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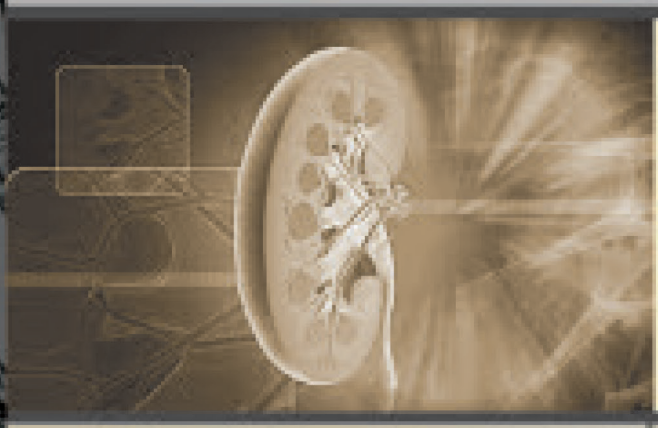

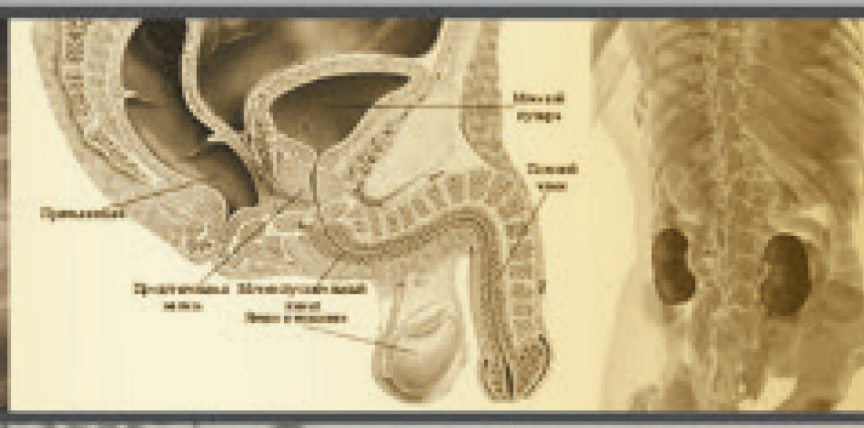

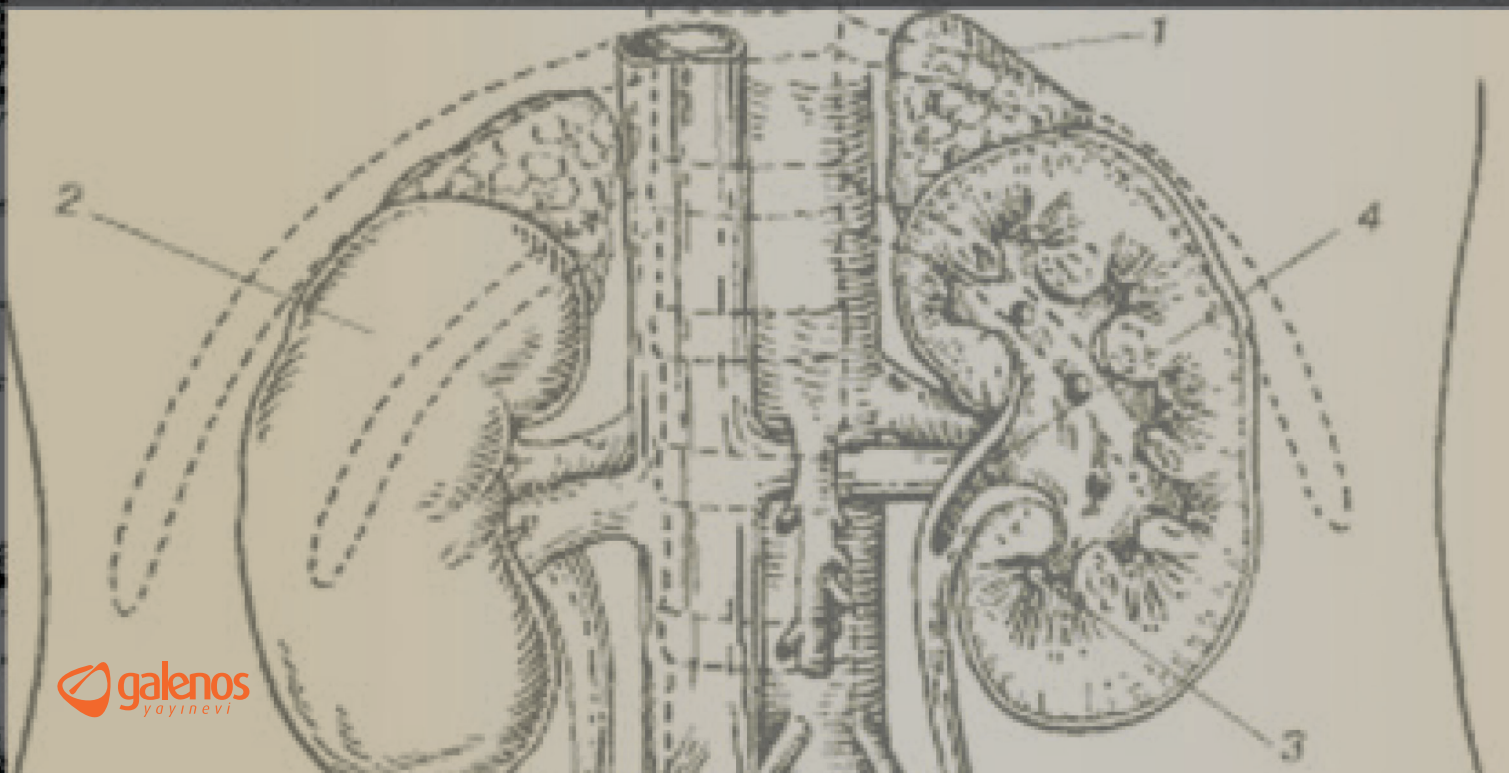

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2. Organization as Author

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

3. Complete Book

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

4. Chapter in Book

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

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5. Abstract

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

6. Letter to the Editor

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

7. Supplement

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

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Original Researches

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ORIGINAL RESEARCH
General Urology

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Journal of Urological Surgery, 2019;6(3):180-183

Prevalence of Polymicrobial Infection in Urethritis

Üretritte Polimikrobial Enfeksiyon Prevelansı

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[1]*Medical Park Hospital, Clinic of Urology, Antalya, Turkiye*
[2]*İstinye University Faculty of Medicine, Department of Urology, İstanbul, Turkiye*

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

Today, the prevalence of polymicrobial infection in acute urethritis is remarkable. It seems that this infection will be more commonly encountered in clinical practice with increasing use of polymerase chain reaction assay for the diagnosis. Empirical antibiotics administration should be avoided for the treatment and the principle for treatment of the pathogen should be adopted.

Abstract

Objective: Urethritis is the most common sexually-transmitted disease in men and is classified as gonococcal (GU) and non-gonococcal (NGU) according to the pathogens. Increased urethritis prevalence in recent years has brought the presence of polymicrobial infection into question. The objective of this study was to investigate the prevalence of polymicrobial infections in patients diagnosed with urethritis in a urology outpatient clinic, based on real-time multiplex polymerase chain reaction (Rt-MPCR) assay outcomes.

Materials and Methods: Data of 171 patients diagnosed with urethritis and undergone Rt-MPCR analysis in a urology outpatient clinic between February 2017 and June 2018 were retrospectively studied. The pathogens that could be detected by the Rt-MPCR were *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum, Ueroplasma parvum, Gardnerella vaginalis, Trichomonas vaginalis, Candida albicans* and *herpes simplex virus* type 1-2.

Results: The mean age of 171 patients was 33.8 (19-56) years. According to the Rt-MPCR outcomes, polymicrobial infections were found in 16.9% (29/171) of patients. Two-pathogen polymicrobial urethritis was found in 14% (24/171) of the patients, and three-pathogen polymicrobial urethritis in 2.9% (5/171). Among the cases of polymicrobial urethritis, coexistence of both GU and NGU pathogens was found in 17.3% (5/29) and that of only NGU pathogens in 82.7% (24/29). Overall distribution of urethritis pathogens was found to be as follows: *Chlamydia trachomatis* 22.9%, *Neisseria gonorrhoeae* 21.7%, *Gardnerella vaginalis* 16.8%, *Ureaplasma urealyticum* 14.2%, *Mycoplasma genitalium* 10.5%, *Ueroplasma parvum* 4.7%, *Mycoplasma hominis* 3.7%, *Trichomonas vaginalis* 3.1%, *Candida albicans* 1.8% and *herpes simplex virus* type -2 1.2%.

Conclusion: The presence of polymicrobial urethritis should be taken into consideration when planning treatment for urethritis. Particularly, the association of NGU urethritis pathogens should be considered in the cases of polymicrobial urethritis.

Keywords: Urethritis, Non-gonogoccal urethritis, PCR, Polymicrobial urethritis

Öz

Amaç: Üretrit erkeklerde en sık görülen cinsel yolla bulaşan hastalıktır ve patojenlerine göre gonokoksik (GU) ve non-gonokoksik üretrit (NGU) olarak sınıflandırılmaktadır. Son yıllarda artan üretrit olguları polimikrobial enfeksiyon varlığını da gündeme getirmiştir. Bu çalışmanın amacı üroloji polikliniğinde üretrit tanısı alan hastalarda gerçek zamanlı multiplex polimeraz zincir reaksiyonu (Rt-MPCR) sonuçlarına göre polimikrobial enfeksiyon prevelansının araştırılmasıdır.

Gereç ve Yöntem: 2017 Şubat - 2018 Haziran arasında üroloji polikliniğinde üretrit tanısı alan ve Rt-MPCR analizi yapılan 171 hastanın dataları retrospektif incelendi. Rt-MPCR kiti tarafından saptanabilen patojenler *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum, Ueroplasma parvum, Gardnerella vaginalis, Trichomonas vaginalis, Candida albicans* ve *herpes simpleks virüsü* tip 1-2 idi.

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Bulgular: Çalışmaya alınan 171 hastanın ortalama yaşı 33,8 (19-56) idi. RT-MPCR sonucuna göre %16,9 (29/171) hastada polimikrobial enfeksiyon mevcuttu. Yüz yetmiş bir hastanın 24'ünde (%14) 2 patojenli, 5'inde (%2,9) ise 3 patojenli polimikrobial üretrit mevcuttu. Polimikrobial üretritli 29 olgu içinde NGÜ patojenlerinin birlikteliği 24'ünde (%82,7) bulunurken, GU ve NGU patojenlerinin birlikteliği 5'inde (%17,3) bulundu. Üretrit patojenlerinin genel dağılımı ise *Chlamydia trachomatis* %22,9, *Neisseria gonorrhoeae* %21,7, *Gardnerella vaginalis* %16,8, *Ureaplasma urealyticum* %14,2, *Mycoplasma genitalium* %10,5, *Ueroplasma parvum* %4,7, *Mycoplasma hominis* %3,7, *Trichomonas vaginalis* %3,1, *Candida albicans* %1,8 ve *herpes simpleks virüsü* tip-2 %1,2 idi.
Sonuç: Üretrit tedavisini planlanırken polimikrobial enfeksiyon varlığı göz önünde bulundurulması gerekmektedir. Polimikrobial üretrit içerisinde ise özellikle NGU üretrit patojenlerinin birlikteliği düşünülmelidir.
Anahtar Kelimeler: Üretrit, Non-gonokoksik üretrit, PCR, Polimicrobial üretrit

Introduction

Urethritis in men is a clinical presentation developing often due to sexually-transmitted pathogens and is characterized by dysuria and urethral discharge (1). Urethritis is an important cause of morbidity in sexually active individuals and remains a major medical, social and economic burden worldwide. Classically, urethritis is classified as non-gonococcal (NGU) and gonococcal (GU) (2). In the world, approximately 62 million new cases of GU and 89 million new cases of NGU are reported each year, and these figures keep increasing (3). With annually increasing prevalence, wrong or incomplete treatment approaches have brought the presence of polymicrobial infection into question (4,5). Urethritis is diagnosed upon the observation of ≥5 polymorphonuclear leukocyte (PMNL/HPF) per high power field in gram staining of urethral smear and/or discharge sample (6). In the identification of urethritis pathogens, nucleic acid amplification tests, such as polymerase chain reaction (PCR) assay, are the diagnostic methods recommended by international guidelines for their ability to identify many pathogens in a single sample within a short amount of time with high sensitivity and specificity (7,8). There is no sufficient data on the prevalence of polymicrobial urethritis in our country. The objective of this study was to investigate the prevalence of polymicrobial infections in patients diagnosed with urethritis in our outpatient clinic, based on real-time multiplex PCR (Rt-MPCR) assay outcomes.

Materials and Methods

Upon receiving ethics committee approval from Antalya Medical Park Hospital Facility (approval no: 011/2018), Rt-MPCR analysis results of 171 patients, who had presented to our outpatient clinic with the complaints of urethral discharge, dysuria and pruritus in the urethra, and had ≥5 PMNL/HPF in the gram staining of urethral discharge/smear sample or had positive leukocyte esterase assay (Combur-Test®-Roche) for their first urine sample, were collected. This retrospective study was performed in accordance with the principles of the Declaration of Helsinki. Pathogens in the urethral discharge/smear samples obtained from the patients were investigated with Rt-MPCR assay. PREP-NA PLUS and PREP-GS PLUS extraction kits manufactured by DNA-Technology® (Moscow, Russia) were used. Results were analyzed by using Elite Prime Real® Time PCR of the same company. Absolute presence of *Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium,* Trichomonas vaginalis and *herpes simplex virus* type 1-2 were considered to be positive. For opportunistic pathogens of *Ureoplasma urealyticum, Ureoplasma parvum, Gardnerella vaginalis,* Candida albicans and *Mycoplasma hominis*, $>10^4$ microbial load was considered positive as per the recommendations of the manufacturer.

Statistical Analysis

All statistical analyses were performed using the SPSS statistical software (SPSS for Windows version 16.0 SPSS Inc. Chicago IL, USA).

Results

The mean age of the 171 patients was 33.8 (19-56) years. At least one pathogen was detected in 124 (72.6%) patients. According to Rt-MPCR results, polymicrobial infections were found in 16.9% (29/171) of patients. There was two-pathogen polymicrobial urethritis in 14% (24/171), and three-pathogen polymicrobial urethritis in 2.9% (5/171) of the patients. Among the cases of polymicrobial urethritis, coexistence of both GU and NGU pathogens was found in 17.3% (5/29) and coexistence of only NGU pathogens was found in 82.7% (24/29) of the patients. Overall distribution of urethritis pathogens was as follows: *Chlamydia trachomatis* 22.9%, *Neisseria gonorrohoea* 21.7%, *Gardnerella vaginalis* 16.8%, *Ureoplasma urealyticum* 14.2%, *Mycoplasma genitalium* 10.5%, *Ureoplasma parvum* 4.7%, *Mycoplasma hominis* 3.7%, *Trichomanas vaginalis* 3.1%, *Candia albicans* 1.8%, and *herpes simplex virus* type-2 1.2% (Figure 1). No pathogens were detected with Rt-MPCR in 47 (27.4%) patients.

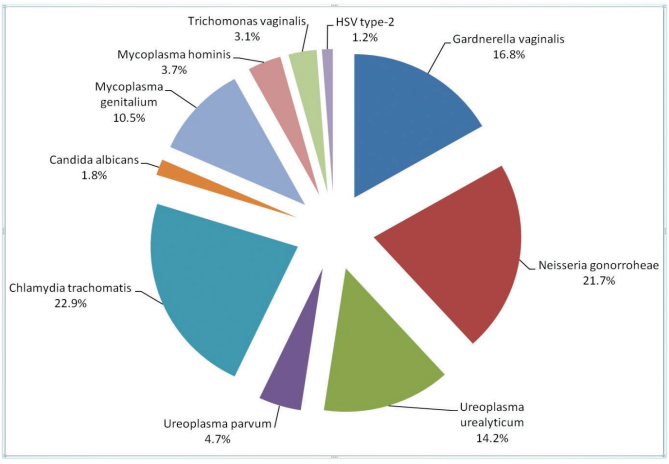

Figure 1. Distribution of urethritis pathogens

Discussion

Urethritis affects the society as an economic and social burden. In the United States, approximately 4 million urethritis cases are being reported every year (7). Unfortunately, there is no sufficient data on this subject in our country. With the widespread use of nucleic acid amplification assays, the number of reported cases of NGU increased at a higher rate compared with GU cases in recent years. As a result, the role of gram staining in the identification of NGU has become questionable. In the classical evaluation, NGU diagnosis is made when intracellular diplococci are not seen on microscopic evaluation of a urethral gram stained smear. Recent studies recommended lowering the diagnostic criteria of the diagnosis to ≥2 PMNL/HPF due to false negative results obtained especially in NGU cases with mild inflammation (9,10). In a recent study conducted by Sarier et al. (11), the authors showed that gram staining had 92.9% sensitivity in GU diagnosis and only 55.6% sensitivity in NGU when the threshold was ≥5 PMNL/HPF, while sensitivity in GU diagnosis increased to 100% and to 92.6% in NGU diagnosis when the cutoff value was lowered to ≥2 PMNL/HPF. Therefore, it must be noted that NGU cases can be missed in clinics where nucleic acid amplification assays such as PCR are not performed. It is also clear that these cases can cause serious economic and social burden due to their infectiousness. This will also lead to increased prevalence of polymicrobial urethritis.

The place of opportunistic pathogens in NGU and sexually transmissibility of NGU are also controversial (12). However, there are publications in the literature suggesting that *Mycoplasma hominis, Gardnerella vaginalis,* Candida albicans, and *Ureaplasma species,* which can be exist as normal commensal flora, cause urethritis at high microbial loads (2,13,14). Among these pathogens, only *Ureoplasma ureolyticum* is specified in the guidelines as a cause of urethritis (8). In such case, Rt-MPCR devices that can perform quantitative measurement of microbial load are very beneficial for preventing false positive results. In a urethritis prevalence study, we conducted in 2016, evaluation using a PCR device without quantitative measurement of microbial load revealed a *Ureoplasma ureolyticum* prevalence of 27.1% (15), while evaluation using PCR with quantitative measurement showed a *Ureoplasma ureolyticum* prevalence rate of 14.2% only. Therefore, we believe that calculation of microbial load in the evaluation of opportunistic pathogens is necessary to avoid false positive diagnoses. Urethritis pathogens mostly develop in association with sexually-transmitted pathogens. However, even if urethritis occurs after sexual intercourse, not only sexually-transmitted pathogens but all of the abovementioned opportunistic pathogens should be taken into consideration as potential factors for both singular and polymicrobial urethritis. It can be considered that the pathogen develops in relation with the disruption of the existing flora, instead of transmission. However, further comparative large-scale studies are warranted. In our study, coexistence of NGU pathogens was observed in 82.7% of polymicrobial urethritis cases. Among all the urethritis pathogens, the rate of approximately 27% for *Mycoplasma hominis, Ureoplasma parvum, Gardnerella vaginalis* and Candida albicans, which have opportunistic characteristics, is of particular interest.

Literature review for polymicrobial urethritis showed that majority of the studies are about the coexistence of both GU and NGU pathogens (16,17). However, coexistence of GU-NGU pathogens was detected only in 17.3% our patients. The reason may be due to the fact that, especially with the increasing use of PCR technology, we detect more NGU pathogens which are difficult to identify with conventional methods.

As conventional methods like culture assays require long time (3-7 days) to identify urethritis pathogens, it is recommended to initiate empiric treatments in an attempt to prevent the patient from infecting other individuals through sexual intercourse during the test period. Urethritis pathogens are very diverse and sometimes can include more than one-species. Therefore, the effectiveness and sufficiency of empiric treatments became questionable. In our study, the prevalence rate of 16.9% for polymicrobial urethritis also suggests this situation. Increasing burden and costs of urethritis treatment led to the necessity of fast and reliable laboratory techniques for the identification of related pathogens. PCR analysis can provide results with 96% sensitivity and 100% specificity in less than 24 hours (18) enabling timely initiation of treatment without any delay. This will lead to an easier infection control. Therefore, recent international guidelines recommend termination of empiric treatment, and using cause-specific treatment after bacterial identification (7,8).

It has been reported that responsible pathogens cannot be identified in 20-30% of men with urethritis (19). In our study, the

rate of the group that can be identified as idiopathic urethritis, for which no agents were determined, was found to be 27.4%. Idiopathic urethritis may not have an infectious etiology, or this condition may be caused by unidentified infectious agents circulating in the sub-groups of the population, different than in ones infected by conventional urethritis pathogens.

This study has some limitations. It was not specified whether the patients included in the study had received prior medical treatment. Therefore, it could not be shown whether the polymicrobial urethritis cases were primary infections or concomitant infections caused by an existing pathogen.

Conclusion

The presence of polymicrobial urethritis should be taken into consideration when planning treatment for urethritis. Particularly coexistence of NGU urethritis pathogens should be considered in the cases of polymicrobial urethritis. Rt-MPCR analysis is a highly effective method for the detection of microbial infection in urethritis. Therefore, clinicians should avoid empiric treatment approaches and prefer pathogen-oriented treatment approaches.

Ethics

Ethics Committee Approval: The study were approved by Medical Park Hospital Local Ethics Committee (protocol number: 011/2018).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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

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Evaluation of Thoracic Complications After Urological Operations: A Single-center Experience

Ürolojik Operasyonlar Sonrası Ortaya Çıkan Torasik Komplikasyoların Değerlendirilmesi: Tek-merkez Deneyimi

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

Thoracic complications are a major complication of urological surgery. Complications are an inevitable part of urological surgery due to the increasing number of cases and complexity in recent years. There are some data on thoracic complications after urological laparoscopic surgery in the literature, while data on a thorough analysis of the thoracic complications of urological surgery is limited. In this study, we present the thoracic complications of the cases operated in our clinic and the treatment methods performed by the thoracic surgery clinic. We concluded that early diagnosis of thoracic complications and coordinated work with thoracic surgery are fundamental.

Abstract

Objective: To present cases of thoracic complications that developed after urologic interventions and were treated in collaboration with thoracic surgery.

Materials and Methods: Patients who were operated in the urology clinic at our hospital between January 2014 and December 2017 and required thoracic surgery consultation were retrospectively reviewed. Forty-two patients with pneumothorax, pleural effusion, hydropneumothorax and diaphragm injury were included in the study. Six patients, who had preoperative diaphragm invasion and underwent preoperative diaphragm incision, were excluded.

Results: Tube thoracostomy (TT) was applied in only 5 patients who developed pneumothorax. Three patients with isolated pleural effusion were treated with TT and 3 with thoracentesis. All patients who developed hydropneumothorax were found to have undergone nephrectomy (3 left, 1 right). All patients with iatrogenic diaphragmatic injury were diagnosed perioperatively and all of these patients were nephrectomized (5 right, 1 left). All the patients underwent primary diaphragm repair and 5 patients underwent TT. The mean duration of tube drainage was 5.5±2.1 (2-13) days. The mean length of hospital stay in patients who underwent percutaneous nephrolithotomy, nephroureterectomy, nephrectomy and prostatectomy with thoracic complications was 4.12±1.08, 8.26±2.87, 4.04±1.23 and 4.17±0.72 days, respectively. There was no significant difference in mean duration of hospital stay between patients with and without thoracic complications (p=0.729).

Conclusion: Thoracic complications may develop after urological interventions. In particular, evaluation of chest pain in patients with right-sided percutaneous nephrolithotomy and nephrectomy by chest X-ray is important for early diagnosis.

Keywords: Pneumothorax, Hydropneumothorax, Complication, Percutaneous Nephrolithotomy, Nephrectomy

Öz

Amaç: Bu çalışmada ürolojik girişimler sonrası torasik komplikasyon gelişen ve göğüs cerrahisi-üroloji işbirliği ile tedavi edilen olgular sunuldu.

Gereç ve Yöntem: Ocak 2014 - Aralık 2017 tarihleri arasında hastanemiz Üroloji Anabilim Dalı tarafından opere edilen ve göğüs cerrahisi konsültasyonu istenilen olgular retrospektif incelendi. Çalışmaya pnömotoraks, plevral effüzyon, hidropnömotoraks ve diyafragma yaralanması

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saptanan 42 hasta dahil edildi. Operasyon öncesi diyafragma invazyonu saptanan ve peroperatif diyafragma insizyonu yapılan altı hasta çalışmadan çıkarıldı.

Bulgular: Pnömotoraks gelişen hastaların sadece 5'ine tüp torakostomi (TT) uygulandı. İzole plevral effüzyon izlenen hastaların 3'ü TT, 3'ü ise torasentez ile tedavi edildi. Hidropnömotoraks gelişen hastaların tamamına nefrektomi (3 sol, 1 sağ) uygulandığı görüldü. İyatrojenik diyafragma yaralanması gelişen hastaların tamamına perioperatif dönemde tanı kondu ve hastaların tamamı nefrektomi (5 sağ, 1 sol) hastası idi. Hastaların tamamında diyafragmanın primer onarımı yapıldı, 5 hastaya TT uygulandı. Hastaların ortalama dren kalış süresi 5,5±2,1 (2-13)/gündü. Toraks komplikasyonu gelişen hastalardan perkütan nefrolitotomi, nefroüreterektomi, nefrektomi ve prostatektomi operasyonu geçiren hastaların ortalama hospitalizasyon süreleri, sırasıyla, 4,12±1,08, 8,26±2,87, 4,04±1,23 ve 4,17±0,72 gündü. Toraks komplikasyonu gelişen ve gelişmeyen hastaların ortalama hospitalizasyon süreleri arasında anlamlı bir farklılık yoktu (p=0,729).

Sonuç: Ürolojik girişimler sonrası torasik komplikasyonlar gelişebilir. Özellikle sağ taraflı perkutan nefrolitotomi ve nefrektomi sonrası göğüs ağrısı tarifleyen hastaların akciğer grafisi ile değerlendirilmesi erken tanı için önemlilik arz etmektedir.

Anahtar Kelimeler: Pnömotoraks, Hidropnömotoraks, Komplikasyon, Perkütan Nefrolitotomi, Nefrektomi

Introduction

Each surgical procedure has a certain risk of complications. Urological surgery, whether open or endoscopic, may be associated with visceral, vascular and thoracic complications. Along with technical and technological advances, in recent years, urologic surgery has evolved from open to endourological methods. With the increase in the number and complexity of cases, the complications caused by surgery have become inevitable. So far, there has been no overrepresentation in the literature on the thoracic complications of urological surgeries, with a focus on vascular and visceral complications (1,2,3). Moreover, most of these complications are related to laparoscopic surgery. A multi-center study focused on pleural damage in laparoscopic renal surgery (4). In another large study, thoracic complications encountered during laparoscopic urology were discussed under the headings medical pulmonary complications, surgical thoracic complications, and subclinical and incidentally detected gas collections in the thorax (5).

Urological surgery itself can often be the cause of thoracic complications, and the position given to the patient may also cause complications. A case of upper lobe atelectasis due to lateral decubitus position during radical nephrectomy under general anesthesia that was successfully treated with saline lavage and bronchoscopic suction has been reported (6). Therefore, urologic surgery-related thoracic complications should be comprehensively considered in conjunction with their etiology and course and treatment methods. In this retrospective analysis, we evaluated thoracic complications occurred in patients, who were operated in our clinic, their etiology and the methods of management performed by thoracic surgery.

Materials and Methods

Patients and Selection Criteria

A total of 48 patients who were operated in the urology clinic and required perioperative and/or postoperative thoracic surgery consultation between January 2014 and December 2017 were the material of this study. Patients, who had pneumothorax, pleural effusion, hydropneumothorax or diaphragm injury due to surgical intervention or anesthesia technique and were managed by the thorax surgery clinic (n=42), were included in the study. Patients who had preoperative diaphragm invasion due to local tumor spread (n=2) and underwent perioperative diaphragm incision (n=4) were excluded. The data of the patients were obtained from the hospital registry system and patient files in the urology and thoracic surgery clinics. The study was carried out in accordance with the principles of the Declaration of Helsinki and all patients included in the study gave consent for research use of their data, provided their identities would be kept confidential.

Management Techniques of Patients

Appropriate follow-up, oxygen inhalation therapy, thoracentesis or tube thoracostomy (TT) treatments were applied by the department of thorax surgery.

Data Collection and Analysis

Demographic data of the patients, urological procedures, thoracic complications and treatment methods applied by the thoracic surgeons were analyzed. The characteristics of the patients with and without thoracic complications were compared by using the unpaired t-test. P values less than 0.05 were considered statistically significant.

Results

Of the 42 patients included in the study, 27 (64.3%) were male and 15 (35.7%) were female. The mean age was 52.81±16.15 (23-85) years. Pneumothorax was the most common thoracic complication (61.9%) followed by pleural effusion, diaphragmatic injury, and hydropneumothorax (17.2%, 17.2% and 9.5%, respectively). It was observed that pneumothorax most often developed after percutaneous nephrolithotomy (PCNL) (n=15).

The other patients who developed pneumothorax were those who have undergone nephrectomy (n=8), prostatectomy (n=2) and laparoscopic nephroureterectomy (n=1). The diagnosis of pneumothorax was most frequently made in the early postoperative period (n=16). In addition, it was made on the postoperative 1st day in 5 patients and postoperative day 4 in 1 patient.

Thoracic complications observed according to urological interventions are given in Table 1.

Only 5 patients required TT. The mean duration of drainage was 4.6±2.1 (2-8) days. Other patients were followed up with oxygen inhalation. Isolated pleural effusion was seen in 6 patients. Three of these patients underwent PCNL and 3 underwent nephrectomy. Three of these patients underwent TT and 3 had thoracentesis. The mean drainage time was 6.66±5.51 (3-13) days in these patients. The implementation of a TT for hemothorax developing in the left thorax after PCNL is shown in Figure 1.

All patients who developed hydropneumothorax had undergone nephrectomy. Three patients underwent TT and the mean drainage time was 5.66±2.89 (4-9) days. Patients with iatrogenic diaphragmatic injury were diagnosed in the perioperative period and all of them had undergone nephrectomy. In these patients, diaphragm was repaired primarily and TT was applied in 5 patients. The mean duration of drainage was 5.2±2.28 (2-8) days in these patients. The management of thoracic complications and the duration of thoracostomy tube drainage are summarized in Table 2.

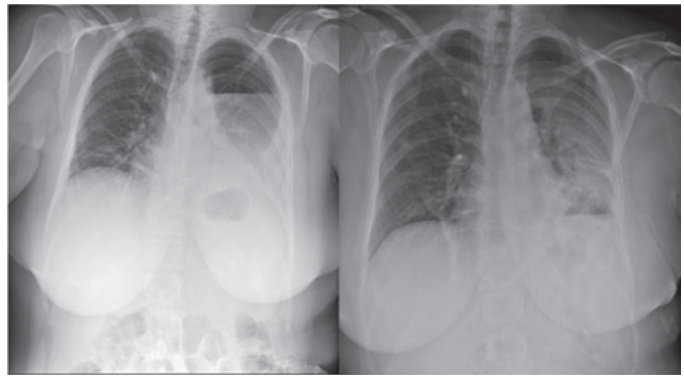

Figure 1. Left-sided thoracic tube application as a result of hemothorax after percutaneous nephrolithotomy

Table 1. Distribution of thoracic complications according to urological interventions

Variable[1]		Thoracic complication				n
		Pneumothorax	Pleural effusion	Diaphragmatic injury	Hydropneumothorax	
Urological intervention	Percutaneous nephrolithotomy	15 (83.3)	3 (16.7)	0	0	18 (100)
	Nephroureterectomy	1 (100)	0	0	0	1 (100)
	Nephrectomy	8 (38.1)	3 (14.3)	6 (28.6)	4 (19.0)	21 (100)
	Prostatectomy	2 (100)	0	0	0	2 (100)
Sex	Female	9 (60)	3 (20)	1 (6.7)	2 (13.3)	15 (100)
	Male	17 (63)	3 (11.1)	5 (18.6)	2 (7.3)	27 (100)
Side	Right	20 (74)	1 (3.7)	5 (18.6)	1 (3.7)	27 (100)
	Left	6 (40)	5 (33.3)	1 (6.7)	3 (20)	15 (100)

[1]Values are given as numbers (percentage)

Table 2. Treatments applied for thoracic complications and duration of the thorax tube drainage

Variable		Thoracic complication				n
		Pneumothorax	Pleural effusion	Diaphragmatic injury	Hydropneumothorax	
Treatment[1]	Follow-up	21 (91.4)	0	1 (4.3)	1 (4.3)	23 (100)
	Thoracentesis	0	3 (100)	0	0	3 (100)
	Tube thoracostomy	5 (31.3)	3 (18.7)	5 (31.3)	3 (18.7)	16 (100)
	Primary repair	0	0	5 (100)	0	5 (100)
	Thorax tube duration time (day)[2]	4.6±2.19 (2-8)	6.66±5.51 (3-13)	5.2±2.28 (2-8)	5.66±2.89 (4-9)	-

[1]Values are given as numbers (percentage)
[2]Values are given as number ± standard deviation (minimum-maximum)

PCNL was performed in 706 patients, nephroureterectomy in 95, nephrectomy in 819 and prostatectomy in 1565 patients during the study period. The rate of thoracic complications for PCNL, nephroureterectomy, nephrectomy and prostatectomy operations was 2.54%, 1.05%, 2.56% and 0.13%, respectively.

The mean length of hospital stay in patients who underwent PCNL, nephroureterectomy, nephrectomy and prostatectomy with thoracic complications was 4.12±1.08, 8.26±2.87, 4.04±1.23 and 4.17±0.72 days, respectively. In the same period, the mean length of hospital stay in patients who underwent PCNL, nephroureterectomy, nephrectomy and prostatectomy without thoracic complications was 3.28±0.68, 7.11±1.79, 3.04±0.62 and 4.13±0.69 days, respectively. There was no significant difference in mean length of hospital stay between the two groups (p=0.729).

Discussion

Different thoracic complications may be encountered after both open and endo-urological operations. This article, in which we presented the thoracic complications and the treatment methods applied for them, revealed that the most common thoracic complication was pneumothorax and nephrectomy was the most common operation following thoracic complications. Follow-up was the most common management method for thoracic complications utilized by the thoracic surgery. TT was the second most commonly used intervention after follow-up. The classification system, which was first described in 1992 by Clavien et al. (7) to convey a recognition and standardization of surgical complications, has been modified in 2004 (8). This system is widely accepted for the classification of surgical complications and classifies them in a spectrum ranging from grade I to V. Pulmonary complications are included in all sub-groups and those constitute important components of the classification. For instance, atelectasis requiring physiotherapy as grade I; pneumonia treated with antibiotics as grade II; bronchopleural fistulas requiring surgical closure after thoracic surgery as grade IIIb; respiratory failure requiring intubation as grade IVa, and renal failure in addition to grade IVa is classified as grade IVb complication.

Pneumothorax may be due to several reasons after abdominal surgery. It can be seen as a complication of anesthesia as well as surgical procedure. Laparoscopic and open surgery may induce pneumothorax with different mechanisms. Congenital diaphragmatic defects may allow peritoneal carbon dioxide (CO_2) to pass into the pleural space in laparoscopic surgery (9,10). CO_2 may cause pneumothorax by dissecting the pulmonary hilum after entering the mediastinum or through a rupture in the mediastinal pleura and entering the pleural cavity (10). In addition, apical pneumothorax may occur due to rupture of apical blebs due to barotrauma caused by positive pressure in mechanical ventilation (9). Needle aspiration of the pleura can help distinguish whether the pneumothorax is due to endotracheal anesthesia or the CO_2 accumulation into the tissue. In our series, pneumothorax most commonly occurred in patients undergoing PCNL. All these patients had upper calyceal stones and had undergone high level-needle access (10-11 or 11-12 rib interspace). During this time, maximum expiratory-inspiration maneuver was performed in coordination with anesthesia. This maneuver and high level-needle access are likely to cause this complication. Asymptomatic CO_2 pneumothorax typically spontaneously resolves with conservative management. It regressed with O_2 support in the majority of our patients; only 5 patients required TT. They were also treated with short-term tube drainage. Two patients who underwent prostatectomy had pneumothorax. These cases were performed by open surgery. We consider that barotrauma was the possible etiologic factor in these patients. In order to prevent abdominal gas collections, it is important to maximize abdominal muscle relaxation and prevent coughing and straining, especially during laparoscopy (11). If an intraoperative pleural or diaphragmatic damage occurs, the anaesthesiologist should be warned immediately. Ventilator parameters should be carefully controlled and allowed to complete the surgical procedure and repair any damage.

The risk of a pleural or lung injury during PCNL operation is about 10% when the puncture is above the 12th rib. If pleural effusion occurs, a thorax tube is required. The choice of lower caliceal access and the combination with flexible nephroscope or extracorporeal shock wave lithotripsy may prevent this complication (12,13). Pleural effusion occurred in our patients who underwent PCNL and nephrectomy. These patients were treated with thoracentesis or TT. The rates of thoracic complications after PCNL have been reported to be between 0% and 11.6% in different studies (14,15,16). In our study, it was found to be 2.54% in accordance with the literature.

Diaphragmatic damage is a rare but well-diagnosed complication of renal surgery. Particularly in upper pole tumors, tear of the diaphragm during dissection due to tumor invasion or injury damage due to the cautery may occur. In this complication, primary repair of the damage site is the most appropriate approach. In open surgery, primary suturing and underwater drainage can be performed, and in laparoscopic surgery, repair of the damaged area by intracorporeal suturing can be performed. A diaphragmatic injury that occurred during laparoscopic nephrectomy was treated with intracorporeal suturing and chest tube, and the CO_2 pneumothorax was rapidly resorbed (9). Gonzalez et al. (17) described an alternative method for repairing diaphragmatic damage occurring during

hand-assisted laparoscopic nephrectomy. The authors patched a polypropylene and polyglactin dual mesh with a laparoscopic stapler on the tear of diaphragm and then inserted a chest tube. The patient recovered without sequelae. In another case, gelatin matrix was used as an alternative to suturing for repairing a diaphragmatic tear. Gelatin thrombin matrix was applied to the tear area through a trocar and the defect was successfully repaired (18). This method can be successfully applied in selected small diaphragmatic defects. The rate of thoracic complications after open renal surgery has been reported to be between 3% and 10% in different studies (19,20). In our study, it was found to be between 1% and 2.5%, less than in the literature. The probable cause of this low rate was our advanced experience in renal surgery and the prevention of high gas pressure by providing coordination with anesthesia during laparoscopic surgery. Recently, in a prospective study, factors that predicted pleural injury during PCNL were evaluated. Three hundred thirty-two patients were divided into two groups according to development of pleural injury and the higher risk of pleural injury was found to be associated only with low body mass index and younger age in multivariate analysis (21).

Study Limitations

Although our study is one of the rare studies presenting thoracic complications of urological surgeries from a single-center, it is not without limitations. Firstly, limited number of cases and its retrospective nature are the main limitations. Second, direct radiography with lower sensitivity was used in the diagnosis of pleural complications instead of computed tomography.

Conclusion

In conclusion, it should be kept in mind that thoracic complications may occur during urological surgeries. It is essential to diagnose complications (perioperative if possible) immediately and to work in coordination with anesthesiologists and to consult with thoracic surgeons.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed written informed consent was obtained from all patients included in our study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.K., T.İ.A., Design: F.K., T.İ.A., Data Collection and/or Processing: F.K., T.İ.A., S.K., A.Ş., B.T., Ö.K., U.Ç., O.N., C.Ö., İ.C. Analysis and/or Interpretation: F.K., T.İ.A., Ö.K. Literature Research: F.K., T.İ.A., Writing: F.K.

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

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Protective Effects of Oral Sirolimus Therapy against ESWL-induced Kidney Tissue Damage in Rats

Ratlarda ESWL Sonrası Oluşan Böbrek Doku Hasarında Oral Sirolimus Tedavisinin Etkisi

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

To date, there are no studies showing the long-term effects of extracorporeal shock wave lithotripsy (ESWL) on the kidney in detail. In experimental studies, only dose-dependent renal fibrosis formation has been demonstrated in dogs and rabbits by different researchers. However, it is unclear whether or not to reduce ESWL-induced tissue damage. In this study, it was determined that sirolimus decreased the histopathological changes related to ESWL on the kidney in long term. To conclude, we think that sirolimus may be beneficial in order to protect the existing renal functions and to decrease the tissue damage in kidney tissue after.

Abstract

Objective: In the present study, we aimed to investigate the short- and long-term protective effects of oral sirolimus therapy on extracorporeal shock wave lithotripsy (ESWL)-induced kidney tissue damage in an experimental rat model.

Materials and Methods: Twenty-four male Spraque-Dawley rats were used in the study. A total of 1000 shock waves (SWs) were applied to the left kidney of all rats at 15 kV, 60 SW/min. Two main groups, ESWL (group 1) and ESWL sirolimus (group 2), were formed. Each group was divided into two subgroups as early (E) and late (L). Left nephrectomy was performed on the 15th day in E groups and on the 60th day in L groups. Tubular injury, interstitial changes, as well as scar formation, were scored semi-quantitatively for at least 10 cortical fields in each sample. An average score was calculated for each subject. Independent samples t-test was used for statistical analysis. The statistical significance was accepted as $p<0.05$.

Results: The mean histopathological score was 0.08 ± 0.94 and 0.15 ± 0.65 ($p=0.332$) in group 1E and 2E and it was 0.27 ± 0.17 in group 1L and 0.05 ± 0.06 in group 2L, respectively ($p<0.05$). When group 1E and group 1L were compared, the mean score was 0.08 ± 0.94 and 0.27 ± 0.17, respectively ($p<0.05$). Furthermore, there was also a statistically significant difference in mean histopathological score between group 2E and group 2L. The mean score was 0.15 ± 0.65 vs 0.05 ± 0.06 ($p<0.05$).

Conclusion: Depending on SW power and frequency, ESWL may cause significant histopathological changes in rat kidneys in the chronic period. In this experimental study, it has been thought that sirolimus treatment may have a tissue protective effect against long-term renal tissue damage.

Keywords: Histopathologic changes, Kidney, ESWL, Sirolimus

Öz

Amaç: Bu çalışmada, deneysel rat modelinde oral sirolimus tedavisinin ekstrakorporeal şok dalgası tedavisi (ESWL) sonrası oluşabilecek böbrek dokusu hasarı üzerine kısa ve uzun dönemde koruyucu etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmada 24 erkek Spraque-Dawley rat kullanıldı. Tüm ratların sol böbreğine 15 kV, 60 SW/dk'da toplam 1000 şok dalgası uyguladı. İki ana grup, ESWL (grup 1) ve ESWL sirolimus (grup 2) oluşturuldu. Her grup erken (E) ve geç (L) olmak üzere iki alt gruba ayrıldı. Sol nefrektomi 15. günde E gruplara, 60. günde L gruplara yapıldı. Tübüler hasar, interstisyel değişiklikler ve skar oluşumu, her denekte en az 10 kortikal alanı için yarı kantitatif olarak skorlandı. Her denek için ortalama bir puan hesaplandı. İstatistiksel analiz için bağımsız örneklem t-testi kullanıldı. İstatistiksel anlamlılık $p<0,05$ olarak kabul edildi.

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Bulgular: Ortalama histopatolojik skor, grup 1E ve 2E'de 0,08±0,94 ve 0,15±0,65 (p=0,332) idi. Grup 1L'de 0,27±0,17 ve grup 2L'de 0,05±0,06 idi (p<0,05). Grup 1E ve grup 1L karşılaştırıldığında, ortalama puan sırasıyla 0,08±0,94 ve 0,27±0,17 idi (p<0,05). Ayrıca, grup 2E ve grup 2L arasında ortalama histopatolojik skor açısından istatistiksel olarak anlamlı fark vardı. Ortalama puan sırasıyla 0,15±0,65'e 0,05±0,06, p<0,05 idi.
Sonuç: Şok dalga gücü ve frekansına bağlı olarak ESWL, kronik dönemde rat böbreklerinde önemli histopatolojik değişikliklere neden olabilir. Bu deneysel çalışmada, sirolimus tedavisinin ESWL'den sonra uzun dönem böbrek dokusu hasarında doku koruyucu bir etkiye sahip olabileceği düşünülmektedir.
Anahtar Kelimeler: Histopatolojik değişiklikler, Böbrek, ESWL, Sirolimus

Introduction

Extracorporeal shock wave lithotripsy (ESWL) is the treatment modality which uses shock waves (SWs) obtained from an external source to break a intra-corporeal stone into small pieces. Since its introduction in the 1980s, it has revolutionized the treatment of urinary stone disease. ESWL has rapidly gained worldwide acceptance because of its non-invasiveness, ease of use, high efficacy in the treatment of kidney and ureteral stones, and the variety of lithotripters (1). SWs carry out stone fragmentation via a number of dynamic and mechanic forces that are simply stated as cavitation and direct stress. It is known that cavitation is the primary mechanism of stone fragmentation. However, SWs that focus on the stone may cause injury to the thin-walled vessels as they pass through the tissues. Vascular injury may lead to bleeding and ischemic areas in the kidney and adjacent organs. At the end, the process in which cytokines and inflammatory cells take part in an active role begins. According to the degree of the vascular damage, fibrosis, scar formation and loss of the tissue function may occur (2).

The crucial cytokine responsible for fibrosis formation is transforming growth factor-β (TGF-β). Many different processes, such as apoptosis, cell differentiation and growth, extracellular matrix (ECM) synthesis are regulated by TGF-β (3). It has been determined by various clinical and experimental studies that sirolimus (rapamycin), an inhibitor of mammalian target of rapamycin (mTOR), has antifibrotic, antiproliferative and neovascularization inhibitory effects. It has been also shown that sirolimus prominently reduced TGF-β expression and suppressed interstitial fibroblast activity, leading to a decrease in the production of ECM and fibrosis (4).

To our knowledge, the protective effects of sirolimus therapy against ESWL-induced kidney tissue damage have not been reported and remain largely unknown. In this study, we aimed to investigate the short- and long-term protective effects of oral sirolimus therapy ageinst ESWL-induced kidney tissue damage in an experimental rat model. The second aim of this study was to evaluate the damage in the renal parenchyma that occurred after acute changes related to ESWL.

Material and Methods

Twenty-four male Spraque-Dawley rats were used in the study. All rats were housed under standard conditions with a temperature-controlled environment and a 12-hour light-dark-cycle and with free access to food and water prior to and after the treatment protocol. All procedures were performed in compliance with the provision of the Strasbourg Universal Declaration on Animal Welfare of 1986 and this study was approved by Ondokuz Mayıs University local ethics committee on animal research (number: 2009/2).

The rats were randomly divided into 2 major experimental groups as ESWL (group 1) and ESWL + sirolimus (group 2). Subsequently, each group was divided into two subgroups as early (E) and late (L) periods. The groups are summarized in Table 1.

Creating Experimental ESWL Model in Rats

General anaesthesia was achieved by intraperitoneal administration of 100 mg/kg ketamine and 20 mg/kg xylazine hydrochloride (Rompun®). A 24 G intravenous catheter was inserted into the rats' tail vein. The rats were fixed on the wooden block and placed on ESWL table as the left lumbar region were open. The left renal collecting system was fluoroscopically visualized by administering sodium amidotrizoate (Urografin® 76%) at a dose of 2 cc/kg via the intravenous catheter at the tail vein of the rats. Furthermore, the middle pole of the left kidney was focused on the F2 focal zone (Figure 1). After the focusing, a total of 1000 SWs were applied to the left kidney of all rats at 15 kV, 60 SW/min. The F2 focus was checked every 200 SWs. As a SWL generator, an Electrohydraulic Stonelith Smart Lithotripter (PCK, Turkiye) was used.

Table 1. Experimental rat model and number of rats per group

	Group 1 (ESWL)	Group 2 (ESWL + sirolimus)
Early (E)	6	6
Late (L)	6	6

ESWL: Extracorporeal shock wave lithotripsy

Group 1: ESWL

After applying ESWL, the rats of the group 1E and group 1L were sacrificed by exsanguination on the 15th and 60th days, respectively.

Group 2: ESWL + sirolimus

On the first-day post-ESWL, 0.8 mg/kg sirolimus was given orally by gastric lavage to the rats of group 2E and group 2L (5). Left nephrectomy was performed on day 15 in group 2E and on day 60 in group 2L.

Histopathologic Evaluation

The extracted left kidneys were macroscopically evaluated for subcapsular haemorrhage on the anterior and posterior sides. Then, they were kept in 10% formaldehyde for 24 hours. Tissue follow-up procedures were followed to prepare 4-micron paraffin-embedded sections. The sections were stained with haematoxylin-eosin (H&E) and periodic acid-schiff. Pathological preparations were evaluated using light microscopy (Olympus BX50, Olympus CO, Japan) by a single pathologist who was blind to the study groups. Tubular damage (tubular dilatation, intratubular bleeding), interstitial inflammation, interstitial haemorrhage, glomerular and vascular congestion in the renal cortex were all examined at a magnification of 200 under a light microscope. In addition, for chronic changes, the presence of tubular atrophy and interstitial fibrosis was also assessed. Modified from the study of Li et al. (6), the prevalence of damage findings was scored on a scale of 0-4 with a semi quantitatively expressed percentile (Table 2). In the present study, tubular injury, interstitial changes, as well as scar formation, were scored semi quantitatively for at least 10 cortical fields in each sample. Average score was calculated for each subject.

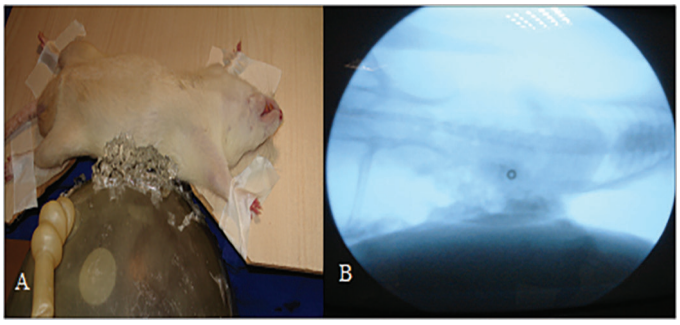

Figure 1. A) Fixation of the rat on wooden blocks; B) F2 focus; after administration of contrast medium

Table 2. Histopathological scoring system

Score	Percent
0	None
1	<10%
2	10-25%
3	26-75%
4	>75%

Scoring system that expresses the prevalence of histopathological findings in percent area

Statistical Analysis

Statistical Package of Social Sciences 15 (SPSS 15, Chicago, IL, USA) was used for statistical analysis. Independent samples t-test was used to compare the groups. The statistical significance was accepted as $p<0.05$.

Results

No subcapsular or intraparenchymal haemorrhage was found on macroscopic examination in any of the subjects. When histopathological evaluation scores were compared between the groups, the mean score was 0.08 ± 0.94 and 0.15 ± 0.65 in group 1E and 2E, respectively ($p=0.332$). The mean score was 0.27 ± 0.17 in group 1L and 0.05 ± 0.06 in group 2L, ($p<0.05$) (Figure 2A and 2B). When group 1E and group 1L were compared, the mean

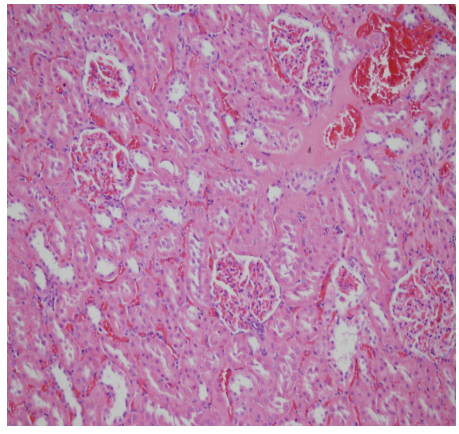

Figure 2A. Group 1L, sample no: 3: H&E x200: Rat with a histopathologic score of 2

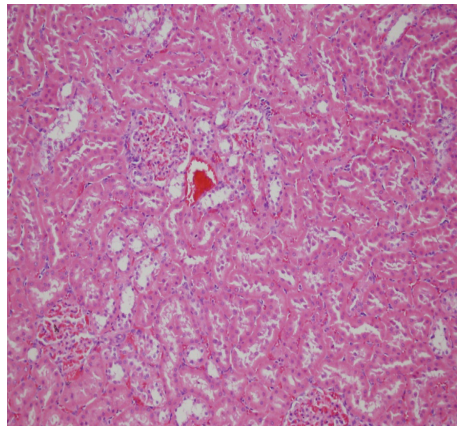

Figure 2B: Group 2L, sample no: 4: H&E x200: Rat with a histopathologic score of 1; Note that interstitial edema is evident. Although edema was a sign of the acute period in histopathologic evaluation in general, it was found in the chronic period rats as a side effect of sirolimus

score was found to be 0.08±0.94 and 0.27±0.17, respectively (p<0.05). Furthermore, a statistically difference was found in mean histopathological score between group 2E and group 2L. The mean score was 0.15±0.65 vs 0.05±0.06, p<0.05 (Figure 3).

When the changes in body weights were examined before and after the study in group 1, the mean body weight in the rats of group 1E and group 1L was 291.5±6.18 g vs 292±5.76 g and 295.1±7.25 g vs 294.8±6.64 g, respectively. The change in body weight in both subgroups of group 1 was not statistically significant (p=0.203 and p=0.638, respectively). Nevertheless, in group 2, the mean body weight in the rats of group 2E and group 2L was 294±5.54 vs 282±5.32 g and 297.5±2.58 vs 273.1±3.76 g, respectively. The change in body weight in both subgroups was statistically significant (p=0.001 and p=0.006, respectively).

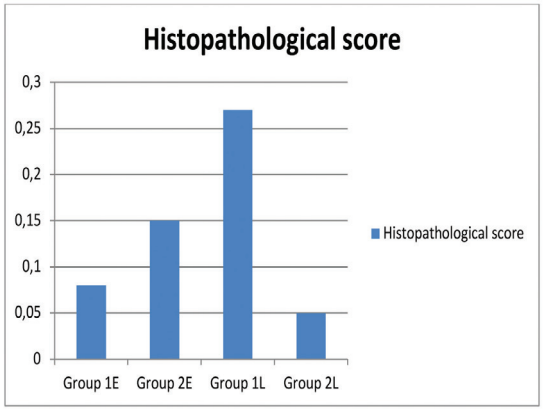

Figure 3. The mean histopathological score of each group

Discussion

ESWL is the only non-invasive treatment modality for the management of stones located in the upper urinary system. The overall risk of side-effect is lower in ESWL compared to other minimally-invasive treatment options such as ureterorenoscopy, retrograde intrarenal surgery, and percutaneous nephrolithotomy (7). Short-term complications of ESWL include perirenal and/or intraparenchymal haemorrhage or hematoma, infectious complications, and adverse events associated with residual stone fragments (8). Furthermore, long-term adverse effects of ESWL on the kidney, which are still a matter of debate, are loss of parenchyma in the functioning kidney that might be related with chronic kidney disease (CKD) and arterial hypertension. Nonetheless, it has been stated in a systematic review that there was no evidence supporting an association between ESWL and long-term adverse effects (8).

Hazardous effects of SWs on blood vessels and renal tubules have been demonstrated in animal studies (6,9). Vascular damage might result in haematuria or hematoma formation as well. However, this tissue damage usually occurs in the field where the focal zone is targeted (1).

In addition, it is asserted that hematuria occurs in all patients who undergo SWL treatment after receiving around 200 SWs. In another human study comparing electromagnetic versus electrohydraulic lithotriptors, it has been reported that electromagnetic lithotriptor caused higher number of red blood cells in the urine compared to electrohydraulic lithotriptor in the early post-SWL period. However, cytologic evaluations performed 10 days after SWL therapy showed recovery of all abnormal cytologic findings (10). On the other hand, an intraparenchymal, subcapsular and perirenal hematoma is another well-known ESWL-induced acute renal complication. The incidence of hematoma detected on ultrasound examination has been reported to be 1%. However, it has been reported that the incidence of hematoma would have increased to 30% when the radiological evaluation was performed by computed tomography or magnetic resonance imaging (MRI). It has also been declared that the frequency of hematoma differs according to the radiological method, time of evaluation as well as lithotripter type (11). Age of the patient, history of hypertension, bleeding diathesis, antiplatelet drug use, body mass index, stone size, diabetes mellitus, frequency and strength of shock wave, and duration of treatment are predisposing risk factors for hematoma formation (11,12,13).

It has been stated in a prospective clinical study that lower energy SW decreases the incidence of renal hematoma detected by MRI. Moreover, it has been reported that a low energy setting caused smaller diameter hematomas and that these hematomas disappeared within 1 week (11). Another study also reported that most of SWL-related renal hematomas resolved within weeks without long-term adverse effects (14). The above-mentioned acute complications have been shown in many experimental and animal studies in the literature. Furthermore, in many studies, acute histopathological changes after ESWL were evaluated immediately after ESWL or within a few weeks (13,15). It is well known that ESWL may cause vascular injury as an acute side effect on kidney parenchyma. Vascular injury and hematoma might initiate an inflammatory response that ends up with scar formation. Morris et al. (16) have shown that dose-dependent scar volume increased 10-fold in rabbits when the number of SWs applied to the kidney was increased from 1000 to 2000 pulses. However, the clinical reflection of chronic scar formation has not been fully clarified for many years. In our study, in the beginning, we planned to apply a total of 2000 SWs but it was reduced to 1000 SWs due to the death of rats during or immediately after the experiment.

It has been reported in a study on pigs that a dose of 2000 SWs using a Dornier HM3 lithotripter operated at 24 kV and SWs

applied at 120 SW/min produced a parenchymal lesion measuring thereabouts 5% to 6% of a functional renal volume (17). In the present study, the first histopathological examinations were made on the 2nd week after ESWL to evaluate the damage that may occur after acute changes in the renal parenchyma. The mean area affected by ESWL in both E groups was less than 15%. Furthermore, there was no subcapsular hematoma detected in both groups. In our opinion, the reduction in total SWs, frequency, and power was associated with the results in E groups. Since intraparenchymal or subcapsular haemorrhage and tubular damage detected in the E period after ESWL are expected to decrease in the second week, the time of examination of the subjects may also be another factor.

To date, there are no studies showing long-term effects of ESWL on the kidney in detail. In experimental studies, only dose-dependent renal fibrosis formation has been demonstrated in dogs and rabbits by different researchers. However, it is still unclear how to prevent SWL-associated kidney tissue damage in clinical practice.

The formation of fibrosis after acute tissue damage is formed over various mediators. In experimental studies, the up-regulation of TGF-β and vascular endothelial growth factor has been proven as a crucial step of the initiation of the process that results in fibrosis. TGF-β also regulates many different biological activities such as cell growth, apoptosis, cell differentiation, and ECM synthesis (18). Sirolimus, an inhibitor of mTOR, has anti-inflammatory and anti-fibrotic effects (19). In *in vivo* studies, it was shown that sirolimus significantly decreased TGF-β expression and suppressed interstitial fibroblast activity and decreased ECM production and fibrosis (4). The main purpose of our study was to investigate the effect of ESWL on histopathological changes in kidney tissue due to the antifibrotic properties of sirolimus, an inhibitor of mTOR. For this reason, two main groups were formed and these groups were divided into two subgroups: E and L period. A control group and sham group were not included.

According to the literature, orally administered low-dose sirolimus (≥0.5 mg/kg/day) had anti-fibroblastic, antiproliferative and neovascularization effects. Stepkowski (5) estimated oral bioavailability of sirolimus at 10%. When the intravenous dose of 0.08 mg/kg/day was compared with an oral dose of 0.8 mg/kg/day, it was found that the average survival time of heart allografts was similar. In our study, we prepared the dose to be given to rats the based on this study (5).

In this study, it was determined that sirolimus decreased histopathological changes in the kidney related to ESWL in long term. However, the effect of sirolimus on histopathological changes in the first two weeks could not be determined.

In another study in which the effect of sirolimus on body weight was evaluated, a significant weight loss was detected after 12 weeks in group administered sirolimus 1.0 mg/kg 3 times a week (20). In our study, the rats were treated with oral sirolimus at a dose of 0.8 mg/kg/day. A statistically significant decrease in body weight was determined in both the E groups ($p<0.05$) and in the L period groups ($p<0.05$).The detection of a statistically significant weight loss among long-term groups was a side effect of sirolimus (20).

In a retrospective study evaluating the effect of ESWL on renal functions in 131 patients with CKD and kidney stones, stone therapy with ESWL delayed the deterioration in renal function in patients with CKD. In patients with chronic renal failure; if there were kidney stones and not treated, annual deterioration in renal function was more common than those treated with ESWL. As a result, it was stated that ESWL could be recommended in patients with CKD and kidney stone (21). Sirolimus provides appropriate immunosuppression without nephrotoxicity, unlike calcineurin inhibitors. It could be used as an alternative drug in a patient with CKD who has organ transplantation (22).

Study Limitations

Several limitations of our study should be noted. First, TGF-β molecule, which is an important marker for the determination of fibrosis, could not be managed at the tissue level due to technical deficiencies. Therefore, evaluations could only be made at the histopathological level. Second, our rat model of ESWL-induced kidney tissue damage is not entirely analogous to clinical conditions seen in patients.

Conclusion

Based on this study, we think that sirolimus may be beneficial in protecting the existing renal functions and in decreasing tissue damage in kidney tissue after ESWL especially in patients with CKD. However, further investigations are needed to confirm or support this theory.

Ethics

Ethics Committee Approval: This study was approved by Ondokuz Mayıs University local ethical committee on animal research (number: 2009/2).

Informed Consent: All procedures were performed in compliance with the provision of the Strasbourg Universal Declaration on Animal Welfare of 1986.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.N.M., Ş.S, E.Ö., Design: M.N.M, E.Ö., Y.B., Data Collection and/or Processing: M.N.M., Y.B., Analysis and/or

Interpretation: E.Ö., Y.B., M.N.M., Literature Research: M.N.M., Writing: M.N.M., Ş.S.

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Fournier's Gangrene: Analysis of Risk Factors Affecting Mortality in a Tertiary Urology Referral Center

Fournier Gangreni: Tersiyer Bir Üroloji Referans Merkezinde Mortaliteye Etki Eden Risk Faktörlerinin Analizi

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

Aggressive treatment is the main approach for the management of Fournier gangrene (FG). The mortality rate is between 3% and 45% in the literature. For this reason, to know the risk factors affecting mortality for FG may help surgeons in their daily practice.

Abstract

Objective: We aimed to investigate the risk factors affecting mortality in patients with Fournier's gangrene (FG).
Materials and Methods: Records of 48 male patients, who were admitted to our urology clinic between November 2011 and June 2018, were analyzed. The patients were divided into two groups according to their survival status. statistical analyses were done to determine the risk factors for mortality.
Results: The mean age was 53.9±12.61 years. 41 patients were discharged (group 1) and 7 were deceased (group 2). The mortality rate was 14.6%. Increased age, Fournier's Gangrene Severity Index (FGSI) scores, prolonged operative time, presence of immunosuppressive diseases, abdominal spread of the disease, history of cystostomy, mechanical ventilation requirement, and multiple micro-organism in wound culture were found to be risk factors for mortality in patients with FG.
Conclusion: Increased age, high FGSI scores, increased operative time, presence of immunosuppressive diseases, history of cystostomy, abdominal spread of the disease, mechanical ventilation requirements, and multiple micro-organism in wound culture were thought to affect mortality in patients with FG.
Keywords: Fournier's gangrene, Mortality, Risk factor

Öz

Amaç: Fournier kangreni (FG) hastalarında mortaliteyi etkileyen risk faktörlerini araştırmayı amaçladık.
Gereç ve Yöntem: Kasım 2011 ve Haziran 2018 arasında 48 erkek hastanın kayıtları analiz edildi. Hastalar sağkalım durumlarına göre iki gruba ayrıldı. Mortaliteye etki eden risk faktörlerini belirlemek için istatistiksel analizler yapıldı.
Bulgular: Ortalama yaş 53,9±12,61 idi. Hastaların 41'i taburcu olmuş (grup 1) ve 7'si vefat etmişti (grup 2). Mortalite oranı %14,6 idi. Artmış yaş, artmış Fournier Gangreni Severity Indeks (FGSI) skorları, artmış operasyon süresi, immünosüpresyon hastalığı olması, sistostomi yapılması, hastalığın abdominal yayılması, mekanik ventilasyon ihtiyacı, yara kültüründe multipl mikroorganizma saptanması FG'de mortalite için risk faktörleri olarak bulundu.
Sonuç: İleri yaş, artmış FGSI skorları, artmış operasyon süresi, immünosüpresyon hastalığı olması, sistostomi yapılması, hastalığın abdominal yayılımının olması, mekanik ventilasyon ihtiyacı, yara kültüründe multipl mikroorganizma saptanmasının FG'si olan hastalarda mortaliteyi etkilediği düşünülmektedir.
Anahtar Kelimeler: Fournier gangreni, Mortalite, Risk faktörü

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Introduction

Fournier's gangrene (FG) is a disease of the perineal, genital or perianal regions characterized by necrotizing fasciitis due to synergistic polymicrobial infection (1). Since delay in diagnosis and treatment can be lethal, it is very important that the symptoms are not missed even if non-specific. It is a serious disease which is seen in emergency departments of general surgery and urology clinics and it is associated with high mortality rates due to its insidious course and requires urgent surgical intervention with appropriate antibiotic therapy (2).

In this retrospective study, we aimed to analyse the factors that affect prognosis in patients treated for FG.

Materials and Method

We retrospectively reviewed the records of patients who underwent surgery with FG diagnosis between 2011 and 2018 in our clinic. A total of 48 male patients were included in the study. Clinical and demographic data such as age, comorbidity, Fournier's Gangrene Severity Index (FGSI) score (Table 1) and perioperative data were recorded. The patients were divided into two groups according to their survival status.

We performed radical debridement of the affected devitalized tissues in all patients after presentation. Initial empiric antibiotherapy with imipenem + teicoplanin and clindamycin was given in the outpatient clinic and continued. The dressings were changed daily. Wound debridement was performed every 48 hours with sedation in the operating room. Vacuum assisted closure (VAC) was used for wound treatment (Figure 1). All necrotic areas were debrided until the healthy tissue was seen in the wound. If necessary, the patients were managed in the intensive care unit (ICU). If the skin defect was not self-healing, treatment with tertiary closure, split-thickness skin grafting (STSG), was performed for reconstruction.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM SPSS Statistics for Windows, version 21.0. monk, NY: IBM Corp., Armonk, NY). The Pearson chi-square and Fisher's exact tests

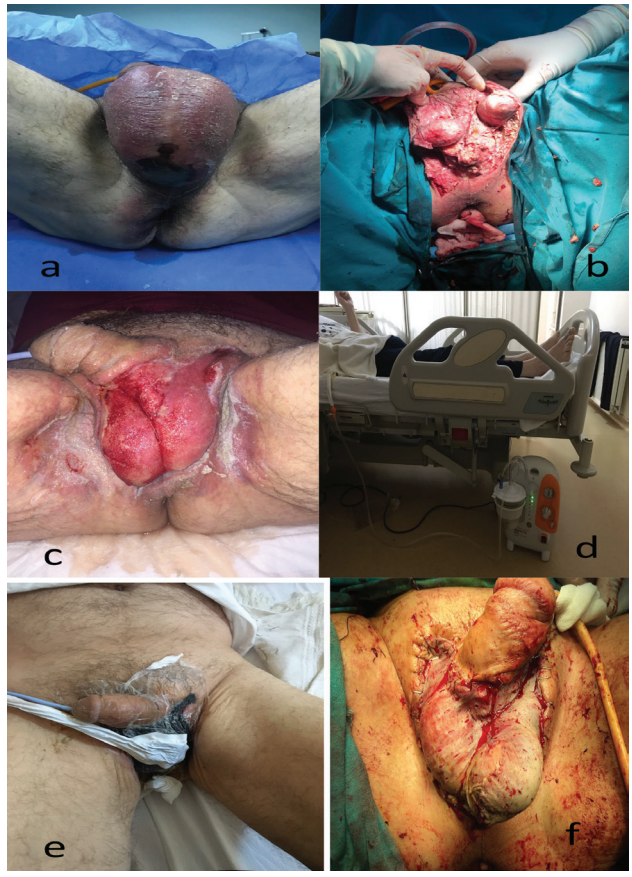

Figure 1. (a) Presentation of a patient with FG (b) Debridement was performed at the operating room (c) Granulation tissue was formed (d,e) VAC therapy procedure (f) Skin graft applied.

Table 1. Fournier Gangrene Severity Index scoring system

Physiologic variable/point assignment	High abnormal values				Normal	Low abnormal values			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	>41	39-40.9	-	38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
Heart rate	>180	140-179	110-139	-	70-109	-	55-69	40-54	<39
Respiratory rate	>50	35-49	-	25-34	12-24	10-11	6-9	-	<5
Serum sodium (mmol/L)	>180	160-179	155-159	150-154	130-149	-	120-129	110-119	<110
Serum potassium (mmol/L)	>7	6-6.9	-	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	-	<2.5
Serum creatine (mg/100 mL) ´2 , acute renal failure	>3.5	2-3.4	1.5-1.9	-	0.6-1.4	-	<0.6	-	-
Hematocrit	>60	-	50-59	46-49	30-45	-	20-29	-	<20
WBC (total/mm^3 ´1000)	>40	-	20-39.9	15-19.9	3-14.9	-	1-2.9	-	<1
Serum bicarbonate (venous, mmol/L)	>53	41-51.9	-	32-40.9	22-31.9	-	18-21.9	15-17.9	<15

WBC: White blood cell

were used for analyzing differences between the categorical variables, and the Kruskal-Wallis and Mann-Whitney U tests were used for analyzing differences between means. A p value of less than 0.05 was considered statistically significant. The study protocol was approved by the ethics committee of Cerrahpasa Faculty of Medicine.

Results

The mean age of the patients was 53.90±12.61 years. Fourty-one patients were discharged (group 1) and 7 deceased (group 2). The demographic data is given in Table 2. The most common cause of the disease was urological causes (25 patients; 52.1%). The most common immunosuppressive disease was diabetes mellitus (12 patients; 25.0%). Two patients were human immunosuppressive virus (HIV)-positive.

The most frequently isolated pathogen in wound culture was *Escherichia coli* (27 patients; 56.2%). Other identified microorganisms were *Klebsiella pneumoniae* in 12 (25.0%), *Streptococcus* in 4 (8.3%), *Staphylococcus* in 3 (6.2%) and *Pseudomonas* in 2 (4.1%). Nineteen patients (39.6%) had polymicrobial infection (≥2 microorganisms identified) .

Table 2. Characteristics of patients

Patient characteristics	n
Number of patients	48
Age (year) Mean (range)	53.9 (36-78)
BMI (kg/m^2) Mean (range)	28.2 (18.7-42.4)
Hematocrite Mean (range)	34.3 (25.6-51.9)
Operation time (min) Mean (range)	162.4 (40-540)
FGSI Mean (range)	3.2 (1-11)
Albumin Mean (range)	3.3 (2.3-4.4)
Leukocyte count value Mean (range)	12.060 (7.320-18.530)
Etiology	
• Urogenital	25 (52.1%)
• Anorectal	19 (39.6%)
• Skin-based	4 (8.3%)
Pathogen in wound culture	
• *E.coli*	27 (56.2%)
• *Klebsiella*	12 (25.0%)
• Other	9 (18.8%)
Length of hospital stay (days) Mean (range)	36.7 (10-93)

FGSI: Fournier Gangrene Severity Index, BMI: Body mass index

VAC therapy was used for wound management in 33 patients. The mean number of debridements was 3 (1-9). Colostomy and cystostomy were established in 5 (10.4%) and 3 (6.3%) patients, respectively. The wound was closed conveniently for tertiary closure in 27 (56.2%) patients. The wounds in 14 (29.1%) patients were reconstructed with STSG.

A total of 14 (29%) patients required treatment in the ICU with a mean duration of 7 days (1-29). Of these, seven underwent mechanical ventilation. The mean duration of postoperative mechanical ventilation was 4±2.1 (1–29) days. A total of 7 patients died due to multi-organ failure associated with septic shock. The mortality rate was found to be 14.6%.

There was a significant difference between the groups in age (p=0.001), FGSI score (p=0.001), operative time (p=0.001), presence of immonosuppressive disease (p=0.001), history of cystostomy (p=0.002), abdominal spread of the disease (p=0.001), mechanical ventilation requirement (p=0.001) and multiple microorganism in wound culture (p=0.001) (Table 3).

Discussion

The rate of mortality associated with FG has been reported to be between 3% and 45% (3). While mortality rate was 80% in the first series published, the rate decreased to 40% in the last 15 years (4). Causes of death from the disease include severe sepsis, coagulopathy, acute renal failure, diabetic ketoacidosis and multiple organ failure (3). Early aggressive treatment reduces mortality. Therefore, the important factor affecting the clinical outcome is timely and adequate surgical debridement. Furthermore, accurate estimation of mortality risk may be a guide for the management of FG. For instance, FGSI is a powerful predictor of mortality associated with FG. In addition, in the literature, many factors have been shown to have a negative effect on survival, e.g., increased age, widespread disease, delay in treatment, presence of shock or sepsis on admission, positive blood culture, increased level of urea, anorectal origin of infection, diabetes mellitus and immunosuppressive condition (5). In our study, the mortality rate was found to be 14.6%. Also, increased age, and operative time, high FGSI score, presence of immonosuppressive disease, history of cystostomy, abdominal spread of the disease, mechanical ventilation requirement and multiple micro-organisms in wound culture were thought to affect mortality in this study.

Perianal infections are the most common cause of FG (4). The most common sites of infection are the gastrointestinal system (30-50%), genitourinary tract (20-40%) and skin (20%). However, in Eke's series, the etiological factors for FG were diabetes mellitus in 20% and alcohol abuse in 9%, and the sources of FG were dermatological in 24%, anorectal in 21%, and urological in 19% (3). In our study, the etiology was urogenital infection in 52.1%

Table 3. The predictive factors for mortality

	Group 1 (n=41)	Group 2 (n=7)	p
Age (year) Mean (+SD)	50.5±9.8	73.4±8.6	0.001
Operation time (min) Mean (+SD)	125.7±97.4	377.1±178.9	0.001
Body mass index (BMI) Mean (+SD)	25.27±4.8	24.82±4.6	0.775
FGSI score Mean (±SD)	2.0±1.0	10.1±1.1	0.001
Hospitalization time (days) Mean (±SD)	38.6±26.8	25.4±8.5	0.258
Immunosuppressive disease			
• Yes	14	0	0.001
• No	27	7	
Cystostomy			
• Yes	0	3	0.002
• No	41	4	
Colostomy			
• Yes	5	0	0.438
• No	36	7	
Abdominal spread			
• Yes	1	6	0.001
• No	40	1	
Orchiectomy			
• Yes	12	0	0.113
• No	29	7	
Mechanical ventilation			
• Yes	13	0	0.001
• No	28	7	
Micro-organism in wound culture	19	7	0.001
• Multiple	22	0	
• Single			

SD: Standard deviation, FGSI: Fournier Gangrene Severity Index, BMI: Body mass index

of patients. Genitourinary tract-related diseases were more common in our patients. This is because the urogenital diseases are being treated by the urology clinic in our hospital.

Increased age, diabetes mellitus, chronic liver disease, chronic renal failure, alcoholism, smoking and immunosuppressive conditions are risk factors for FG. Diabetes mellitus, the most common concomitant disease (12-70%) in patients with FG, is a predisposing factor for the disease (6). There is a decrease in chemotaxis, phagocytosis and cellular digestive function in diabetes mellitus leading to increased susceptibility to infections (7). Similarly, we found that diabetes mellitus, was the most common comorbid disease in this study (25% of the patients). In addition, 2 patients (4.2%) were found to be HIV-positive.

The FGSI was developed by Laor et al. (8) using vital findings and some laboratory data to determine the severity and prognosis of infection in FG patients. In their 15-year study, they found that a FGSI score of >9 was associated with a 75% probability of death and a score of <9 with a 78% probability of survival. FGSI score is a valid and effective tool commonly used in many studies for determining the clinical outcome in patients with FG (9). Different scoring systems have been studied to predict survival and prognosis. Bozkurt et al. (9) evaluated mortality associated with FG using three different scoring systems.

As a result, FGSI score, laboratory risk indicator for necrotizing fasciitis score and neutrophil-to-lymphocyte ratio were all found to be capable of predicting worse prognosis. We used the FGSI in our study. Similarly, FGSI scores were significantly higher in group 2 than in group 1 in our study (p=0.001) and an increased FGSI score was thought to correlate with mortality.

Aerobic and anaerobic bacteria can be isolated in patients with FG. The most commonly isolated microorganisms are *E. coli* (80-43%), *Klebsiella pneumoniae*, *Bacteroides*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Clostridium*, *Peptostreptococcus* and *Enterobacteriaceae* (10,11). These infections are frequently polymicrobial (12). It is recommended to start a broad-spectrum antibiotic treatment with double and triple combinations before surgery (13). Depending on culture-antibiogram results, the same treatment may be continued or proper antibiotic substitution may be required. Our patient group was similar to the previous publications in terms of the most common microorganisms and reproduction of more than one microorganism. The most frequently isolated pathogens in the wound culture were *E. coli* (56.2%) and *Klebsiella* (25%). Also, multiple microorganisms were isolated in 39.6% of the patients. When FG was detected, empiric antibiotherapy with a combination of intravenous imipenem + teicoplanin and clindamycin was started. According to the culture-antibiogram results, the antibiotic treatment was revised.

Aggressive resuscitation, broad spectrum antibiotic use and early surgical drainage are important in the treatment of FG (12,13). All necrotic tissues are removed by debridement and the procedure is repeated to control infection. If the anorectal area and sphincters are involved, colostomy may be preferred to reduce contamination. Urinary catheterization or cystostomy is also recommended (11,12,13,14). Similarly, 5 of our patients underwent colostomy and 3 patients underwent cystostomy. Also, the mean number of debridement was 3 (1-9) in our study. The number of patients undergoing cystostomy was significantly higher in group 2 (p=0.002). Mortality rate was also found to be higher in patients with abdominal distention (p=0.001). However, no significant difference was found between group 1 and group 2 in terms of mean duration of hospitalization or length of hospital stay in the ICU. However, mechanical

ventilation requirement was significantly higher in group 2 than in group 1 (p=0.001).

The last step in the treatment of FG is the process of closing the large wound defect. In most cases, especially small defect wounds simply improve as secondary healing. However, STSG is the most widely used and preferred method for wounds with large defects. VAC procedure, which has gained popularity in the recent years, has contributed significantly to this period of the treatment by accelerating wound healing. (14). By placing sterile foam dressing with an evacuation tube connected to an adjustable vacuum pump into the wound bed, thus, applying negative pressure to the entire wound bed, VAC accelerates wound healing by reducing edema, increasing blood flow, fibroblast migration and cell proliferation. In our study, VAC therapy was used for wound management in 33 patients (68.7%).

Study Limitations

This study has several limitations. Firstly, it was a retrospective study. Secondly, we could not perform logistic regression analyses. FG patients are treated in the general surgery or urology clinics depending on the affected area and system. In some cases, co-operation of both clinics is needed. The fact that only the outcomes of patients treated in the urology department were evaluated and the small sample size were other limitations of this study. Future prospective studies are warranted in order to overcome all the aforementioned limitations.

Conclusion

In conclusion, in this retrospective study, increased age, high FGSI scores, increased operative time, presence of immunosuppressive disease, history of cystostomy, abdominal spread of the disease, mechanical ventilation requirement, multiple micro-organism in wound culture are thought to associate with mortality in patients with FG.

Ethics

Ethics Committee Approval: The study protocol was approved by the ethics committee of Cerrahpaşa Faculty of Medicine (approval number: 83045809/604.01/02).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions:

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

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Effects of Laser Probes and Computed Tomography Findings on Ureterorenoscopic Laser Lithotripsy Success Rate, Laser Time, Laser Energy Level and Operative Time for Distal Ureteral Stones

Distal Üreter Taşlarında Lazer Probunun ve Bilgisayarlı Tomografi Bulgularının Üreterorenoskopik Lazer Litotripsi Başarısı, Lazer Süresi, Lazer Enerji Düzeyi ve Operasyon Süresi Üzerine Etkileri

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

Stone diameter, volume and Hounsfield units values were significant predictors of laser energy level, ureterorenoscopy and laser time for distal ureteral stones. Also, use of a thinner probe decreased total laser time, laser energy level and laser energy/time ratio.

Abstract

Objective: To investigate the effect of preoperative non-contrast computed tomography (NCCT) findings and peroperative laser probe selection on total laser time, energy level and ureterorenoscopy (URS) time for distal ureteral stones.

Materials and Methods: We prospectively evaluated 72 patients with single distal ureteral stone measuring 5-25 mm in diameter on NCCT, who were treated with ureteroscopic lithotripsy (URSL) between June 2015 and October 2016. The patients were divided into two groups according to probe selection as 365 µm and 550 µm groups. Stone diameters, stone volume and Hounsfield units (HU) measured on NCCT, and URSL findings were noted at the end of the treatment. These findings were compared between the groups. Also the possible predictive value of NCCT findings was evaluated for URSL data.

Results: There were 17 patients in the 365 µm and 55 patients in the 550 µm groups. There was no significant difference in URSL success rate and other predictive data between the groups. However, among the peroperative data, laser time, laser energy level and laser energy/time ratio were significantly lower in the 365 µm group compared to the 550 µm group ($p<0.05$). Correlation analysis indicated that total laser time and URS time were correlated with stone diameter, stone volume, HU values and density (HD). Laser energy level was only correlated with longitudinal stone diameter and HD.

Conclusion: Stone diameter, volume and HU values are significant predictors of laser energy level, URS and laser time for distal ureteral stones. Also, use of a thinner probe decreases total laser time, laser energy level and laser energy/time ratio. In addition, thinner laser probe shortens URS time.

Keywords: Distal ureteral stone, Hounsfield units (HU), Laser lithotripsy, Non-contrast computed tomography (NCCT), Ureterorenoscopy (URS)

Öz

Amaç: Distal üreter taşlarında, preoperatif kontrastsız bilgisayarlı tomografi (BT) bulgularının ve peroperatif lazer prob seçiminin toplam lazer süresi, enerji düzeyi ve üreterorenoskopi (URS) zamanı üzerine etkisini araştırmayı amaçladık.

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Gereç ve Yöntem: Haziran 2015 - Ekim 2016 tarihleri arasında, URS ile tedavi edilen ve BT'de 5-25 mm çaplı, tek, distal üreter taşı olan 72 hasta prospektif olarak değerlendirildi. BT'de ölçülen taş çapı, taş hacmi ve hounsfield ünitesi (HU) ile URS bulguları not edildi. Prob seçimine göre 365 µm ve 550 µm olarak iki gruba ayrılan hastalarda tüm veriler lazer prob grupları arasında karşılaştırılarak değerlendirildi. Ayrıca URS verilerini etkileyebilecek olası BT bulgularının tahmini prediktif etkileri incelendi.

Bulgular: Toplam 72 hastadan, 365 µm prob grubunda 17 hasta ve 550 µm prob grubunda 55 hasta mevcuttu. URS başarı oranı ve diğer prediktif veriler gruplar arasında anlamlı değildi. Ancak, peroperatif verilerden lazer süresi, lazer enerji düzeyi ve lazer enerji/süre oranı 365 µm prob grubunda 550 µm prob grubuna göre anlamlı daha düşüktü ($p<0,05$). Korelasyon analizinde toplam lazer süresi ve URS süresinin taş çapı, taş hacmi, HU değeri ve HU dansitesi (HD) ile korele olduğu gözlendi. Lazer enerji düzeyi ise sadece longitudinal taş çapı ve HD ile koreleydi.

Sonuç: Distal üreter taşlarında taş çapı, hacmi ve HU değerleri lazer enerji düzeyi, URS ve lazer süresini öngören faktörlerdir. Ayrıca, daha ince lazer prob kullanımı toplam lazer süresini, lazer enerji düzeyini ve lazer enerji/süre oranını azaltmaktadır. Ayrıca, ince lazer probu URS süresini kısaltmaktadır.

Anahtar Kelimeler: Distal üreter taşı, Hounsfield units (HU), Lazer litotripsi, Kontrastsız bilgisayarlı tomografi (BT), Üreterorenoskopi (URS)

Introduction

Ureteroscopy (URS) procedure is an appropriate treatment modality for ureteral stones (1). The holmium:yttrium-aluminum-garnet (Ho:YAG) laser has been considered the standard lithotripsy modality for ureteroscopic lithotripsy (URSL) for the past 2 decades (2,3). With the development of semirigid and flexible URS technology and introduction of better instrumentation, including the Ho:YAG laser, URSL has improved in efficacy while sustaining a low morbidity and high success profile (4,5). In current studies, URSL stone-free (SF) rates were reported as 94.2%, 89.4%, and 84.5%, for distal, mid, and proximal ureteral stones, respectively (6).

Non-contrast computed tomography (NCCT) is the gold standard imaging modality to evaluate patients with urinary stones, providing predictive information for treatment planning (7,8). NCCT provides stone measurements (size and volume), stone location and stone density [Hounsfield units (HU) measurements]. Absolute HU inversely correlates with the effectiveness of extracorporeal shock wave lithotripsy (SWL) and has also been proposed to affect SF rates after URSL and percutaneous nephrolithotomy (PNL) (9-12). Stone fragmentation is an important factor for SF status, laser and operative times. Therefore, it is important to define the predictive factors affecting stone fragmentation and these factors may also be useful in predicting SF status, laser and operative times for URSL. In a recent study, URSL procedures were retrospectively analyzed and predictive factors for operative time and success were investigated and identified (13).

The purpose of our investigation was to prospectively evaluate the effect of preoperative NCCT findings and peroperative laser probe selection on treatment success rate, cumulative Ho:YAG laser time, URS time and laser energy level for single distal ureteral stones.

Materials and Methods

After approval was obtained from the Local Ethics Committee, we prospectively evaluated patients >18 years old who underwent URSL for single distal ureteral stone 5-25 mm in diameter from March 2015 to October 2016. The patients were evaluated with NCCT before URSL. The exclusion criteria were stones of <5 or >25 mm in diameter, obstructive and multiple stones, stones requiring emergency drainage (fever, Systemic Inflammatory Response syndrome, sepsis, urinary tract infection), patients with solitary kidney and patients with congenital urinary tract anomalies. Mid-proximal ureteral stones were also excluded. NCCT images using 2 mm sections with the liver's dome as cranial border and the pubis joint as caudal border at 100 mA 120 kV (Brilliance 64, Philips®, Best, The Netherlands) were taken. All NCCT findings were evaluated by a radiologist. Stone diameters (longitudinal and transverse) were calculated in 2 different planes and the maximum diameters of the stones were taken into consideration. Stone volumes were measured using a computer programme. HU values were measured as previously described by Celik et al. (12) for the largest diameter of the stone (longitudinal or transverse) with bone window and large magnification. After serial measurements of the highest HU value (HUmax) and the lowest HU value (HUmin), HU value was calculated as the average of these two values (HUave). The difference in HU (HUdiff) was calculated as the difference between the HUmax and the HUmin values, as previously defined by Celik et al. (14,15) Hounsfield density (HD) was calculated as HUmax divided by stone size (16). All URSL treatments were performed with a 8/9.8 F rigid ureteroscope (Karl Storz®, Tuttlingen, Germany), 365 µm PercuFib or 550 µm RigiFib laser probes (LISA® laser products OHG, Katlenburg-Lindau, Germany) and a 80 watt Ho:YAG laser device (Sphinx®, Livermore, CA, USA). Laser probe was randomly selected during the the operation. Stone fragmentation was monitored using the Storz endovision system (Karl Storz®, Tuttlingen,

Germany) throughout the procedure. All laser procedures were performed with 1.5 joules energy, 12 watts power and 8 hertz frequency. Usage of forceps and/or basket catheter and the data on obstruction (no obstruction/partial obstruction/complete obstruction) and impaction (no impaction/partial impaction/complete impaction) were noted according to URS observation during the procedure. The total laser energy level, laser time, URS time and operative time were noted at the end of the operation. Necessity of J stent placement was decided according to the operation findings. Status of stone impaction and obstruction and J stent placement were also noted. URSL success was defined as SF (absence of all of clinical significant and insignificant stones) status at the end of the operation.

Statistical Analysis

Success status was evaluated as SF and residual fragments (RF). Type of laser probe used was also evaluated and divided into two groups as 365 and 550 µm laser probe groups. Data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) software program. Nonparametric correlations between possible predictive parameters for URSL success were compared by using Pearson's correlation coefficient. The Mann-Whitney U test and Pearson chi-square test were used to compare demographic and radiologic parameters between 365 and 550 µm groups. Data are given as mean ± standard deviation. However, the results of analysis are given as median data. Statistical significance was defined as $p<0.05$.

Results

A total of 72 patients with distal ureteral stones were included. Patient and stone characteristics are given in Table 1. Correlation between predictive radiologic parameters measured on NCCT images and peroperative URSL data was investigated in all the 72 patients. Correlation results are given in Table 2. In correlation analysis of 72 patients, laser time was strongly correlated with longitudinal and transverse diameters of stone, stone volume, HUmax, HUmin and HUave and negatively correlated with HD. URS time was found to positively correlate with longitudinal and transverse stone diameters and negatively correlate with HD. Laser energy was also positively correlated with only longitudinal stone diameter and negatively correlated with HD. However, energy/time ratio was not found to correlate with any predictive data. Stone diameters, volume and HU measurements were not significantly different between the groups with presence of obstruction and impaction. There were 17 patients in the 365 µm group and 55 patients in the 550 µm probe group. Patients and stone characteristics of the groups and comparison of statistical analysis results are given in Table 3. The rate of patients treated with SWL before the URSL procedure was found to be significantly higher in the 365 µm group compared to 550 µm group ($p<0.05$). There was no significant difference in URSL success rate and other predictive data between the groups. However, in the peroperative data, laser time, laser energy level and laser energy/time ratio were significantly lower in the 365 µm group compared to the 550 µm group ($p<0.05$). After exclusion of patients with previous SWL, 61 patients were evaluated (11 patients in the 365 µm group and 50 patients in the 550 µm group) and almost all parameters were similar between the groups. However, URS time was found to be shorter in the 365 µm group than in the 550 µm group (17.5 min vs 24.4 min, $p=0.036$).

Table 1. Patient and stone characteristics

		All patients (n=72) mean ± SD (minimum-maximum)
Mean age (year)		46.9±13.2 (18.6-71.7)
BMI (kg/m^2)		25.8±3.1 (15.7-32)
Longitudinal diameter of stone (mm)		10.6±3.7 (5-21)
Transvers diameter of stone (mm)		8.3±3.1 (3.5-25)
Stone volume (mm^3)		416.1±578.3 (41.6-3900)
HUmax (HU)		1116.8±281.3 (270-1596)
HUmin (HU)		780.5±257.5 (204-1435)
HUave (HU)		948.6±252.3 (252-1515.5)
HUdiff (HU)		336.3±190.3 (36-824)
HD (HU/mm)		111.8±38.9 (24.8-213.9)
Laser time (min)		9.5±6.1 (1-25)
Laser energy (joule)		2409.9±2928.3 (17-18900)
Laser energy/time ratio (J/min)		218.5±179.5 (2.8-821.7)
URS time (min)		23.6±10.6 (3-50)
Laser probe, n (%)	365 µm	17 (23.6%)
	550 µm	55 (76.4%)
J stent status, n (%)	Yes	49 (68.1%)
	No	23 (31.9%)
Previous SWL status, n (%)	Yes	11 (15.3%)
	No	61 (84.7%)
Obstruction presence, n (%)	No	37 (51.4%)
	Partial	24 (33.3%)
	Complete	11 (15.3%)
Impacte stone presence, n (%)	No	40 (55.6%)
	Partial	21 (29.2%)
	Complete	11 (15.3%)

SD: Standard deviation, BMI: Body mass index, HU: Hounsfield units, HUmax: Highest hounsfield units value, HUmin: Howest hounsfield units value, HUave: The average of hounsfield units values, HUdiff: The difference of hounsfield units values, HD: Hounsfield density, SWL: Extracorporeal shock wave lithotripsy, URS: Ureterorenoscopy

Table 2. Correlation between preoperative predictive radiologic findings and ureteroscopic lithotripsy findings

	Laser time	Laser energy	Laser energy/time ratio	URS time
Age	R=0.199	R=0.106	R=0.031	R=0.169
	p=0.093	p=0.376	p=0.796	p=0.156
BMI	R=0.106	R=0.025	R=0.029	R=0.083
	p=0.376	p=0.833	p=0.811	p=0.490
Longitudinal diameter of stone	R=0.528**	R=0.407**	R=0.188	R=0.409**
	p<0.001	p<0.001	p=0.115	p<0.001
Transvers diameter of stone	R=0.317**	R=0.179	R=0.001	R=0.265*
	p=0.007	p=0.133	p=0.993	p=0.024
Stone volume	R=0.305**	R=0.231	R=0.042	R=0.215
	p=0.009	p=0.050	p=0.724	p=0.070
HUmax	R=0.323**	R=0.193	R=0.135	R=0.207
	p=0.006	p=0.104	p=0.258	p=0.081
HUmin	R=0.278*	R=0.090	R=0.057	R=0.173
	p=0.018	p=0.451	p=0.633	p=0.147
HUave	R=0.322**	R=0.154	R=0.104	R=0.203
	p=0.006	p=0.197	p=0.383	p=0.087
HUdiff	R=0.101	R=0.164	R=0.122	R=0.072
	p=0.397	p=0.169	p=0.307	p=0.547
HD	R=-0.300**	R=-0.242*	R=-0.074	R=-0.312**
	p=0.010	p=0.040	p=0.537	p=0.008

**Correlation is significant at the 0.01 level, *Correlation is significant at the 0.05 level
BMI: Body mass index, HUmax: Highest Hounsfield units value, HUmin: Lowest hounsfield units value, HUave: Average of hounsfield units values, HUdiff: Difference of hounsfield units values, HD: Hounsfield density, URS: Ureterorenoscopy

Discussion

NCCT images provide more information about stone characteristics and stone density including HU measurements. HU measurements have been researched many times to date and an absolute inverse correlation has been found between high HU level and SF rates after SWL, URSL and PNL procedures. (9,10,11,12). Especially for URSL, stone fragmentation during the procedure is the most important factor for laser energy level, laser time and operative time. Therefore, defining the predictive factors affecting stone fragmentation is one of the major areas of research for URSL in recent years. In a recent study designed by Ito et al. (10), 219 patients who underwent URSL procedures for renal stones were retrospectively analyzed. There was a significant difference in the fragmentation efficiency and operative time in favor of the low HUave group (<1061 HU) compared to the high HUave group (≥1061 HU) in URSL procedures for <20.0 mm renal stones (10). However, we agreed with Ofude et al. (13) and we also evaluated both total laser time and URS time because laser time is more predictive than operative time. Ofude et al. (13) found that stone attenuations such as HUave and stone volume predicted laser energy level during URSL with Ho:YAG laser. Also, maximum stone diameter and severe hydronephrosis rate were found to be associated with laser energy amount. However, other radiological findings were not found to predict the laser energy levels, such as HD, whereas HD was found to be inversely correlated with stone volume. Therefore, the authors considered that HD was insufficient as an indicator of stone density. Also, Seitz et al. (17) retrospectively analyzed 543 patients with ureteral stones who underwent URS. The degree of hydronephrosis was found to be positively correlated with stone size (17). In contrast, stone diameter, volume and HU measurements were not found to be significantly different between the groups with presence of obstruction and presence of impaction in our study.

In an important study published by Molina et al. (18), stone volume, presence of renal stone and HD were found to be significantly positively correlated with laser energy level and stone volume and HD were significantly positively correlated with laser time. Also, size of laser probe and laser power setting were found to be positively correlated with laser energy level. In addition, another study reported that increasing laser settings that may increase laser energy level is associated with high intraluminal temperature, potentially causing ureteral tissue injury (19). When we look at our study; first, laser time was strongly correlated with stone diameter, stone volume, HUmax, HUmin and HUave measurements and negatively correlated

Table 3. Patients and stone characteristics in laser probe groups and comparison of preoperative predictors and peroperative laser data between the groups in distal ureteral stones by Mann-Whitney U and Pearson chi-square tests

		Laser probe 365 µm (n=17)	Laser probe 550 µm (n=55)	p
Mean Age (year)		45.8±13.7	47.2±13.1	0.591
BMI (kg/m2)		25.1±3.2	26±3	0.353
Longitudinal diameter of stone (mm)		10.3±3	10.7±3.9	0.968
Transvers diameter of stone (mm)		9±4.3	8±2.7	0.619
Stone volume (mm^3)		470±890.8	399.4±450.9	0.868
HUmax (HU)		1113.9±252.9	1117.7±291.7	0.921
HUmin (HU)		794.4±274.1	776.2±254.7	0.842
HUave (HU)		954.1±248.4	947±255.8	0.974
HUdiff (HU)		319.5±177	341.5±195.5	0.822
HD (HU/mm)		111.5±33.8	111.9±40.6	0.942
Laser time (min)		6.4±4.9	10.5±6.1	**0.007**
Laser energy (joule)		580.8±1028.1	2975.2±3095.6	**<0.001**
Laser energy/time ratio (J/min)		85.8±85.6	259.5±181.4	**<0.001**
URS time (min)		20.6±10.3	24.5±10.6	0.149
Single session URSL success, n	Yes	16	52	0.946
	No	1	3	
Usage of forceps and/or basket catheter	Forceps	12	39	0.888
	Basket	4	11	
	Forceps and basket	1	5	
J stent status, n	Yes	12	37	0.798
	No	5	18	
Previous SWL status, n	Yes	6	5	**0.009**
	No	11	50	
Obstruction presence, n	No	12	25	0.091
	Partial	2	22	
	Complete	3	8	
Impacted stone presence, n	No	12	28	0.192
	Partial	2	19	
	Complete	3	8	

BMI: Body mass index, HU: Hounsfield units, HUmax: Highest hounsfield units value, HUmin: Lowest hounsfield units value, HUave: Average of hounsfield units values, HUdiff: Difference of hounsfield units values, HD: Hounsfield density, SWL: Extracorporeal shock wave lithotripsy. URS: Ureterorenoscopy, URLS: Ureteroscopic lithotripsy

with HD. Second, URS time was found to be positively correlated with stone diameter and negatively correlated with HD. Last, laser energy level was also positively correlated with only longitudinal stone diameter and negatively correlated with HD. In contrast, the energy/time ratio was not found to correlate with any predictive data.

When we look at previous literature on the type of laser probe, Vassar et al. (20) reported that higher energy level was generated by smaller laser fibers than by larger fibers. In our study, in the analysis of laser probe groups, laser time, laser energy level and laser energy/time ratio were found to be significantly lower in the 365 µm group compared to the 550 µm group ($p<0.05$). In addition, the 365 µm probe shortened URS time compared to the 550 µm probe, although not statistically significant. Interestingly, the rate of previous SWL was found to be higher in the 365 µm probe group. Although SWL may affect stones, stone characteristics were found to be similar between the groups in the study. Therefore, all parameters were evaluated after the exclusion of patients with previous SWL. Similar results were achieved and also URS time was statistically shorter in the 365 µm group.

Study Limitations

There are several limitations in this study. The most important limitation is the small number of patients in the study because of the different laser setting selection by different surgeons. Therefore, many patients who underwent URSL with different laser settings for distal ureteral stone were not included in the study. Other limitation is that previous SWL status was different between the groups. However, similar results were achieved after the exclusion of patients with previous SWL. Another limitation is that the distribution of patients according to laser probe selection was not similar between the groups because of the limited number of times the 365 µm probe was used during the study. Nonetheless, the results of this study showed that stone diameter, stone volume and HU parameters measured by NCCT are predictors of laser energy level and laser time. Also, the 365 µm laser probe decreases the laser energy level, laser time and laser energy/time ratio compared to the 550 µm probe.

Conclusion

In conclusion, for URSL procedures, it is important to acknowledge that NCCT measurements of the stone are effective predictive factors for operative time and laser energy level. Thinner probe usage decreases total laser time, laser energy level and laser energy/time ratio. In addition, thinner laser probe shortens URS time. Nevertheless, for clarification of these results further randomised, prospective studies with large series are warranted.

Ethics

Ethics Committee Approval: Dokuz Eylul University Ethics Committee, ethical protocol number: 1966 GOA, 2015/06-16.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç, O.B, I.B., Ö.G., Design: S.Ç, O.B, I.B., Ö.G., Data Collection and/or Processing: S.C, O.B, I.B., O.G., Analysis and/or Interpretation: Ö.D., M.S., A.E., Literature Research: S.Ç, O.B, I.B., Ö.G., Writing: S.Ç., O.B.

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Efficacy and Predictive Factors of the Outcome of Extracorporeal Shock Wave Lithotripsy: A Review of One-thousand-nine-hundred-ninety-seven Patients

Ekstrakorporeal Şok Dalga Litotripsisinin Etkinliği ve Başarısındaki Belirleyici Faktörler: Bin Dokuz Yüz Doksan Yedi Hastanın Derlemesi

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

Extracorporeal shock wave lithotripsy (ESWL) is an easy, effective, reliable and non-invasive method and therefore is an alternative modality to surgery in patients with urinary stone disease. However, with the development of endoscopic treatment methods, it has become less preferred by urologists. ESWL can be used effectively and safely in appropriate patients.

Abstract

Objective: The aim of this study was to evaluate the efficacy and safety of extracorporeal shock wave lithotripsy (SWL) in a large patient group treated with SWL due to kidney stone.

Materials and Methods: Data of 1997 patients, who underwent SWL due to renal stone in the at Atatürk University Medical Faculty Clinic of Urology between 2008 and 2013, were evaluated retrospectively. The effect of age, gender, stone location, size and opacity on SWL success, additional procedure requirement and complication rates were evaluated.

Results: Six hundred eighty-six patients were female and 1311 were male. The overall rate of success of SWL was found to be 82.6%. The rate of success of SWL was 82.1% in female patients and 82.9% in male patients ($p>0.05$). Gender, stone location, stone size and opacity were significant predictive factors for the success of SWL ($p<0.05$). The complication rate in stones >15 mm was 5.8% ($p<0.05$). Age, gender, stone size, stone location and stone opacity were not predictive factors for additional treatment after SWL ($p>0.05$).

Conclusion: Although SWL is less preferred today with the increase of endourological interventions, it remains an effective treatment method in appropriate patients.

Keywords: Extracorporeal shock wave lithotripsy, Urinary stone, Complication

Öz

Amaç: Bu çalışmamızdaki amacımız böbrek taşı nedeniyle ekstrakorporeal şok dalga litotripsinin (ESWL) ile tedavi edilen geniş hasta grubunda etkinliğinin ve güvenirliğinin değerlendirilmesidir.

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Gereç ve Yöntem: 2008-2013 yılları arasında Atatürk Üniversitesi Tıp Fakültesi Üroloji Kliniğinde böbrek taşı nedeniyle ESWL yapılan 1997 hastaya ait veriler retrospektif olarak değerlendirildi. Yaş, cinsiyet, taş lokalizasyonu, taş boyutu ve taş opasitesinin ESWL başarısına etkisi, ek prosedür gereksinimi ve komplikasyon oranları değerlendirildi.

Bulgular: Hastaların 686'sı kadın ve 1311'i erkekti. ESWL'nin tüm hastalardaki başarısı %82,6 olarak bulundu. Kadın hastalarda ESWL başarısı %82,1, erkek hastalarda %82,9 idi (p>0,05). ESWL başarısında cinsiyet, taş lokalizasyonu, taş boyutu ve opasite önemli belirleyici faktörler olarak öne çıktı (p<0,05). Komplikasyon oranı >15 mm ebatlı taşlarda %5,8 ile yüksek bulundu (p<0,05). Ek prosedür gereksiniminde değerlendirilen faktörler arasında anlamlı fark bulunmadı (p>0,05).

Sonuç: ESWL günümüzde endoürolojik girişimlerin artması ile ikinci plana düşse de uygun hastalarda etkili bir tedavi yöntemi olarak değerini korumaktadır.

Anahtar Kelimeler: Ekstrakorporeal şok dalga litotripsi, Taş, Komplikasyon

Introduction

Urinary stone disease is an important public health problem with a prevalence of about 8.8% worldwide. It has been reported that urinary stone disease has an annual health care cost of $3.8 billion in the United States (1). Extracorporeal shock wave lithotripsy (SWL) has been widely accepted as a non-invasive treatment method after it was first described by Chaussy et al. (2) in 1980. With the developments in endoscopic treatment techniques, ureteroscopy has replaced SWL as the most commonly performed treatment for renal stones in recent years. However, SWL is still an important treatment option in patients with stone disease because it is an easy, practical, effective, non-invasive and mostly non-anesthetic treatment method. However, SWL can cause complications such as hemorrhage, infection, hematoma and renal colic. The widespread availability of alternative treatment methods, such as percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS), in urology practice forced urologists to be more careful in SWL indications. In this study, we aimed to investigate the success and side effects of SWL in a large group of patients retrospectively. To our knowledge, this study that investigated the effectiveness of SWL in the highest group of patients in Turkiye and it is among the top ten studies according to the number of patients in the English literature.

Materials and Methods

A total of 1997 patients treated with SWL at Atatürk University Medical Faculty Research Hospital between 2008 and 2013 were evaluated retrospectively. The demographic data of the patients, including age, gender, stone size, stone opacity and stone location, were recorded. Stone size was obtained by measuring the largest diameter in millimeters using ultrasonography (US), X-ray or computed tomography (CT).

All patients were treated using a Siemens Lithostar Modularis device. In our clinic, SWL is not performed in patients with urinary tract infection, stenosis distal to stone, morbid obesity, staghorn stone, aortic aneurysm, cardiac pacemaker and bleeding diathesis and those using antiplatelet agents. All patients were evaluated by X-ray, urinary US and, if necessary, intravenous urography and/or non-contrast CT. Each patient was treated with a minimum of 8 hours of fasting, and a maximum of 3 sessions of SWL. No routine general anesthesia was performed before SWL. However, children and patients, who could not tolerate SWL, were treated with sedation by the anesthesia team before the procedure. The SWL was performed with a dose of 2000-3000 shocks. For each patient, low-energy operation was initiated, and the energy increased by assessing the patient tolerance and whether or not the stone was fragmented. Radiopaque stones were visualized with fluoroscopy, radiolucent stones with special probe integrated into the US device. In patients with radiopaque stones, the stone was checked with fluoroscopy in every 500 shock. In patients with radiolucent stones, the procedure was continuously monitored with US. No routine antibiotic or medical expulsive treatment was performed before or after the treatment. The patients were advised to consume plenty of fluid after the procedure. After the treatment, all patients were given an appointment for SWL. All patients were re-evaluated by kidney, ureter, and bladder (KUB) X-ray or US before the second and third session. The procedure was considered to be successful in patients with no stone fragments or with any stone fragments smaller than 4 mm in size. Stones smaller than 4 mm were considered clinically insignificant stone fragments (3). Patients, who had fragmented stones but were not stone-free, were followed. Patients who had a significant residual stone (>4 mm) or stones not fragmented after SWL were treated with alternative treatment methods. The success of SWL was evaluated according to age, sex, stone location, stone opacity, stone size, complication rate and additional procedure in all patients. The patients were divided into two groups based on age greater or less than 40 years old (3). We also evaluated patients under the age of 18 as a separate group. We defined the stone size range values (<10 mm, 10-15 mm, >15 mm) according to the European Association of Urology (EAU) Guidelines On Urolithiasis and the Study by Politis and Griffith (4). We calculated efficiency quotient (EQ) of SWL in respect to stone location. EQ was assessed using

the following formula EQ = percentage stone free /[100% (1 treatment) + percentage requiring retreatment + percentage requiring auxiliary procedure]×100% (5,6). The problems that required hospitalization after a SWL session were stone-street, severe renal colic or retroperitoneal hematoma. Alternative treatment techniques were recommended in patients without SWL response. Patients who did not accept additional treatment and/or patients with non-obstructive stone were followed up.

Statistical Analysis

The data were analyzed with SPSS version 25.0. The stone-free status was correlated with patient characteristics and various stone features with the aid of t-test and Pearson's chi-squared test. Factors with a significant impact on success rate were further analyzed using multivariate analysis (stepwise logistic regression model with backward elimination using the likelihood ratio) to identify independent predictors of the success of SWL treatment. A p value of less than 0.05 was considered statistically significant.

Results

Of the 1997 patients, 686 (34.3%) were female and 1311 (65.6%) were male. The patients were evaluated in three different age groups: 0-18, 18-40 and >40 years. SWL success rates were 90.2%, 84.5% and 79.2%, respectively (Table 1). Age was a statistically significant predicting factor for SWL success. SWL success rate decreased as the age of the patients increased (p<0.001). The success rate of SWL was 82.1% in male patients and 82.9% in female patients (p>0.05). The rate of success of SWL in the lower pole, middle pole-pelvis and upper pole stones was 73.7%, 83.4%, and 88.5%, respectively. The success rate of SWL was lower in the lower pole than in the middle pole and pelvic stones (p<0.001). SWL success rates for stone groups <10 mm, 10-15 mm and >15 mm were found to be 89.9%, 81.7% and 60.8%, respectively. The rate of success of SWL in radiopaque stones was 80.6%, and in non-radiopaque stones was 88.6% (p<0.001) (Table 1).

Four factors (age, stone location, stone opacity and stone size) were further analyzed using a logistic regression model, which resulted in the exclusion of the nature of the stones from the model, while the other prognostic factors maintained their statistically significant effect on ESWL outcome, indicating that they acted independently (Table 1). The sensitivity of the model was 60.7%, the specificity 83.2% and the overall accuracy was 82.9%. Using the regression model, we can define the stone-free ratio of a certain category in comparison to the reference category (Table 1), as Exp (B) sets for the odds ratio. For example,

Table 1. Demographic data and stone parameters were provided with stepwise logistic regression model

Variable	n	Stone free n (%)	p value of chi-square test	B[a]	Exp B[b]	p value of regression analysis
Age (year)						
0-18*	315	284 (90.2)	<0.001	0	1	0.006
18-40	634	536 (84.5)		0.632	1.881	0.003
>40	1048	830 (79.2)		0.237	1.267	0.086
Gender						
Female*	686	563 (82.1)	0.636	Not studied within the logistic regression model		
Male	1311	1087 (82.9)				
Localization						
Lower pole	357	332 (73.7)	<0.001	0.616	1.851	0.000
Mid pole-pelvis	1265	1055 (83.4)		0.873	2.393	0.000
Upper pole*	375	263 (88.5)		0	1	0.000
Opacity						
Radiopaque*	1488	1199 (80.6)	<0.001	0	1	
Radiolucent	509	451 (88.6)		-0.493	0.611	0.002
Size (mm)						
<10 mm*	703	632 (89.9)	<0.001	0	1	0.000
10-15 mm	1105	903 (81.7)		1.593	4.917	0.000
>15 mm	189	115 (60.8)		0.970	2.637	0.000
Total/constant	1997	1650 (82.6%)		0.243	1.275	0.304

NS: Not significant
[a]Regression coefficient, [b]Stone-free rate when the category of a certain variable is compared to the reference category which is indicated with*

the probability of stone-free status is 4.917 times greater for patients with stones 10-15 mm in size in comparison to patients with stones <10 mm in size.

68 patients had stone-street, 4 patients had renal hematoma and 2 patients had urinoma after procedure. The complication rate was found to be 5.8% in stones >15 mm (p<0.001) (Table 2). A total of 141 patients underwent additional procedures as complementary or secondary to complications. 49 patients were treated with ureterorenoscopy, 49 patients with PCNL, 42 patients with double J stent placement and 1 patient with ureterolithotomy (Table 3). In our study, it was observed that age, gender, stone location, stone size and opacity parameters did not create any statistically significant difference in the need for additional procedure (p>0.05).

EQ values were calculated based on stone locations. EQ rates were 45.7% for lower pole, 55.9% for middle pol-pelvis, 65% for upper pole and total EQ was found to be 55.5% (Table 4).

Table 2. Complication rates with demographic data and stone parameters

	Number (n)	Complication (%) (n)	p
Age (year)			
0-18	315	0.6% (2)	0.063
18-40	634	1.9% (12)	
>40	1048	2.8% (29)	
Gender			
Female	686	2.9% (20)	0.090
Male	1311	1.8% (23)	
Localization			
Lowerpole	357	3.4% (12)	0.155
Midpole-pelvis	1265	2.1% (26)	
Upperpole	375	1.3% (5)	
Opacity			
Radiopaque	1488	2.3% (34)	0.488
Radiolucent	509	1.8% (9)	
Size (mm)			
<10 mm	703	1.0% (7)	0.001
10-15 mm	1105	2.3% (25)	
>15 mm	189	5.8% (11)	
Total	**1997**	**2.1% (43)**	

Discussion

SWL has been recognized as a safe and non-invasive treatment method for ureteral stones smaller than 20 mm and uncomplicated kidney stones since its introduction in the 1980s. In most cases, SWL can be performed without anesthesia or with minimal anesthesia (7). Many studies have shown that factors such as stone size, skin-to-stone distance, severity of obstruction, obesity, urinary tract anatomy and the type of device used are effective in predicting SWL success. As we retrospectively evaluated the data, we could not provide data for stone density, distance, energy applied per session and obesity. In our study, the effect of age, gender, stone size, location and opacity on SWL results was evaluated. The effect of the age factor on SWL success is controversial. In a few studies, the age factor was found to be important in predicting SWL

Table 3. Additional procedure with demographic data and stone parametres

	Number (n)	Additional procedure (%) (n)	p
Age(year)			
0-18	315	7.6% (24)	0.516
18-40	634	7.0% (45)	
>40	1048	6.8% (72)	
Gender			
Female	686	7.4% (51)	0.692
Male	1311	6.8% (90)	
Localization			
Lowerpole	357	7.8% (28)	0.584
Midpole-pelvis	1265	7.0% (89)	
Upperpole	375	6.4% (24)	
Opacity			
Radiopaque	1488	7.3% (108)	0.556
Radiolucent	509	6.5% (33)	
Size (mm)			
<10 mm	703	6.0% (42)	0.372
10-15 mm	1105	7.6% (84)	
>15 mm	189	7.9% (15)	
Total	**1997**	**7.1% (141)**	

Table 4. Efficiency quotient of shock wave lithotripsy in respect to stone location

Stone location	Patients (n)	No. of stones retreated (%)	No. of additional procedures (%)	No. of stone free (%)	Effectiveness quotient (%)
Lower	357	190 (53.2)	28 (7.8)	332 (73.7)	45.7
Mid-pelvis	1265	533 (42.1)	89 (7.0)	1055 (83.4)	55.9
Upper	375	111 (29.6)	24 (6.4)	263 (88.5)	65
Total	1997	834 (41.7)	141 (7.1)	1650 (82.6%)	55.5

success (8). In a study evaluating 3023 patients treated with SWL, stone free rates were reported to be significantly lower in the elderly patient group (9). In another similar study evaluating 2954 patients who underwent SWL for kidney stones, stone-free rates were reported to be significantly low in patients over the age of 40 years (3). In our study, it was observed that SWL success decreased with age ($p<0.001$).

In a study evaluating 235 adult patients treated with SWL, gender was reported as a predicting factor for SWL success. In this study, the rate of success of SWL in men was 82.4% and 66% in women (8). In a retrospective study of 145 patients, age, gender and stone location were not statistically significant in predicting SWL success (10). In our study, there was no significant difference in SWL success between female and male patient groups ($p>0.05$).

Stone location is another important predicting factor for SWL success. In the EAU Guidelines, SWL is recommended as a first-line treatment with RIRS for renal pelvis, middle and upper pole stones smaller than 2 cm. In a meta-analysis evaluating SWL, PCNL and RIRS results, PCNL was found to be more effective at the end of three months, but the duration of treatment, the need for additional treatment and the duration of hospital stay were lower in the SWL group. There was no significant difference between SWL and RIRS results in the same meta-analysis (11). In many studies, high success rates for treatment with SWL have been reported in upper, middle and pelvic stones. However, the best treatment for lower pole stones is still controversial (7). In the literature, the results of SWL for lower pole stones are variable. Stone-free rates for SWL-treated lower pole stones have been reported to be between 47% and 84% (8). There are also studies that have different interpretations of the low success rate in SWL for lower pole stones. Nafie et al. (12) reported a stone-free rate of 49% in lower pole stones; but in this study, the low stone-free rate was attributed to a large number of patients with lower pole stones (43.3%). In a study of 246 patients with lower pole stones, stone size was reported to be an important predictive factor for SWL success rather than lower pole caliceal anatomy (13). In another study conducted on 714 renal units of 687 patients investigated for isolated calyceal stones, no significant difference was found between treatment of lower, middle or upper pole stones (14). In our study, stone location was prominent as a predictive factor. We found SWL to be more successful in upper pole and middle pole-pelvis stones than those in the lower pole ($p<0.05$).

In their meta-analysis, Torricelli et al. (15) emphasized that stone size was an important predictive factor for SWL success. In a study of Al-Ansari et al. (16), the success rate in SWL in stones of less than and above 10 mm was reported to be 90% and 70%, respectively. Furthermore, in the same study, the authors reported that SWL treatment was more successful in patients with single stone than in those with multiple stones ($p<0.01$). SWL success was found to be significantly higher in single and middle pole stones (16). In the present study, SWL success in patients with stones <10 mm, 10-15 mm and 15 mm was 89.9%, 81.7% and 60.8%, respectively ($p<0.001$). We concluded that SWL success rate decreased significantly as the stone size increased. According to our study, other minimally-invasive treatments, such as PCNL and RIRS, may be recommended as first-line treatment in patients with stones greater than 15 mm located in the lower pole.

Elbahnasy et al. (17) reported inferior pole infundubulopelvic (LIP) angle, infundibular length (IL) and infundibular width to be more important in predicting SWL success. In their study, the patients with LIP angle >70°, IL <3 cm and IW >5 mm were found to be excellent candidates for SWL. Same study suggested to offer PCNL or URS to patients with lower pole stones less than 17 mm and unfavorable anatomies (LIP angle <70° and IW <5 mm or IL >3 cm) as SWL success is low in such patients. SWL success rates are adversely affected in patients with congenital renal abnormalities, stone density greater than 1000 Hounsfield Units and a skin-to-stone distance greater than 9 cm (16,18). Compared to SWL, RIRS and PCNL are more invasive treatment options in pediatric patients. Thus, for any pediatric patient, SWL should be preferred if they are eligible for the treatment. Considering the smaller body size of pediatric patients, higher SWL success rates could be due to shorter skin-to-stone distance. Therefore, SWL must be chosen as the first-line treatment in pediatric patients whenever possible.

Some radiological parameters have been evaluated for their ability to predict stone fragility. Bon et al. (19) reported that smooth, uniform calculi that seems denser than bone on KUB responded poorly to SWL. Mandhani et al. (20) concluded in their study that the patients with high stone mineral content should be offered other treatment methods rather than SWL. In our study, the rate of success of SWL in 509 patients with radiolucent stone and 1488 patients with radiopaque stone was 88.6%, and 80.6%, respectively. The success of SWL was statistically significant in patients with radiolucent stone ($p<0.05$). We assume that the lower mineral content of radiolucent stones and US monitoring during the procedure played a role in the success of SWL.

SWL has several advantages over other minimally-invasive surgical techniques. In a meta-analysis by Junbo et al. (21), it has been reported that SWL offered shortest length of hospital stay and shorter operative time compared to PCNL and RIRS. SWL usually can be applied without anesthesia especially in adult patients. Also cost of operation is another important superiority of SWL. We calculated costs of SWL, RIRS and PNL separately by the fees of Turkish Social Security Institution. 3 sessions of SWL

cost about $85, 1 session of RIRS about $160 and 1 session of PNL costs about $510.

Study Limitation

The study has some limitations. We could not provide data for stone density, skin-to-stone distance, energy applied per session and obesity due to the retrospective design of the study. A follow-up was not done following the last treatment session. Previous treatments were not recorded in the data collection phase.

Conclusions

The widespread availability and effectiveness of alternative minimally-invasive treatment modalities in urinary stone disease makes us prefer SWL less. However, SWL is a non-invasive treatment that should always be kept in mind because of its high success in suitable stones. In our study, age, stone location, size and opacity were prominent predictive factors for SWL success.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: H.K., Design: H.K., Data Collection and/or Processing: H.K., A.H.Y., Analysis and/or Interpretation: H.K., F.Ö., Literature Research: H.K., Writing: H.K., Ç.A.Ş., Y.T.

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Simultaneous Measurement of Pressure in the Calyces During RIRS in a Human Cadaver Model

İnsan Kadavra Böbrek Modelinde RIRS Sırasında Kalikslerin Eş Zamanlı Basınç Ölçümü

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

In previous studies in literature, intrarenal pressure measurement has been made at the renal pelvis level. To the best of our knowledge, there has been no study in the English literature that has shown whether the renal pelvis pressure is reflected at the same level in the renal calyces or that has evaluated the effect of the pressure in the examined calyx on the other calyces.

Abstract

Objective: The aim of this study was to evaluate calyceal pressure caused by irrigation of the upper, mid and lower calyces in a cadaver kidney model and to examine the interactions.

Materials and Methods: The kidney was dissected together with the ureter from a human cadaver from a 75-year-old without a history of renal disease. Catheters were placed in the bases of the calyces to perform pressure measurements. After recording baseline pressures while the flexible ureteroscope working channel was empty during irrigation, pressures were then measured by administering fluid with a hand pump, 5 cc and 50 cc syringe. Then, 272 µ and 350 µ laser probes were placed in the flexible ureteroscope and, after recording the baseline calyceal pressures, the measurements were repeated 3 times during hand pump irrigation.

Results: Lowest calyceal pressures were measured when a 300 µ laser probe in the working channel of the flexible ureteroscope was placed in the upper calyx during irrigation at 60 cm H2O. Independent of the location of the flexible ureteroscope, the pressure in all the calyces was observed to be ≥50 mmHg during all types of fluid irrigation. All the calyceal pressures were observed to be affected by each other. The pressure within the calyx where the flexible ureteroscope was located was statistically significantly higher than in the other calyces ($p<0.001$).

Conclusion: Application of additional fluid irrigation during flexible ureteroscopy causes a serious increase in intrarenal pressure. If fluid irrigation is to be applied, it should be done using a very small amount of fluid and for a very short duration.

Keywords: Intrarenal pressure, Retrograde intrarenal surgery, RIRS, Calyx pressure

Öz

Amaç: Çalışmamızda kadavra böbrek modelinde üst, orta ve alt kalikste farklı irrigasyon uygulamaları ile oluşan kaliksiyel basınçları ve birbirleri ile etkileşimlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Yetmiş beş yaşında bilinen böbrek hastalığı öyküsü olmayan insan kadavra böbreği üreteri ile birlikte diseke edildi. Kateter uçları kaliks tabanına gelecek şekilde yerleştirildi. Flexible ureteroskop çalışma kanalı boş iken bazal basınçlar kayıt edildikten sonra pump, 5 cc ve 50 cc enjektör ile sıvı verilerek basınçlar ölçüldü. Daha sonra flexible ureteroskopun içinden 272 ve 350 µ lazer probu yerleştirilerek bazal ve pump yapılarak 3 kez aynı işlemler tekrarlandı.

Bulgular: Tüm kalikslerin basınçları en düşük 60 cm H20 irrigasyon sırasında flexible urs üst kalikste çalışma kanalı 300 µ lazer var iken ölçüldü. Flexible URS lokalizasyonundan bağımsız olarak uygulanan her türlü sıvı irrigasyonunda tüm kalikslerde basıncın 50 mmHg ve üzerine çıktığı izlendi.

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Tüm kaliks basınçlarının birbirinden etkilendiği gözlendi. Flexible URS'nin bulunduğu kaliks içinde basınçlar diğerlerinden daha yüksek ölçüldü ve bu istatistiksel olarak anlamlı idi (p<0,001).
Sonuç: Flexible ureteroskopi sırasında ek sıvı irrigasyonu yapılması böbrek içi basınçlarında ciddi artışa neden olmaktadır. Sıvı irrigasyonu yapılacaksa çok kısa süreli ve mümkün olduğunca az uygulanmalıdır.
Anahtar Kelimeler: İntrarenal basınç, Retrograd intrarenal cerrahi, RIRC, Kaliks basınç

Introduction

Technological developments in flexible ureteroscopy (fURS) aim to increase image quality (1,2,3). By increasing pixel resolution of digital ureteroscopes, it is aimed to obtain better vision. However, even though developments in optical sources continue, another factor defining vision quality during ureteroscopy is fluid irrigation. Especially during stone breakage with laser, the stone dust cloud disrupts the view and it is attempted to correct this with fluid irrigation. Irrigation may lead to an increase in intrarenal pressure. The use of a ureteral access sheath is recommended to decrease elevated intrarenal pressure (4). There are reports showing that even if a ureteral access sheath is used, intrarenal pressures reach a critical level (5). In previous studies in the literature, intrarenal pressure measurement has been made at the renal pelvis (6,7). To the best of our knowledge, there has been no study in the English literature investigating whether the renal pelvis pressure was reflected at the same level in the renal calyces or evaluating the effect of the pressure in the examined calyx on the other calyces.

The aim of this study was to evaluate calyceal pressure caused by irrigation of the upper, mid and lower calyces in a cadaver kidney model and to examine the interactions.

Materials and Methods

The kidney was dissected together with the ureter from a human cadaver of a 75-year-old without a history of renal disease. An Elite Flex (Istem Medikal, Ankara, Turkiye) 10/12 Fr, 35 cm ureteral access sheath was placed in the ureteral lumen below the ureteropelvic junction and the sheath was fixed to the lumen with a 2.0 vicryl suture. The calyx structures were identified with retrograde pyelography. Under fluoroscopic guidance, catheters were placed in the upper, mid and lower calyces for pressure measurements. The pressure values were recorded by attaching the catheters to a Dräger Fabius plus XL (Dräger Medical GmbH, Germany) arterial pressure monitor (Figure 1). A Storz Flex-x^{2s} (Tuttlingen/Germany) flexible ureteroscope was rotated to the pelvis, the upper calyx, the mid calyx and the lower calyx. The catheters were observed to be placed within the calyx structures. The ends of the catheters were placed to be at the base of the calyx.

The calyceal pressure where the measurement was made and the simultaneous pressures formed in the other calyces were recorded during the measurement process. After recording the baseline pressures while the flexible ureteroscope working channel was empty during irrigation at 60 cm H_2O level, pressures were then measured by administering fluid with a hand pump, and 5 cc and 50 cc syringe. Each procedure was repeated 3 times; irrigation was applied for about 3 sec and repeated when the pressure levels reached the baseline levels. Maximum pressure values were noted and average pressure values were calculated. Then, 272 and 350 µ laser probes were placed inside the working channel of the flexible ureteroscope and after recording the baseline calyceal pressures, the measurements were repeated 3 times during hand pump irrigation.

Statistical Analyses

Statistical analyses of the study data were made using IBM SPSS Statistics 21.0 software (IBM SPSS Statistics for Windows, version 21.0 (2012 release) Armonk, NY, USA). Conformity of the data to normal distribution was evaluated using the Shapiro-Wilks test. In the comparison of values at different measurement times, the Wilcoxon test was used when there were 2 groups and the Friedman test when there were 3 or more groups. For repeated measurements, the two-way repeated measures ANOVA (one factor repetition) was applied. Pearson's chi-square test was used to analyse the cross-tables formed. A p value of less than 0.05 was considered statistically significant.

Results

Figure 1. Simultaneous measurement of pressure of the calyces on cadaver kidney model

In this study, the lowest pressures in all the calyces were measured when a 300 µ laser probe in the working channel of the flexible ureteroscope was placed in the upper calyx during irrigation at 60 cm H_2O. The pressures were measured to be <10 mmHg. The highest calyceal pressure values were measured when the pump was applied in the middle calyx while the working canal was empty and the flexible ureteroscope was in the pelvis. The pressures were >100 mmHg (Figure 2).

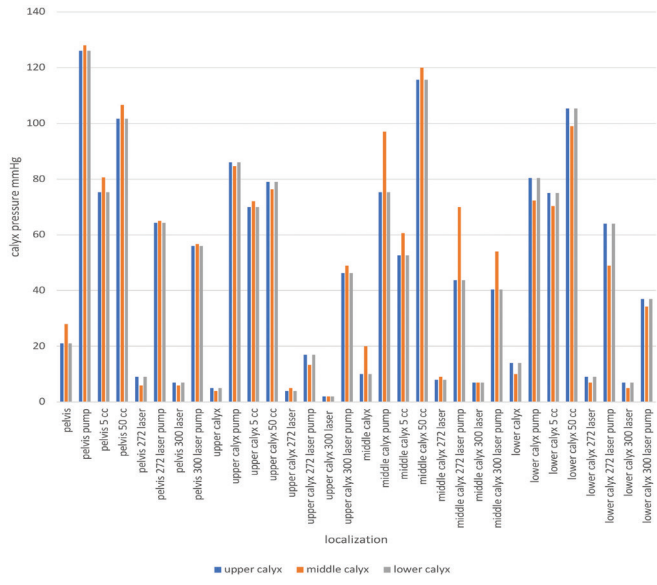

Figure 2. Average pressure of calices

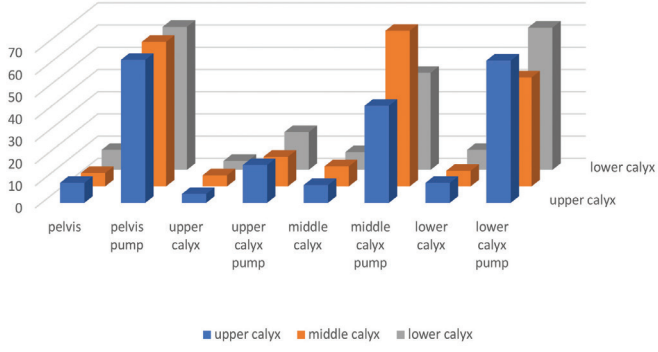

Figure 3. Working chanel with 272 µ laser

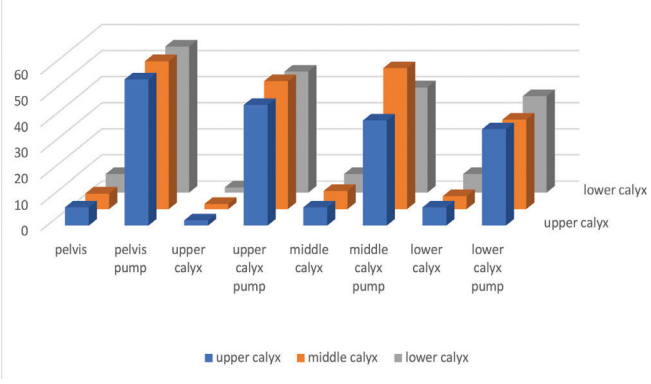

Figure 4. Working chanel with 300µ laser

Independent of the flexible ureteroscope location, the pressure in all the calyces was observed to be ≥50 mmHg during all types of fluid irrigation (p=0.610). With 5cc irrigation, there was a 12.98-fold increase in the risk of pressures >50 mmHg in all the calyx groups even with a laser probe in the working canal, compared to the baseline pressure measurements (p<0.001). The greatest difference in the measurements made with 5 cc irrigation and when the working canal was empty was observed to be in the upper calyx group (p<0.001).

Using a hand pump together with 272 µ laser created a 4.27-fold increase in the risk of developing pressures more than 50 mmHg compared to baseline value with 272 µ laser. A difference was observed in all the calyx groups during the procedure with the greatest difference when the flexible ureteroscope was in the pelvis (p<0.001) (Figure 3).

Using a hand pump together with 300 µ laser created a 2.89-fold increase in the risk of developing pressures >50 mmHg compared to the baseline value (p<0.001). A difference was observed in all the calyx groups during the procedure with the greatest difference when the flexible ureteroscope was in the ureter. The lowest difference was observed when the flexible ureteroscope was in the lower calyx (p<0.001) (Figure 4).

All the calyceal pressures were observed to be affected by each other. The pressure within the calyx where the flexible ureteroscope was located was found to be statistically significantly higher than in the other calyces (p<0.001). When the flexible ureteroscope was located in the pelvis and the upper and mid calyx, the highest pressures were reached with pump applied while the working canal was empty, and the highest pressure was obtained with 50 cc irrigation when the flexible ureteroscope was in the lower calyx (p<0.001).

Discussion

Endoscopic imaging and treatment of the upper urinary system is greatly facilitated with fURS. It is the first-line recommended method in the guidelines for the treatment of upper urinary system stones in particular (8). However, there are still some problems associated with the currently increasing widespread use of this method. In this respect, there are developments in finer instruments, digital camera systems to increase image quality, the use of different laser probes and endoscopic basket catheters specific for this procedure. While developments are increasing success of the procedure, there are also ongoing studies investigating the effects on kidney.

Fluid irrigation applied to increase the vision quality causes an increase in intrarenal pressure. Under physiological conditions,

the intrarenal pelvic pressure has been reported to vary between 0 mmHg and 15 mmHg (5). When a ureteral access sheath with a semi-rigid or flexible ureteroscope, intrarenal pressure has been reported to increase to 100-300 mmHg with irrigation (5,9). Auge et al. (10) evaluated intrarenal pressure with measurements made via a nephrostomy catheter in different ureter segments without the use of a ureteral access sheath and determined a decrease of 57%-75% in intrarenal pressure with the use of a ureteral access sheath. There is a greater reduction in intrarenal pressure with larger sized ureteral access sheaths. However, even though the use of a large ureteral access sheath may lead to lower intrarenal pressure, there is an increased risk of ureteral damage (11). Al-Qahtani et al. (12) reported the ideal access sheath diameter to be 10/12 Fr. For this reason, we used 10/12 Fr ureteral access sheath in the study.

As it is known from animal and human studies, with an increase of intrarenal pressure to 20-30 mmHg, pyelo-tubular backflow develops and blood circulation of the kidney decreases (13,14). When intrarenal pressure increases to 30-50 mmHg, the pyelovenous backflow becomes more evident and an increase in both pyelosinus and pyelolymphatic pressures results in forniceal rupture (14,15). It has been reported that a pelvic pressure of ≥30 mmHg during rigid nephrolithotomy was associated with higher pain score and longer hospital stay (16). Therefore, pyelo-tubular and even pyelovenous and pyelolymphatic backflow almost always occurs with the intrarenal pressure seen during routine fURS, and this can potentially cause infectious and hemorrhagic complications in addition to impaired renal function (5). In the current study, even in the presence of a laser probe in the working canal, pressures were observed to be ≥50 mmHg in all types of additional fluid irrigation.

In association with increasing intrarenal pressure, fluid passes into the bloodstream. Guzelburc et al. (17) reported that fluid absorption ranged between 20 mL and 573 mL in patients undergoing RIRS. An increased fluid volume can create problems in cardiac patients and those with renal failure. In the current study, there was fluid extravasation from the kidney parenchyma during the procedure. According to the results of this study, administration of diuretics may be recommended in the presence of contraindications found during fURS to avoid fluid overload and to reduce the risk of parenchymal fluid transfer. In the current study, it was observed that the calyceal pressures were increased during fluid administration with flexible ureteroscope while the working canal was empty. It is recommended to avoid fluid irrigation while the working canal is empty during fURS. Long duration of irrigation can increase the risk of the development of complications. Intrarenal pressure was observed to significantly increase even during irrigation made using a 5 cc syringe. All the calyceal pressures were observed to be affected by each other. It is possible to reach high pressures even with a small amount of fluid due to low renal pelvic capacity. Different results can be obtained in different pelvic volumes. The lowest pressures in the calyces were obtained with a 300 µ laser probe in the 3.6 Fr working channel of the fURS. As the diameter of the laser fiber increases, the amount of fluid passing through the working channel decreases and the intrarenal pressure remains low. However, in our study additional 5 cc fluid applications were sufficient to increase intrarenal pressure. When a manual pump is used in clinical practice, the applied force will be different every time, resulting in different amounts of fluid. Waiting for intra-renal pressure to decrease after each additional fluid applied for dust removal may be a solution to avoid possible complications.

Different approaches for reducing intrarenal pressure can be found in the literature. In a study performed in a porcine model by Zhu et al. (18), success was reported in maintaining low renal pelvic pressure with flexible ureteroscope at different flow rates with the use of a smart pressure control device. In the same study, following perfusion applied while the flexible ureteroscope was in the upper calyx, the upper calyceal pressure was temporarily higher than the pelvic outlet pressure. Huang et al. (19) successfully treated patients with a solitary kidney and upper urinary tract calculus by protecting low renal pressure using a device with a suction system. With endoluminal application of 0.1 µg/mL isoproterenol to reduce intrarenal pressure, Jung et al. (9) reported that intrarenal pressures were reduced without any cardiac side-effects.

Study Limitations

There are some limitations in the current study. The measurements were made on a single cadaver kidney. The effect on pressures in different calyx structures and length of the calyx neck could not be evaluated. As this was a cadaver kidney, the tissue elasticity and resistance were different from that of a normal kidney. Therefore, the pressures in this study may be different than in those in routine procedures. Fluid extravasation during the procedure caused a decrease in the measured calyceal pressures, and the amount of fluid returning from the access sheath could not be evaluated because of the extravasation. Fixing the sheath to the ureteropelvic junction with suturing may also affect the pressures. In addition, the effect of different diameters of ureteral access sheaths on calyceal pressures could not be evaluated.

Conclusion

Application of additional fluid irrigation during fURS causes a serious increase in intrarenal pressure. Even in irrigation made using a 5 cc syringe, intrarenal pressure was found to be significantly increased. If fluid irrigation is to be applied, it

should be done using a very small amount of fluid and for a very short duration. During fURS, diuretics can be useful for avoiding fluid overload. Although the upper calyx is the most affected, there the pressure may increase in all calyces.

Ethics

Ethics Committee Approval: There is no need ethics committee approve for cadaveric study.

Informed Consent: You can't get a consent if you can do cadaver work.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection and/or Processing: Z.Ö., Ö.B., C.K., Analysis and/or Interpretation: Ö.B., C.K., Literature Research: A.A., Ö.B., Writing: A.A. Content and Supervision: U.Ö., M.S.

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

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Evaluation of the Prognostic Value of Preoperative Neutrophil-to-lymphocyte Ratio in Renal Cell Carcinoma

Renal Hücreli Kanserlerde Preoperatif Nötrofil Lenfosit Oranının Prognostik Belirteç Olarak Değerlendirilmesi

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

Neutrophil/lymphocyte ratio (NLR) has been investigated as a prognostic marker in many cancers. In this article we aimed to investigate the prognostic value of NLR in renal cell carcinoma.

Abstract

Objective: To investigate the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in renal cell carcinoma (RCC).
Materials and Methods: Preoperative NLR value in 125 patients who underwent surgical treatment for renal tumor between January 2012 and September 2017 and and received the pathological diagnosis of RCC, was evaluated. The patients were initially divided into two groups as patients with and without metastases at the time of diagnosis.
Subsequently, the patients were divided into two groups according to the pathological stage. In the first group, patients with localized RCC (pT1 and pT2) were evaluated and in the other group, those with advanced RCC (pT3 and pT4) were evaluated, and then, these two groups were compared.
Results: The mean NLR was higher in group with metastasis than in group without metastasis at the time of diagnosis (4.4±2.8 and 2.9±1.6, respectively; p=0.029). When a NLR of 3.1 was taken as the cut-off value; it was observed that the NRL value in 7 of 8 patients with metastasis at diagnosis was above 3.1. (p=0.002, OR=14.6). Overall survival was 59.8±2.7 months and 49±4.5 months in patients with a NLR of <3.1 and >3.1, respectively (p=0.045).
Conclusion: We assume that preoperative NLR can be evaluated as a prognostic marker for overall survival in patients with RCC.
Keywords: Renal cell carcinoma, Neutrophil-to-lymphocyteratio, Prognostic marker

Öz

Amaç: Renal hücreli kanserlerde (RHK) prognostik belirteç olarak nötrofil lenfosit oranının (NLO) etkinliğini araştırmak.
Gereç ve Yöntem: Ocak 2012 - Eylül 2017 tarihleri arasında böbrek tümörü nedeniyle cerrahi tedavi uygulanan ve RHK patolojisi olan 125 hastanın preoperatif NLO'su değerlendirildi. Hastalar ilk tanı anında metastaz olanlar ve olmayanlar olarak iki gruba ayrıldı. Ardından hastalar patolojik T evresine göre iki gruba ayrıldı. İlk grupta T1 ve T2 evreli lokalize hastalar, diğer grupta T3 ve T4 evreli invaziv hastalar değerlendirilerek veriler bu iki grup arasında karşılaştırılarak incelendi.
Bulgular: NLO tanı anında metastazı olan grupta, metastazı olmayan gruba oranla daha yüksekti (sırasıyla 4,4±2,8 ve 2,9±1,6; p=0,029). NLO=3,1 değeri sınır değer olarak alındığında tanı anında metastatik olan 8 hastanın 7'sinin değeri 3,1'in üzerinde olduğu gözlendi (p=0,002, OR=14,6). NLO <3,1 olan hastalarda genel sağkalım 59,8±2,7 ay iken NLO >3,1 olan hastalarda 49±4,5 ay olarak saptandı (p=0,045).
Sonuç: Bu çalışmada preoperatif NLO, RHK hastalarında genel sağkalım açısından prognostik belirteç olarak değerlendirilebileceği gösterilmiştir.
Anahtar Kelimeler: Renal hücreli kanser, Nötrofil lenfosit oranı, Prognostik belirteç

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Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers, and is the most common genitourinary malignancy after prostate and bladder cancer (1). As a result of the increased widespread use of computed tomography (CT) and ultrasonography (USG), the frequency of incidental identification of early stage tumors has increased (2,3). Nearly 8% of patients with localized disease, who undergo partial or radical nephrectomy, develop metastatic disease during follow-up (4). A variety of models based on clinicopathological findings, such as TNM stage and Fuhrmann nuclear grade have been developed to estimate the outcomes for RCC patients to determine postoperative risks and to develop individualized treatments (5,6). Other well-known prognostic factors are lymphocyte infiltration and histological subtype. However, not all of these prognostic factors are reliable (7). In clinical practice, a prognostic factor will have a great potential if it is easily evaluated, cheap and can be used in routine practice.

Many studies have shown the role of local and systemic inflammation in the development of cancer metastasis (8). Due to this effect, neutrophil-to-lymphocyte ratio (NLR) has been assessed as an independent prognostic factor for inflammation and many cancer types (9). A high NLR has been defined as a prognostic factor for poor overall survival, disease-free survival and progression-free survival in cancer patients (9). Our aim in this study was to assess the prognostic value of preoperative NLR in predicting survival and tumor recurrence in RCC patients.

Materials and Methods

Records of 153 patients, who underwent surgical treatment due to kidney tumors at our clinic from January 2012 to September 2017, were retrospectively analyzed in accordance with the ethical principles of the Helsinki Declaration. Twenty-eight patients, including 10 with benign results, 8 with urothelial carcinoma, 1 with lymphoma and 9 with missing data, were excluded from the study. The remaining 125 patients were included in the study.

Demographic data (age and sex), preoperative radiological findings (presence of invasion and metastasis at the time of diagnosis), preoperative laboratory data (serum neutrophil and lymphocyte levels and neutrophil/lymphocyte ratio), operation data, operation side, pathologic data (pathologic T stage, tumor size, Fuhrmann nuclear grade, tumor histology) and postoperative follow-up data (follow-up imaging) were investigated. All patients were assessed preoperatively with thoracic, abdominal and pelvic CT. According to the pathologic T stage determined by the 2010 TNM classification system, cellular evaluation was made using the Fuhrmann grading system (10,11). Preoperative full blood count was evaluated 1 day before the operation with no blood transfusion, no active infection or fever. Preoperative NLR was calculated by dividing neutrophil count by lymphocyte count.

For patient follow-up, the kidney tumor follow-up protocol stated in the EAU 2010 guidelines was used (12). Accordingly, low-risk patients (pT1a, pT1b) underwent USG and chest X-ray once every 6 months in the first postoperative year and once a year after that. Intermediate-risk patients had thoracic and abdominal CT at 6 months, 2 and 5 years postoperatively and annual USG and chest x-ray at 1, 3, 4 and 5 years postoperatively. High-risk patients underwent thoracic and abdominal CT every 6 months in the first year and every year afterwards. Mortality data for patients were obtained from the Turkish Statistical Institute database and the hospital database. The patients were last assessed in October 2017. Overall survival was calculated as the duration in months from the date of operation until death due to any cause. Presence of metastasis at the time of diagnosis was identified with preoperative radiological investigation and patients with metastasis after surgical treatment were referred to medical oncology. Patients without preoperative clinical metastasis were assessed according to radiological evaluation results for recurrence and metastasis presence during follow-up.

The patients were initially divided into two groups as those with and without metastasis according to the presence of clinical metastasis at the time of diagnosis. All data were compared between the groups. Then patients were further divided into two groups according to pathologic T stage. The first group included patients with pT1 and pT2 stage localized RCC and the other group pT3 and pT4 stage invasive RCC. The data in these two groups were compared and investigated.

Statistical Analysis

Continuous data from the demographic information of patients were analyzed descriptively, while categorical data were analyzed according to frequency and proportion. Firstly, patients with and without metastasis at the time of diagnosis were compared. Then, the pT1 and pT2 patients were compared with pT3 and pT4 patients. In the comparisons the Mann-Whitney U test, binary logistic regression analysis and Pearson's chi-square test were used. Survival analysis was done using the Kaplan-Meier method. All data were analyzed with the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) software program. Data were given as mean ± SD. A p value of less than 0.05 was considered statistically significant.

Results

The data on demographic characterstics, preoperative radiological and clinical findings, pathological findings and follow-up data for the 125 patients [79 (63.2%) male and 46

(36.8%) female] included in the study are shown in Table 1. The median follow-up duration was 24.6 (0.03-68.6) months and the mean age of the patients was 58.6±12.3 years. The mean tumor size was 5.6±3.3 cm, and when patients were assessed in terms of histologic subtypes, 88 (70.4%) had clear-cell RCC, 19 (15.2%) had papillary RCC and 18 (14.4%) had chromophobe RCC. The mean overall survival was 56.2±2.4 months, with 21 patients (16.8%) exitus during follow-up.

When the patients were initially evaluated in two groups according to clinical metastasis status at the time of diagnosis, it was found that 117 patients did not have metastasis and 8 patients had metastasis and these two groups were compared. Comparative results for the data in both groups are given in Table 2. The mean Fuhrmann nuclear grade was 2.2±0.6 in the non-metastasis group and 3±0.5 in the metastasis group (p<0.001). NLR was higher in the metastasis group compared

Table 1. Demographic, pathological and laboratory data of patients

		n=125	Percentage (%)
Age (years) (mean ± SD)		58.56±12.349	
Sex	Male	79	63.2
	Female	46	36.8
Site of surgery	Right	57	45.6
	Left	68	54.4
NLR (mean ± SD)		2.96511±1.753766	
Tumor size (cm) (mean ± SD)		5.620±3.2781	
Pathological subtype of RCC	CCRCC	88	70.4
	PRCC	19	15.2
	CRCC	18	14.4
Fuhrmann grade	1	9	7.2
	2	85	68
	3	26	20.8
	4	5	4
Microscopic surgical margin status	Negative	118	94.4
	Positive	7	5.6
Tumor stage according to the TNM classification (Pt)	T1a	48	38.4
	T1b	33	26.4
	T2a	13	10.4
	T2b	7	5.6
	T3a	20	16.0
	T3b	3	2.4
	T4	1	0.8
Lymph node according to the TNM classification (N)	N0	122	97.6
	N1	3	2.4
Metastasis according to the TNM classification (M)	M0	117	93.6
	M1	8	6.4
TNM stage	1	81	64.8
	2	19	15.2
	3	24	19.2
	4	1	0.8
Overall survival	Alive	117	83.2
	Deceased	8	16.8
Duration of follow-up (months), median (min-max)	-	24.6 (0.03-68,6)	-
Overall survival (months) (mean ±SD)	-	56.2±2.4	-

NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma, TNM: Tumor, node, metastases

to the non-metastasis group (4.4±2.8 and 2.9±1.6, respectively, p=0.029). Multivariate analysis also revealed a significant difference in NLR between the groups (p=0.035). Receiver operating characteristics curve analysis identified that the sensitivity and specificity of the NLR cut-off value of 3.1 were 87.5% and 67.5%, respectively (AUC=0.731, p=0.029). When a NLR of 3.1 was taken as a cut-off value, the NLR value in 7 of 8 patients with metastasis at the time of diagnosis was observed to be above 3.1 (p=0.002, OR=14.6). However, this value did not show a significant correlation with T stage, Fuhrman nuclear grade, lymph node (LN) involvement, surgical margin positivity, local recurrence and development of metastasis during follow-up. In the group without metastasis, there were 19 patients with invasive disease (pT3-4) (16%), while in the metastasis group 6 patients had invasive disease (75%) (p<0.001). The number of patients with LN metastasis was 1 in the non-metastasis group (0.8%) and 2 in the clinical metastasis group (25%) (p=0.01). The number of patients with positive surgical margins in the non-metastasis and metastasis groups were 4 (3.4%) and 3 (37.5%), respectively (p<0.001). The mean survival duration in the non-metastasis group was longer compared to that in the metastasis group (58.4±2.3 months and 18.5±4.5 months, respectively, p<0.001). During follow-up, 16 patients in the non-metastasis group (13.6%) and 5 patients in the metastasis group (62.5%) were exitus (p<0.001). There were no significant differences for other statistical data.

According to pathological stage, there were 100 patients with pT1-2 and 25 patients with pT3-4. Comparative results for data in the two groups are given in Table 3. Fuhrmann nuclear grade was lower in the pT1-2 group compared to the pT3-4 group

Table 2. Comparison of demographic, pathological and laboratory data of metastatic and non-metastatic patients at the time of diagnosis

			Group of patients without metastasis (n=117)	Group of patients with metastasis (n=8)	p
Age (years) (mean ± SD)			58.54±12.57	58.88±9.12	0.984†
Sex (n)	Male		72	7	0.141•
	Female		45	1	
Site of surgery	Right		54	3	0.634•
	Left		63	5	
NLR (mean ± SD)			2.87±1.63	4.41±2.80	0.029†
Tumor size (cm) (mean ± SD)			5.337±3.0651	9.763±3.7025	<0.001†
Pathological subtype of RCC		CCRCC	83	5	0.727•
PRCC		17	2		
CRCC		17	1		
pT		T1a	48	0	<0.001•
T1b		33	0		
T2a		11	2		
T2b		6	1		
T3a		17	3		
T3b		2	1		
T4		0	1		
pN		N0	116	6	0.01
N1		1	2		
Microscopic surgical margin status		Negatif	113	5	<0.001•
Pozitif		4	3		
Duration of follow up (months), median (min-max)			26.5 (0.03-68.6)	13.7 (1.9-39.8)	0.050†
Overall survey (month) (mean ± SD)			58.4±2.3	18.5±4.5	<0,001*
Overall survival		Alive	101	3	<0.001•
Deceased		16	5		

†Mann-Whitney U test, •chi-square test, *Kaplan-Meier survival analysis
NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma

(2.1±0.5 and 2.7±0.8, respectively, p<0.001). The mean tumor size was 5.2±3.1 cm in the pT1-2 group and 7.5±3.2 cm in the pT3-4 group (p<0.001). NLR was higher in the pT3-4 group compared to the pT1-2 group (3.8±2.6 and 2.8±1.4, respectively) and multivariate analysis also showed a significant difference in NLR between the groups (p=0.035). While LN metastasis was not observed in patients in the pT1-2 group LN metastasis was present in 3 patients (13.6%) in the pT3-4 group. The number of patients with clinical metastasis on preoperative assessment was 2 (2%) and 6 (24%) in the pT1-2 and pT3-4 groups, respectively (p<0.001). The number of patients with positive surgical margins was 3 (3%) in the pT1-2 group and 4 (25%) in the pT3-4 group (p=0.011). On follow-up, the time to recurrence was longer in the pT1-2 group compared to that in the pT3-4 group (63.4±1.9 months and 28.7±3.1 months, respectively, p<0.001). The mean overall survival was longer in the pT1-2 group than in the pT3-4 group (62.8±1.9 months and 26±3.1 months, respectively; p<0.001). During follow-up, 8 patients in the pT1-2 group (8%) and 13 patients in the pT3-4 group (54.1%) were exitus (p<0.001). There were no significant differences identified for other statistical data. According to the NLR cut-off value of 3.1, the patients were divided into two groups as NLR <3.1 and >3.1. There was no significant difference observed in recurrence-free survival between the two groups (Figure 1, NLR <3.1 - 60.8±2.6 months, NLR >3.1 - 56.5±3.9 months, p=0.409). However, when

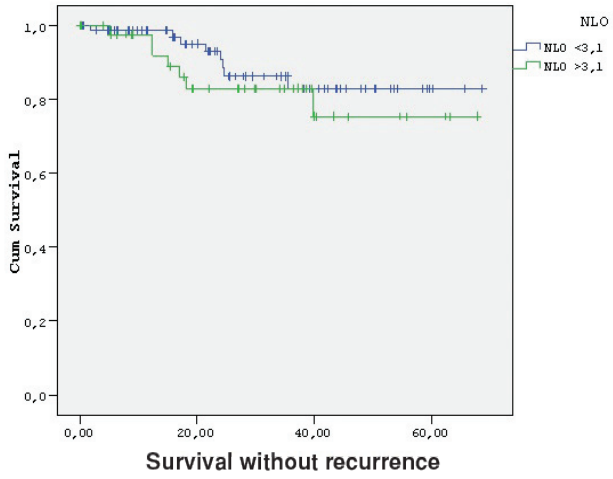

Figure 1. Kaplan-Meier survival plot for relapse-free survival and analysis result

Table 3. Comparison of demographic, pathological and laboratory data of pT1-2 and pT3-4 patients

			pT1-2 (n=100)	pT3-4 (n=25)	p
Age (years) (mean ± SD)			58.19±12.42	60.04±12.17	0.509†
Sex (n)	Male		62	17	0.578•
	Female		38	8	
Site of surgery	Right		45	12	0.788•
	Left		55	13	
NLR (mean ± SD)			2.77±1.43	3.76±2.57	0.071†
Tumor size (cm) (mean ± SD)			5.16±3.14	7.47±3.23	<0.001†
Pathological subtype of RCC		CCRCC	68	20	0.470•
PRCC		16	3		
CRCC		16	2		
pN		N0	100	22	0.007•
N1		0	3		
Metastasis according to TNM classification (M)		M0	98	19	<0.001•
M1		2	6		
Microscopic surgical margin status		Negative	97	21	0.011•
Positive		3	4		
Duration of follow-up (months), median (min-max)			27.9 (0.03-68.63)	17 (0.2-39.9)	0.003†
Time to recurrence (months) (mean ± SD)			63.4±1.9	28.7±3.1	<0.001*
Overall survival (months) (mean ± SD)			62.8±1.9	26±3.1	<0.001*
Overall survival		Alive	92	12	<0.001•
Deceased		8	13		

†Mann-Whitney U test, •chi-square test, *Kaplan-Meier survival analysis
NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma, TNM: Tumor, node, metastases

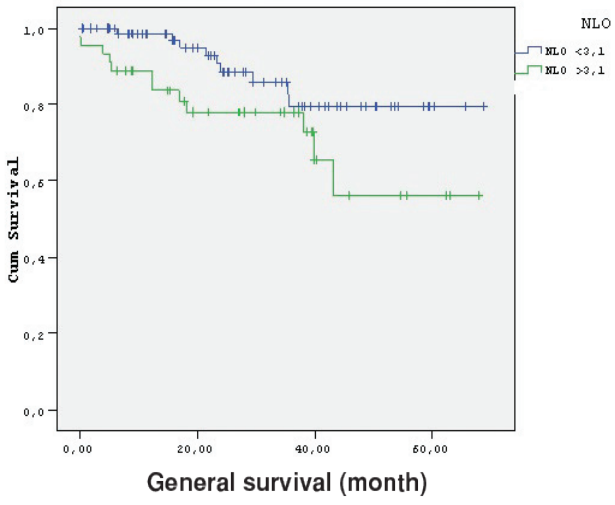

Figure 2. Kaplan-Meier survival plot for OS and analysis result

overall survival was assessed, this value was 59.8±2.7 months for patients with a NLR <3.1 and 49±4.5 months for patients with a NLR >3.1 (Figure 2, p=0.045).

Discussion

In recent years, many laboratory markers and risk scores associated with these markers have been defined to predict prognosis for RCC patients. Of these, the Leibovich prognosis score, the Mayo clinic stage, size, grade and necrosis score, and ULCA integrated staging system to assess metastasis-free survival and additional immunohistochemical evaluation of biological markers and genomic assessments for RCC follow-up in the postoperative period to assess cancer-free survival are recommended to predict prognosis (13,14,15,16). As a result, we assessed preoperative and postoperative data forming the basis of scoring in our study. In line with this, when we examined our results, NLR in the group with metastasis at the time of diagnosis was identified to be significantly higher compared to that in the group without metastasis. When the patients were grouped according to pathologic stage, NLR was significantly higher in the pT3-4 group than in the pT1-2 group.

Inflammation in the microenvironment of the tumor plays an important role in angiogenesis, proliferation and tumor invasion. Additionally, the intrinsic effect of inflammation is required to inactivate tumor suppressor genes and for oncogene activation (8). High percentage of neutrophil values is associated with chemokines, growth factors and proteases associated with angiogenesis. These neutrophil-associated factors help tumor cells to invade extracellular matrix and vascular wall and development of metastasis (17). Low lymphocyte values are a marker of reduced cellular immune response. Cytokine release preventing tumor distribution and development and cytotoxic cell death occurs due to lymphocytes (18).

The prognostic value of NLR in predicting recurrence was first investigated by Ohno et al. (19) in a study including 192 patients with non-metastatic RCC. This study revealed that patients with a NLR >2.7 had worse recurrence-free survival. A study by Tanaka et al. (20) in 2014 found that a high NLR value (>3 threshold value) was associated with advanced T stage, lymphovascular invasion, LN involvement and poor cancer-specific survival. Similarly, in a review of 15 studies, Boissier et al. (21) observed that a NLR <3 predicted reduced recurrence risk, with better overall survival and disease-free survival in patients with localized RCC than in those with metastatic and locally advanced RCC. In our study, NLR was higher in the group with metastasis at the time of diagnosis compared to the group without metastasis. In multivariate analysis, NLR was found to be an independent factor for metastasis. When a NLR of 3.1 was accepted as a cutoff value, there was no significant difference in recurrence-free survival, but overall survival was longer in patients with a NLR <3.1.

Study Limitations

Limitations of the study include the retrospective nature of the study and the low number of patients (especially in the metastasis group).

Conclusion

This study shows that preoperative NLR may be considered a prognostic factor in terms of general survival in RCC patients.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç., İ.B., T.D., S.Y., Design: İ.B., Data Collection and/or Processing: İ.H.B., S.Ç., İ.B., E.Ş., S.Y., E.A., Analysis and/or Interpretation: S.Ç., İ.B., E.Ş., E.A., Literature Research: S.Ç., İ.B., T.D., S.Y., Writing: İ.B.

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

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Do Renal Tumor Characteristics Affect the Number of Hemostatic Agents Used During Partial Nephrectomy?

Böbrek Tümörü Özellikleri Parsiyel Nefrektomi Sırasında Kullanılan Hemostatik Ajan Sayısını Etkiler mi?

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

Hemostatic agents (HAs) are frequently used worldwide to achieve hemostasis during partial nephrectomy (PN). Cellulose based agents (78.8%) and polytetrafluoroethylene pledgets (38%) are the more commonly used HAs during the PN in our clinic. There is no publication that shows the relationship of the number of HAs used with tumor size, RENAL nephrometry score, ischemia time, and tumor pathology results. Therefore, despite our limitations, our work is valuable in this respect.

Abstract

Objective: The aim of this study was to investigate the use and types of hemostatic agents (HAs) used during partial nephrectomy (PN) and the relationship of the number of these agents used during surgery with tumor size, RENAL nephrometry score (NS), peroperative ischemia time, and postoperative pathology results.

Materials and Methods: Records of patients, who had undergone PN in our clinic due to renal mass between January 2013 and February 2019, were retrospectively reviewed. Our study included 71 patients who were administered one or more HAs during PN. Demographic characteristics, operative data, and pathological results of patients, who were administered one or more HAs during PN, were recorded.

Results: Cellulose-based agents and polytetrafluoroethylene pledgets were the most frequently used HAs (78.8% and 38%, respectively). The patients were divided into two groups according to tumor size (0-4 cm and larger than 4 cm tumors), RENAL NS (low and intermediate-high score), ischemia time (0-20 min and longer than 20 min), and tumor pathology result (benign and malignant tumor), and the number of HAs used in each group was compared. When the groups were compared separately in terms of number of HAs used, no statistically significant difference was found between the groups (p=0.323, p=0.183, p=0.618, and p=0.131, respectively).

Conclusion: HAs are frequently used in our clinic to achieve hemostasis. There was no statistically significant difference in the number of HAs used between the groups.

Keywords: Renal mass, Partial nephrectomy, Hemostatic agents

Öz

Amaç: Çalışmamızın amacı parsiyel nefrektomi (PN) operasyonu sırasında hemostatik ajan (HA) kullanımının yaygınlığı ve bu kullanılan HA sayısının hastaların tümör boyutu, RENAL nefrometri skoru (NS), iskemi zamanı ve tümör patoloji sonucu ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Kliniğimizde renal kitle nedeniyle Ocak 2013 - Şubat 2019 tarihleri arasında PN operasyonu geçiren hastaların kayıtları tarandı. PN sırasında HA kullanılan 71 hasta çalışmaya dahil edildi. PN sırasında HA kullanılan hastaların demografik özellikleri, operasyon bilgileri, patolojik sonuçları ve komplikasyonları kaydedildi.

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Bulgular: Selüloz bazlı ajanlar (%78,8) ve politetrafloroetilen pledgets (%38) PN sırasında en sık kullanılan HA'lardır. Tümör boyutu (0-4 cm ve 4 cm'den büyük tümorler), RENAL NS (düşük puan-orta puan-yüksek puan), iskemi süresi (0-20 dk ve 20 dk'dan uzun iskemi süresi) ve tümör patoloji sonucu (benign tümör-malign tümör), kendi içerisinde gruplara ayrıldı ve gruplar içerisinde kullanılan HA sayıları karşılaştırıldı. Kullanılan HA sayısı açısından gruplar ayrı ayrı karşılaştırıldığında, gruplar arasında istatistiksel anlamlı fark saptanmamıştır (p=0,323, p=0,183, p=0,618, p=0,131 sırasıyla).
Sonuç: HA'lar PN sırasında hemostaz aşamasında kliniğimizde çok sık kullanılmaktadır. Çalışma grupları arasında, PN sırasında kullanılan HA sayısı açısından istatistiksel fark saptanmamıştır.
Anahtar Kelimeler: Renal kitle, Parsiyel nefrektomi, Hemostatik ajanlar

Introduction

Partial nephrectomy (PN) surgery, including open partial nephrectomy (OPN), laparoscopic partial nephrectomy (LPN) and robotic partial nephrectomy (RPN), are favored for the management of T1 masses when technically feasible (1). Bleeding is among the most important complications associated with this surgery. While the rate of this complication is 1.6% following OPN, it is 4-6% after LPN (2,3). The most important stage at which bleeding can be prevented is ensuring good hemostasis during surgery. At this stage, various hemostatic agents (HAs) are utilized either alone or in combination with hemostatic suturing of the excision base in order to make hemostasis safer and minimize the bleeding complication. These HAs have been used in renal surgery for 40 years and they act by mimicking, facilitating, or bypassing certain steps of the coagulation cascade (4,5) (Figure 1).

HAs are commonly used throughout the world in both OPN and LPN (6,7). Multicenter studies conducted in Europe and the United States have determined the rates of using at least one HA in OPN or LPN to be between 67.5% and 86% (6,7). Some of these agents facilitate hemostasis during surgery, while others contribute to renography by filling the parenchymal defect created by tumor excision in addition to facilitating hemostasis (5,8,9). On the other hand, other studies have stated that HA use did not cause a difference in the bleeding complication and could only have an effect in cases of minor bleeding (6,7). Some recent studies argue that HAs do not have any effect on bleeding complication rates (10,11,12,13,14).

This study aims to investigate the use and types of HAs used during PN and the relationship of the number of these agents used during surgery with tumor size, nephrometry score (NS), peroperative ischemia time, and postoperative pathology results.

Materials and Methods

Records of 91 patients, who had undergone OPN or LPN operation in our clinic due to renal mass between January 2013 and February 2019, were retrospectively reviewed. A retrospective review and analysis was performed following the approval of the institutional ethics committee. Patients who had not been administered HA during PN (n=8), and patients whose imaging records were incomplete (n=12) were excluded from the study. Demographic characteristics, operative data, pathological results, and complications of patients, who were administered one or more HAs during the PN operation, were recorded. Two urologists (E.K. and M.Y.Y) used preoperative contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (diffusion-weighted imaging and/or dynamic contrast-enhanced imaging) images to determine RENAL NSs. The results were crosschecked and confirmed by an uro-radiologist (H.S.). The masses were classified into low, intermediate, and high-risk tumors based on RENAL. NSs as suggested by Kutikov et al. (15). The types and number of HAs used during surgery, as well as the total number of HAs used were recorded.

Open Partial Nephrectomy or Laparoscopic Partial Nephrectomy Surgical Technique and the Use of Hemostatic Agent

The decision for choosing OPN or LPN was determined according to the RENAL NS and surgeon's experience. During the PN, both the renal artery and the renal vein were dissected and prepared. Only the renal artery was clamped during warm ischemia. The tumor was excised with cold scissors and removed en-bloc. After removal of the mass, excision bed hemostasis was achieved with absorbable sutures (2.0 vicryl). The collecting system was checked for leaks and if present, the leaks were closed with absorbable sutures (3.0 vicryl). The excision cavity was then filled with either a cellulose-based agent (Surgicel®; Ethicon, Somerville, NJ, USA), gelatin-based sponge (Spongostan® (Ferrosan, Copenhagen, Denmark), fibrin sealant (Tachosil®; Nycomed, Zurich, Switzerland) or autologous perirenal fat, based on the surgeon's choice and the size of the cavity. Polytetrafluoroethylene (PTFE) pledgets (Syneture®; Covedien, Mansfield, MA) were used during the renal parenchymal approximation to prevent sutures from tearing the parenchyma and then the renography was completed. In addition, Weck Hem-o-lok clips (Weck Closure Systems Research, Triangle Park, NC) were used during suturing and parenchymal approximation in LPN. Then, in case of need and based on the surgeon's choice, either hemostatic powder (Bloodcare powder®; Life Line, Brno, Czech Republic) or adhesives (Bioglue®; CryoLife, Kennesaw,

GA, USA) alone or in combination were used on the renography area. After the reconstruction was completed, the arterial clamp was removed and after the bleeding control, the procedure was completed.

Statistical Analysis

The groups were assessed for normal distribution using the Shapiro-Wilk test. None of the evaluated parameters was normally distributed. The Mann-Whitney U test was used for pairwise comparisons and the Kruskal-Wallis Test was used for three or more groups. A p value of less than 0.05 was considered statistically significant. All analyses were made using the IBM SPSS V22.

Results

Our study included 71 patients who were administered one or more HAs during the PN operation. The patients' demographic characteristics, operative data, pathology results, and complications are summarized in Table 1.

Table 1. Patient Characteristics

Number of patients	71
Median age, year (min-max.)	62 (63-77)
Mean ± SD	59.1±13.6
Sex n, (%)	
Male	42 (59.1%)
Female	29 (40.8%)
Operation side n, (%)	
Right	30 (42.2%)
Left	41 (57.7%)
Renal tumor location n, (%)	
Anterior	37 (52.1%)
Posterior	34 (47.8%)
Upper pole	14 (19.7%)
Mid pole	28 (39.4%)
Lower pole	29 (40.8%)
Median preoperative renal tumor size, cm (min-max.)	3.5 (1-15)
Mean ± SD	4.2±2.3
Median RENAL N.S, (min-max.)	6 (4-12)
Mean ± SD	6.3±2.1
RENAL N.S	
Low	40 (56.3%)
Intermediate	24 (33.8%)
High	7 (9.8%)
Operation type	
Open	63 (88.7%)
Laparoscopic	8 (11.2%)
Median HA used, min. (min-max)	2 (1-7)
Mean ± SD	2.5±1.4

Patients and HAs Used: The types and distribution of HAs used during the PN operations are summarized in Table 2. In 35.2% of cases, single HA was sufficient for achieving hemostasis. Two HAs were needed in 28.1% and 3 or more additional HAs were needed in 36.6% of the patients. Cellulose-based agents (Surgicel®) and PTFE pledgets (Syneture®; Covedien, Mansfield, MA) were the most frequently used HAs during PN (78.8% and 38%, respectively).

The patients were divided into two groups based on tumor size (0-4 cm and larger than 4 cm tumors), RENAL NS (low and intermediate-high score), ischemia time (0-20 min and longer than 20 min), and tumor pathology result (benign-malignant tumor) and the number of HAs used in each group was compared. When the groups were compared separately in terms of the number of HAs used, no statistically significant

Table 1 contiuned

Median operative time, min. (min-max)	140 (100-350)
Mean ± SD	154.4±47.6
Median ischemia time, min. (min-max)	11 (0-45)
Mean ± SD	12±11.1
Median hospitalization time, day, (min-max)	3 (2-14)
Mean ± SD	3.7±1.7
Pathology	
Benign	15 (21.1%)
- Oncocytoma	7 (9.8%)
- Angiomyolipoma	3 (4.2%)
- Simple Cyst	1 (1.4%)
- Chronic Pyelonephritis	2 (2.8%)
- Hydatid Cyst	2 (2.8%)
Malignant	56 (78.8%)
- Clear cell type	35 (49.2%)
- Papillary type 1	7 (9.8%)
- Papillary type 2	1 (1.4%)
- Chromophobe type	11 (15.4%)
- Multilocularcyst type	2 (2.8%)
Complications	
Intraoperative complications	
- Transfusion	4 (5.6%)
- Pleural injury	6 (8.4%)
- Ureteral injury	1 (1.4%)
- Fragmentation of renal mass	1 (1.4%)
Postoperative complications	
- Urinary leakage, DJ stent	2 (2.8%)
- Arteriovenous fistula, embolization	1 (1.4%)
- Urinary Tract Infection	1 (1.4%)

SD: Standard deviation HA: Hemostatic agent, NS: Nephrometry score, min: Minimum, max: Maximum

Table 2. Patients and hemostatic agents used

Hemostatic agents	n, (%)
- Fibrin sealant (Tachosil®)	3 (4.2%)
- Cellulose based agents (Surgicel®)	56 (78.8%)
- Gelatin based sponge (Spongostan®)	9 (12.6%)
- Gelatin based sealent (FloSeal®)	4 (5.6 %)
- Adhesives (Bioglue®)	17 (23.9%)
- Hemostatic powder (Bloodcare powder®)	16 (22.5%)
-Autologous perirenal fat	12 (16.9%)
- Hem-O clips	8 (11.2%)
- Metal clips	8 (11.2%)
- PTFE pledgets (PLEDGETS®)	27 (38%)

PTFE: Polytetrafluoroethylene

Table 3. Comparison of groups in terms of number of hemostatic agents used

	Number of HA used	p
Median (Q1-Q3), preoperative renal tumor size		
0-4 cm	2 (1-3)	0.323
>4 cm	3 (1-4)	
Median (Q1-Q3), RENAL N.S		
Low	2 (1-3)	
Intermediate	2 (1.25-4)	0.183
High	3 (2-3)	
Median (Q1-Q3), ischemia time		
0-20 min	2 (1-3.75)	0.618
>20 min	2 (1.75-3.25)	
Median (Q1-Q3), pathology		
Benign	3 (2-4)	0.131
Malignant	2 (1-3)	

HA: Hemostatic agent, NS: Nephrometry score

difference was found between the groups (p=0.323, p=0.183, p=0.618, and p=0.131, respectively) (Table 3).

Discussion

It has been shown that in renal mass treatment, PN results in better protection of the renal reserve and decreases the risk of metabolic and cardiovascular disorders compared to radical nephrectomy (16). During PN, after the tumor is excised, the important step is to quickly control bleeding by providing a good hemostasis in order to see surgical margins clearly and to achieve reconstruction of the renal parenchyma in a shorter time. HAs have been in use for many years for the purpose of accelerating and facilitating the hemostasis stage in both the open, laparoscopic, and robotic types of PN (6-14). In a multicenter study conducted by Lang et al. (6) in France, at least one HA was used in OPN or LPN surgery at a rate of 71.4%. Again, a multi-center study conducted by Breda et al. (7) in the United States and Europe determined that 16 of 18 centers used HAs and 80% of surgeons at these centers used HAs during LPN. In the study that we performed at our clinic, the rate of HA use in OPN or LPN surgery was 91.2%. All LPN cases involved one or more HAs. We associate our frequent use of HAs during PN to the fact that approximately 45% of the renal masses we treated with PN had an RENAL. NS categorized as intermediate-high score.

Previous studies in the literature have shown the association between ischemia time and NSs such as RENAL., preoperative aspects and dimensions used for an anatomical, C-index, and diameter-axial-polar during PN (15,17,18,19). In a study comparing these NSs, RENAL. NS has been shown to be most correlated with ischemia time, tumor margin and occurrence of complications during PN (20). In this study, we divided the patients based on tumor size (0-4 cm and larger than 4cm tumors), RENAL NS (low -intermediate-high score), ischemia time (0-20 min and longer than 20 min), and tumor pathology result (benign-malignant tumor) and compared the number of HAs used among these groups. Although the groups such as tumor size greater than 4 cm, higher RENAL score, ischemia time longer than 20 min, and malignant pathology were expected to have higher HA use, there was no statistically significant difference between the groups. We believe that the technique and effectiveness of the suture applied to the excision base during surgery comprises the most important step for hemostasis, as stressed in recent studies, and is the reason we did not observe significant difference between the groups. Secondly, HAs used for hemostasis can be applied in combination with bipolar coagulation or Harmonic/LigaSure. Lastly, identifying the relationship between the number of HAs used and the evaluated parameters was complicated due to the heterogeneity created by the variability in different surgeons' HA preferences.

HAs have been used in PN surgery for many years. It was stressed that these agents had potential benefits associated with decreasing complications, such as bleeding and urinary leakage, and shortening ischemia time in both laparoscopic and robotic surgery (8,9). Meanwhile, years of accumulated experience and advances in suture techniques called the hemostatic effect of these HAs into question. Some studies conducted in the recent years suggested that HAs had a very limited contribution to hemostasis or had no contribution at all (6,7,10,11,12,13,14). In these publications, the authors emphasized that suturing after tumor excision comprised the most important step in hemostasia rather than the use of HAs. They stated that the effect attributed to HAs in earlier studies decreased due to advanced surgical experience and suturing techniques, and therefore, with regard to the bleeding complication, there were no differences between the cases where HAs were used

and where HAs were not used (10,11,12,13,14). Moreover, they suggested that the cost that emerges due to the use of these agents, their effectiveness and their safety must also be taken into consideration (6). In this study, we were not able to perform a statistical comparison between the group operated with HAs and the group operated without HAs in terms of complications such as bleeding and urinary leakage because the number of patients operated without HAs was very low (n=6, 7.7%). However, based on our experience in PN surgery, during the OPN or LPN, HAs help to achieve hemostasis after tumor excision, to fill the cavity after tumor excision, and to prevent sutures from tearing the parenchyma during the approximation of the parenchyma. We still believe that hemostasis suture thrown into the tumor base at the hemostasis stage is the most important step in terms of bleeding control and that HAs play more of a supportive and complementary role.

Study Limitations

The limitations of this study can be listed as the lack of randomization in the study design, its retrospective nature, and being a single-center study. Moreover, the inability to standardize the selection of HA types based on tumor characteristics, evaluating procedures performed by various surgeons, as well as heterogeneity of HAs, and variation in dimensions of the HAs (Surgicel®, Spongostan® and PTFE Pledgets) may be listed as limitations. The strengths of this study include the fact that, to our knowledge, it is the first study that has evaluated the relationship of the number of HAs used during PN with tumor size, RENAL NS, ischemia time, and renal mass pathology.

Conclusion

PN is a standardized method in the treatment of small renal masses. The most important stage of PN is hemostasis. HAs are frequently used worldwide and in our clinic to achieve hemostasis. Although the groups such as tumor size greater than 4 cm, higher RENAL score, ischemia time longer than 20 min, and malignant pathology were expected to have higher HA use, there was no statistically significant difference between the groups. However, future prospective randomized controlled studies are needed to strengthen our findings.

Ethics

Ethics Committee Approval: A retrospective review and analysis was performed following the approval of the institutional ethics committee.

Informed Consent: All patients had given written informed consent before the surgery for giving permission for the use of the collected data at any time.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K, M.Z.K., M.Y.Y., C.Y., Ö.Ç., Y.Ö.İ., Concept: E.K., H.Ş Design: E.K., H.Ş, Data Collection and/ or Processing: E.K., M.Z.K., H.S., M.Y.Y., C.Y., Ö.Ç., Analysis and/ or Interpretation: E.K., M.Z.K., H.Ş., M.Y.Y., C.Y., Ö.Ç., Y.Ö.İ., Literature Research: E.K, H.Ş, Ö.Ç Writing: E.K.

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The Use of Tubularized Incised Plate Urethroplasty to Repair Distal Hypospadias in A Peripheral State Hospital

Perifer Devlet Hastanesinde Distal Hipospadias Onarımında TIPU Kullanımı

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

Tubularized incised plate urethroplasty is a successful method in the treatment of hypospadias, and various medical therapies can be used to increase patient comfort in postoperative period. Tubularized incised plate urethroplasty is a surgical treatment of distal hypospadias in the periphery could also be performe and Glans-Urethral Meatus-Shaft and hypospadias objective scoring evaluation scores are useful evaluating the hypospadias and surgery results.

Abstract

Objective: Hypospadias is a congenital anomaly of the male urethra that is becoming increasingly prevalent. In this paper, we share the results of our series of 45 distal hypospadias cases treated with tubularized incised plate urethroplasty (TIPU) at a single center in Şanlıurfa, Turkiye.

Materials and Methods: Hypospadias repairs were made by two urologists who had completed their urology residencies at the same clinic in a state hospital. The TIPU technique was used for all 45 patients. To prevent bladder contractions and reduce anal itching during hospitalization, the patients were administered low-dose oxybutynin and 2 mg/mL hydroxyzine hydrochloride; they were also followed up postoperatively for a mean duration of 9.3 (6-12) months.

Results: The average age of the patients was 9.5±0.5 (2-24) years. Ten patients had been circumcised previously, preoperative skin chordee was observed in 35, and none experienced preoperative complications. Postoperative catheterization lasted seven days. Postoperatively, one patient developed a fistula and two developed meatal strictures. No other complications were observed in the other patients.

Conclusion: Hypospadias is an anomaly frequently seen in pediatric urology practice and requires considerable attention and experience. TIPU is an ideal technique for correcting hypospadias, especially distal hypospadias, due to its low complication rate and favorable cosmetic results. Although hypospadias surgery requires experience, it can be done quite easily in peripheral hospitals by surgeons who have trained in clinics experienced in this field, provided that they follow the rules pertaining to surgery.

Keywords: Hypospadias, TIPU, Snodgrass method, Dystal hypospadias, Hypospadias surgery, GMS score, HOSE score

Öz

Amaç: Hipospadias son yıllarda prevalansı giderek artan konjenital bir anomalidir. Şanlıurfa'da tek merkezde tübülarize insize plak üretroplasti (TİPU) yapılarak tedavi edilen 45 olguluk distal hipospadias serimizin sonuçlarını paylaştık.

Gereç ve Yöntem: Hipospadias onarımları tek merkez devlet hastanesinde aynı klinikten uzmanlığını almış 2 adet ürolog tarafından gerçekleştirildi. Tüm hastalarda TİPU tekniği kullanıldı. Mesane kontraksiyonlarını ve anal kaşıntıyı azaltmak için hastanede kalış süresince hastalara düşük doz oksibutinin ve hidroksizin HCL 2 mg/mL verildi. Hastalar ortalama 9,3 (6-12) ay takip edildi.

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Bulgular: Toplam 45 distal hipospadiaslı hastaya cerrahi uygulandı. Hastaların ortalama yaşı 9,5±0,5'di (2-24). 10 hasta daha önce sirkumsizyon operasyonu geçirmişti. Otuz beş hastada preoperatif deri kordisinin olduğu görüldü. Ameliyat süresi 90±10 dk idi. Peroperatif hiçbir hastada komplikasyon izlenmedi. Postoperatif kateterizasyon süresi 7 gündü. Postoperatif 1 hastada fistül, 2 hasta da meatal darlık tespit edildi. Bu hastalara lokal anestezi altında mea dilatasyonu yapıldı ve dilatasyon tarif edildi. Ancak hastaların mea dilatasyonunu aktif yapamadıkları ve mea darlığının tekrarlaması üzerine bu hastalara postop 3. ayda meatoplasti yapıldı. Diğer hastalar da fistül veya başka bir komplikasyon görülmedi.
Sonuç: Hipospadias çocuk ürolojisi pratiğinde sık görülen ancak tedavisi zahmetli, büyük dikkat ve tecrübe gerektiren bir anomalidir TİPU özellikle distal hipospadiaslarda komplikasyon oranı az olması ve daha güzel bir kozmetik görünüm elde edilmesi nedeniyle distal hipospadias cerrahisinde ideal bir tekniktir. Hipospadias cerrahisi tecrübe isteyen bir cerrahi olmakla birlikte bu konuda tecrübeli kliniklerde eğitimini tamamlamış hekimlerin cerrahi kurallara uymak zorunluluğu ile mecburi hizmette (periferde) gayet rahat yapabilecekleri bir cerrahidir.
Anahtar Kelimeler: Hipospadias, TİPU, Snodgrass yöntemi, Distal hipospadias, Hipospadias cerrahisi, GMS skor, HOSE skor

Introduction

Hypospadias, which occurs in approximately 1 out of 200-300 live births, is a condition in which the urethra opens to the ventral side of the penis. It is the second most common congenital defect seen in males, after cryptorchidism, and its prevalence has doubled over the past 30 years. The initial diagnosis of hypospadias is typically made during the physical examination after birth. In hypospadias patients, there is a ventral skin deficiency with a dorsal foreskin hood and an abnormally located meatus, with varying degrees of ventral penile curvature (1,2).

Since it is one of the cities in Turkey with highest birth rate, hypospadias is a common occurrence in Şanlıurfa, and thus hypospadias repair is one of the most common surgical procedures done by pediatric urologists. The aim of hypospadias repair is to create a functional urethra and a normal penile appearance with a meatus at the tip of the penis. Single-session methods, such as urethral advancement, urethral plate tubularization [tubularized incised plate urethroplasty (TIPU), and Thiersch-Duplay], and urethral lengthening using a flap are standard treatments for distal hypospadias (3). In this paper, we share the results of our series of 45 cases of distal hypospadias treated with TIPU at a single center in Şanlıurfa.

Materials and Methods

The hypospadias repairs were performed by two urologists who had completed their urology residency at the same clinic in a state hospital. The hypospadias patients were evaluated retrospectively. Written informed consent was obtained from all participants or their legal guardians. The research was conducted according to the principles of the World Medical Association's Declaration of Helsinki. The series consisted of 45 distal hypospadias patients aged between 2 and 24 (9.5±0.5) years. The meatus level varied between the coronal and distal level. Ten patients were circumcised; the remaining 35, who were uncircumcised, underwent surgery for the first time. Skin chordee was observed in 35 patients. The TIPU technique was used in all patients. The characteristics of hypospadias are presented in Table 1. Additionally, the patients were evaluated using the Glans-Urethral Meatus-Shaft (GMS) score (4), representing preoperative glans size, meatal location, and degree of shaft curvature, and the hypospadias objective scoring evaluation (HOSE) score (5), indicating postoperative meatal location and shape, urinary stream, straightness of erection, and any presence of urethral fistulae.

Surgical Technique (TIPU Method)

After injecting each patient with lidocaine solution with 1/80.000 adrenaline using a 26 G injector in the operating room, two deep and parallel incisions were made in the urethral plate in the distal of the present mean. A U-shaped incision was made to preserve the urethral plate. Some subglanular tissue was excised beneath each glans wing on the sides. A 6-14 f feeding catheter was placed in the urethra for diversion. Penile skin was incised from the circumcision line and degloved. A duct-shaped urethral plate located in the hypospadiac meatus was incised, encompassing the whole epithelium from the hypospadiac meatus to the tip of the penis. Urethral formation was started from the tube proximal. Polydioxanone (6/0) sutures were used for urethra formation. The first suture was done very carefully to ensure that the urethral catheter would not be

Table 1. Hypospadias characteristics of the patients

Meatus localization	Number	Previous circumcisions	Skin chordee	Uncircumcised skin chordee	Circumcised skin chordee
Coronal level	21	5	17	14	3
Sub coronal level	17	4	15	13	2
Distal penile level	7	1	3	2	1
Total	45	10	35	29	6

constricted and the new meatus would not have a stricture. The urethra was formed using a subepithelial transitive inverting continuous suturing technique. The new urethra was covered with a subdartos fascia flap prepared with paraurethral and dorsolateral tissues. During the glanduloplasty, the circumcision line was sutured with 4/0 or 5/0 polyglactin 910. The penis was wrapped with a Coban bandage at medium tightness. The bandages were removed on the fourth day. The urethral catheter was removed on the seventh day and the patient's urination was checked (Figure 1,2,3,4).

Results

The GMS scores representing the preoperative penile appearance are presented in Table 2. The patients were followed up for 6-12 months. It was observed that the skin chordee recovered after deglovation during surgery. The surgical site was wrapped with Coban bandage after the surgery for four days and a feeding tube of an appropriate size was used as a urethral catheter. Each patient was followed in the hospital for seven days after the surgery. On the seventh day, the patient's urination was observed after removing the catheter; a meatal dilatator was suggested and defined and then the patient was discharged once an easy flow from the new meatus was observed after

Figure 1. Coronal mea cateterization

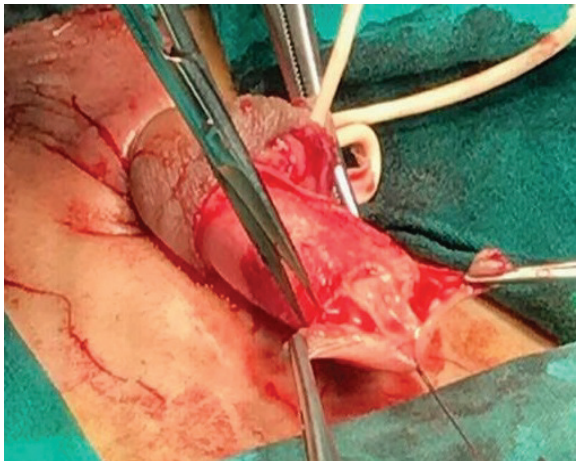

Figure 2. Urethral plate dissection

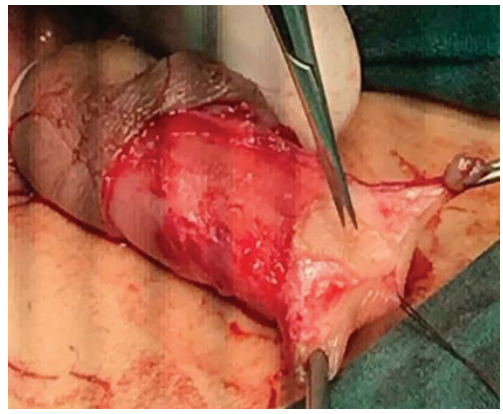

Figure 3. Urethral plate insicion

Figure 4. Postoperative image

Table 2. The Glans-Urethral Meatus-Shaft scores of patients

Score parameters	n (%)	Mean score
Glans (G) score:		
1. Glans good size; healthy urethral plate, deeply grooved	25 (55.5)	
2. Glans adequate size; adequate urethral plate, grooved	15 (33.3)	1.55
3. Glans small in size; urethral plate narrow, some fibrosis or flat	5 (11.1)	
4. Glans very small; urethral plate indistinct, very narrow or flat	0	
Meatus (M) score:		
1. Glanular	0	
2. Coronal sulcus	38 (84.4)	2.15
3. Mid or distal shaft	7 (15.5)	
4. Proximal shaft, penoscrotal	0	
Shaft (S) score:		
1. No chordee	10 (22.2)	
2. Mild (<30°) chordee	30 (66.6)	**1.88**
3. Moderate (30-60°) chordee	5 (11.1)	
4. Severe (>60°) chordee	0	
		Total score
		5.58

the catheter was removed. No fistulae or strictures were observed during urination on the seventh postoperative day in any patient. To prevent bladder contractions and decrease anal itching during hospitalization, each patient was administered low-dose oxybutynin suspension and 2 mg/mL hydroxyzine hydrochloride. When the patients were being treated, it was observed that they were comfortable and did not have bladder contractions, related urethral catheter dislocations, or anal itching. The medications were administered after nearly 10 patients developed these symptoms, and the treatment was observed to allay the symptoms. Prior to being discharged, each patient or his primary caregiver was shown how use a meatal dilator, as well as the capillary tube of a glass thermometer if they could not find a meatal dilatator. The patients were asked to continue meatal dilatation for one month. All patients were evaluated at the first postoperative check in the second week and at one, three, six, and 12 months postoperatively. It was observed that complications were most likely to occur in the first month. The formation of a fistula wider than coronal level was observed in a patient during the follow-up in the first month and a band of nearly 0.8 mm was observed to have formed in the new formed meatus. It was found that this patient had not made an effective meatal dilatation. As the patient was 20 years old and lacked a congenital left tibia and fibula, the wound recovery was not considered to be very good and he refused to undergo a second operation.

Table 3. The hypospadias objective scoring evaluation scores of patients

Score parameters and score values	n (%)	Mean score
1.Meatal Location		
Distal glanular =4	35 (77.7)	
Proximal glanular =3	10 (22.2)	**3.77**
Coronal =2	0	
Penile shaft =1	0	
2.Meatal shape		
Vertical slit =2	40 (88.8)	**1.88**
Circular =1	5 (11.1)	
3.Urinary stream		
Single stream =2	38 (84.4)	**1.84**
Spray =1	7 (15.5)	
4. Erection		
Straigh t=4	39 (86.6)	
Mild angulation (<10^0) =3	6 (13.3)	**3.86**
Moderate angulation (>10^0 but <45^0) =2	0	
Severe angulation (>45^0) =1	0	
5.Fistula		
None =4	44 (97.7)	
Single-subcoronal or more distal =3	1 (2.2)	**3.97**
Single-proximal =2	0	
Multiple or complex =1	0	
		Total score 15.32

Table 4. Postoperative general findings of patients

Operation duration	90±10 minutes
Follow-up duration	Average 9.3 months
Preoperative complication	0
Catheterization duration	7th day
Postoperative stricture	2
Postoperative fistula	1

A meatal stricture was detected in the postoperative first month controls in two patients. Dilatation was performed under local anesthesia and meatal dilatation was demonstrated again. However, it was observed that the patients did not perform active meatal dilatation and meatoplasty was therefore required in the third postoperative month, as the meatal stricture recurred due to this reason. When these patients were examined in detail, it was noticed that they were blonde, fair-skinned, and had allergies. No fistulae or other complications were observed in the other patients.

The values for HOSE scores reflecting the postoperative results are presented in Table 3. It was observed that the anal itching and bladder contractions that frequently affect hypospadias patients were reduced by the postoperative drug treatment given to the patients; furthermore, patient comfort increased and the risk of urethral catheter dislocation decreased. Using a meatal dilatator or the capillary tube of a glass thermometer was observed to be beneficial in preventing the formation of meatal strictures after urethral catheter removal. The postoperative general findings are presented in Table 4.

Discussion

Most urologists tend to avoid performing hypospadias surgery, as it has a high rate of complications such as fistulae when performed in peripheral hospitals; furthermore, surgeons' experience of the procedure is limited due to the low number of hypospadias clinics across Turkiye. We performed hypospadias surgery on 45 patients in a peripheral state hospital because both surgeons performing the operations had worked in centers that took hypospadias cases during their urology training. There are no other centers with staff experienced in dealing with hypospadias in our peripheral location and our patients could not afford to seek treatment further away from home.

Distal hypospadias cases constitute 85% of hypospadias patients. Although many surgical techniques have been defined

for the repair of distal hypospadias, the most commonly used methods are Mathieu (flip-flap) and TIPU. A vertical meatus and conical glans cannot be created using the Mathieu method, and its reported duration of operation and complication rate are higher (6).

Multiple studies have shown that the TIPU technique has a low rate of complications and provides very successful surgical results, even in proximal hypospadias cases. In distal hypospadias in particular, the width proportion of the urethral plate to the glans is reported to be better than that achieved using other techniques. Not requiring separate skin flaps to form a vertical meatus and neourethra is one of the notable advantages of the procedure (7,8). In addition to these causes, we preferred to use the TIPU method in all our patients because we have greater individual experience with it.

Our average operation duration was 90 (±10) minutes. By forming a conical glans and an angular meatus using the TIPU method, we achieved a good cosmetic appearance that more closely resembled normal anatomy.

GMS scores provide a brief and reproducible way to define the severity of hypospadias and correlates with the risk of surgical complications. Merriman et al. (4) reported that patients with a GMS score of 6 or below had fewer complications. In our study, the average G score was 1.55, the average M score was 2.15, the average S score was 1.88, and the total average GMS score was 5.58; these scores were found to correspond to those in the literature.

Using the HOSE system makes it easier to evaluate both the corrective operations for hypospadias and the surgical results. A HOSE score >14 has been reported to be acceptable for hypospadias surgery (5). Our results, which achieved an average HOSE score of 15.32, were in line with literature in terms of both surgical results and patient satisfaction. We think that our work in this study is successful as we have achieved acceptable HOSE scores based on the low preoperative GMS scores and the distal hypospadias repairs made.

In a series of 16 patients, Snodgrass reported that he encountered no meatal problems or urethral fistulae (9). The TIPU technique was applied on 148 patients in the United States and Europe, and a 7% complication rate and good cosmetic appearances were reported (10).

Snodgrass et al. (11) reported complications in 19 out of 426 patients (4%) (9 fistulae, 9 glans dehiscences, and one meatal stricture) after distal TIPU procedures. In a meta-analysis including 23 papers comprising 1872 TIPU repairs and 1496 Mathieu repairs published between 1994 and 2009, Wilkinson et al. (12) reported an increased incidence of urethral fistulae with the Mathieu technique (3.8% vs 5.3%) and meatal stenosis with the TIPU technique (3.1% vs 0.7%). Snodgrass later reported that the complication rate increased from 0 to 24% in patients who underwent distal TIPU between 1994 and 2009; another 25 articles reported rates of 10% or less, which were mostly fistulae and meatal strictures (13). In our series, three of our patients (6.6% in total) experienced complications: a urethral fistula was observed in 1 patient (2.2%) and meatal strictures in two patients (4.4%), in line with the literature. In their retrospective study of 492 patients, Oztorun et al. (14) compared distal hypospadias repairs and found no significant differences in the incidence of complication between Mathieu urethroplasty, and TIPU which is in line with the literature. Serrano Durbá et al. (15) found that 12% of 124 patients experienced complications following the Snodgrass procedure; nine of these were fistulae (7.2%) and six were meatal strictures (4.8%). Castellan et al. (16) used the Snodgrass method in 97 patients and reported that they achieved a perfect cosmetic appearance in all cases, with complications occurring in only four patients. In 300 distal hypospadias cases, Rudin et al. reported that Snodgrass TIPU was more suitable in cases where the urethral plate and glans were of normal size; when these was smaller than normal, Mathieu urethroplasty was preferred. They reported fistulae and strictures as late-developing complications (17). In our series, we observed that all complications occurred in the first postoperative month. Viseshsindh performed TIPU in 80 hypospadias patients and observed the following complications: 12 cases of fistula (15%), three complete openings (3.75%), and four cases of meatal stenosis (18). These complications in particular depend on hypospadias type and occur more often in proximal hypospadias cases; interestingly, age did not increase the rate of complications (18). In our series, a fistula occurred in one 20 year-old patient, but that patient had congenital anomalies. Although there were 16 patients over 10 years of age, we observed this complication only in the 20-year-old patient. While two recent studies stated that the most important factors causing meatal stricture were technical mistakes and surgeons' lack of experience, another stated that meatal strictures and obstructions could be evaluated objectively through preoperative and postoperative uroflowmetry and were more common after TIPU (19,20). Another study reported that fistulae occurred less often in dorsal dartos flaps and preputial flaps (21). We covered the neourethra with a subdartos flap in all our patients, and believe that our fistula rate is low compared to that reported in the literature.

As recorded in the literature, using a meatal dilatator once the flap is placed and after the urethral catheter is removed decreases complications in distal hypospadias repairs made using the TIPU technique. Although we had a large number of uncircumcised patients in series (22%), we found that covering the neourethra with a dorsal or ventral subdartos flap decreased the likelihood of fistulae developing.

In hypospadias surgery, postoperative care, follow-up, and complication management is as important as the surgical technique used. A lack of assistant doctors in peripheral hospitals and patients' postoperative follow-up being done only by nurses increases the burden on surgeons and intense shifts are required for these patients during the postoperative period. Living in peripheral areas with poor socioeconomic conditions makes it harder for patients to manage their catheters; it also makes it harder to care for patients who develop complications. Despite all these difficulties, we found that our complication rate was low and our successful surgical results were comparable to those reported in the literature.

In order to overcome these difficulties, we think that better training of assisting medical staff, particularly nurses, on issues relating to hypospadias surgery and postoperative care is required, especially in inexperienced centers. We also think that taking sufficient time to explain the procedure and after-care to all patients, regardless of their socioeconomic condition, would make patient follow-up easier.

Study Limitations

This study is limited in that it does not include patients with proximal hypospadias, our study sample was relatively small, and we reviewed the application of only one technique in a single center.

Conclusion

Hypospadias is an anomaly that is frequently seen in pediatric urology practice and correcting it requires considerable attention and experience. TIPU is an ideal technique for surgically correcting distal hypospadias, as the complication rate is low, especially in distal hypospadias repairs, and it achieves a better cosmetic appearance. This surgical technique is preferred because it provides good results when attention is paid to basic steps that can be learned through experience in hypospadias clinics. It is also a relatively simple procedure that can be applied easily in any medical facility with an operating room and by any surgeon with sufficient experience. It should not be forgotten that surgeons become experts in specific techniques and fields by working with them regularly. Thus, although hypospadias surgery requires experience, it is a surgery which can be done quite easily in rural and suburban areas by doctors who have completed their residency in a hypospadias clinic, as long as they respect surgical rules. It is also vital that doctors inexperienced in this particular technique transfer such patients to experts. Finally, we observed that treating patients with low-dose antihistamines and anticholinergic therapy during hospitalization increased both their comfort and that of their doctors. Using a meatal dilatator or the capillary tube of a glass thermometer was observed to be beneficial in preventing meatal strictures.

Ethics

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association eclaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., M.B., R.S., Design: A.A., M.B., R.S., Data Collection and/or Processing: A.A., M.B., R.S., M.G.S., Analysis and/or Interpretation: A.A., S.Ö., Y.E.G., Literature Research: A.A., M.B., Writing: A.A., M.G.S., M.B.

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Local Anesthetic Infiltration During Pediatric Percutaneous Nephrolithotomy Improves Postoperative Analgesia

Çocuklarda Perkütan Nefrolitotomi Sırasında Uygulanan Lokal Anestezik İnfiltrasyonunun Ameliyat Sonrası Analjezi Üzerine Etkisi

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

There is limited number of studies reporting pain management after pediatric percutaneous nephrolithotomy. Our study is the first to report the importance of preemptive local anesthetic use in pediatric percutaneous nephrolithotomy.

Abstract

Objective: Percutaneous nephrolithotomy is not pain-free due to the procedure itself and presence of post-operative diversion. Our purpose was to evaluate the efficacy of local anesthetic infiltration in postoperative analgesia in children who undergo percutaneous nephrolithotomy.

Materials and Methods: Forty-two renal units were included to our study. Local anesthesia group received prilocaine and bupivacaine injection through the percutaneous access line where patients received no local anesthetic constituted the control group. All patients received the same anesthesia protocol and 15 mg/kg paracetamol infusion postoperatively four times a day. Post-operative pain scores of patients were evaluated by using FLACC-FPS scales. Patients with pain scores ≥4 received meperidine 1 mg/kg as rescue analgesic.

Results: Between the two groups there was no significant difference in pain scores except 24th hour, where the local anesthesia group found to be favorable. The need (p=0.040) and total number (p=0.018) of rescue analgesic was significantly less in local anesthesia group. According to need for repetitive analgesic dose, the local anesthesia group was founded to be more advantageous (p=0.017). The postoperative analgesic satisfaction of parents' was favorable in local anesthesia group (p=0.002).

Conclusion: In pediatric percutaneous nephrolithotomy, preemptive local anesthetic infiltration reduces postoperative pain, the need for analgesics, the number of analgesics used and also improves patient comfort and analgesic satisfaction.

Keywords: Percutaneous nephrolithotomy, Local anesthetic, Pain, Patient satisfaction with pain management

Öz

Amaç: Perkütan nefrolitotomi uygulama yolu ve ameliyat sonrasında diversiyon konulması sebebiyle ağrısız bir cerrahi değildir. Çalışmamızda perkütan nefrolitotomi uygulanan çocuk hastalarda lokal anestezik uygulamasının, ameliyat sonrası ağrıya etkisini araştırmak amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 42 renal ünite dahil edilmiştir. Lokal anestezik grubuna perkütan giriş hattı boyunca prilokain ve bupivakain enjeksiyonu yapılmıştır. Lokal anestezik uygulanmayan çocuklar kontrol gurubunu oluşturmuştur. Tüm hastalarda aynı anestezi protokolü kullanılmış olup ameliyat sonrası günde dört kez 15 mg/kg parasetamol infüzyonu uygulanmıştır. Ameliyat sonrası ağrı değerlendirmesi FLACC-FPS skorlamaları ile yapılmıştır. Ağrı skoru ≥4 olan hastalara kurtarıcı analjezik olarak meperidine 1mg/kg uygulanmıştır.

Bulgular: Gruplar arasında ağrı skorları açısından 24 saat dışında anlamlı fark saptanmamıştır. Lokal anestezik grubunda 24. saat ağrı skorları daha düşük bulunmuştur. Kurtarıcı analjezik ihtiyacının (p=0,040) ve kullanılan toplam analjezik sayısının (p=0,018) lokal anestezik grubunda anlamlı derecede az olduğu saptanmıştır. Tekrar eden analjezik ihtiyacı değerlendirildiğinde, lokal anestezik grubunun daha avantajlı olduğu görülmüştür

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(p=0,017). Ebeveynlerin ameliyat sonrası analjezi memnuniyeti değerlendirildiğinde lokal anestezik grubunun daha avantajlı olduğu belirlenmiştir (p=0,002).
Sonuç: Çocuk hastalarda perkütan nefrolitotomide uygulanan preemptif lokal anestezik uygulaması ameliyat sonrası ağrıyı, analjezik ihtiyacını ve uygulanan analjezik sayısını azaltır, hasta konforunu ve analjezik memnuniyetini artırır.
Anahtar Kelimeler: Perkütan nefrolitotomi, Lokal anestezik, Ağrı, Analjezi memnuniyeti

Introduction

Percutaneous nephrolithotomy (PCNL) is the preferred treatment option in whom the other minimally-invasive modalities failed or are inappropriate. Remarkable changes in PCNL technique have been made in order to reduce pain and minimize complications. Reduction of the sheath size led to minimally-invasive approaches such as mini-PCNL, ultramini-PCNL and micro-PCNL (1). Then, the "tubeless" and "totally tubeless" PCNL emerged as methods promising less post-operative pain and faster recovery (2). However, standard PCNL with a nephrostomy tube is still the routine practice for adult and pediatric stone patients.

Post-operative pain management and patient comfort are also important in pediatric patients. To reduce post-operative pain, preemptive analgesia and multimodal protocols are used. Preemptive analgesia is described as analgesic administration before a painful stimulus. In this manner, local anesthetics (LAs) are widely used where they can block the sensation of pain before surgical incision, resulting less need for anesthetic drugs intra-operatively and less pain post-operatively (3). This multimodal approach increases the safety of general anesthesia and reduces the amount of drugs needed for general anesthesia as well as analgesic drugs including opioids (3). There are several studies on LA use in adult PCNL suggesting benefit but there is no study on pediatric population on this issue (4,5).

Our purpose was to assess the effect of preemptive LA infiltration on postoperative analgesic need and patient comfort after pediatric PCNL.

Materials and Methods

The study was conducted after approval of the Hacettepe University Institutional Clinical Ethics Committee with the IRB number 16969557-331. A total of 42 renal units of 40 children who underwent PCNL between February 2015 and February 2017 were included in this study. One patient with neurological disorder and one patient with orthopedic disorder were excluded for that pain scoring would be misleading.

We constituted the control group of 21 cases who did not receive any LA before PCNL (control group, n=21). The study group (LA group, n=21) was constituted by 21 patients who received LAs before PCNL. Prilocaine and bupivacaine mixture was used as LAs in pediatric PCNL (2 mg/kg of 0.2% prilocaine and 2 mg/kg of 0.5% bupivacaine). The LA group received prilocaine and bupivacaine at all layers through the access line (including skin, subcutaneous tissues, perirenal muscles and fascia) before the puncture. Surgeries were performed by the same surgeon (H.S.D.). All children were operated in the prone position with a standard pediatric PCNL approach via a 24 F sheath with a 17 F nephroscope by a single access made from the lower pole. After fragmentation with a pneumotic lithotripter, the stones were removed and a 14 F re-entry nephrostomy catheter was placed in each patient.

All patients received the same protocol for general anesthesia. The routine general anesthesia protocol for pediatric PCNL in our clinic is induction with 2.5 mg/kg propofol, 1 mcg/kg fentanyl, 0.6 mg/kg rocuronium and, for maintenance, 2% sevoflurane with remifentanil infusion. Remifentanil infusion is set to maintain blood pressure within 20% of baseline value. Ten minutes before the end of PCNL, remifentanil is stopped and, before 30 minutes, 15 mg/kg paracetamol infusion is started. We prefer routine paracetamol (4 times a day, 15 mg/kg) infusion for post-operative analgesia. None of the patients received non-steroid anti-inflammatory drugs (NSAIDs).

We routinely use the face, legs, activity, cry, consolability (FLACC) scale to assess post-operative pain in all pediatric patients and the Faces Pain Score-Revised (FPS-R) scale for children 8 years of age and older (6,7). Post-operative pain assessment in children is done at post-operative 15th minute, 30th minute, 1st hour, 6th hour, 24th hour, and at every nurse visit afterwards routinely. The pain scores within the first 24 hours were included in our study.

Pain scores of 4 and higher are considered moderate pain and pain scores higher than 7, severe pain. All patients who had a pain score of 4 and higher received 1 mg/kg of intramuscular meperidine as rescue analgesic. The same nurse at the recovery unit and ward assessed pain scores and administered the analgesics. Also the nurse was blind to patient groups.

The patients were monitored for drug-related side effects (nausea, vomiting, hypotension, allergic reactions and respiratory depression) post-operatively. On the post-operative first day, the children were evaluated by a kidney-ureter-bladder radiography for residual fragments and place of the nephrostomy catheter. At the third post-operative day, the nephrostomy tube was removed under fluoroscopy in all patients. The patients were

discharged after leakage at the tract site stoped. At the end of the first day, the parents were asked about their satisfactions with their child's pain management in the post-operative first 24 hours. Parents's satisfaction was assessed by a 5-point Likert scale (1=poor to 5=excellent).

Statistical Analysis

The results of our study were analyzed using the SPSS version 23.0. Chi-square test was used to compare categorical data and the Mann-Whitney U test was used to compare groups with non normal distribution. A p value of less than 0.05 was considered statistically significant.

Results

There was no significant difference in age, stone size, stone number, operative time, postoperative hospital stay, blood transfusion rate and drug-related side effects between LA and control groups (Table 1).

Nausea, vomiting and hypotension were the side effects. Hypotension was observed in only one patient who was in the control group and needed two doses of meperidine. All of our patients were clinically stone-free after PCNL (complete or with a residual stone smaller that 3 mm).

Although pain scores at the first 15 minutes were higher in control group, statistical analysis showed no significant difference in FLACC and FPS scores between the two groups at 15 minutes, 30 minutes, 1 hour and 6 hours post-operatively. FLACC and FPS scores at post-operative 24th hour were significantly lower in LA group than in controls (p=0.023, p=0.038 respectively, Table 2). There was no significant difference in the number of patients who had severe pain between the groups (control group n=6, LA group n=5, p=0.726).

We observed that post-operative pain was felt more in the first 15 minutes after PCNL as the pain scores were higher (p=0.034). Pain after PCNL was found to be decreasing in time but the rate of decrease in LA group was distinctive. The analysis of the rate of decline in FLACC scores through post-operative 15th minute, 30th minute, 1st hour, 6th hour, and 24th hour revealed that in the control group, FLACC scores decreased in the first hour where in LA group FLACC scores kept decreasing significantly also in the further 6th and 24th hour evaluations.

Twelve out of 21 (57.1%) children in LA group and 18 out of 21

Table 1. Medians of patients' age, stone size, stone number, operation time, post-operative hospital stay and blood transfusion rate

	Control group	LA group	p
Age, months (median, min-max)	60 (21-204)	59 (9-204)	0.320[a]
Stone Size, mm (median, min-max)	18 (9-36)	17 (10-40)	0.930[a]
Stone number, n (median, min-max)	2 (1-7)	2 (1-7)	0.240[a]
Operation time, minutes (median, min-max)	120 (60-180)	120 (60-130)	0.355[a]
Postoperative hospital stay, days (median, min-max)	5 (4-7)	5 (4-7)	0.360[a]
Blood transfusion (positive/negative)	3/18	3/18	1.000[b]

LA: Local anesthetic, min: Minimum, max: Maksimum
[a]Mann-Whitney U test, [b]Chi-square

Table 2. Face, legs, activity, cry and consolability scale score medians at 15th minute, 30th minute, 1st hour, 6th hour and 24th hour post-operatively

	Control group (median, min-max)	LA group (median, min-max)	p (Mann-Whitney U test)
15 minutes FLACC score	4 (0-10)	2 (0-8)	0.065
30 minutes FLACC score	2 (0-8)	2 (0-8)	0.295
1 hour FLACC score	2 (0-6)	2 (0-5)	0.481
6 hours FLACC score	1 (0-5)	0 (0-3)	0.091
24 hours FLACC score	0 (0-5)	0 (0-2)	0.023

FLACC: Face, legs, activity, cry and consolability scale, LA: Local anesthetic, min: Minimum, max: Maksimum

Table 3. The need for rescue analgesic in groups

Rescue analgesic administration	Control group (n)	LA group (n)
None	3	9
Just one dosage needed	13	12
Second dosage needed	5	0
Total number of dosage administered	23 (13+2×5)	12

LA: Local anesthetic

(85.7%) children in control group needed rescue analgesic. The LA group needed significantly less rescue analgesia (p=0.040). The patients in our study required rescue analgesic up to two doses at most. In control group, 13 patients needed one dose and 5 patients needed 2 doses of meperidine. Meperidine was administered in 12 patients once and second dose was not needed in LA group. The total number of analgesic requirement was significantly lower in LA patients compared to that in controls [12 doses and 23 doses, respectively (p=0.018)]. The need for second dose rescue analgesic was significantly higher in control group (p=0.017) (Table 3).

Parents' satisfaction with their child's post-operative pain management was found to be significantly higher in LA group (p=0.002). The median of satisfaction score in LA group was 4 (2-5) and the median in control group was 3 (1-5).

Discussion

Despite being a minimally-invasive surgery, PCNL is not pain-free due to the procedure itself and the presence of postoperative diversion. Pediatric PCNL has evolved from adult size instruments to Micro-PCNL in time. It has been reported that the use of smaller access sheaths was associated with less complication and less post-operative pain (8,9,10,11). A study on patients with 1-2 cm stones, mini-PCNL and standard PCNL showed same stone-free rates where mini-PCNL was found to be advantageous in terms of analgesic requirement, hemoglobin drop and hospital stay (11).

Also, tubeless and totally tubeless PCNL were developed in order to reduce post-operative pain. In a retrospective study on 1469 patients, who underwent PCNL, the subjects were divided into three groups. In the first group, a 14 F nephrostomy catheter was placed, the second group received ureteral catheter and the third group received double J stent. In the nephrostomy group the length of hospital stay, need for blood transfusion, post-operative narcotic analgesic requirement and the complication rates were higher than in other groups (12). A study comparing tubeless PCNL with PCNL with a 14 F malecot catheter revealed that the tubeless group had shorter hospital stay, decreased NSAIDs requirement and decreased narcotic analgesic need (13). Tubeless PCNL and pain in pediatric age group was also studied. A study on 54 children undergoing PCNL in 60 renal units showed that children who underwent tubeless PCNL had less pethidine requirement and shorter hospital stay than 16 F nephrostomy group (14). Despite the different PCNL techniques described, indications for tubeless surgery are limited and not applicable for every case. Therefore, placing a nephrostomy tube for drainage after PCNL is the standard practice. A nephrostomy tube is the safest way of good drainage, managing bleeding and allowing second-look procedures. We aimed to evaluate the efficacy of LA infiltration in a standard pediatric PCNL patient. Our results showed that the FLACC scores in LA group were lower than in controls in all evaluation times though reaching statistical significance at postoperative 24th hour.

Preemptive analgesia is the easiest and the safest way of managing surgical pain. However, the modern understanding of postoperative analgesia starts with sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia (15). Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs (16). LAs or non-steroidal analgesics are given intra-operatively to delay post-operative pain and to decrease post-operative analgesic consumption. A LA administered before surgery may help preventing the adverse effects of NSAIDs and narcotic analgesics because it reduces the need for additional analgesic drugs (3). Bupivacaine infiltration before surgical incision is recommended by the American Society of Anesthesiologists because it has been shown to reduce post-operative pain scores (17). We prefer prilocaine and bupivacaine combination as LAs in our daily practice. Prilocaine is a short-acting LA where bupivacaine is a long-acting agent effective for 4-8 hours (18). In our study, pain scores after PCNL were highest in the first 15 minutes. Pietrow et al. (19) reported that patients with a 10 F nephrostomy tube placed after PCNL had lower post-operative pain scores than patients with 22 F tube. Also they found that pain scores were similar between the two groups at 6 hours post-operatively (19). Regarding the duration of analgesic effects of the drugs and the pain intensity after PCNL, we can postulate that especially bupivacaine is the suitable LA for preemptive analgesia in PCNL. In this study, we observed no severe analgesic-related side effects. Only nausea, vomiting and hypotension were observed and we found no significant difference between the groups. Our study revealed that the need for and total number of rescue analgesic was significantly less in LA group with no difference in drug-related side effects. This finding supports the logic of preemptive analgesia and favors the use of LA infiltration in children in terms of decreasing post-operative analgesic need.

Application of LA in adult PCNL patients has also been studied. In their randomized controlled study including 60 adult PCNL patients, Gokten et al. (4) used levobupivacaine as preemptive

LA (4). They evaluated the patients post-operatively at the 6th and 24th hour with a visual analogue scale (VAS) and they used meperidine as rescue analgesic. The data showed that preemptive LA use in PCNL provided lower VAS scores, less amount and frequency of opioid use, less opioid-related side effects, higher satisfaction with analgesia, and early mobilization post-operatively. Parikh et al. (5) conducted a study on adult patients and preferred bupivacaine as LA after PCNL (5). They reported that in bupivacaine group, VAS scores and analgesic requirement were significantly lower. In another study, 10 mL of bupivacaine was infiltrated around nephrostomy tube in 53 adults during PCNL. They stated that peritubal LA infiltration was effective in reducing post-operative pain after PCNL even with supra-costal access (20). Likewise, the adult studies revealing a better self-reported analgesia satisfaction, our study -although depending on parental observation in some patients- also supports better postoperative analgesic satisfaction in LA group (4,5).

We use the FLACC scale primarily for pain scoring in children because we believe that the FLACC scale provides more objective measurement of pain than VAS. Since the FLACC scale is applicable in all age groups (from newborns to adults), it is recommended by many authors as a reliable pain assessment tool in children after surgery (21).

The former studies on the preemptive use of LAs in PCNL were all conducted in adults. Our study is the first in the literature demonstrating the effects and safety of preemptive LA use in pediatric PCNL patients. We assume that the results of our study may provide guidance for further studies assessing and manipulating post-operative pain in children.

Study Limitations

This study is not without limitations. The limited number of patients may be the main cause of statistical indifference in the early pain evaluation despite the lower scores in the LA group. The efficacy of the protocol could be compared in different diversion (14 F vs 8 F nephrostomy vs tubeless) or instrument size (pediatric PCNL vs mini-PCNL vs micro-PCNL) groups.

These kinds of studies need very large number of patients with multi-institutional collaboration.

Conclusion

In pediatric PCNL, preemptive use of LA infiltration reduces postoperative pain, need for analgesics and number of analgesics used, in addition, improves patient's comfort and satisfaction with pain management with no increased drug-related side effects. These results support that routine use of LA seems beneficial also in children as we promote LA use in our daily practice.

Disclosure of Interest

The authors declare no conflict of interest including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript. The authors have no ethical conflicts to disclose.

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Ethics

Ethics Committee Approval: The study were approved by the Hacettepe University Ethics Committee (protocol number: GO17/122-19.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.C., H.S.D., Ö.C., A.A.Y., S.T., Design: E.C., H.S.D., Ö.C., A.A.Y., S.T., Data Collection and/or Processing: E.C., F.İ., A.C.B., H..S.D., Analysis and/or Interpretation: E.C., A.C.B., H.S.D., S.T., Literature Research: E.C., H.S.D., Ö.C., A.A.Y., S.T., Writing: E.C., H.S.D., A.A.Y., S.T.

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Effects of Vitamin B12 Deficiency on Ejaculation Time in Patients with Chronic Gastritis

Kronik Gastritli Hastalarda Vitamin B12 Eksikliğinin Ejakulasyon Süresine Olan Etkileri

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

Vitamin B12 deficiency may be observed in young men population due to chronic gastritis. Vitamin B12 is an important cofactor in synthesis of serotonin which acts a major role in ejaculation physiology. In our study; patients with B12 deficiency had lower intravaginal ejaculation time and higher premature ejaculation diagnostic tool scores. Men with vitamin B12 deficiency should be evaluated for sexual dysfunction especially premature ejaculation.

Abstract

Objective: Vitamin B12 deficiency is a common problem among chronic gastritis (CG) patients due to various factors. Vitamin B12 is involved in the regulation of the central nervous system and plays an active role in the synthesis of serotonin and catecholamines. This study aims to reveal the relationship between premature ejaculation (PE), which is a common sexual dysfunction in men, and B12 deficiency detected in patients with CG.

Materials and Methods: A total of 155 patients enrolled in the study between May 2017 and December 2017 were evaluated in three groups; CG with and without B12 deficiency and healthy volunteers. The patients were assessed with intravaginal ejaculatory latency time (IELT) and the premature ejaculation diagnostic tool (PEDT) to evaluate PE. Depression status of the patients was evaluated by the Beck Depression Inventory (BDI-II).

Results: The mean age of the patients was 36.04±9.53 years. Patients in the CG with B12 deficiency group had statistically significantly shorter IELT times (137.12±93.58) and higher PEDT scores (11.96±4.66) ($p<0.001$). Receiver operating characteristic analysis demonstrated a significant correlation between low levels of vitamin B12 and PE, and the cut-off value found in our study was 167.5 pg/mL. No significant differences were determined in BDI-II scores between the groups, however, patients with CG and B12 deficiency had higher scores.

Conclusion: While the cause of vitamin B12 deficiency in CG patients is multifactorial, our study revealed a relationship between B12 deficiency and PE. Vitamin B12 deficiency was found to have significant relationship with IELT times and PEDT, while no significant association between vitamin B12 deficiency and depression was determined.

Keywords: Premature Ejaculation, Chronic Gastritis, Vitamin B12

Öz

Amaç: Vitamin B12 eksikliği kronik gastrit (KG) hastalarında çeşitli faktörlere bağlı sık gözlenen bir durumdur. Vitamin B12 santral sinir sisteminin regülasyonunda görev almakta olup özellikle serotonin ve katekolaminlerin sentezinde aktif rol oynamaktadır. Erkeklerde sık gözlenen bir seksüel disfonksiyon olan prematür ejakulasyon (PE) ile KG hastalarında saptanan vitamin B12 eksikliğinin ilişkisi çalışmamızda ortaya konmaya çalışılmıştır.

Gereç ve Yöntem: Mayıs 2017 - Aralık 2017 tarihleri arasında çalışmaya dahil edilen toplam 155 hasta vitamin B12 eksikliği olan KG (grup 1), vitamin B12 eksikliği izlenmeyen KG (grup 2) ve sağlıklı gönüllülerden (grup 3) oluşan üç gruba ayrılmıştır. Erektil disfonksiyonu olmayan ve orta-ağır depresyonu bulunmayan hastalar PE açısından değerlendirilmek için self-reported intravaginal ejaculatory latency time (IELT) ve five-item premature ejaculation diagnostic tool (PEDT) anketleri ile değerlendirilmiştir.

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Bulgular: Ortalama yaşları (36,04±9,53) ve ortalama vücut kitle indeksleri (24,21±2,59) olan hastalardan vitamin B12 seviyesi düşük olan KG hastalarında diğer gruplara göre anlamlı derecede kısa IELT süreleri (137,12±93,58) ve yüksek PEDT skorları (11,96±4,66) saptanmıştır (p<0,001). Yapılan ROC analizine görede düşük vitamin B12 düzeyleri ile PE arasında anlamlı korelasyon saptanmış ve çalışmamıza ait cut-off değeri 167,5 pg/mL olarak belirlenmiştir. Beck Depression Inventory-II anketine göre değerlendirilen hastalar arasında anlamlı fark saptanmamış; ancak vitamin B12'si düşük KG hastalarında diğer gruplara göre yükseklik saptanmıştır.
Sonuç: KG hastalarında vitamin B12 eksiklinin nedeni multifaktöriyel olmakla beraber çalışmamızda eksikliğinin görüldüğü olgular ile PE arasındaki ilişkisi ortaya konmuştur. Vitamin B12 eksikliği ile IELT süreleri ve PEDT arasında anlamlı ilişki bulunmuş olup depresyon durumları açısından anlamlı fark saptanmamıştır.
Anahtar Kelimeler: Prematür Ejakülasyon, Kronik Gastrit, Vitamin B12

Introduction

Chronic gastritis (CG) is defined as chronic inflammation of the gastric mucosa and is considered the most common endoscopic finding in the world's population (1). The most widely accepted classification was established by the Sydney System Working Party and it provided a well-accepted common language to clinicians for the evaluation of the biology and natural course of CG (2). On the other hand, the morphological evaluation of gastritis pivots on five key parameters. These parameters can be listed as chronic inflammation (plasma cells are dominant), activity level revealed by investigating the presence of polymorphonuclear leukocytes among mononuclear inflammatory cells, intestinal metaplasia currently diagnosed when the epithelium resembles the small intestinal phenotype, atrophy defined as the loss of normal mucosal glands, and the presence of *Helicobacter pylori* (Hp) (positive or negative) (3,4). The risk factors for gastric cancer are Hp infection, salt intake, smoking, alcohol consumption, family history of gastric cancer, atrophic gastritis, and intestinal metaplasia. Particularly atrophic gastritis and intestinal metaplasia are considered to be premalignant lesions of gastric cancer (5). For this reason, early diagnosis and management are important in preventing gastric cancer (6,7,8). The majority of stomach cancers are classified as adenocarcinomas and, rare type of gastric cancers are lymphomas, gastrointestinal stromal tumors and carcinoid tumors.

Gastritis results in a decrease in acid secretion and bicarbonate production regardless of its etiology, and consequently, creates a reduction in mucosal blood flow, causing damage to the gastric epithelium and nutritional deficiencies, such as vitamin B12 (vit B12) and iron deficiency which are most commonly identified (9). Vit B12 is an essential water-soluble vitamin that is also known as cobalamin and requires adequate dietary intake and absorption to maintain its optimal level. Binding proteins such as haptocorrin, intrinsic factor (IF), transcobalamin II, and other specific cellular receptors are required for its absorption, transport, and cellular uptake. Clinically, vit B12 deficiency can manifest in a variety of forms ranging from asymptomatic clinical findings to macrocytic anemia, neuropsychiatric findings, cardiovascular diseases, and serious forms of cancer (10). Premature ejaculation (PE) is among the forms of sexual dysfunction that are commonly encountered in men and is defined in the diagnostic and statistical manual (DSM) of mental disorders, 5th edition as a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within 1 minute after vaginal penetration and before the individual wishes present for at least 6 months and experienced in almost all or all (75-100%) sexual activities (11). According to the most recent description of PE by the International Society for Sexual Medicine, lifelong PE where ejaculation takes place almost always before or within one minute of vaginal penetration since the first sexual experience and acquired PE where the Intravaginal ejaculation latency time (IELT) is significantly reduced with a duration of 3 minutes or less, are accompanied by a failure to delay ejaculation on nearly all vaginal penetrations, and consequently, stress, disappointment, and avoidance of sexual intercourse can be observed (12). Prevalence studies have reported the prevalence of PE to be approximately between 20% and 30%, however, most of these studies were conducted based on DSM-IV-TR, which offers unsatisfactory objective diagnostic criteria (13). Multinational prevalence studies investigating IELT in the general population have reported that the rate of patients who had an average latency time of 1 minute was 2.95% (14). Studies done in Turkey and China with a focus on PE subtypes determined that the prevalence of lifelong PE was 2.3% and 3%, and the prevalence of acquired PE was 3.9% and 4.8%, respectively (15,16).

While the pathophysiology of PE has not yet been revealed, it is commonly thought that neurobiological and psychogenic factors, such as anxiety, penile hypersensitivity, and dysfunction of the 5-hydroxytryptamine (5-HT) receptors, play a major role in the etiology (17). In addition, it can also develop due to organic factors (thyroid disease, diabetes, prostatitis, medication use, glans hypersensitivity) and genetic predisposition (18,19,20,21). 5-HT is known to be a potent inhibitor of ejaculation and a reduction in its levels is considered a significant risk factor for PE (22). Vit B12 is an important cofactor in nitric oxide (NO), homocysteine, and 5-HT metabolisms and provides the methyl group for the conversion of methionine to S-adenosylmethionine (SAM) (23). Therefore, low serum levels of vit B12 is considered closely related with PE. The aim of this study was to investigate the relationship between vit B12 deficiency that can develop secondary to CG and clinical manifestations of PE.

Material and Methods

Ethical Approval and Study Design

Our study had a prospective design and was conducted with the voluntary participation of patients, who were referred to the Gastroenterology and Urology clinics at the Cumhuriyet University Hospital from other departments due to non-specific upper gastrointestinal system findings or to investigate the etiology of anemia and were diagnosed with CG based on oesophagogastroscopic biopsy (corpus and antrum) between the dates May 2017 and December 2017, and healthy volunteers. Approval was obtained from the ethics committee prior to the study and the patients were asked to sign a written consent prior to evaluation (ethics approval number: 2017-02/24).

Patient Selection

A total of 155 patients of whom 50 had a diagnosis of CG with vit B12 deficiency (group 1), 53 had a diagnosis of CG without B12 deficiency (group 2), and 52 were healthy volunteers (group 3), were assigned to three groups. Inclusion criteria were being in the age range 18-50, having a body mass index (BMI) <30, having monogamous and heterosexual intercourse for a period of six months, having normal erectile function, not having been treated for depression, not using alcohol and not smoking, not possessing any anatomical or endocrine causes for PE (malignity, diabetes, thyroid disease), not using medications, retardant condoms and topical agents, and not having undergone urogenital and pelvic surgery. Patients who described lifelong PE were excluded from the study. Detailed medical and sexual anamnesis was obtained from the participants, who were enrolled in the study, and urogenital examinations were performed. Then, they were asked to complete self-estimated IELT (the time between the start of vaginal intromission and the start of intravaginal ejaculation), Premature Ejaculation Diagnostic Tool (PEDT) which is a brief measure to assess PE, 15-Question International Index of Erectile Function (IIEF-5) and the Beck Depression Inventory (BDI-II) (0-13: minimal, 14-19: mild, 20-28: moderate, 29-63: severe) in order to investigate their sexual and psychological states and the results were recorded (24,25,26). According to the study criteria, volunteers with normal erectile function who obtained scores ≥22 on the IIEF-5, and who presented minimal and mild depressive findings according to their scores on the 21-question BDI-II (<19) were included in the study. In order to make a PE diagnosis, an IELT time <3 minutes and/or a five-question PEDT score ≥11 scores were required (9).

Measurement of Vitamin B12 Levels

For all groups, venous blood samples were collected into EDTA tubes after approximately 12 hours of fasting. Centrifuged samples were stored at -70 °C until analysis. Prepared samples were analyzed using the cobas e 601 (Roche Diagnostics, Turkiye) device with the immunoassay method to produce results in the form of picogram/milliliter (pg/mL). The reference value for vit B12 deficiency was 200 pg/mL and below.

Chronic Gastritis Classification

In classifying chronic inflammation, which is among the parameters used in the histopathological evaluation of CG, infiltration of less than 1/3 of the mucosa with mononuclear cells was considered mild, denser infiltration that did not exceed 2/3 of the mucosa was considered moderate, and infiltration of all layers of the mucosa was considered severe. In the evaluation of activity, infiltration of the lamina propria with few neutrophils was classified as mild, presence of more neutrophils in the mucosal layer that extend between surface and gland epithelial cells was classified as moderate, and dense infiltration with neutrophils accompanied by abscess or pits is classified as severe. Loss of gastric mucosal glands is considered atrophic gastritis (27).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, (version 22, Armonk, NY, USA). Normally distributed data was analyzed using the Kolmogorov-Smirnov test. Data is given as mean ± standard deviation (SD), with minimum and maximum values for continuous variables. The categorical data is defined as the number and percentage. One-way ANOVA and post-hoc Tukey tests were used in parametric variables. Categorical data was analyzed using a chi-square test. Correlations between non-normally distributed data were assessed using the Pearson correlation coefficient (r). Statistical significance was considered at $p \leq 0.05$. The receiver operating characteristic curve cut-off value was estimated with the Youden index. In addition, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

The mean age of the 155 patients was 36.1±9.5 (19-50) and the mean BMI value was 24.2±2.5 (18.3-29.8) with no difference between the groups (p=0.442 and p=0.073, respectively). Clinical and demographic data of the patients are shown in Table 1. BDI and IIEF-5 scores were determined to be similar across the three groups (p=0.406 and p=0.997, respectively). Twenty-six patients in group 1, 10 patients in group 2 and 8 patients in group 3 had a IELT less than 3 minutes. Mean self-reported IELT values and vit B12 levels in group 1 were 137.1±93.5 and 150.5±33.8, respectively and significantly lower than those in the other two groups (p<0.001), however, no differences were found between

group 2 and group 3 (p=0.937 and p=0.336, respectively). While the mean PEDT score in group 1 was significantly higher than in the other two groups (11.9±4.6) (p<0.01), group 2 and group 3 presented similar results. No differences were found between the groups in terms of hemoglobin (Hb, g/dL), hematocrit (Hct, %) and mean corpuscular volume values. Statistical power analysis done with regard to plasma vit B12 levels produced a value of 95.2% (α=0.05).

Among oesophagogastroscopic biopsy findings that included activity, chronic inflammation, intestinal metaplasia, presence of Hp, and Hp severity in group 1 and group 2 patients, only metaplasia demonstrated a significant difference (p<0.05); whereas no statistical differences were detected between the three groups in terms of the other parameters. All the biopsy findings were normal in healthy group. Gastroscopic biopsy results of the patients are presented in Table 2.

Table 1. Clinical characteristics of the patient

	Group 1 (n=50)	Group 2 (n=53)	Group 3 (n=52)	p
Age (year)	35.65±10.62	37.79±9.94	34.61±7.98	0.442
BMI (kg/m^2)	23.66±1.99	23.59±2.45	24.25±2.92	0.073
BDI	688±3.47	3.79±2.95	2.25±2.27	0.206
IIEF-5	24.31±1.16	24.48±0.74	24.36±1.06	0.997
PEDT	11.96±4.66[a,b]	6.59±4.56	5.89±4.49	0.007*
IELT	137.12±93.58[a,b]	246.21±114.91	248.57±124.06	<0.001*
Vit B12 (pg/mL)	150.54±33.85[a,b]	344.40±99.00	323.49±92.19	<0.001*

BMI: Body mass index, IIEF-5: International Index of Erectile Function-5, BDI: Beck Depression Inventory, IELT: Intravaginal ejaculatory latency time, PEDT: Premature ejaculation diagnostic tool, Vit: Vitamin
[a]p<0.01 when compared with group 2, [b]p<0.01 when compared with group 3

Table 2. Oesophagogastric biopsy findings of chronic gastritis patients

Chronic inflammation	Group 1 n (%)	Group2 n (%)	p
Mild	15 (30)	18 (33.9)	-
Moderate	27 (54)	26 (49.1)	0.877
Severe	8 (16)	9 (16.9)	-
Activity			
None	14 (28)	21 (39.6)	-
Mild	14 (28)	13 (24.5)	0.650
Moderate	17 (34)	14 (26.4)	-
Severe	5 (10)	5 (9.5)	-
Atrophy			
Absent	41 (82)	46 (86.7)	0.502
Present	9 (18)	7 (13.3)	-
Intestinal metaplasia			
Absent	36 (72)	48 (90.5)	0.015*
Present	14 (28)	5 (9.5)	-
Hp			
Absent	14 (28)	16 (30)	0.807
Present	36 (72)	37 (70)	-
Hp severity			
Mild	13 (36.1)	12 (32.4)	-
Moderate	11 (30.5)	13 (35.1)	0.908
Severe	12 (33.4)	12 (32.5)	-

Hp: Helicobacter pylori

Parameters of both only CG patients and all participants including the healthy control group were investigated for correlations and it was found that serum vit B12 values were positively correlated with IELT values and negatively correlated with PEDT scores, with statistical significance. The results of analysis investigating correlations between vit B12 levels and other parameters are summarized in Table 3.

A receiver operating characteristic (ROC) curve analysis was referred to in order to determine the diagnostic value of serum vit B12 in all groups and the area under the curve was determined as 0.75 for vit B12 (95% CI: 0.590-0.910; p=0.002). The cut-off value for vit B12 determined by the ROC analysis was 167.5 pg/mL. The sensitivity and specificity of this value were 55.5% and 90.7%, respectively. Based on this analysis, the PPV was calculated as 62.5, the NPV as 88.1, and accuracy as 83.1%. The ROC curve analysis is demonstrated in Figure 1.

Table 3. Correlation between serum vitamin B12 levels and other parameters

	Chronic gastiritis patients (group 1 and 2) (n=103)		Entire patients (All groups) (n=155)	
	Vit B12		Vit B12	
	r	p	r	p
Age	0.03	0.411	0.10	0.177
BMI	-0.03	0.405	-014	0.111
IELT	0.47	<0.0001*	0.33	0.001*
PEDT	-0.50	<0.0001*	-0.38	<0.0001*
BDI	0.09	0.268	-0.03	0.384
IIEF-5	0.10	0.231	0.14	0.110

BMI: Body mass index, IIEF-5: International Index of Erectile Function-5, BDI: Beck Depression Inventory, IELT: Intravaginal ejaculatory latency time, PEDT: Premature ejaculation diagnostic tool, Vit: Vitamin

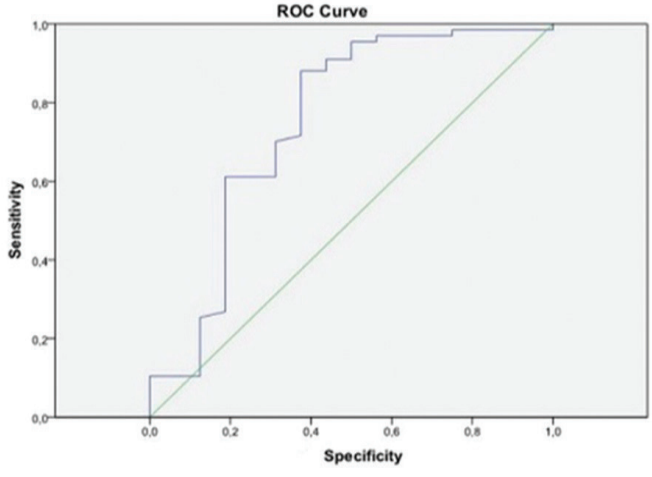

Figure 1. Receiver operating characteristic analysis for the diagnosis of premature ejaculation by plasma vitamin B12 levels

Discussion

Ejaculation is mediated by two primary neurological reflexes termed emission and expulsion, which involve different neural pathways. The sensation of orgasm is considered to be a distinct sensation that occurs simultaneously with these events. Emission is the movement of seminal fluid and sperm to the posterior urethra with sympathetic nervous system-mediated (T10-L2) rhythmic contractions of the seminal vesicle and prostate. In ejection, forcible expulsion takes place primarily under the control of somatic nerves (S2-S4) with the relaxation of the external urethral meatus in parallel to pulsatile contractions of the bulbocavernous and pelvic floor muscles (28). These complex pathways are enabled by the interaction of central serotonergic and dopaminergic neurons with secondary adrenergic, cholinergic, oxytocinergic, and gamma aminobutyric acid neurons (22). Serotonin (5-HT) found in the hypothalamus, brain stem, and the spinal cord plays an important role in the regulation of ejaculation. 5-HT acts as an ejaculation inhibitor and it delivers this effect through the 5-$HT_{1A,}$ 5-HT_{1B} and 5-HT_{2C} receptors in particular (29). While the activation of the receptors 5-HT_{2C} and 5-HT_{1B} at the postsynaptic level prolongs ejaculation time, activation of the 5-HT_{1A} receptor at the presynaptic level causes a decrease in serotonin release and negatively affects ejaculation time (30). Particularly in those with lifelong PE, 5-HT_{2C} hyposensitivity and/or 5-HT_{1A} receptor hypersensitivity have been considered responsible (22).

Aside from being an essential, a water-soluble vitamin that plays a role in DNA regulation and synthesis in the central nervous system, vit B12 also acts as a catalyzer and provides the methyl group in the conversion of homocysteine to methionine and in the subsequent events required for the formation of SAM (31). SAM is involved in the synthesis of serotonin and catecholamines and, vit B12 deficiency indirectly causes a negative effect on the production of serotonin (23). This role as a methyl provider is necessary for many methylation reactions in the brain and the 5-HT metabolism. Vit B12 therapy has also been reported to take effect by allowing communication between noradrenergic (α1 and α2) and serotonergic receptors (5-HT_{1A} an $HT_{2A/2C}$) (32).

Vit B12 deficiency can arise from insufficient dietary intake, disorders of cobalamin absorption, metabolism, or transport, and factors such as small intestinal malabsorption (33). The prevalence of vit B12 deficiency reported in the literature varies depending on the cut-off value and has been found to be 5-40% in the older population; whereas its prevalence based on age reveals rates of 3% for ages 29-39, 4% for ages 40-59, and 6% for ages 60 and above (34,35). The absorption of vit B12 involves active and passive mechanisms and a small portion (1-5%) of free form is absorbed in the jejunum and ileum through passive diffusion independently from IF. This usually occurs due

to vitamin intake at a supraphysiological dose and can result in a misevaluation of vit B12 levels absorbed from the stomach. Vit B12 deficiency can also be observed when antibodies against IF develop due to congenital, pernicious anemia-related, or gastric mucosal disorders. Furthermore, hypochlorhydria that develops in patients, who underwent gastrectomy or long-term use of proton-pump inhibitors, metformin, cholestyramine, and antacids, can also result in vit B12 deficiency (36). As opposed to studies that reported rates of combined pernicious anemia and vit B12 deficiency within the 15-25% range, one study that investigated 181 patients with megaloblastic anemia and vit B12 deficiency determined a pernicous anemia prevalence of 65% (37,38). These results raise the question whether there are other factors affecting vit B12 absorption besides autoimmune causes.

Our study determined significantly shorter self-estimated IELT times and higher PEDT scores in CG patients with low vit B12 levels compared to those in the other two groups ($p<0.001$). According to the results of the ROC analysis, vit B12 levels had a strong negative correlation with PEDT and a strong positive correlation with IELT. The determined cut-off value was calculated as 167.5 pg/mL and was found to have high specificity. There exist very few studies in the literature investigating the relationship between vit B12 and PE, and one study comparing PE patients and a healthy control group determined significantly lower vit B12 levels in patients with PE (39).

It is known that patients with low levels of serum vit B12 experience depressive disorders due to disruption of serotonin synthesis and their treatment requires long-term vitamin replacement (40). On the other hand, a recent meta-analysis showed that vit B12 deficiency was encountered more frequently in advanced age and in women (41). In our study, patients with moderate and severe depression were specifically excluded, and although group 1 received a higher score on the BDI-II compared to the other groups, no statistically significant differences were determined between the groups ($p=0.206$).

While gastritis is usually localized in the antrum in the case of Hp-related disease, stress, or medication use, inflammation in atrophic and autoimmune gastritis is usually localized in the fundus and corpus where parietal cells are found. Atrophy is also thought to develop independently of etiology (Hp gastritis or autoimmune) as a result of chronic inflammation. Half of patients with CG were shown to manifest atrophy at levels that varied throughout their lives (42). Studies done on older patients reported a higher prevalence of atrophy in those with vit B12 deficiency (43). Meanwhile, our study found a prevalence of atrophy and Hp of 16.5% and 70.8%, respectively in our CG patients (group 1 and group 2). We think that our atrophy rates were similar across groups in contradiction to the literature because the patients enrolled in the study belonged to a younger age group. In evaluations of our CG patients according to the Sydney classification, the prevalence of intestinal metaplasia was the only parameter that demonstrated a significant difference. In our study, the higher prevalence of intestinal metaplasia observed in group 1 patients was also related to corpus-predominant gastritis in the young population that did not manifest atrophy, and the group that had metaplasia was the one with lower serum vit B12 levels as expected.

We know in the light of recent genetic studies that vit B12 levels are affected by single nucleotide polymorphisms in multiple genes. Genetic variants can alter tissue levels of vit B12 by affecting the proteins involved in certain stages of absorption, cellular intake, and intracellular metabolism (44). Investigating the genetic factors will allow for more objective evaluation of vit B12 levels.

Study Limitation

The limitations of our study are the small sample size and inability to investigate plasma serotonine, IF antibody levels and tests associated with the genetic disorders that affect vit B12 absorption. Other limitation might be using self-estimated IELT measurement in our study, but self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with higher sensitivity and specificity (45).

Conclusion

The measurement and evaluation of vit B12 levels are multifactorial and especially dietary intake, malabsorption, and genetic factors that affect absorption must be considered holistically. In our study, which aims to reveal the relationship between vit B12 levels and PE in the cohort of CG patients, CG patients with B12 deficiency demonstrated shorter IELT times and higher PEDT scores compared to the healthy control group and CG patients without B12 deficiency, regardless of CG etiology. Beyond the known symptoms of vit B12 deficiency, determining the effects of its clinical manifestations on ejaculation and depression plays a key role in improving the quality of life of the patients. There is a need for specific studies that will focus on etiology and publications that will corroborate the relationship between diseases such as CG that are frequently accompanied by vit B12 deficiency and PE and other sexual dysfunctions.

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The authors have read the STROBE Statement and the manuscript was prepared and revised according to the STROBE Statement.

Ethics

Ethics Committee Approval: Approval was obtained from the ethics committee prior to the study and the patients were asked to sign a written consent prior to evaluation (no: 2017-02/24).

Informed Consent: Approval was obtained from the ethics committee prior to the study and the patients were asked to sign a written consent prior to evaluation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.G., Design: K.G., Data Collection and/or Processing: K.G., P.G., Analysis and/or Interpretation: K.G., P.G., Literature Research: K.G., P.G., Writing: K.G., P.G.

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CASE REPORT
Urooncology

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Leydig Cell Tumor of the Testis: A Case with Incidental Diagnosis

Testisin Leydig Hücreli Tümörü: İnsidental Tanı Alan Bir Olgu

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Abstract

Leydig cell tumors account for approximately 1-3% of adult testicular tumors. These tumors are the most common type of gonadal stromal tumors and most commonly seen in the third to sixth decades of life, and about 10% of them are malignant. This case is about an incidentally diagnosed Leydig cell testis tumor in a patient who was investigated for primary infertility. A 28-year-old male patient presented with primary infertility and scrotal ultrasonography examination revealed a heterogeneous hypoechoic mass in the left testicle. He underwent left radical orchiectomy and pathological diagnosis was testicular Leydig cell tumor. There was no distant metastasis and the patient is being followed for metastasis.
Keywords: Infertility, Leydig cell tumor, Testicular neoplasms, Inguinal orchiectomy

Öz

Leydig hücreli tümörler, yetişkin testis tümörlerinin yaklaşık %1-3'ünü oluşturmaktadır. Bu tümörler gonadal stromal tümörlerin en sık rastlanan türü olup, erkeklerde en yaygın 3 ile 6. dekatlarda görülürler. Leydig hücre tümörlerinin yaklaşık %10'u maligndir. Bu yazıda primer infertilite nedeniyle araştırılan bir hastada insidental tanı konan bir Leydig hücreli testis tümörü olgusu sunmaktayız. Yirmi sekiz yaşında evli bir erkek hasta primer infertilite şikayeti ile kliniğimize başvurdu ve skrotal ultrasonografi incelemesinde sol testiste heterojen ve hipoekoik bir kitlesi olduğu görüldü. Hastaya sol radikal orşiektomi uygulandı ve patoloji sonucu testis Leydig hücreli tümörü olarak raporlandı. Toraks ve batın bilgisayarlı tomografisinde uzak metastaz saptanmadı ve hasta takibe alındı.
Anahtar Kelimeler: İnfertilite, Leydig hücreli tümör, Testiküler neoplaziler, İnguinal orşiektomi

Introduction

Leydig cell tumors account for 1-3% of all adult testicular tumors. These tumors are the most common type of gonadal stromal tumors and most commonly seen in the third to sixth decades (1). New developments in ultrasound imaging have increased the number of Leydig cell tumors discovered (2).

In this report, we present a case of Leydig cell testis tumor incidentally diagnosed during primary infertility investigation.

Case Presentation

A 28-year-old married male patient presented to our clinic with the complaint of primary infertility. The patient had no additional diseases, such as undescended testes, and history of surgery or trauma. Physical examination was unremarkable. On scrotal examination, the left testis was 7x5x4 cm in size with a mass measuring approximately 15x20 mm in the middle part of the left testicle, and the right testis was normal. No other

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signs, including gynecomastia and enlarged or superficial lymph nodes, were observed.

FSH, LH, testosterone, prolactin, cortisol, progesterone, and estrogen levels and testicular tumor markers (alpha-feto protein, beta-human chorionic gonadotropin and lactate dehydrogenase) were normal and no abnormality was detected in the spermiogram (Table 1). Scrotal ultrasonography revealed that the left testicle was measured 7x4x3 cm with a heterogeneous hypoechoic mass of 14x22 mm in size in the middle part of the left testicle.

He underwent left radical orchiectomy after sperm cryopreservation was performed. The patient was discharged on the postoperative 2nd day. Pathological investigation revealed a testicular Leydig cell tumor measuring 15 mm in diameter, diffuse positive for inhibin and calretinin while surgical margins were negative and no tumor necrosis, nuclear atypia or vascular invasion was detected (Figure 1). There was no distant metastasis on thoracic and abdominal contrast-enhanced computed tomography (CT). Subsequently, the patient was referred to the in vitro fertilization center for assisted reproductive techniques.

Table 1. The patient's tumor markers, hormonal evaluation and semen parameters

	Preoperative	Normal range
Hormon/tumor marker		
FSH (mIU/mL)	6.69	1.27-19.26
LH (mIU/mL)	3.52	1.24-8.62
Testesterone (ng/mL)	2.05	1.75-7.81
Prolactin (ng/mL)	5.14	2.64-13.13
Progesterone (ng/mL)	0.68	0.14-2.06
Ostrogen (pg/mL)	17.1	15-31.5
AFP (ng/mL)	2.69	0-9
β-hCG (mIU/mL)	0.12	0.5-2.67
LDH (U/l)	155	0-248
Spermiogram		
Semen volume (mL)	1.6	
Sperm concentration (10^6/mL)	32	
Total sperm count (10^6)	53	
Total motility (%)	51	
Progressive motility (%)	40	
Sperm morphology (normal forms, %)	5	

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, AFP: Alpha-fetoprotein, β-hCG: β-human chorionic gonadotropin, LDH: Lactate dehydrogenase
Normal ranges are according to hospital reference

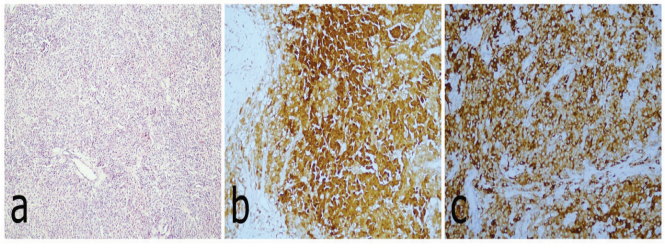

Figure 1. a) Sharp-limited, broad and eosinophilic cytoplasmic tumor cells with solid growth pattern (HE; x100); b) Diffuse calretinin (+) in tumor cells (IHC, Calretinin; x200), c) Diffuse inhibin (+) in tumor cells (IHC, Inhibin; x200)

The patient is still followed regularly at 6-month intervals with thoracic and abdominal contrast-enhanced CT. No distant metastases were seen during the follow-up period. Written informed consent was obtained from the patient.

Discussion

Leydig cell tumors are relatively rare testicular tumors accounting for 1-3% of all testicular tumors in adults (1). They are usually diagnosed incidentally as a palpable mass during manual testicular exam or during ultrasonography.

These tumors usually produce hormones. Suardi et al. (3) reported that 80% of 37 patients with Leydig cell tumor had low testosterone and high estrogen, estradiol, LH and FSH levels while no patient showed increased testicular markers. In our case, testicular tumor markers were negative and LH, FSH, testosterone and estrogen levels were normal (Table 1).

It is estimated that about 30% of patients with Leydig cell tumors have endocrine symptoms due to abnormal hormone levels (4). Scrotal ultrasonography is the primary imaging method used in the diagnosis, however, investigation of tumor markers, hormones (testosterone, LH, FSH, estrogen, estradiol, progesterone and cortisol) and CT examination of chest and abdomen for distant metastasis should be performed. As in our patient, cases of Leydig cell tumors incidentally diagnosed during infertility investigation have been reported in the literature (5,6).

Malignant transformation of Leydig cell tumors occurs in approximately 10% of patients. Orchiectomy is the standard treatment. Histopathological and clinical findings of malignant Leydig cell tumors include increased mitotic activity, vascular invasion, large size (>5 cm), necrosis, cytological atypia, extension beyond the testicular parenchyma, increased MIB-1 expression, infiltrative margins and DNA aneuploidy (7). However, the strongest indicator of malignancy is the presence of metastases (8). Malignant tumors occur exclusively in adults and are unaccompanied by endocrine changes (1,9). In our case, the tumors size was 15 mm, the patient was young, there were no vascular invasion, cytological atypia or necrosis and surgical margins were negative and no distant metastasis was found. Thus, this case should not be considered malignant.

In all high-risk patients, physical examination, scrotal and abdominal ultrasonography, evaluation of hormones and CT of the chest and abdomen are recommended every 3-6 months for follow-up (3).

The rate of metastatic tumors among all reported cases is less than 10%. In three older series, 18 metastatic tumors were found in 83 cases (21.7%) (1,2,10), while 5 recently published studies reported only 2 metastatic tumors in 156 cases (1.3%) (3,11,12,13,14). The most common sites of metastasis are the regional lymph nodes, followed by the liver, lungs, and bones (1). The metastases respond poorly to radiation or chemotherapy and overall survival is poor (15). There is no recommended option for the treatment of metastatic Leydig cell tumors yet. In this case, the patient was followed with every 3-6 month controls and no distant metastasis was seen in radiological exams.

In conclusion, Leydig cell tumors are rare tumors developing from gonadal stroma. They are usually diagnosed incidentally. These tumors are important for their endocrine effects because they often produce hormones. However, normal hormone profile does not exclude Leydig cell tumor. Radical orchiectomy should be performed for the treatment and the patient should be closely monitored for metastasis.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E.A., Design: M.E.A., Ö.K., Data Collection and/or Processing: A.E.E., E.A., Analysis and/or Interpretation: A.E.E., Literature Research: E.A., Ö.K., Writing: M.E.A., F.T.

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CASE REPORT
Pediatric Urology

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Testis Sparing Surgery in Children

Çocuklarda Testis Koruyucu Cerrahi

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Abstract

Although the standard treatment for testicular tumors is radical orchiectomy in children, testis-sparing surgery (TSS) is an alternative method in selected cases according to tumor size, tumor markers and histopathological findings. In this paper, we present two patients aged 11 and 12 years who underwent TSS in our clinic. Frozen section examination was performed in both patients. Intraoperative ultrasound-guided mass excision was performed in one patient. Histopathological examination revealed an epidermoid cyst in one patient and Leydig cell hyperplasia in the other. TSS may be performed in children with a small testicular mass and negative tumor markers.
Keywords: Child, Testicular tumors, Minimally invasive surgical procedures

Öz

Çocuklarda testis tümörünün standart tedavisi radikal orşiektomi olmasına rağmen tümör boyutları, belirteçleri ve histopatolojik bulgulara göre uygun olgularda testis koruyucu cerrahi (TKC) alternatif bir yöntemdir. Bu olgu sunumunda yaşları 11 ve 12 olan TKC uygulanan iki hastanın sunulması amaçlanmıştır. İki hastada da frozen incelemesi yapılmıştır. Bir hastada peroperatif ultrasonografi eşliğinde kitle eksizyonu yapılmıştır. Histopatolojik incelemede bir hastada epidermoid kist ve diğer hastada leydig hücre hiperplazisi olarak raporlanmıştır. Testis koruyucu cerrahi küçük testis kitlesi ve negatif tümör belirteçleri olan çocuklarda uygulanabilir.
Anahtar Kelimeler: Çocuk, Testis Tümörü, Minimal İnvaziv Cerrahi Yöntemler

Introduction

The majority of testicular masses in children are benign. Characteristics of testicular masses cannot be fully evaluated by imaging methods such as ultrasound (US) and magnetic resonance imaging (MRI). Small size and cystic characteristics increase the likelihood of a mass having a benign etiology. Radical orchiectomy is the gold standard of treatment for childhood testicular tumors. Testis-sparing surgery (TSS) is one of the methods that can be used to prevent loss of organ due to surgery and overtreatment in selected patients with benign masses. In this article, we aimed to share our experience in TSS in children.

Case Presentations

Case 1

An 11-year-old male patient presented with the complaint of inguinal pain. Physical examination revealed a left testicular mass measuring approximately 5 mm in diameter. Development of external genitalia and pubic hair were Tanner stage 2. Scrotal Doppler US revealed a solid mass in the left testis 5.5 mm in diameter with central anechoic area. Tumor markers were normal. A 6 mm mass inferior to the left testis was detected on MRI. TSS was planned. Under general anesthesia, the testis and spermatic cord were released with inguinal incision. The testicular mass

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was excised after the spermatic cord was clamped with bulldog clips. Frozen section examination revealed a 7 mm keratinous cyst. The testis was placed in the scrotum and the operation was terminated (Figure 1). Postoperative follow-up was uneventful. Pathological diagnosis was epidermoid cyst.

Case 2

A 12-year-old male patient was admitted to our clinic due to trauma that occurred during sports. He had a history of hormone therapy due to left undescended testis at the age 1.5 years. Physical examination was normal. Development of external genitalia and pubic hair were Tanner stage 2. A scrotal Doppler US revealed a 2.5 x4 mm hyperechoic mass in the left testis. Tumor markers were normal (Beta-hCG<0.5 mIU/mL, AFP: 1.06 ng/mL). MRI showed a 4 mm focal area with intratesticular contrast enhancement in the left testis. TSS was planned. Intraoperative US was used to locate the mass and a 4 mm mass in the left testis was excised (Figure 2). Frozen section examination revealed a 4 mm Leyding cell hyperplasia. Postoperative follow-up was uneventful. Pathological diagnosis was Leyding cell hyperplasia (Figure 3).

Discussion

Testicular tumors are very rare in children. Testicular tumors account for 1-2% of all solid tumors in children and 3% of all testicular tumors. The incidence of testicular tumor is approximately 0.5-2 per 100.000 children and adolescents (1). In past years, most testicular tumors in children were thought to be malignant. However, in recent years, it has been shown that benign lesions, especially teratomas, were more common (2,3).

Figure 1. Testis Sparing Surgery. Enucleation of testis mass, testis mass, excision area, closure of tunika albuginea

According to the German Cancer Study Group, TSS is only recommended in patients with a mass in solitary testis or patients with bilateral tumors of less than 2 cm, no rete testis invasion and normal preoperative luteinizing hormone levels. The European Association of Urology Guidelines recommends TSS for synchronous bilateral tumors, metachronous contralateral tumors or normal preoperative testosterone levels and solitary testis with a tumor volume of less than 30% of the testicular volume. Intraoperative US and frozen examinations can provide information about the character of the mass in the testis, allowing prevention of recurrences (4).

Figure 2. Leydig cell hyperplasia

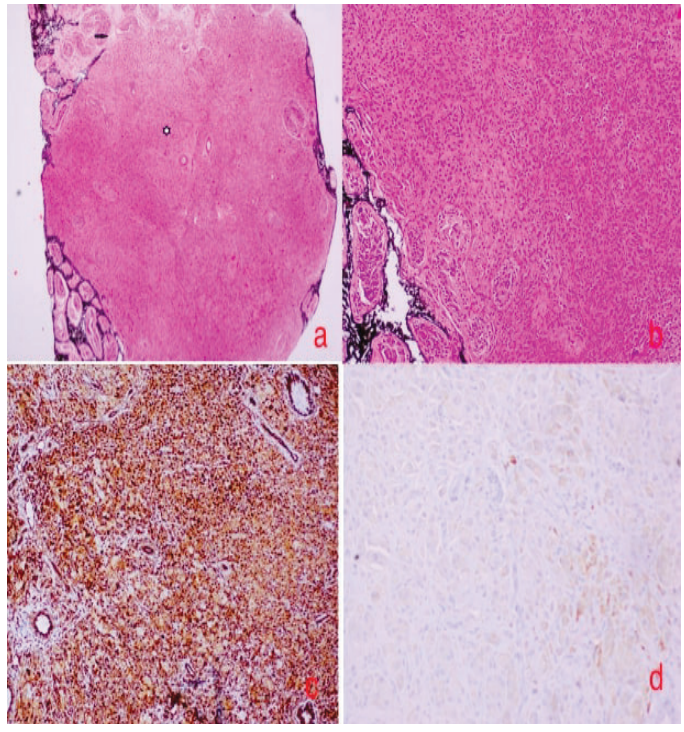

Figure 3. Pathological images of leydig cell hyperplasia: a) HEX10, arrow shows the normal tubule structure, star leydig cells. This picture shows normal tubule structure and non-destructive leydig cell hyperplasia. b) HEX20. c) VimentinX20 (immunohistochemical staining, Vimentin +). d) Inhibin X20 (Immunohistochemical staining, Inhibin weak +)

Organ-sparing surgery has begun to replace radical orchiectomy in childhood testicular tumors. The most important reason for this is the fact that most testicular tumors are benign in childhood. Teratoma, epidermoid cysts and stromal tumors constitute two-thirds of testicular tumors in children under 12 years of age. Yolk sac tumors account for less than 15% of pediatric testicular tumors. The organ-sparing approach is recommended in children with normal tumor markers, benign US findings and intraoperative frozen section (5).

In the case series of Emre et al. (6) , 4 patients underwent TSS, 3 patients had Leyding cell hyperplasia and 1 patient had a Leyding cell tumor. None of the patients had recurrence and testicular atrophy. In one patient, contralateral metachronous lesion was detected and treated successfully. This suggests that orchiectomy should not be performed in benign lesions (6). In a study by Friend et al. (7), TSS was recommended as standard treatment for epidermoid cysts, however, it was not recommended for follow-up of patients with testicular epidermoid cyst. In one case, orchiectomy was performed because of the fact that distinguishing malignant from benign tumor could not be made in frozen examination (7). In their study, Bujons et al. (8) reported that 15 children in pre-pubertal period underwent TSS and 4 patients had epidermoid cysts. There was no recurrence, metastasis or testicular atrophy.

In a study by Mennie et al. (9), TSS was performed in 3 patients with Leyding cell hyperplasia, two of whom were diagnosed incidentally. No recurrence was observed in follow-up. Testicular tumors in children with normal biochemical markers without findings of precocious puberty can be followed by US and unnecessary surgeries are prevented. However, if the lesions do not regress in follow-up, excisional biopsy and frozen section examination may be necessary (9).

It is thought that the remaining testis may provide normal hormonal and reproductive functions after unilateral orchiectomy. However, some studies have shown that loss of testicular tissue is related to infertility, endocrine deficiencies and sexual and psychological problems (10,11,12). In a study by Heidenreich et al. (13), 84 of 101 patients treated with TSS for germ cell tumors showed normal postoperative testosterone levels. Ten patients had hypogonadism and received androgen supplementation postoperatively and 6 remained on preoperative hypogonadism. To prevent irreversible damage, a warm ischemia time not exceeding 30 minutes is recommended during TSS (14). It has been reported that fertility is maintained in 50% of patients with intraepithelial neoplasia and normal testosterone levels (15).

In conclusion, testis-sparing procedure may be performed in children with a small testicular mass and negative tumor markers. To prevent recurrence, the lesion should be completely excised. If necessary, radical orchiectomy should be performed.

Ethics

Informed Consent: Written consent from the parents before.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ş., Ç.A.Ş., Design: A.Ş., Ç.A.Ş., Data Collection and/or Processing: A.Ş., Ç.A.Ş., Analysis and/or Interpretation: A.Ş., A.Ö.G., Ç.A.Ş., D.A., H.K., Literature Research: A.Ş., A.Ö.G., Ç.A.Ş., Writing: A.Ş., A.Ö.G., Ç.A.Ş.

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

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'No Residual Tumor' Rate in Radical Cystectomy Specimens

Radikal Sistektomi Spesmenlerinde Rezidüel Tümör Görülmeme Oranı

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Bladder cancer, which is the 9th most common type of cancer and the 13th cause of death from cancer, is a worldwide health problem (1). According to the GLOBOCAN, the highest incidence rates were in Western countries and Western Europe (2). Turkiye is one of the five countries with the highest age-standardized death rate (6.6/100.000) (3).

To achieve initial diagnosis, transurethral resection of the bladder tumor (TURBT) is usually performed (4). Some patients undergo radical cystectomy, which is the surgical procedure performed as standard therapy for locally confined, muscle-invasive, or highly aggressive superficial primary tumors of the bladder (5). Even though pathologists examine such specimens vigorously, no tumor can be detected because of several reasons, and such cases have been reported as pT0 tumor (6). No residual tumor (pT0) on cystectomy specimens may be related with completeness of TURBT, time frame of TURBT, neoadjuvant radio- and chemotherapy, small tumor size, initial misdiagnosis, and delayed formaldehyde fixation (6). Stage pT0 has been found to be associated with improved survival (7).

As a general rule, all cystectomy specimens are inked and immediately opened with Y-shaped incision through anterior wall when still fresh and fixed in 10% buffered formaldehyde overnight. Specimens are processed according to the international gross examination guidelines. Mucosa is inspected thoroughly and any suspicious area (irregularity, ulceration, solid or papillary mass, etc.) is described, and measured. After locating these lesions, already opened and fixed bladder is cut into horizontal slices of 0.5 cm thickness. Samples are taken from the determined suspicious areas, and depth of invasion is recorded if present. Also at least one sample is taken from each wall of the bladder even no lesion is detected. In histological examination if no tumor is noted, specimen is reexamined, and the entire suspicious areas including the surrounding walls are sampled extensively.

Despite the fact that extensive measures are taken, cystectomy specimens with no residual tumor may still exist. In the literature, the rate of pT0 cystectomy specimens is found in 5.1-20.1% of cases (8). While the highest rate (20.1%) was reported in a dataset of 900 patients, the lowest rate (5.1%) was reported in a dataset of 4430 patients (9,10). Both of these were multi-center studies, and patients who received neoadjuvant radio- and/or chemotherapy were excluded (9,10). Different findings were reported by means of prognosis in pT0 patients. While these studies stated a relationship with better prognosis, others found none.

In our institution, 185 robotic radical cystectomy surgeries were performed between 2014 and 2018. Patients who received neoadjuvant radio- and/or chemotherapy were 30 in number. Out of 155 patients, who did not receive neoadjuvant radio- and/or chemotherapy, 15 were detected as having pT0 (9.6%). Our pT0 rate (9.6%) is in accordance with the previous reports.

Reporting 'no residual tumor' is a distress for the pathologist all the time because of potential pitfalls, such as delayed fixation, small tumor size or initial misdiagnosis, although no residual tumor in cystectomy specimen is a finding which may herald better prognosis.

Keywords: Cystectomy, pT0, Urothelial carcinoma, Residual tumor

Anahtar Kelimeler: Sistektomi, pT0, Ürotelyal karsinom, Rezidü tümör

Ethics

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Surgical and Medical Practices: B.G., Concept: B.G., Design: B.G., Data Collection and/or Processing: M.M.K., Analysis and/or Interpretation: M.M.K., Literature Research: M.M.K., Writing: B.G.

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Transplant Survey

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Re: Incidences and Oncological Outcomes of Urothelial Carcinoma in Kidney Transplant Recipients

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EDITORIAL COMMENT

The increased number of successfully performed kidney transplantations increases, life expectancy and the chance for urologists to treat urothelial carcinoma (UC) in kidney transplant (KTs) recipients. In this non-randomized retrospective single-center study, the authors aimed to investigate the incidence of UC by calculating age-standardized rates (ASRs) in 2186 KT recipients and the general population and to determine the treatment outcomes. ASRs of bladder cancer and upper urinary tract UC (UTUC) in KT recipients were 25.5 and 129.5 times higher than that in the general population and the proportion of female UC patients was 2.5 times higher, reflecting a reversed gender disparity. No significant difference was observed in treatment outcomes between KT recipients and non-KT patient, however, the rate of progression to bladder cancer was higher with a relative risk of 10.53 (p=0.0481) compared to the general population. In the light of these data, urologic screening, and active treatment should be offered to identify the UC cases in KT recipients.

Yarkın Kamil Yakupoglu, MD

Transplant Survey

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Re: Significance of Atypical Urinary Cytology in the Evaluation of Patients with End-stage Renal Disease for Kidney Transplantation - A Retrospective Study

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EDITORIAL COMMENT

Active malignancy is a contraindication to kidney transplantation (KT) since immunosuppression may exacerbate an underlying malignancy. In this single center retrospective cohort study, the authors aimed to evaluate the incidence of urothelial carcinoma (UC) in end-stage renal disease (ESRD) patients presenting for KT work up and establish the incidence of UC in ESRD patients with atypical urinary cytology. Out of 703 patients, 430 ESRD patients with sufficient urine had been screened with urinary cytology and those with atypical cytology (151patients, 35%) or risk factors for bladder cancer had undergone cystoscopy. A total of 6 (0.85%) patients (only 3 with atypical cytology) were found to have bladder cancer and treated with transurethral resection of the bladder and eventually underwent KT. One patient, who had been diagnosed with high-grade non-muscle invasive bladder cancer during double-J stent removal after KT, progressed to metastatic disease. The rate of atypical cytology in ESRD population in this study (35%) was high compared to that in the general population, which has been reported as low as 1.9%. However, lack of high-grade lesions in this study makes it hard to exclude urinary cytology in the evaluation of these patients. The results of this study indicate that the incidence of bladder cancer is higher in ESRD patients compared to that in the general population, however, in this population, atypical cytology alone should not be an indication for cystoscopy.

Yarkın Kamil Yakupoglu, MD

Andrology

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Male Infertility as A Window to Health

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EDITORIAL COMMENT

Male factor infertility thought to affect approximately 50% of infertile couples worldwide. In the literature, there is a growing body of evidence that suggest associations between male infertility and other medical conditions such as oncological, cardiovascular, autoimmune, and other chronic diseases. Although the exact nature of these associations remains unclear, it has been hypothesized that genetic, developmental, and lifestyle-based factors might play a role. This review article provides overall knowledge of the relationship between male infertility and men's health in the literature.

Emre Bakırcıoğlu, MD

Andrology

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Microsurgical Varicocele Ligation: Surgical Methodology and Associated Outcomes

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EDITORIAL COMMENT

Microsurgical varicocelectomy is accepted as the criterion standard for therapy and that the use of microscope reduced postoperative complications such as hydrocele and varicocele recurrence. The authors described very nicely the tips and tricks of subinguinal and inguinal varicocelectomy operations utilizing an operating microscope. In the light of current literature, the authors concluded that both subinguinal and inguinal approaches of varicocelectomy under an microscope with high magnification offer excellent potential for reproductive success.

Emre Bakırcıoğlu, MD

Basic Research

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Diagnostic Classification of Cystoscopic Images Using Deep Convolutional Neural Networks

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EDITORIAL COMMENT

Recently, we are talking about some new concepts like Deepmind, Artificial Intelligence (AI), neural networks, big data, etc. The near future heralds a new era of medicine. Advances in information and communication technologies contribute to the development of new algorithms for the diagnosis and treatment of diseases. Some researches on this subject can be found in the field of urology in the literature. Data-driven tools and techniques, particularly machine learning methods that underpin artificial intelligence, offer promise for improving healthcare systems and services. Moreover, DeepMind announced its first major health project to assist in the management of acute kidney injury. Digital technology companies such as Google, Facebook, Microsoft, Amazon, Apple, IBM, and others are all preparing, in their own ways, bids on the future of health and on various aspects of the global healthcare industry. In this work, the authors suggested the usability of deep learning to predict and classify cystoscopic findings with high accuracy. In this research, the digital atlas covering 44 cystoscopic findings that frequently observed during the clinical routine was used. After image preprocessing, they developed deep convolutional neural network (CNN) models. The deep-learning model can be integrated into the artificial intelligence-aided cystoscopic imaging diagnostic tool (AI cystoscopy) that supports urologists during the cystoscopic examination. Computer-aided diagnosis tools using feature extraction and deep learning show promise as instruments to perform diagnostic classification. The results of this study show the potential of deep learning for the diagnostic classification of cystoscopic images and have proven the potential of CNN for that. Future work will focus on integration of artificial intelligence–aided cystoscopy into clinical routines. Although some subsets were falsely recognized, the neural network architecture can be improved to increase the accuracy performance for diagnosis of cancer.

Fehmi Narter, Prof, MD, PhD

Basic Research

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The Electromagnetic Spectrum: Current and Future Applications in Oncology

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EDITORIAL COMMENT

The electromagnetic spectrum is the foundation of physics. The electromagnetic spectrum includes radio waves, infrared radiation, visible light and ultraviolet radiation, X-rays, and gamma-rays. The electromagnetic spectrum is composed of waves of various energies that interact with matter. These energy sources can be used for cancer ablation. Different types of energy in the electromagnetic spectrum can be a potential application for the diagnosis and treatment of cancer. Radio waves, microwaves and infrared waves, electroporation, light-based therapies [e.g. photo-chemotherapy, photodynamic therapy (PDT)], and radiation-based therapies are new opportunities for cancer treatment. Radio frequency ablation (RFA), microwaves, ultrasounds, lasers and magnetic resonance imaging are actual members of this concept. Many of them have some disadvantages such as tissue warming, lack of miniaturized probes and high cost. In the context of warming, new dosimetry apparatus are being developed for cancer ablation. It is also likely that for PDT, perhaps RFA and MW therapy will be pioneer of nanoparticle-based treatment. Ultrasound and laser energy could also heat nanoparticles for precise therapy. These data would usher in a new age of minimally-invasive oncologic therapy. On the other hand, radiation therapy is a well known technique for cancer treatment. It is anticipated that image-guided radiation delivery systems will enable a greater degree of personalization of radiotherapy thus increase the precision and accuracy of radiation delivery. Robotic radiosurgery devices are becoming far more common. No doubt nanoparticles directed to the tumor will allow for enhanced lesion imaging to better target the tumor. The future will also bring more widespread use of particle (Hadron) therapy as particle radiations (i.e. protons and carbon ions). Clearly, the future application of the electromagnetic spectrum will help ultra-precise treatment of cancer. Moreover, I believe that more accurate and timely diagnosis of cancer may be possible with the discovery of all the parts of the electromagnetic spectrum.

Fehmi Narter. Prof, MD PhD