent removal at 1 week and routine ureteral stent removal at 4 weeks in living kidney transplant recipients. In order to be able to perform power calculations on the incidence of major urologic complications, at least 271 patients are required in both groups. However, first 111 cases are described and minor urologic complications are given in this interim report. Stent removal was delayed in 3 patients due to increased serum creatinine levels and 5 patients were lost-to-follow-up due to loss of renal functions, thus 8 patients were excluded from the study. The patients were randomised to stent removal either at 1 week without local anesthesia by pulling the silk suture tied on the double-J catheter or cystoscopy or 4 weeks with cystoscopy under local anesthesia. All patients received intravenous antibiotics until 3 days posttransplant except co-trimoxazole. The 3-month incidence of urinary tract infection was 5.9% and 29% in the 1-week and 4-week stent removal groups, respectively. Also, there was a marked health care cost advantage of 1-week stent removal over 4-week stent removal because of the stent removal procedure and consumption of antibiotics.

Yarkın Kamil Yakupoğlu, MD

Transplant Survey

Doi: 10.4274/jus.2017.04.027

Re: Deep Neuromuscular Blockade Improves Surgical Conditions During Low-Pressure Pneumoperitoneum Laparoscopic Donor Nephrectomy

Özdemir-van Brunschot DMD[1], Braat AE[2], van der Jagt MFP[1], Scheffer GJ[3], Martini CH[4], Langenhuijsen JF[5], Dam RE[2], Huurman VA[2], Lam D[2], d'Ancona FC[5], Dahan A[4], Warlé MC[1]

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Surg Endosc 2017. doi: 10.1007/s00464-017-5670-2.

EDITORIAL COMMENT

In this small blinded randomized controlled multicenter trial, the authors have evaluated the effect of deep neuromuscular blockade (NMB) on surgical conditions during-low pressure pneumoperitoneum (PNP) laparoscopic donor nephrectomy. Previous evidence supports that low-pressure PNP (6 mmHg) reduces post-operative pain, but sometimes may restrain visibility and surgical access. By applying deep NMB authors were able to demonstrate lower post-operative opiate requirement besides improvement in surgical conditions. Although not significant, insufflation pressures were lower in the deep NMB group. In four patients in the moderate NMB group, major intraoperative complications occurred in whom two required conversion to open procedure have had occurred. Given the relatively high incidence of intraoperative complications and conversions to open donor nephrectomy, the use low-pressure PNP with moderate NMB may compromise safety during surgery.

Yarkın Kamil Yakupoğlu, MD

Andrology

Doi: 10.4274/jus.2017.04.028

Re: Varicocelectomy to "Upgrade" Semen Quality to Allow Couples to Use Less Invasive Forms of Assisted Reproductive Technology

Samplaski MK[1], Lo KC[2], Grober ED[2], Zini A[3], Jarvi KA[4]

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Fertil Steril 2017;108:609-612. doi: 10.1016/j.fertnstert.2017.07.017.

EDITORIAL COMMENT

Varicocele is the most common etiology of male-factor infertility. Varicocele repair is the simplest and the most cost-effective treatment way for infertile couples for natural conception. Recent data suggested that varicocele repair may reduce the need for invasive modalities of assisted reproductive technology (ART) for infertile couples. In this study, the authors tried to determine the degree of semen improvement after varicocelectomy and the effect of semen improvement on the need for ARTs. A total of 373 men who underwent varicocele repair were evaluated. Varicocelectomy was bilateral in 46.6% of patients and left in 53%. Radiographic embolization was performed in 18% of patients and 82% was operated by microsurgical procedure. Overall total motile sperm count (TMSC) increased from 18.22±38.22 to 46.72±210.92 (p=0.007). The most significant increase was observed in men with baseline TMSC <5 million and almost 60% of men were upgraded from *in vitro* fertilization (IVF) candidacy to intrauterine insemination or natural pregnancy. In conclusion, varicocelectomy has an important role in the treatment of male infertility and reduces the need for IVF treatment even in men with very low TMSCs.

Emre Bakırcıoğlu, MD

Andrology

Doi: 10.4274/jus.2017.04.029

Re: Reproductive Outcomes of Testicular Versus Ejaculated Sperm for Intracytoplasmic Sperm Injection Among Men with High Levels of DNA Fragmentation in Semen: Systematic Review and Meta-Analysis

Esteves SC[1], Roque M[2], Bradley CK[3], Garrido N[4]

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Fertil Steril 2017;108:456-467.e1. doi: 10.1016/j.fertnstert.2017.06.018.

EDITORIAL COMMENT

Since its introduction in 1992, intracytoplasmic sperm injection (ICSI) has been widely used for different levels of spermatogenic failure in infertile men. However, still reliable methods are not widely accepted for sperm selection for ICSI in male-factor infertility. Sperm DNA plays critical role in embryo development and high sperm DNA fragmentation (SDF) is more common in infertile men compared to fertile individuals (1). In this meta-analysis, the authors aimed to investigate the evidence of potential role of using testicular sperm (testi-ICSI) and ejaculated sperm (ejac-ICSI) for ICSI in nonazoospermic infertile men with confirmed post-testicular SDF. In eligible five studies involving 143 patients, it was found that SDF rate was lower in testicular sperm than in ejaculated sperm. Evaluation of the clinical outcomes of testi-ICSI and ejac-ICSI revealed that, fertilization rates were not different but higher clinical pregnancy and live birth rates were observed in testi-ICSI group whereas miscarriage rates were reduced. In conclusion, in male-factor infertility men with high SDF levels, testicular sperm may have lower SDF compared to ejaculated sperm and couples may benefit from testi-ICSI in terms of better chance of clinical pregnancy and live birth.

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Emre Bakırcıoğlu, MD

Basic Research

Doi: 10.4274/jus.2017.04.030

Re: Regulation of Cancer Cell Metabolism

Cairns RA, Harris IS, Mak TW

The Campbell Family Cancer Research Institute, Toronto, Ontario, Canada

Nat Rev Cancer 2011;11:85-95. doi: 10.1038/nrc2981.

EDITORIAL COMMENT

For basic needs of dividing cells, three main molecular mechanisms include rapid adenosine triphosphate (ATP) generation for providing energy, increased biosynthesis of macromolecules, and maintenance of appropriate cellular redox status. Metabolic changes in cancer cells have not been well described yet. The best described metabolic mechanism observed in tumour cells is the Warburg effect which is a shift from ATP generation through oxidative phosphorylation to ATP generation through glycolysis, even under normal oxygen concentrations. This effect is regulated by several pathways such as the phosphatidylinositol 3-kinase pathway, hypoxia-inducible factor, p53, MYC and AMP-activated protein kinase (AMPK). The tumor microenvironment is characterized by hypoxia, low extracellular pH and low glucose concentration. Mutations in oncogenes and tumor suppressor genes cause alterations in intracellular signalling pathways that affect tumour cell metabolism. A key molecule produced as a result of altered cancer metabolism is reduced nicotinamide adenine dinucleotide phosphate (NADPH), which functions as a cofactor and provides reducing power in many enzymatic reactions crucial for macromolecular biosynthesis. NADPH is also an antioxidant and forms part of the defense against reactive oxygen species (ROS) produced during rapid proliferation. High levels of ROS can cause damage to macromolecules, which can induce apoptosis. These antioxidant systems rely on the reducing power of NADPH to maintain their activities. In the near future, anticancer treatments will focus on energy metabolism of the cancer cell.

Fehmi Narter, MD, PhD

Basic Research

Doi: 10.4274/jus.2017.04.031

Re: Application of Virtual, Augmented, and Mixed Reality to Urology

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[3]Hallym University College of Medicine, Department of Urology, Seoul, Korea
[4]Kwangwoon University, Graduate School of Information Contents, Seoul, Korea

Int Neurourol J 2016;20:172-181.

EDITORIAL COMMENT

In addition to virtual reality (VR), new developments in augmented reality (AR) (i.e., google glass), and mixed reality (MR) have been introduced in the field of medicine. This review presents an overview of significant developments in VR, AR, and MR technologies which are currently in use in urology, and the future development trends that could be expected. This spectrum depicts a continuum from the real world to the virtual world, leaving space in between for AR as well as for augmented virtuality and considering everything between these two worlds the MR. Usage of AR, VR, and MR in medicine is especially focused on neuroscience/psychotherapy, hepatology and orthopedics. However, recent papers reporting 3D image-guided surgery show that AR with visual cues to the subsurface anatomy could be a substitute in minimally invasive surgery in urology. These developments are used for education, 3D modeling of medical imaging visualizations, training, planning, therapy, assisting, telesurgery, telementoring, and augmented biofeedback in pelvic floor muscle re-education. AR and VR have the potential to reduce risk through improved planning and relying on their assistance would reduce the time spent in the operating room. In the near future, these techniques will provide the potential to further increase efficiency in the urological usage.

Fehmi Narter, MD, PhD

Doi: 10.4274/jus.1690
Journal of Urological Surgery, 2017;4(4):224-225

Bladder Neck Involvement in Radical Prostatectomy Specimens is not a pT4 Disease

Radikal Prostatektomide Saptanan Mesane Boynu İnvazyonu pT4 Değildir

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Introduction

Prostatic carcinoma is the most common cancer in men in the USA and Europe. It is the second cause of cancer death among men (1). Bladder neck (BN) involvement (BNI) after radical prostatectomy has been a matter of debate for many years. In the fourth edition of the American Joint Committee on Cancer (AJCC) staging manual published in 1992, it was classified in pT4 category, showing the extension of the tumor into the adjacent organs such as the rectum, external sphincter or the pelvic wall musculature (2). Since then, several studies have been published discussing whether it should be classified as pT3 or pT4. Since BN sparing surgeries are preferred to avoid postoperative incontinence, it is important to make a proper substaging. In radical prostatectomy materials, there were many different BNI definitions. Consequently, it is classified as microscopic and macroscopic involvement (3). One of the two studies by Yossepowitch et al. (4) with a larger population cohort study with heterogeneous features, it was reported that sole BNI did not predict prostate-specific antigen (PSA) recurrence in a multivariate model and pT4 was suggested to be reserved for macroscopic or radiographic BNI instead of microscopic BNI. In their multiethnic, multicenter study, Buschemeyer et al. (5) concluded that a positive BN margin associated with other positive margins had a progression risk similar to seminal vesicle (SV) invasion (pT3b), however, an isolated BN margin was found to be a rare event. However, this data needs to be supported by large cohorts due to the limited number of patients. Additionally, patients with positive BN margin had higher PSA level, greater Gleason score, higher rates of extraprostatic extension (EPE), SV involvement, and positive surgical margins (5). Zhou et al. (6) grouped microscopic BNI as true and false. True BNI had prostatic carcinoma within thick smooth muscle bundles without intermixed benign prostatic glands (Figure 1a), and false BNI had prostatic carcinoma intermixed with benign prostatic glands (Figure 1b). Regardless of this categorization, both groups had increased biochemical recurrence risk. According to this study, microscopic BNI should be staged between pT2 and pT3, and pT4 should be limited to gross or radiographic invasion, consistent with some of the previous studies (6). A large study (17000 patients) with a long time period (1982-2008) by Pierorazio et al. (7) supported the significance of a BNI after radical prostatectomy concordant with the study by Zhou et al. (6). They also used the true-false BNI term and found that biochemical recurrence-free and cancer-specific survival rates were similar to pT3a and pT3b,

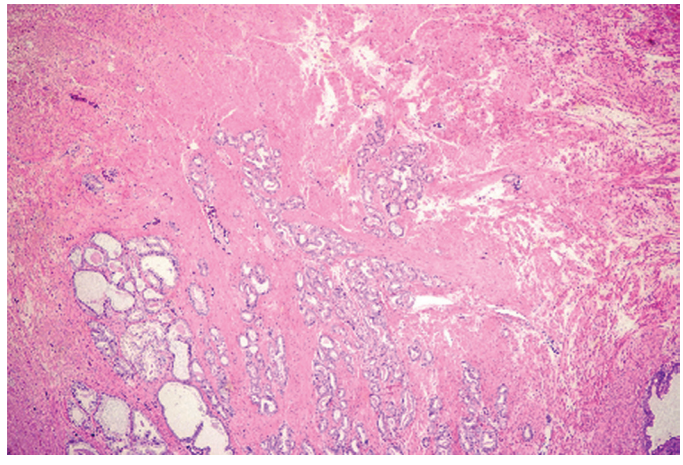

Figure 1a. True bladder neck involvement: Prostatic adenocarcinoma within thick smooth muscle bundles without intermixed benign prostatic glands (Hematoxylin-Eosin x40)

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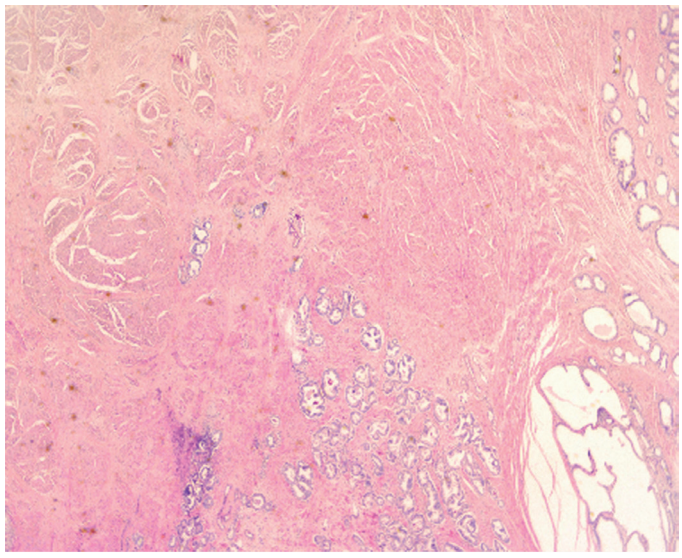

Figure 1b. False bladder neck involvement: Prostatic adenocarcinoma within thick smooth muscle bundles intermixed with benign prostatic glands (Hematoxylin-Eosin x40)

respectively. They also suggested that BNI could be settled into pT3a similar to EPE or placed into pT3b by pushing SV involvement to pT3c. The study emphasized that BNI should not be designated as stage pT4, in which the patients were rarely treated by surgery. On the contrary, this group of tumors can be resected or treated. This study also advocates their data's reliability with their quite large cohort and 25-year single institution follow-up (7). After similar several studies, change was inevitable, and microscopic BNI was carried from pT4 to pT3a category in the seventh edition of the AJCC manual (3). Recently, a group of Korean urologists published a study supporting the validity of this change both in isolated positive BNI and BNI with another surgical margin positivity (8). After well designed and multiple large studies conducted with appropriate patient populations, BNI substaging remained the same in the 8th edition of the AJCC manual (9). However, as both the prostate team of the AJCC and Silberstein and Eastham (10) mentioned, we still need further investigations to determine the significance of BNI substaging because of the rarity of this population.

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Keywords: Bladder, neck, involvement, pT4

Anahtar Kelimeler: Mesane, boyun, invazyon, pT4

Ethics

Peer-review: Externally peer-reviewed.

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

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