

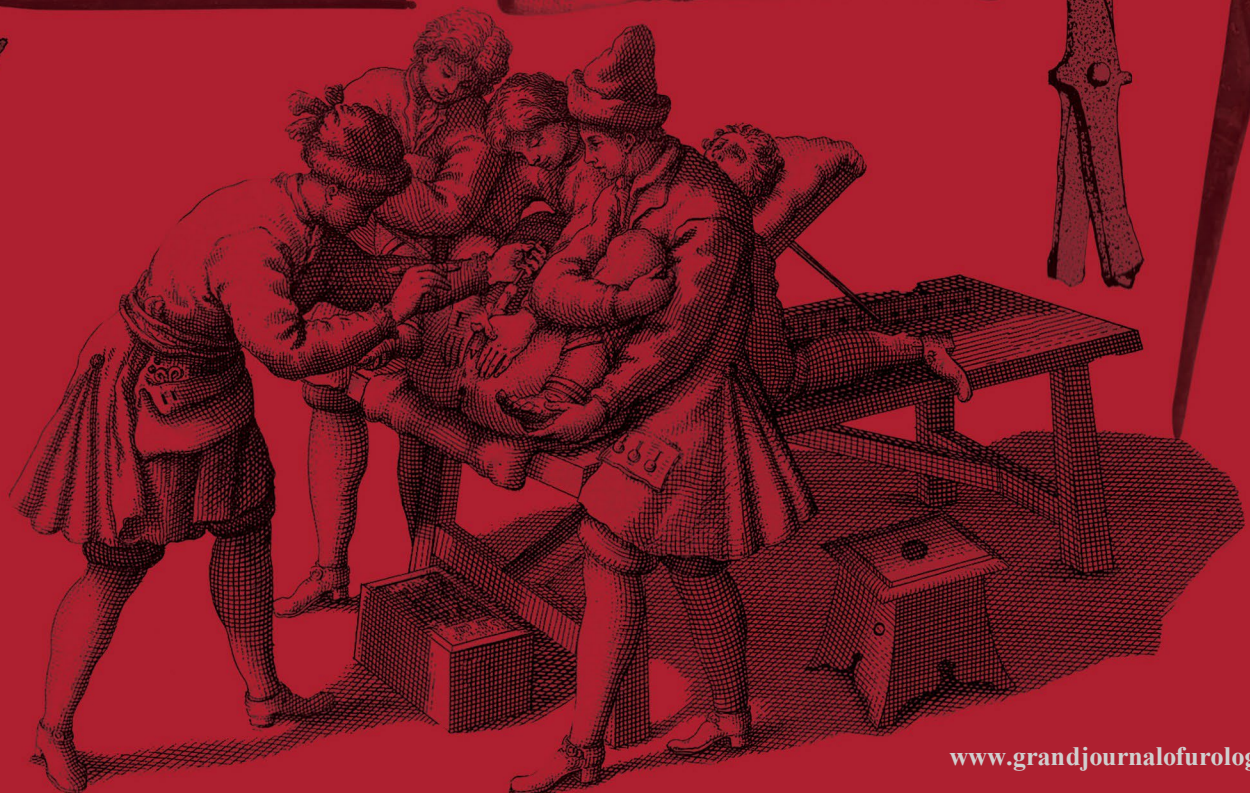


Grand Journal of UROLOGY

January 2024

Volume: 4

Issue: 1



ISSN: 2757-7163 | January 2024 | Volume: 4 | Issue: 1

Grand Journal of UROLOGY

Grand Journal of Urology is published three times a year
(January, May, September)
GJU is an open access, free and peer-reviewed journal

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Publication Type

Periodicals Electronic

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The target audience of the journal includes, urology specialists, residents in urology and other specialists who are interested in the field of urology. The journal aims to publish original scientific articles, clinical research, reviews, case reports, clinical images, editorial comments, and letters to the editor that are prepared in accordance with the ethical guidelines. Mini reviews, clinical updates, surgical techniques, and a guideline of guidelines that are in the scope of the journal are considered for publication and/or invited by the editor. All manuscripts must be submitted via the online submission system at www.grandjournalofurology.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications in the World.

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Keywords

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Research	12	4000	450	30	5
Review	5	5000	400	100	5
Case Report	8	1500	250	15	1
Clinical Image	5	500	N/A	10	0
Letters to the Editor	5	500	N/A	5	1

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[1], [3-5], [6,9], [8-12,16].

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- Book

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Contents

Editorial

Ekrem Guner

XII

Original Article

A Novel Hybrid Urology Education Model for Medical Students: A Urology Clinic Experience

Tıp Öğrencileri İçin Orijinal Hibrid Üroloji Eğitimi: Bir Üroloji Kliniği Deneyimi

Erdem Akbay, Erim Erdem, Selahittin Çayan, Murat Bozlu, Ercüment Ulusoy, Hasan Erdal Doruk, Mesut Tek

1-5

Does Migraine Prophylaxis Improve Overactive Bladder Symptoms? Prospective Observational Study

Migren Profilaksisi Aşırı Aktif Mesane Semptomlarını İyileştirir mi? Prospektif Gözlemsel Çalışma

Sinan Eliaçık, Aykut Başer, Funda Uysal Tan

6-11

Activity of Diosmin-Hesperidin in Kidney Ischemia-reperfusion Injury in Rats: Experimental Study

Ratlarda Böbrek İskemi-Reperfüzyon Hasarında Diosmin-Hesperidin'in Etkinliği: Deneysel Çalışma

Kenan Yalçın, Erim Ersoy

12-18

Effect of the Hounsfield Unit Calculated on the Non-contrast Computed Tomography of Kidney and Ureteral Stones on the Success of Fragmentation with a Holmium: YAG Laser in Ureterorenoscopy and Retrograde Intrarenal Surgery

Böbrek ve Üreter Taşlarının Kontrastsız Bilgisayarlı Tomografi Üzerinde Hesaplanan Hounsfield Ünitesinin Holmium Yag Laser ile Yapılan Üreterorenoskopi ve Retrograd İntrarenal Cerrahi Tedavisinde Fragmantasyon Üzerindeki Etkisi

Muhittin Atar, Abdullah Turan, Ali Haydar Yılmaz, Fatih Kürsat Yılmazel, İbrahim Karabulut, Sercan Sarı, Abdullah Gürel

19-24

Case Report

Partial Nephrectomy in Wilms Tumor: A Rarely Implemented Surgical Method

Wilms Tümöründe Parsiyel Nefrektomi: Çok Nadir Uygulanan Bir Cerrahi Yöntem

Kenan Yalçın

25-27

Prostate Cancer with Osteolytic Sternal Metastasis: A Rare Clinical Presentation

Osteolitik Sternal Metastazlı Prostat Kanseri: Nadir Bir Klinik Sunum

Somanatha Sharma, Kiritha Ranjani Ac, Sethu Ram Sharma

28-31

A Rare Clinical Condition That Can Mimic Bladder Malignancy: Primary Bladder Amyloidosis

Mesane Malignitesini Taklit Edebilen Nadir Bir Klinik Durum: Primer Mesane Amiloidozu

Saurabh Kumar Negi, Sandip Desai, Gaurav Faujdar, Ram Dayal Sahu, Somendra Bansal, Shivam Priyadarshi

32-34



Editorial

Dear colleagues,

I am honored to share with you the third issue of 2023 (volume 3, issue 3) of the Grand Journal of Urology (Grand J Urol) with the contributions of many respected researchers and authors.

Grand Journal of Urology (GJU) aims to carry written and visual scientific urology studies to academic platforms and to make significant contributions to the science of urology.

Our journal has been abstracted/indexed in Tubitak Ulakbim TR Index, DOAJ, EBSCOhost, J-Gate, Index Copernicus International, EuroPub, SciLit, ResearchGate, ScienceGate and Google Scholar international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by national and international databases.

In this issue of our journal, there are many valuable articles under the subheadings of General Urology, Neurourology, Urolithiasis and Urological Oncology. I hope that these carefully prepared articles will make important contributions to valuable readers, researchers and the urology literature.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles.

Respectfully yours

January 2024

Assoc. Prof. Ekrem GUNER, MD

Editor-in-Chief

A Novel Hybrid Urology Education Model for Medical Students: A Urology Clinic Experience

Tıp Öğrencileri İçin Orijinal Hibrid Üroloji Eğitimi: Bir Üroloji Kliniği Deneyimi

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Cite as: Akbay E, Erdem E, Çayan S, Bozlu M, Ulusoy E, Doruk HE, Tek M. A novel hybrid urology education model for medical students: A urology clinic experience. Grand J Urol 2024;4(1):1-5

Submission date: 03 April 2023 **Acceptance date:** 19 September 2023 **Online first:** 29 September 2023 **Publication date:** 19 January 2024

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Abstract

Objective: To compare traditional and hybrid model of education in urology among 4th-year medical students in terms of training success

Materials and Methods: In our urology clinic, the training success scores of seven randomly selected training groups among 4th-year medical students, who were trained with the traditional model between 1998-2018, and the 4th year medical students who were trained with the hybrid model between 2018-2020 and constituted five randomly selected training groups were compared. Of the total 582 medical students, included in the study, 278 (47.8%) were enrolled in the traditional model group, and 304 (52.2%) in the hybrid model group. The training was evaluated with hands-on applications and theoretical and oral exams. Differences between both male and female students and differences that may vary depending on different faculty members teaching the students were evaluated using multivariate logistic regression analysis.

Results: The training success rates were significantly higher in the hybrid model group (300/304; 98.7%) than in the traditional model group (261/278; 93.9%) [p:0.002]. Multivariate logistic regression analysis found that factors such as the number of training groups, gender of medical students, and evaluations of different faculty members did not affect the educational success rate.

Conclusion: The hybrid model could be accepted as a mobile education model in a sense. The exam results of medical students educated with the hybrid model were better than those receiving training with the traditional model which can be explained by the increased accessibility of medical students to education in the hybrid model without constraints of time and place. Additionally, it is thought that conducting the oral exam as a “structured oral exam” also contributed to these results.

Keywords: Traditional urology education model, hybrid urology education model, structured oral exam, mobil devices, youtube channel

Özet

Amaç: Dördüncü sınıf tıp öğrencilerinde üroloji stajı eğitimlerinde geleneksel ve hibrit eğitim modelinin eğitim başarısı açısından karşılaştırılması.

Gereçler ve Yöntemler: Üroloji kliniğimizde 1998-2018 yılları arasında geleneksel modelle eğitim gören 4.sınıf tıp öğrencileri arasından rastgele seçilmiş yedi eğitim grubu ile 2018-2020 yılları arasında hibrit modelle eğitim almış ve rastgele seçilmiş beş eğitim grubunu oluşturan 4. sınıf tıp öğrencilerinin eğitim başarı puanları karşılaştırıldı. Araştırmaya dahil edilen toplam 582 tıp öğrencisinin 278'i (%47,8) geleneksel model grubuna, 304'ü (%52,2) hibrit model grubuna kayıtlıydı. Eğitim, klinik uygulamalar, teorik ve sözlü sınavlarla değerlendirildi. Hem erkek hem de kız öğrenciler arasındaki farklar ve öğrencilere ders veren farklı öğretim elemanlarına bağlı değişebilecek farklılıklar çok değişkenli lojistik regresyon analizi kullanılarak değerlendirildi.

Bulgular: Eğitim başarı oranları hibrit model grubunda (300/304; %98,7), geleneksel model grubuna (261/278; %93,9) göre önemli ölçüde daha yüksekti [p:0,002]. Çok değişkenli lojistik regresyon analizinde eğitim gruplarının sayısı, tıp öğrencilerinin cinsiyeti ve farklı öğretim üyelerinin değerlendirmeleri gibi faktörlerin eğitim başarı oranını etkilemediği saptandı.

Sonuç: Hibrit eğitim modeli bir anlamda mobil eğitim modeli olarak kabul edilebilir. Hibrit modelle eğitim gören tıp öğrencilerinin sınav sonuçlarının geleneksel modelle eğitim alan öğrencilere göre daha iyi olması, tıp öğrencilerinin hibrit modelde zaman ve mekân kısıtlaması olmaksızın eğitime erişimlerinin artmasıyla açıklanabilir. İlave olarak sözlü sınavın “yapılandırılmış sözlü sınav” olarak yapılmasının da bu sonuçlara katkısı olduğu düşünülmektedir.

Anahtar kelimeler: Geleneksel üroloji eğitim modeli, hibrid üroloji eğitim modeli, yapılandırılmış sözlü sınav, mobil cihazlar, youtube kanalı

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Introduction

Advances in telecommunication technology such as mobile internet devices have changed medical educational practices in academic centers. Today, the biggest benefit of the use of mobile phones and laptops for education is that they provide a great deal of freedom regarding the time and place at which information is obtained [1]. In recent years, the transfer of educational programs to virtual platforms has begun to take its place in medical education. Applications used in other fields of education have become important tools when used for medical education [2]. The development of instant messaging applications, especially on mobile phones, has gained popularity among healthcare professionals and medical students.

Traditional medicine education continues to be the cornerstone of many educational institutions in the world. In addition to traditional education, the use of mobile devices will be essential for the education and exams of medical students, interns, and medical residents [3-5]. There is limited information in the literature about the place of hybrid models in urology. In this study, we have compared training success rates between traditional and hybrid model of education among 4th-year medical students rotating in urology clinics of a university hospital.

Materials and Methods

At the beginning of training, all 4th-year medical students downloaded urology training applications and, subscribed to the urology training videos channel from YouTube, administered by our clinics, and were informed with detail concerning hybrid structured-oral exams in the hybrid model group.

The total duration of teaching in urology for 4th-year medical students was 3 weeks. In either group, the theoretical lessons were presented by seven academic members during training period. Practical activity report cards were given to the students at the start of training which they filled out with practical activities they carried out such as patient examinations, urethral catheterization, minor surgical intervention, etc. The two groups had the same practical and theoretical objectives. The students that had $\geq 60/100$ grades on their report cards were considered successful at the practical exam at the end of training and gained the right to sit for the theoretical exam. Unsuccessful students were excluded from the training program.

In either group, the theoretical exam consisted of two parts; a test exam and an oral exam (traditional or hybrid). The test exam was organized as a multiple-choice test. The overall theoretical grade was calculated by the arithmetic mean of the test and oral exam grades.

In the hybrid group, the hybrid oral exam was applied with the help of software developed by our clinic using Microsoft Access. The questions, asked in an oral exam by an academic member, were randomly chosen among question groups at Urology Training Applications that also had the answers to them.

In either group, theoretical oral exams were done by seven academic members for seven student groups. The students were examined again by a different academic member in case they failed the oral exam, and then the theoretical oral exam grades were estimated, and expressed as the arithmetic mean of the final grades assigned by both academic members. The medical students who had both practical and theoretical exam grades of ≥ 60 were evaluated as successful. The final grade was estimated, and

expressed as the arithmetic mean of the practical and theoretical exam grades. The students who scored less than 60 in the practical exam weren't allowed to enter the theoretical exam and had to repeat the internship. However, students who scored less than 60 on the theoretical exam were given a chance to resit the exam. If they failed to surpass 60 points after the resit exam, they had to repeat the internship as well. The study protocol was reviewed and approved by the Mersin University Clinical Research Ethics Committee (04.26.2023/294).

Statistical Analysis

Descriptive statistics for continuous variables were expressed and also tabulated as mean \pm standard deviation, and for categorical variables as frequencies, and percentages (%). T-test were used to compare continuous variables between the two groups. One-way ANOVA and post- hoc tests were used to compare continuous variables among the groups, and chi-square test was used for qualitative variables in patient groups. In addition, multivariate logistic regression analysis was done to present factors predicting training success. Statistical analysis was performed using Statistical Package for the Social Sciences software (version 21.0, IBM SPSS), and a p-value of less than 0.05 was considered statistically significant.

Results

Of the total 582 medical students (352 males and 230 females), included in the study, 278 (47.8%) were in the traditional model group, and 304 (52.2%) were in the hybrid model group. The mean grades for all items of the exam were higher in the hybrid model group (**Table 1**). All students were divided into four groups by gender and education model. The hybrid model group that consisted of female students had the highest mean grades in all items of the exam (**Table 2**). All results of these groups are shown clearly in **Figure 1**.

Multivariate logistic regression analysis was done to present factors predicting training success among the students. The number of training groups, gender of the medical students and evaluation by a different academic member have predicted the training success in both groups ($p > 0.05$ and $p > 0.05$, respectively). Based on results of the one-way ANOVA test, the mean training grades evaluated by different academic members were not significantly different in the hybrid model ($p: 0.072$), but they differed significantly in the traditional model ($p: 0.004$).

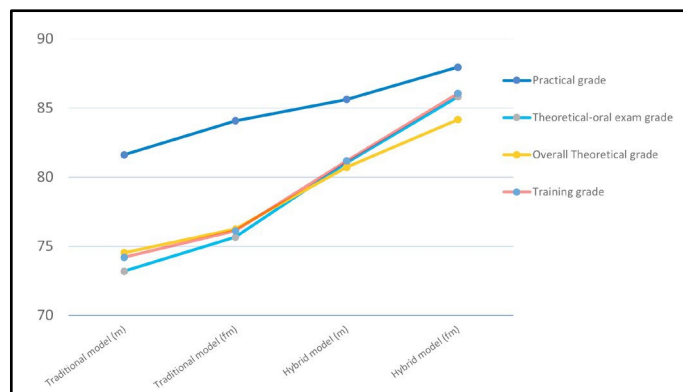


Figure 1. Mean grades by education model and gender

Table 1. Comparisons of the mean grades for all items of exam in education model groups

Item	Group*	Mean	Std. deviation	Std. error mean	P**
Practical grade	1	82.45	7.52	0.45	0.000
	2	86.65	6.64	0.38	
Theoretical (test exam grade)	1	76.20	9.71	0.51	0.000
	2	81.40	9.50	0.54	
Theoretical (oral exam grade)	1	74.04	18.82	1.13	0.000
	2	83.15	17.52	1.00	
Overall theoretical grade	1	75.11	11.89	0.71	0.000
	2	82.28	10.75	0.62	
Final grade	1	75.06	20.06	1.20	0.000
	2	83.68	11.12	0.64	

* Group 1: Traditional model; Group 2: Hybrid model; ** Student's t test

Table 2. Comparisons of the mean grades for all items of exam in education&gender groups

Item	Group*	Mean	Std. deviation	Std. error mean	p (Anova)	Post Hoc Tests (Tamphane)
Practical grade	1	81.61	7.87	0.58	0.000	1 - 2 : p = 0.033 1 - 3 : p = 0.000 1 - 4 : p = 0.000 2 - 3 : p = 0.363 2 - 4 : p = 0.000 3 - 4 : p = 0.012
	2	84.08	6.52	0.67		
	3	85.62	6.89	0.52		
	4	87.95	6.09	0.52		
Theoretical (test exam grade)	1	75.87	10.85	0.80	0.000	1 - 2 : p = 0.939 1 - 3 : p = 0.000 1 - 4 : p = 0.000 2 - 3 : p = 0.004 2 - 4 : p = 0.000 3 - 4 : p = 0.340
	2	76.83	7.02	0.72		
	3	80.54	10.37	0.79		
	4	82.49	8.19	0.70		
Theoretical (oral exam grade)	1	73.19	19.67	1.45	0.000	1 - 2 : p = 0.860 1 - 3 : p = 0.001 1 - 4 : p = 0.000 2 - 3 : p = 0.111 2 - 4 : p = 0.000 3 - 4 : p = 0.087
	2	75.66	17.07	1.75		
	3	81.04	19.07	1.46		
	4	85.82	14.98	1.29		
Overall theoretical grade	1	74.53	12.85	0.94	0.000	1 - 2 : p = 0.766 1 - 3 : p = 0.000 1 - 4 : p = 0.000 2 - 3 : p = 0.006 2 - 4 : p = 0.000 3 - 4 : p = 0.029
	2	76.24	9.74	0.99		
	3	80.71	11.95	0.91		
	4	84.16	8.69	0.75		
Final grade	1	74.20	20.59	1.52	0.000	1 - 2 : p = 0.892 1 - 3 : p = 0.000 1 - 4 : p = 0.000 2 - 3 : p = 0.132 2 - 4 : p = 0.000 3 - 4 : p = 0.002
	2	76.11	18.99	1.95		
	3	81.17	13.93	1.07		
	4	86.05	4.99	0.43		

* Group 1: Traditional model (male); Group 2: Traditional model (female); Group 3: Hybrid model (male); Group 4: Hybrid model (female)

Discussion

In this study, in addition to the traditional model, we have created a hybrid model with applications that were accessed through mobile devices for the 4th-year medical students rotating in urology. In addition, we have supported this hybrid model by changing traditional oral exams to structured oral exams with the use of a Microsoft Access application.

Although traditional medical education is the cornerstone, the development of new methods such as mobile messaging attracts the attention of educators [6]. Especially during the COVID-19 pandemic, medical education had to be carried out virtually in many countries of the world. Indeed, Pandya et al. have shown that the use of these easily accessible applications can improve nephrology education [1]. Various studies have examined the use of instant messaging applications in medical education and have shown that students' learning motivation and satisfaction increase depending on these applications [7,8]. In studies evaluating online and offline education in dermatology, it has been suggested that online teaching presents some difficulties [9,10]. Recently, Shahar et al. evaluated the role of secure instant messaging applications, and Siilo which is also a secure instant messaging application in medical education [11]. They demonstrated that the "Siilo" appeared to be a promising tool for facilitating case-based learning in a medical setting and it was found to be user-friendly and secure, with a high level of satisfaction reported by participants.

To the best of our knowledge, these two educational models for medical students rotating in urology have not been compared so far. In our study, the mean success grades for all items of the exam were significantly higher in the hybrid education model compared to the traditional education (**Table 1**). A remarkable amount of increase was observed in success rates of both male and female students in the hybrid group, compared to the traditional model. Female medical students in both groups were more successful than their male counterparts (**Table 2, Figure 1**). In multivariate logistic regression analysis, the sample size of the training group, students' gender, and evaluation by different academic members did not predict the training success in either group. However, based on the one-way ANOVA test results, the mean training grades given by academic members were not significantly different in the hybrid model ($p:0.072$) but differed significantly in the traditional model ($p:0.004$). We have attributed this issue to the standardization of questions and answers in the structured oral exams.

This study has several limitations. First of all, it was done only in our own center. Second, different applications were not compared in our study. On the other hand, the strength of our study is that it will shed light on future multicenter studies performed with a larger sample size in the field of urology education.

Conclusion

We have observed that medical students who received training with our hybrid model were greatly interested in urology residency programs. We have arrived at the conclusion that a hybrid model, coupled with structured oral exams, can create an environment where medical students will achieve the maximum possible success.

Ethics Committee Approval: The study protocol was reviewed and approved by the Mersin University Clinical Research Ethics Committee (ethics committee approval date and number: 26.04.2023/294).

Informed Consent: An informed consent was obtained from all the patients.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.A., E.E.; Design – E.A., E.E.; Supervision – S.C., M.B., E.U.; Resources – H.E.D., M.T.; Materials – H.E.D., M.T.; Data Collection and/or Processing – E.U., H.E.D., M.T.; Analysis and/or Interpretation – E.U., H.E.D., M.T.; Literature Search – H.E.D., M.T.; Writing Manuscript – E.A., E.E.; Critical Review – E.A., E.E., S.C.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors state that they have not received any funding.

Supplementary Materials

1. Urology Internship- Mobile Application (Google Play)
<https://play.google.com/store/apps/details?id=com.akbay.erdem.urologytraining&gl=TR>
2. Mobile Urology Internship & Internship Exam Guide (App Store)
http://www.mersinuroloji.com/?smd_process_download=1&download_id=542
3. Urology False-True Hybrid Quiz (Google Play)
<https://play.google.com/store/apps/details?id=com.akbay.erdem.urologyhibridquiz>
4. Urology Multiple Choice Quiz (Google Play)
<https://play.google.com/store/apps/details?id=com.akbay.erdem.multiplechoice>
5. Mersin Urology Structured Oral Exam
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Does Migraine Prophylaxis Improve Overactive Bladder Symptoms? Prospective Observational Study

Migren Profilaksisi Aşırı Aktif Mesane Semptomlarını İyileştirir mi? Prospektif Gözlemsel Çalışma

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Cite as: Eliaçık S, Başer A, Uysal Tan F. Does migraine prophylaxis improve overactive bladder symptoms? Prospective observational study. Grand J Urol 2024;4(1):6-11

Submission date: 19 May 2023 **Acceptance date:** 20 September 2023 **Online first:** 02 October 2023 **Publication date:** 19 January 2024

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Abstract

Objective: In this study, we aimed to investigate whether there would be any improvement in symptoms of overactive bladder (OAB) after migraine prophylaxis in patients with chronic migraine (CM) and OAB.

Materials and Methods: The study group consisted of women aged 19 to 64 years diagnosed as CM according to current International Headache Society criteria, and OAB using the OAB-V8 (Overactive Bladder Inquiry Form - V8) and ICIQ-SF (International Consultation on Incontinence Questionnaire Short Form) forms as well as clinical evaluation in the neurology and urology clinics. 63 patients informed and agreed to enter the study were started migraine prophylaxis and evaluated after 6 months for comparison of pre-treatment and post-treatment VPS (visual pain scale), OAB-V8, and the ICIQ-SF scores. Flunarizine, topiramate, venlafaxine and propranolol were used in the treatment of patients.

Results: The mean age of 63 women included in the study was 39.15 ± 8.74 (19-64) years. The mean Body Mass Index (BMI) of the patients was determined as 25.41 ± 3.64 (16.4-35.6) kg/m². After migraine prophylaxis, VPS, OAB-V8 and ICIQ-SF scores decreased significantly in the entire patient group ($p < 0.05$). Statistically significant changes were found in the values of VPS, OAB-V8 and ICIQ-SF in the topiramate or propranolol treated groups. In the flunarizine group, there was a significant statistical response in the VPS and OAB-V8 scores, while there were no significant changes in the ICIQ-SF and OAB-V8 scores in the venlafaxine-treated group.

Conclusion: The beneficial effect of migraine prophylaxis on OAB symptoms support somewhat shared etiopathogenesis for both disorders. However, the series is small and considering the involvement of multifactorial factors and complex physiopathology for both disorders further studies are necessary to reveal the underlying mechanisms and clinical impacts.

Keywords: Migraine, overactive bladder, incontinence, neurourology, functional urology

Özet

Amaç: Bu çalışmada kronik migren ve komorbid olarak aşırı aktif mesane semptomları olan hastalarda migren profilaksisi sonrası aşırı aktif mesane semptomlarında düzelme olup olmayacağını araştırmayı amaçladık.

Gereçler ve Yöntemler: Çalışma grubu, mevcut Uluslararası Baş Ağrısı Derneği kriterlerine göre kronik migren tanısı alan 19-64 yaş arası kadınlardan oluşmaktaydı. Kronik migrene komorbid olarak aşırı aktif mesanesi olan vakalar çalışmaya dahil edilme kriterlerine göre seçildi. OAB-V8 (Aşırı Aktif Mesane Sorgulama Formu - V8) ve ICIQ-SF (Uluslararası İnkontinans Danışma Anketi Kısa Formu), VAS (vizüel ağrı skala) formları uzman nörolog ve ürolog tarafından değerlendirildi. Bilgilendirilen ve çalışmaya katılmayı kabul eden 63 hastaya migren profilaksisi başlandı. Tedavi başlangıcında ve tedavi sonrası altıncı ayda anketler tekrar uygulandı. Hastaların tedavisinde flunarizin, topiramet, venlafaksin ve propranolol kullanıldı.

Bulgular: Çalışmaya dahil edilen 63 kadının yaş ortalaması 39.15 ± 8.74 (19-64) yıldı. Hastaların ortalama vücut kitle indeksi 25.41 ± 3.64 (16.4-35.6) kg/m² olarak belirlendi. Migren profilaksisinden sonra; VAS, OAB ve ICIQ skorları anlamlı olarak azaldı ($p < 0.005$). Topiramet veya propranolol ile tedavi edilen gruplarda VAS, OAB-V8 ve ICIQ-SF değerlerinde istatistiksel olarak anlamlı değişiklikler bulundu. Flunarizin grubunda VPS ve OAB-V8 skorlarında anlamlı istatistiksel değişiklikler saptanırken, venlafaksin ile tedavi edilen grupta ICIQ-SF ve OAB-V8 skorlarında anlamlı bir değişiklik tespit edilmedi.

Sonuç: Migren profilaksisinin aşırı aktif mesane semptomları üzerindeki yararlı etkisi, her iki hastalık içinde ortak olabilecek etiopatogenezi desteklemektedir. Ancak, çalışma serimiz küçüktür ve her iki hastalık için de çok faktörlü ve karmaşık fizyopatolojinin katılımı göz önüne alındığında, altta yatan mekanizmaları ve klinik etkileri ortaya çıkarmak için daha geniş kapsamlı çalışmalar gereklidir.

Anahtar kelimeler: migren, aşırı aktif mesane, inkontinans, nöroüroloji, fonksiyonel üroloji

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Introduction

Chronic migraine (CM) is a disease that negatively affects the quality of life of individuals, and it is more common in women, it affects approximately 12% of the general population. Similarly, overactive bladder (OAB), the most common subtype of urinary incontinence, has also an adverse effect on life quality. Unfortunately, most women hardly reveal their complaints, living with the course despite worsening of OAB symptoms. Altman et. al. have documented the association between OAB and various somatic disorders [1]. The comorbidity between CM and OAB was also supported by other studies, however, both disorders have complex multifactorial etiopathogenesis affected by both environmental and genetic factors [2]. Thus, the physiopathological basis of the possible association between CM and OAB remains obscure. Based on the study in which we found an association between CM and OAB; suspecting a common etiopathogenesis behind the comorbidity, we aimed to determine whether migraine prophylaxis would affect the symptom severity of OAB [3]. Thus, we evaluated the changes in OAB symptoms in patients given migraine prophylaxis treatment.

Materials and Methods

The study was a cross-sectional prospective study approved by the Hitit University School of Medicine Ethics Committee (349/06.01.2021) and conducted by STROBE guidelines for reporting observational studies (www.strobestatment.org) and the Declaration of Helsinki. All participants gave informed consent for this study.

This study group consisted of women aged 19 to 64 years diagnosed as CM according to the International Headache Society (IHS) criteria [4]. Patients were evaluated by urology and neurology physicians according to exclusion and inclusion criteria and participated in the study. The exclusion criteria were determined as follows: Urinary tract infection, neurogenic bladder and other etiology that can cause a neurogenic bladder (such as spinal cord injury, peripheral nerve disease), history / diagnosis of interstitial cystitis, lower urinary tract symptoms due to bladder stone and pelvic mass, symptomatic or severe pelvic organ prolapse, vaginal cancers, concomitant diseases that cause fluid shifts, such as congestive heart failure, cirrhosis, and pulmonary edema, use of diuretics and similar medicines, excessive fluid consumption (assessed by at least 3 days of voiding diary).

Questionnaires and Definitions

The individuals participating in the study were evaluated by the neurology and urology physician with a study questionnaire consisting of four parts; (I) Patient demographics; the gender, age, body mass index (BMI) of the participants, (II) Migraine ID test for the diagnosis of CM, which was any headache occurring ≥ 15 days per month for at least 3 months with migraine features on ≥ 8 days every month, headache without excessive drug use and non-attributable to another reason, and the visual pain scale (VPS) scored between 0 and 10 points for qualitative evaluation of migraine pain, (III) OAB-V8 (Overactive Bladder Inquiry Form - V8) [5], (IV) ICIQ-SF (International Consultation on Incontinence Questionnaire Short Form) [6].

Accordingly, patients diagnosed as having both CM and OAB were identified and evaluated as reported before [3]. In this study, we aimed to investigate whether there would be any improvement in symptoms of OAB after migraine prophylaxis in patients with CM and OAB, as a follow-up. Patients informed and agreed to enter the study who were started migraine prophylaxis were evaluated after 6 months using the VPS, OAB-V8, and ICIQ-SF forms. Pre-treatment (before prophylaxis) and post-treatment (after prophylaxis) symptoms were compared. There was a total of 63 women patients included in the study. Migraine prophylaxis was made using topiramate (22 patients), venlafaxine (14 patients), propranolol (12 patients), and flunarizine (15 patients), according to doctor and patient preference and related health issues, however, drugs that would affect bladder dynamics and used in the treatment OAB were avoided. Multiple agents were used and randomly selected (if no comorbid condition necessitating the need for a particular preference was present such as depression or epilepsy) to prevent selection bias and specific drug effects. None of the patients included in the study was given any medication for the treatment of OAB as this could certainly affect the results.

Statistical Analysis

Statistical analyses were performed using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA Hitit University Licensed) package program. The mean age of 63 women included in the study was 39.25 ± 9.21 (19-64) years. The mean BMI of the patients was determined as 25.29 ± 3.61 (16.4-33.3) kg/m^2 . Our analyses were performed with the SPSS 22.0 program and were studied at a 95% confidence level. In our analysis, parametric dependent groups t-test and ANOVA test were used. The Analysis of the pre-and post-treatment in the group separation and the whole group was analyzed by the dependent group's t-test.

Results

In the topiramate group; the VPS score change is significant ($p < 0.05$). While the mean before the treatment was 6.77, it decreased to 3.91 with a decrease of 2.86 points after treatment. OAB score change is significant ($p < 0.05$). While the average was 15.23 before treatment, it decreased to 10.55 with a decrease of 4.68 points after treatment. ICIQ-SF score change is significant ($p < 0.05$). While the average was 5.95 before treatment, it decreased to 4.45 with a decrease of 1.50 points after treatment.

In the venlafaxine group; the change in VPS score is significant ($p < 0.05$). While the average was 6.64 before treatment, it decreased to 4.50 with a decrease of 2.14 points after treatment. The change in OAB-V8 and ICIQ-SF scores is not significant ($p > 0.05$).

In the propranolol group; the change in VPS score is significant ($p < 0.05$). While the average was 7.00 before treatment, it decreased to 3.25 with a decrease of 3.75 points after treatment. OAB-V8 score change is significant ($p < 0.05$). While the average was 15.58 before treatment, it decreased to 9.42 with a decrease of 6.17 points after treatment. ICIQ-SF score change is significant ($p < 0.05$). While the average was 7.33 before the treatment, it decreased to 4.42 with a decrease of 2.92 points after treatment.

Table 1. Investigation of pre-and post-treatment variation in the whole group and between drug groups

Group		Mean	SD	Change	t	p
Topiramate	Pre. T. VPS.	6,77	0,97	2,86	5,016	,000*
	Post. T. VPS.	3,91	2,16			
	Pre. T. OABS	15,23	7,46	4,68	4,092	,001*
	Post. T. OABS	10,55	5,27			
	Pre. T. ICIQS	5,95	3,68	1,50	2,925	,008*
	Post. T. ICIQS	4,45	3,05			
Venlafaxine	Pre. T. VPS	6,64	1,08	2,14	3,944	,002*
	Post. T. VPS	4,50	2,10			
	Pre. T. OABS	13,86	6,68	3,50	2,147	,051
	Post. T. OABS	10,36	5,14			
	Pre. T. ICIQS	6,00	3,14	1,36	2,032	,063
	Post. T. ICIQS	4,64	2,87			
Propranolol	Pre. T. VPS	7,00	1,41	3,75	7,156	,000*
	Post. T. VPS	3,25	1,82			
	Pre. T. OABS	15,58	5,21	6,17	5,679	,000*
	Post. T. OABS	9,42	5,33			
	Pre. T. ICIQS	7,33	2,19	2,92	4,037	,002*
	Post. T. ICIQS	4,42	1,83			
Flunarizine	Pre. T. VPS	6,27	1,10	1,53	3,617	,003*
	Post. T. VPS	4,73	1,44			
	Pre. T. OABS	14,73	7,87	3,40	2,241	,042*
	Post. T. OABS	11,33	6,01			
	Pre. T. ICIQS	5,93	4,38	1,47	1,798	,094
	Post. T. ICIQS	4,47	4,03			
Total	Pre. T. VPS	6,67	1,12	2,56	8,991	,000*
	Post. T. VPS	4,11	1,96			
	Pre. T. OABS	14,87	6,88	4,40	6,489	,000*
	Post. T. OABS	10,48	5,34			
	Pre. T. ICIQS	6,22	3,48	1,73	5,200	,000*
	Post. T. ICIQS	4,49	3,03			

Pre-T VPS: Pre-treatment visual pain scale; Post-T VAS: Post-treatment visual analog scale; Pre-T OABS: Pre-treatment Overactive Bladder Inquiry Form Score; Post-T OABS: Post-treatment Overactive Bladder Inquiry Form Score; Pre-T ICIQS: Pre-treatment International Consultation on Incontinence Questionnaire Score; Post-T ICIQS: Post-treatment International Consultation on Incontinence Questionnaire Score

In the flunarizine group; the change in VPS score is significant ($p < 0.05$). While the average was 6.27 before treatment, it decreased to 4.73 with a decrease of 1.53 points after treatment. OAB-V8 score change is significant ($p < 0.05$). While the average was 14.73 before treatment, it decreased to 11.33 with a decrease of 3.40 points after treatment. ICIQ-SF score change is not significant ($p > 0.05$).

In the whole patient group; the change in VPS score is significant ($p < 0.05$). While the average was 6.67 before treatment, it decreased to 4.11 with a decrease of 2.56 points after treatment. OAB-V8 score change is significant ($p < 0.05$).

While the average was 14.87 before treatment, it decreased to 10.48 with a decrease of 4.40 points after treatment. ICIQ-SF score change is significant ($p < 0.05$). While the average was 6.22 before treatment, it decreased to 4.49 with a decrease of 1.73 points after treatment.

ANOVA test was used to examine the pre-and post-treatment questionnaires in terms of drug groups. There were no significant differences between the drug groups in terms of VAS, OAB-V8, and ICIQ-SF measurements before and after treatment ($p > 0.05$). Table 1 summarized the investigation of pre-and post-treatment variation in the whole group and between drug groups.

Discussion

Migraine is a lifespan neurological disorder. Migraine involves recurrent, severe head pain and associated various symptoms while attacks evolve over different phases with specific neural mechanisms and symptoms. In some patients, migraine can develop into a chronic form and adversely affect a person's social life. The mechanisms behind the chronic migraine remain detailed and unknown, genetic, epigenetic factors, inflammatory processes, environmental triggering, and central sensitization might play an important role [7].

Preventive therapy for migraine aims to decrease headache frequency and severity for a better quality of life and progression to CM for episodic patients. There are many agents used for migraine prophylaxis with individual benefits and drawbacks affecting the selection. Beta-blockers; metoprolol, and propranolol are beneficial in hypertensive while the antidepressants like amitriptyline and venlafaxine are preferred in patients with depression or anxiety disorders, and insomnia. Anticonvulsants; valproate acid and topiramate can be used. Especially in women of childbearing age or patients with Raynaud's phenomenon calcium channel blockers, verapamil, and flunarizine might be prescribed. Among other agents are calcitonin gene-related peptide antagonists like erenumab, and galcanezumab [8].

OAB is a condition defined as urinary urgency, usually accompanied by frequent urination and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [9]. Urinary incontinence, like a migraine, negatively affects the psychological health and quality of life of women [10]. Unfortunately, few people seek help for this symptom because of embarrassment and stigma [11]. Urinary incontinence accompanying CM will worsen both the quality of life and stigmatization. Both CM and OAB are common in women over the age of 40 and their prevalence will increase over the years due to increasing awareness [12,13].

The comorbidity between CM and OAB will also be supported by comprehensive studies. Both disorders have common factors underlying the relationship in etiopathogenesis, as well as their complex multifactorial etiopathogenesis that remains unclear.

When we examined the literature, we encountered publications that could explain similar etiopathogenesis. Activation of the trigeminovascular system results in the release of vasoactive neuropeptides particularly calcitonin gene-related peptide (CGRP) that induce vasodilation and neurogenic inflammation in leptomeningeal and extracranial vessels causing acute migraine pain. Repeated peripheral activation might sensitize central pain pathways, transforming episodic migraine into a chronic condition in predisposed patients. Similarly, women with OAB have increased density of suburothelial nerve fibers that are immune-reactive for CGRP supporting that increased, aberrant sensory afferent activity might be a factor in OAB pathophysiology [14,15].

Botulinum toxin A treatment is effective in both OAB and CM [16]. Botulinum toxin A has been shown to reduce increased CGRP levels in CM patients [17] and to inhibit CGRP release in the bladder of experimental animals [18]. Finally, central brain structures implicated in OAB and CM pathophysiology, such as the prefrontal cortex, hypothalamus, or periaqueductal grey nuclei are common [19]. The association between CM and OAB based on shared pathophysiological mechanisms should be supported by

further epidemiological studies. In clinical practice, CM as well as OAB patients could be warned about possible comorbidity. In this study, we aimed to determine whether migraine prophylaxis would affect the symptom severity of OAB, and to our knowledge, this is the first study. Based on our previous "Clinical Reflection of OAB Migraine Comorbidity: Prospective Cross-sectional study" data, we compared the VPS scores and OAB symptom scores of CM patients with OAB after six months of prophylactic migraine treatment and found that patients had a regression in both VPS, ICIQ-SF scores and OAB symptoms.

Migraine and OAB are two diseases that both affect the quality of life and psychosocial health. Getting relief, the migraine pain might provide better tolerance and struggle for OAB symptoms. Thus, a psychological benefit and better self-esteem might be responsible for the beneficial effect of migraine prophylaxis on OAB symptoms. It is important not only to feel healthy but also to get rid of the psychological stress of CM and/or OAB symptoms. However, symptoms of OAB hurt the quality of life as these patients are required to identify toilet locations before leaving home and avoid collective activities. Thus, the physical and psychosocial problems of OAB might be hardly bearable in some patients themselves. Similarly, migraine attacks also cause a person to stay away from social activities.

Similar lifestyle changes are recommended in the treatment of migraine and OAB. Lifestyle changes are advised in both disease processes and found to be beneficial but usually insufficient. For OAB, adequate and appropriate fluid intake is advised. Insufficient fluid intake or fluid restriction may play a role in the development of urgency, frequent urination, and urinary tract infections by increasing urine concentration, irritating the bladder mucosa, and reducing the functional capacity of the bladder [19,20]. Studies have shown that the removal of artificial sweeteners and food such as highly spicy foods, citrus fruits, and tomato-containing products from the diet can play a role in the treatment of incontinence [21]. It is recommended to use similar dietary restrictions in migraine patients to reduce the frequency of attacks. As stated, before none of the patients included in the study was given any medication for the treatment of OAB, such as muscarinic receptor antagonists, beta-3 agonists, and desmopressin as this could certainly affect the results. Also, conservative measures specific to OAB were neglected such as timed voiding, special dietary habits (like avoidance of caffeine), and so on. Sleep adjustment, adequate fluid intake, diet, and weight control in necessary patients were recommended for migraine patients. Similar measures might be beneficial for OAB symptoms. Adequate and appropriate fluid intake serves as a quick washout of irritants from the bladder and produces diluted urine [19,20]. Nuotio et al., in their population-based study involving 1059 women and men between the ages of 60 and 89, found a relationship between smoking and urinary urgency, but it was not confirmed by others [22-24]. As studies have shown the relationship between smoking and migraine, cessation of smoking should be recommended in comorbid patients [25]. Nevertheless, lifestyle and dietary adjustments can help manage both migraine and OAB symptoms and quality of life improvement. We have recommended the above-mentioned lifestyle recommendations in addition to prophylactic treatment in CM, thus the regression in OAB symptoms might be partially

influenced. In OAB clinical spectrum conservative measures are usually insufficient in most of the patients, thus attributing the benefit solely to lifestyle changes is not logical.

OAB results in a decrease in the quality of life and an increase in both sensory and affective qualities of pain [26]. The severity of pain is increased in parallel with the severity of symptoms in OAB patients. This result, independent of the effect of OAB on emotional state, supports the hypothesis that central sensitization predisposes to pain syndromes in the pathophysiology of OAB. According to these results, it can be emphasized that patients with OAB may be predisposed to pain syndromes as well as lower urinary tract symptoms and that clinicians should consider this during the evaluation of patients [27].

A study in the literature found that about 30% of OAB patients were accompanied by depression, and these patients complained of more severe OAB symptoms [28]. Some of the agents used in migraine prophylaxis are antidepressants and serve dual benefits, especially in these cases. Tricyclic antidepressants are competitive antagonists of muscarinic acetylcholine receptors, the predominant class of acetylcholine receptors in the brain. However, these agents also block muscarinic receptors in other sites of the body producing symptoms such as blurred vision, dry mouth, and urinary retention. Antidepressants particularly amitriptyline are used in migraine prophylaxis and avoided in this study because of marked anticholinergic properties that are beneficial for OAB patients. Topiramate is an antiepileptic and carbonic anhydrase inhibitor used to treat chronic migraines and does not affect the bladder. Antidepressants, venlafaxine is a serotonin-norepinephrine reuptake inhibitor and receptor data state anticholinergic effects are minimal. However anticholinergic side effects including dry mouth and constipation might be encountered. It is not expected to be beneficial for symptoms of OAB in its therapeutic range. Flunarizine is a calcium antagonist and does not affect the bladder. As stated before drugs that would affect bladder dynamics and be used in the treatment of OAB were excluded and multiple agents were used and randomly selected to prevent selection bias and specific drug effects. None of the patients included in the study was given any medication for the treatment of OAB as this could certainly affect the results. Although the small number of cases in our study is considered a limitation, statistically we obtained significant results in all drug subgroups. We could not obtain statistically significant results in OAB-V8 and ICIQ-SF in the venlafaxine group and ICIQS total scores in the flunarizine group. We think that we will shed light on studies aimed at etiopathogenesis with extensive studies involving more cases.

Conclusion

The association between migraine and OAB was confirmed and supported by the favorable effect of CM prophylaxis on OAB symptoms in this study. The beneficial effect of migraine prophylaxis on OAB symptoms supports somewhat shared etiopathogenesis for both disorders. However, the series is small, and considering the involvement of multifactorial factors and complex physiopathology for both disorders further studies are necessary to reveal the underlying mechanisms and clinical impacts.

Ethics Committee Approval: The study was a cross-sectional prospective study approved by the Hitit University School of Medicine Ethics Committee (ethics committee approval date and number: 06.01.2021/349).

Informed Consent: An informed consent was obtained from all the patients.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – S.E., A.B., F.U.T.; Design – S.E., A.B., F.U.T.; Supervision – S.E., A.B., F.U.T.; Resources – S.E., A.B., F.U.T.; Materials – S.E., A.B., F.U.T.; Data Collection and/or Processing – S.E., A.B., F.U.T.; Analysis and/or Interpretation – S.E., A.B., F.U.T.; Literature Search – S.E., A.B., F.U.T.; Writing Manuscript – S.E., A.B., F.U.T.; Critical Review – S.E., A.B., F.U.T.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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

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Activity of Diosmin-Hesperidin in Kidney Ischemia-reperfusion Injury in Rats: Experimental Study

Ratlarda Böbrek İskemi-Reperfüzyon Hasarında Diosmin-Hesperidin'in Etkinliği: Deneysel Çalışma

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Cite as: Yalçın K, Ersoy E. Activity of diosmin-hesperidin in kidney ischemia-reperfusion injury in rats: Experimental study. Grand J Urol 2024;4(1):12-8

Submission date: 16 August 2023 **Acceptance date:** 02 November 2023 **Online first:** 06 November 2023 **Publication date:** 19 January 2024

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Abstract

Objective: We aimed to investigate the activity of diosmin-hesperidin (DAFLON®) in ischemia-reperfusion injury in the rat kidney.

Materials and Methods: Twenty-four Wistar rats were used for the experimental study. Each group comprised of 8 subjects. Sham group (Group 1) was nephrectomized for histopathologic examination and blood samples were obtained for biochemical analysis. Control group (Group 2) was subjected to ischemia for 1 hour and reperfusion for 24 hours, then they were nephrectomized for histopathologic examination and blood samples were taken for biochemical analysis. Treatment group (Group 3) was given 80 mg/kg diosmin-hesperidin combination (DAFLON®) for 10 days and subjected to ischemia for 1-hour and reperfusion for 24 hours, then they were nephrectomized for histopathologic examination and blood samples were obtained for biochemical analysis.

Results: As a result of biochemical analysis and histopathologic examination, more significant results were acquired in regard to other groups. Serum urea values were statistically significant ($p<0.05$). Consistent with the results of the studies previously performed, higher creatinine values were detected in the control and treatment groups. Enzymatic activities of superoxide dismutase and glutathione peroxidase were significantly lower in the treatment group when compared with the control group. When groups were compared based on histopathologic examination findings, cell necrosis and ischemic alterations were statistically significant parameters ($p<0.05$). When all parameters were analysed, values indicating any histopathologic abnormalities were at the lowest level in the treatment group. Histopathologic alterations were most frequently detected in the control group.

Conclusion: Anti-inflammatory activity of diosmin-hesperidin which is used experimentally in the treatment of ischemia-reperfusion injury was evaluated both biochemically and histopathologically. Based on the literature data, it is thought that the damage occurring after ischemia-reperfusion injury can be prevented with diosmin-hesperidin treatment.

Keywords: kidney, ischemia-reperfusion injury, diosmin-hesperidin

Özet

Amaç: Rat böbreğinde iskemi-reperfüzyon hasarında diosmin-hesperidin'in (DAFLON®) etkinliğini deneysel bir çalışma ile araştırmayı amaçladık.

Gereçler ve Yöntemler: 24 adet Wistar rat deneysel çalışma için kullanıldı. Her grup 8 adet denekten oluşmaktaydı. Sham grubu (Grup 1) histopatolojik inceleme için nefrektomi ve biyokimyasal analiz için kan alınan gruptu. Kontrol grubu (Grup 2) 1 saat iskemi ve 24 saat reperfüzyon yapıldı sonrasında histopatolojik inceleme için nefrektomi ve biyokimyasal analiz için kan alınan gruptu. Tedavi grubu (Grup 3) ise 10 gün boyunca 80mg/kg/gün dozunda diosmin hesperidin (DAFLON®) verildikten sonra 1 saat iskemi ve 24 saat reperfüzyon yapıldı sonrasında histopatolojik inceleme için nefrektomi ve biyokimyasal analiz için kan alınan gruptu.

Bulgular: Yapılan biyokimyasal analizler ve histopatolojik değerlendirmeler sonucunda tedavi grubunda diğer gruplara göre daha anlamlı sonuçlar elde edildi. Serum üre değerleri istatistiksel olarak anlamlıydı ($p<0.05$). Diğer biyokimyasal parametrelerden kreatinin değeri ise yapılan çalışmalarla doğru orantılı olarak kontrol grubu ve tedavi grubunda yüksek bulundu. Süperoksit dismutaz ve Glutatyon peroksidaz enzim aktiviteleri de tedavi grubunda kontrol grubuyla karşılaştırıldığında anlamlı derecede düşük bulundu. Histopatolojik değerlendirmeler sonucunda da gruplar karşılaştırıldığında hücre nekrozu ve iskemik değişiklikler istatistiksel olarak anlamlıydı ($p<0.05$). Bütün parametreler incelendiğinde histopatolojik bozukluğu gösteren değerler tedavi grubunda en alt düzeydeydi. En fazla ise kontrol grubunda değişimler mevcuttu.

Sonuç: İskemi reperfüzyon hasarında deneysel olarak kullanılan diosmin-hesperidin etkinliği hem biyokimyasal hem de histopatolojik olarak değerlendirildi. Literatür gözden geçirildiğinde, iskemi- reperfüzyon hasarı sonrası diosmin-hesperidin tedavisi ile oluşan hasarın engellenebileceği düşünülmektedir.

Anahtar kelimeler: böbrek, iskemi-reperfüzyon hasarı, diosmin-hesperidin

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Introduction

With the higher prevalence of surgical interventions that reduce renal blood flow such as transplantation, trauma, anatomic nephrolithotomy, nephron-sparing surgery, and renal artery surgery ischemia-reperfusion injury has been more frequently cited in the literature. In ischemia, oxygen required to maintain aerobic metabolism is not supplied to the living tissue. Recovery of normal blood flow after a period of ischemia is called reperfusion. Since the self-control of the metabolism of the oxygen entering the atmosphere with reperfusion of the organ that remains ischemic for a while deteriorates, free oxygen radicals (FORs) with their toxic effects become manifest and cause ischemia-reperfusion injury in the tissue. Along with emerging FORs, activation of various proteases and phospholipase A2 by calcium entering the cell during ischemia is also a response to ischemia-reperfusion injury [1-5].

The response that organs give to experimental ischemia-reperfusion injury was very well specified in the rats and rats were preferred as experimental animals in most of the literature studies [2-6]. During ischemia, the tissue is damaged by asphyxiation and when the normal blood flow is retrieved, tissue damage aggravates greatly as a result of a series of events caused by the oxygen entering the atmosphere [7,8].

Mitochondrial electron transport chain reactions, inhibition of arachidonic acid metabolites, increase in intracellular calcium levels, xanthine oxidase system, iron ion, etc. involve in the production of FORs which induce ischemia-reperfusion injury in the kidney tissue. These factors affect each other sequentially and disrupt cell functions, increase membrane destruction, and result in the production of endogenous toxins [9-13].

The only way of treatment in ischemic kidneys is to increase the renal blood flow through reperfusion. Yet in that case reperfusion damage inevitably occurs. In such a case, since the increase of blood supply is inevitable, it is necessary to look for solutions to prevent reperfusion damage. Many agents such as vitamin E, melatonin, phospholipase type 3 enzyme inhibitors (amrinone, olprinone), adenosine, n-acetyl cysteine, nitric oxide (NO), calcium channel blockers, mycophenolate mofetil have been used in order to prevent or alleviate renal ischemia-reperfusion injury associated with various etiologic factors [10,11].

Diosmin-hesperidin is produced by the purification of flavonoid extracts of a plant found in the nature. Daflon is a phlebotonic and vasculoprotector agent that is comprised of 90% diosmin and 10% hesperidin. Hesperidin reinforces the activity of diosmin, improves wound recovery by acting against inflammatory mediators and protects microcirculation via decreasing blood viscosity [14].

Diosmin-hesperidin has also shown anti-inflammatory effects through many mechanisms of action in our study. Many studies have been conducted on significant ischemia-reperfusion injury preventing effects of diosmin-hesperidin in multiple organs such as heart, brain muscle tissue, and peritoneum [14,15].

Diosmin-hesperidin is an important antioxidant drug combination. Leukocyte aggregation is important in ischemia-reperfusion injury and damage can be prevented with diosmin-hesperidin at daily oral doses of 500 mg. Also, this drug combination reduces the amount of H₂O₂ released from leukocytes by suppressing activity of myeloperoxidase (MPO).

A decrease in the MPO activity can explain the decrease in H₂O₂ in the group that received diosmin-hesperidin at doses protecting against oxidative stress associated with glutathione (GSH). Diosmin-hesperidin given at doses protecting against oxidative stress associated with GSH guards the escape of macromolecules from the microvascular structures. According to histopathological data, diosmin-hesperidin prevents infiltration of leukocytes into the perivascular area. Although it does not totally prevent leukocyte infiltration, a significant reduction in leukocyte accumulation in the perivascular area in the kidney was observed [16].

We have aimed to experimentally investigate the activity of diosmin-hesperidin, which acts against inflammatory mediators in ischemia-reperfusion injury and protects microcirculation by decreasing blood viscosity in cases with renal ischemia-reperfusion injury.

Materials and Methods

Twenty-four healthy adult Wistar rats weighing between 300-380 gr (average 340 gr) were used in the study. Experimental animals were tracked by keeping them at normal room temperature and in separate cages during preoperative and postoperative periods. Anesthesia was provided with the combination of ketamine IM (40 mg/kg, Ketalar 50 mg/cc, Parke-Davis) and xylazin HCl IV (10 mg/kg, Rompun, 23-32 mg/cc, Bayer). According to experimental protocol maintenance of anesthesia was provided with the same doses. Ethics committee approval for the study was acquired from the Ethics Committee of Ankara Training and Research Hospital (Date: 18.02.2009, Decision No: 2347).

In this study, rats were separated into three groups of 8 subjects. Experimental animals were tracked for 10 days by being kept at normal room temperature and in separate cages during preoperative and postoperative periods. Groups 1 and 2 were followed up without giving any treatment. Daily doses of 80 mg/kg diosmin-hesperidin (DAFLON®) were given to Group 3 subjects for 10 days by crushing film-coated tablets and adding them in their drinking water. At the end of the 10th day, only Group 1 rats underwent nephrectomy through laparotomy incision. In Groups 2 and 3, ischemia was induced in the renal artery for 60 minutes. After 24 hours, for the subjects in each group, before the procedure, serum samples were collected for the measurement of glutathione peroxidase, superoxide dismutase and urea creatinine. Then nephrectomy specimens in 10% formaldehyde solution were sent for histopathologic evaluation (**Figure 1**).

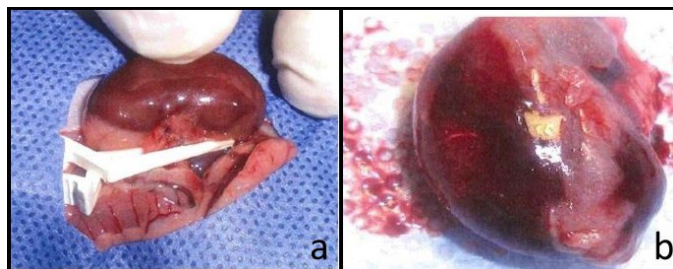


Figure 1a. Right kidney on which warm ischemia model with microvascular clamp constituted (Groups 2 and 3) **1b.** Nephrectomy performed right kidney after ischemia-reperfusion injury

After tissue samples in 10% formaldehyde were embedded in paraffin blocks and stained with hematoxylin-eosin, all preparations were examined under light microscope by a pathologist blinded to the study protocol. A semiquantitative scale defined by Paller et al. who evaluated, and scored the alterations in acute renal insufficiency was used [1].

Modified scoring system defined by Paller et al:

- 1- Chronic inflammation (0, +, ++)
- 2- Tubular epithelial cell flattening (0, +, ++)
- 3- Cytoplasmic vacuolization (0, +, ++)
- 4- Cell necrosis and ischemic changes (0, +, ++)
- 5- Tubular lumen obstruction (0, +, ++)

Statistical Analysis

Data analysis was performed using the SPSS 15 package program. While descriptive statistics were shown as mean \pm standard deviation for blood creatinine values, alterations in histopathologic results and blood parameters were shown as average (minimum-maximum) values. One-Way Anova analysis was used in the comparisons of blood parameters both within and between groups. T-test with Bonferroni correction was used to investigate whether there is a significant alteration in the groups in regard to serum urea creatinine levels. Percent changes between groups in serum urea creatinine levels within 24 hours were calculated, and intergroup comparisons were performed. The statistical significance of histopathologic scores between groups was analyzed using the Kruskal-Wallis test. The results were accepted as statistically significant at $p < 0.05$.

Results

Serum Urea Values

Average serum urea values were significantly higher in the control (Group 2) and treatment (Group 3) groups compared to the sham group (Group 1). The highest value was found in the control group. A statistically significant difference was detected between the groups ($p < 0.05$) (Figure 2).

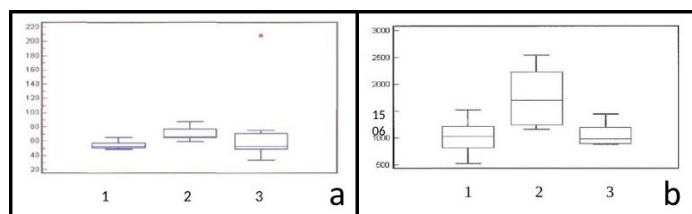


Figure 2a. Range of urea values between groups **2b.** Range of creatinine values between groups

Serum Creatinine Values

Average serum creatinine values were higher in the control and the treatment groups compared to the sham group. There was no statistically significant difference between the groups in this regard ($p > 0.05$) (Figure 2).

Superoxide Dismutase Enzyme Values

Superoxide dismutase enzyme values were higher in the control group compared to the other groups. The sham group and treatment group had approximately the same values. There

was no statistically significant difference between the groups in this regard ($p > 0.05$).

Glutathione Peroxidase Enzyme Values

Highest glutathione peroxidase enzyme values were found in the control group. The sham group and treatment group had approximately the same values. There was no statistically significant difference between the groups in this regard ($p > 0.05$).

Results of Histopathological Evaluation

According to histopathological classification defined by Paller et al., a total of 100 cortical tubules from 10 different microscopic field of views were evaluated in the kidney preparation of each experimental animal. An average score for each case was stated by averaging the scores. From the average scores of 8 rats in each group, the general average and standard deviation were calculated.

Histopathological evaluation revealed the presence of significant intergroup differences. Especially cell necrosis, tubular lumen obstruction, chronic inflammation, cytoplasmic vacuolization, and epithelial cell flattening were more common in the control and treatment groups when compared with the sham group. The most distinct histopathological alterations were cell necrosis and inflammation which were observed significantly less frequently in the treatment group relative to the control group (Figure 3).

There were histopathological differences between the control group and the treatment group. Histopathological alterations which are the indicator of kidney insufficiency were more common in the control group. The frequency of histopathological alterations in the treatment group was nearly close to the sham group. The most distinct alteration was cell necrosis and ischemic changes were less common in the treatment group. Cell necrosis and ischemic alterations were statistically significant findings ($p < 0.05$).

Histopathological alterations indicating all reperfusion injuries were observed more commonly in the control group. In the treatment group, severe histopathological alterations were observed less frequently compared to the control group. The histopathological alterations caused by kidney reperfusion injury in the treatment group were observed significantly less frequently compared to the control group. The most distinct alteration was cell necrosis and ischemic changes were less common in the treatment group ($p < 0.05$) (Table 1).

As a result of histopathological evaluations, the most distinct alteration was found in the treatment group. As a critically important finding cell necrosis and ischemic alterations were significantly different between the treatment, and control groups. There were partial cell necrosis and ischemic alterations in the treatment group, while cell necrosis and ischemic alterations were more frequently seen in the control group with a statistically significant intergroup difference ($p < 0.05$) (Figure 3).

Discussion

There is no need for specifying a specific ischemia time for the revelation of the effects of experimental ischemia-reperfusion injury. In experiments performed with rat kidneys, Williams et al. [5] indicated that reperfusion injury emerged after ischemia lasting for 45 minutes, while Paller et al. [1]

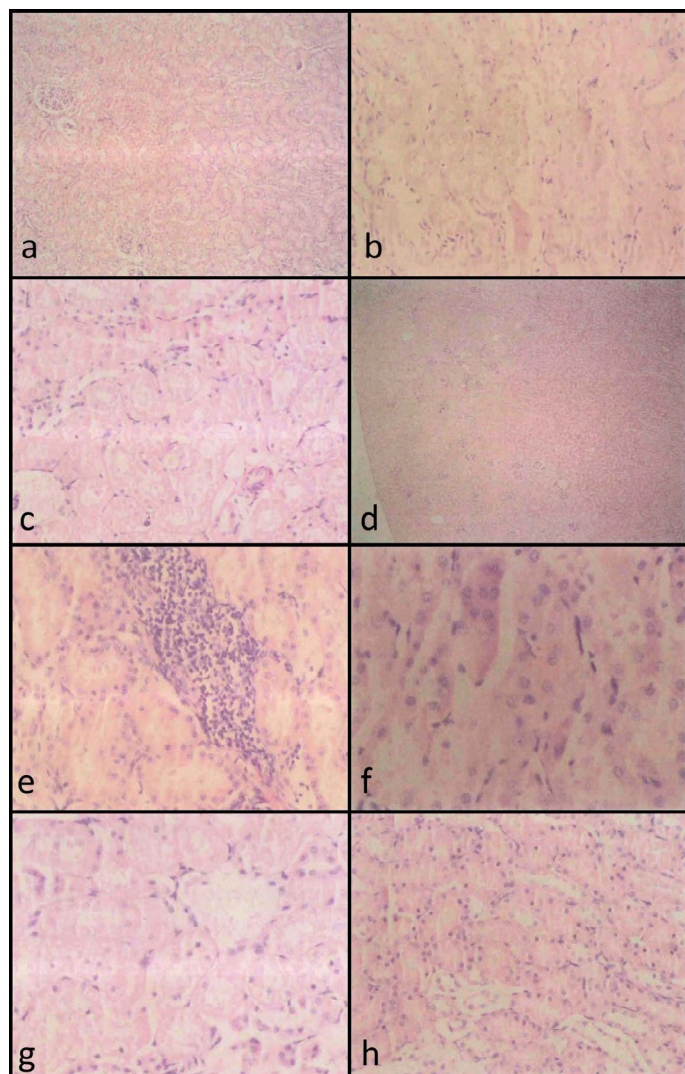


Figure 3a. Histopathological analysis of the kidney, all histopathological sections were dyed with hematoxylin-eosin (HEEx100). Necrosis in the tubules of the sham group and cell casts (debris) in the tubule were followed insignificantly. **3b.** Ischemia-reperfusion + Daflon (80 mg/kg/day) performed treatment group. It was observed that in necrosis in the tubular cells decreased at the $p < 0.05$ level compared to the control group, and there was a significant decrease in the intratubular caste deposition at the $p < 0.05$ level. **3c.** Distinct tubular cell necrosis and intratubular caste deposition were noticed in the control group. In the treatment group, these changes were less than in the control group and were in the form of focal alterations. **3d.** Ischemic alterations were noticed in the control group. In the treatment group, these changes were less than in the control group and could be observed focally. **3e.** Alterations related to chronic inflammation were noticed in the control group. In the treatment group, these changes were less than in the control group and were focal. **3f.** Alterations related to tubular lumen obstruction were noticed in the control group. In the treatment group, these changes were less than in the control group. **3g.** Alterations related to the flattening in the tubular luminal epithelium were noticed in the control group. In the treatment group, these changes were less than in the control group and were focal. **3h.** Alterations related to the cytoplasmic vacuolization were noticed in the control group. In the treatment group, these changes were less than in the control group and were at a focal level.

Table 1. Histopathological data

	Group1		Group 2		Group 3		p
	n	%	n	%	n	%	
Chronic inflammation	7	87.5	3	37.5	5	62.5	0.253
	1	12.5	4	50	3	37.5	
	0	0	1	12.5	0	0	
Tubular epithelial cell flattening	6	85.7	4	50	5	62.5	0.261
	1	14.3	2	25	3	37.5	
	0	0	2	25	0	0	
Cytoplasmic vacuolization	6	75	1	12.5	3	37.5	0.126
	2	25	5	62.5	3	37.5	
	0	0	2	25	2	25	
Cell Necrosis and ischemic changes	8	100	0	0	5	62.5	0.000
	0	0	2	25	3	37.5	
	0	0	6	75	0	0	
Tubular lumen obstruction	8	100	3	37.5	5	62.5	0.127
	0	0	3	37.5	2	25	
	0	0	2	25	1	12.5	

stated that it emerged after ischemia persisting for 60 minutes. In this study, renal ischemia applied for 60 minutes was preferred in consistent with literature data. It has been reported that renal ischemia-reperfusion injury becomes manifest at the earliest within 4 hours based on the analyzes of tissue samples and serum analytes and reached its peak at 24 hours [9]. As we desired to investigate the effects of renal ischemia-reperfusion injury clearly in our study, other procedures were also initiated 24 hours after reperfusion.

In our study; we observed that in the model we formed by applying ischemia for 60 minutes and reperfusion for 24 hours, the levels of plasma urea and creatinine which are indicators of renal glomerular insufficiency in the treatment and the control groups increased. While serum urea values were statistically significantly higher ($p < 0.05$), creatinine values were not. However, their median average values were significantly increased. Scarce number of data, uncertainties about the dosages and time periods specified for the treatment were thought to be the reasons for not obtaining statistically significant results .

A significant reduction in activities of renal antioxidant enzymes and histopathological manifestations suggestive of

necrosis was observed. Low antioxidant enzyme activity is an indicator of a mild ischemia-reperfusion injury. Enzyme activities were at the highest level in the control group. Because this group was exposed most often to the adverse effects of ischemia-reperfusion injury compared to the other groups. In the sham and treatment groups, enzyme activities were almost at the same level and quite low compared to the control group. As a result of this finding, it can be interpreted that the treatment group was least affected by ischemia-reperfusion injury.

When studies were reviewed, there was no specific dosage used for the prevention of renal ischemia-reperfusion injury [1,5]. An average dose used in our study was determined based on the studies conducted on other organs.

Histopathologically there was a statistically significant decrease, especially in cell necrosis and ischemic alterations ($p < 0.05$). The scoring system defined by Paller et al. [1] and used in acute kidney insufficiency was modified and applied in our study. We detected that the treatment group was more effective in improving all parameters taken into consideration and less damaging to the cell relative to the control group. Our findings were consistent with those of many studies investigating therapeutic activity of diosmin-hesperidin in muscle tissue, brain tissue, peritoneum, and heart tissue with ensuing histopathologically significant results [14,15].

Dobashi et al. applied renal ischemia (30, 60, 90 min.) and reperfusion (2, 24, 72, 120 hours) for different time periods, and noticed a significant decrease in superoxide dismutase and glutathione peroxidase activities and increase at the level of lipid peroxidation in the group in which they applied ischemia for 60 minutes and reperfusion for 24 hours [15]. Also in the studies where ischemia and reperfusion were applied for different durations, decrease in glutathione levels whereas increase in peroxidation and plasma urea and creatinine levels were indicated. Our findings were consistent with the results of previous studies [15,17].

Many studies cited in the literature have shown the favorable effect of diosmin-hesperidin on alleviating or preventing ischemia-reperfusion injury [14,15]. In our study, diosmin-hesperidin at a dose of 500 mg that prevented the development of ischemia-reperfusion injury in other organs was also found to be effective in preventing renal ischemia-reperfusion injury.

Diosmin-hesperidin is a medication used in venous insufficiency of extremities and venous system diseases such as hemorrhoids. Its venous tone enhancing, capillary resistance, and capillary permeability regulating, and lymphatic drainage enhancing effects are known. Besides, its free radical scavenging and leukocyte adherence-reducing effects have been shown. Duchene-Marullaz et al. demonstrated that it significantly reduced free radical activity, chemotactic reaction, and free radical activity induced by leukocyte phagocytosis consistent with our findings [18].

Stucker et al. conducted a microvascular permeability study using fibrils of cremaster muscle, and indicated that the treatment with diosmin-hesperidin also significantly reduced the residue induced by ischemia and bradykinin in vascular permeability [19]. In *in vitro* and *in vivo* studies, Di Peri and Auteri demonstrated that diosmin-hesperidin reduced the activity of the complement system, and this mechanism of action was considered to constitute one of the anti-inflammatory

effects of this drug therapy which also contributes favorably to the ulcer recovery [20].

Schoab et al. conducted a study on patients with chronic venous insufficiency using diosmin-hesperidin, and showed that it increased wound recovery by reducing oscillations in endothelial VCAM1 and ICAM1 expressions, preventing leukocyte adhesion, activation, and migration which consequently shortening the recovery time in patients with venous insufficiency [21]. Coloridge-Smith et al. conducted a meta-analysis on patients with venous ulcers developed as a result of chronic venous insufficiency, and showed that administering diosmin-hesperidin in addition to conventional treatment was effective in the rapid reduction of ulcer-related symptoms and sizes of ulcers compared to conventional treatment only [22].

Hasanoğlu et al., showed that diosmin-hesperidin was systematically and topically effective in infected skin injuries and improved wound recovery [23,24]. Pecking et al. investigated the effects of diosmin-hesperidin in upper extremity lymphedema developed after breast cancer surgery, and showed that diosmin-hesperidin was an effective treatment of lymphedema by increasing lymphatic flow in lymphedema, significantly reducing intralymphatic pressure and at the same time increasing the return of interstitial fluid to the capillaries [16]. Hasanoğlu et al. used diosmin-hesperidin systematically and topically in infected second-degree burns and showed that wound recovery was faster and better in patients in whom diosmin-hesperidin was used [24].

Many above-mentioned studies have indicated that diosmin-hesperidin was effective in preventing inflammatory effects and injury caused by free oxygen radicals. Therefore, frequent use of diosmin-hesperidin at the experimental level as an anti-inflammatory drug in ischemia-reperfusion injury conveys extreme importance as has been always observed in previously performed studies. Our study has shown that diosmin-hesperidin exerted anti-inflammatory effects that prevented development of ischemia-reperfusion injury.

Conclusion

In this study, the effect of diosmin-hesperidin on renal ischemia-reperfusion injury and whether this drug treatment can be used before development of ischemia-reperfusion injury were investigated. The effects of diosmin-hesperidin on ischemia-reperfusion injury were histopathologically and biochemically evaluated. As a result of histopathological and biochemical evaluations, favorable results of diosmin-hesperidin on the prevention of ischemia-reperfusion injury were obtained. When the literature is reviewed, it has been concluded that the damage caused by ischemia-reperfusion injury can be prevented with diosmin-hesperidin treatment.

Ethics Committee Approval: Ethics committee approval for the study was acquired from the Ethics Committee of Ankara Training and Research Hospital (Date: 18.02.2009, Decision No: 2347).

Informed Consent: An informed consent was obtained from all the patients.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – K.Y., E.E.; Design – K.Y., E.E.; Supervision – K.Y., E.E.; Resources – K.Y., E.E.; Materials – K.Y., E.E.; Data Collection and/or Processing – K.Y., E.E.; Analysis and/or Interpretation – K.Y., E.E.; Literature Search – K.Y., E.E.; Writing Manuscript – K.Y., E.E.; Critical Review – K.Y., E.E.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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

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Effect of the Hounsfield Unit Calculated on the Non-contrast Computed Tomography of Kidney and Ureteral Stones on the Success of Fragmentation with a Holmium: YAG Laser in Ureterorenoscopy and Retrograde Intrarenal Surgery

Böbrek ve Üreter Taşlarının Kontrastsız Bilgisayarlı Tomografi Üzerinde Hesaplanan Hounsfield Ünitesinin Holmium Yag Laser ile Yapılan Üreterorenoskopi ve Retrograd İntrarenal Cerrahi Tedavisinde Fragmantasyon Üzerindeki Etkisi

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Cite as: Atar M, Turan A, Yılmaz AH, Yılmazel FK, Karabulut I, Sarı S, Gürel A. Effect of the Hounsfield unit calculated on the non-contrast computed tomography of kidney and ureteral stones on the success of fragmentation with a Holmium: YAG laser in ureterorenoscopy and retrograde intrarenal surgery. Grand J Urol 2024;4(1):19-24

Submission date: 31 October 2023 **Acceptance date:** 16 December 2023 **Online first:** 23 December 2023 **Publication date:** 19 January 2024
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Abstract

Objective: This study aimed to investigate the effect of stone density on the success of ureterorenoscopy (URS) and retrograde intrarenal surgery (RIRS).

Materials and Methods: The data of patients who underwent URS or RIRS due to kidney and ureteral stones between January 2013 and March 2018 were retrospectively screened. For all patients, age, gender, comorbidities, the American Society of Anesthesiologists (ASA) score, the presence of preoperative double-J (DJ) stents, extracorporeal shock wave lithotripsy (ESWL) history, ipsilateral stone surgery history, the presence of renal anomalies, stone laterality, stone opacity, stone density, stone size, stone volume, operative time, stone-free status, and the presence and size of residual stones were recorded.

Results: The study included 566 patients who underwent URS or RIRS, including 186 women (32.9%) and 380 (67.1%) men. The mean age of the patients was 47 years. The mean stone size was 10 mm, and the mean stone density was 886 Hounsfield units. The mean stone volume was 426.13 mm³. The mean operative time was 31 minutes. The stone-free rate was 89.4%. Stone density, stone size, and stone volume were positively correlated with operative time (p<0.001) and residual stone size (p<0.001). Additionally, stone density and residual stone size were positively correlated in the group that did not achieve stone-free status (p=0.003).

Conclusion: In this study, it was determined that stone density, stone size, and stone volume were positively correlated with residual stone size and operative time. In addition, stone density was positively correlated with residual stone size among patients who were not stone-free after treatment, indicating that high stone density negatively affects the success of treatment even in cases presenting with small stone size and volume preoperatively.

Keywords: ureteroscopy, retrograde intrarenal surgery, stone density, stone size, stone volume

Özet

Amaç: Bu çalışmada, taş dansitesinin üreterorenoskopi (URS) ve retrograd intrarenal cerrahi (RIRS) başarısı üzerine etkisini araştırmayı amaçladık.

Gereçler ve Yöntemler: Ocak 2013-Mart 2018 tarihleri arasında böbrek ve üreter taşı nedeniyle URS veya RIRS yapılan hastaların verileri retrospektif olarak tarandı. Hastaların yaşı, cinsiyeti, eşlik eden hastalıkları, ASA (American Society of Anesthesiologists) skoru, preoperatif double-J (DJ) stent varlığı, ESWL öyküsü, ipsilateral taş cerrahisi öyküsü, renal anomalinin varlığı, taş lateralitesi, taş opasitesi, taş dansitesi, taş boyutu, taş hacmi, operasyon süresi, taşsızlık durumu ve rezidü taş varlığı kaydedildi.

Bulgular: Çalışmamızda 186 kadın (%32.9), 380 (%67.1) erkek olmak üzere URS ve RIRS yapılan 566 hasta mevcuttu. Hastaların yaş ortalaması 47 idi. Hastaların ortalama taş boyutu 10 mm, ortalama taş dansitesi (HU) 886 idi. Ortalama taş hacmi ise 426.13 mm³'tü. Ortalama operasyon süresi 31 dakikaydı. Taşsızlık oranı %89.4 idi. Taş dansitesi, taş boyutu ve taş hacminin operasyon süresi (p<0.001) ve rezidü taş (p<0.001) boyutuyla pozitif korele olduğu belirlendi. Ayrıca, stone free olmayan hastalarda taş dansitesi ile rezidü boyutunun pozitif korele olduğu belirlendi (p=0.003).

Sonuç: Çalışmamızda taş dansitesi, taş boyutu ve taş hacminin rezidü taş boyutu ve operasyon süresiyle pozitif korele olduğu belirlendi. Ayrıca, stone-free olmayan hastalarda taş dansitesinin rezidü boyutu ile pozitif korele olması yüksek taş dansitesinin taş boyutu ve hacmi düşük olsa dahi taşsızlığı olumsuz etkilediğini göstermektedir.

Anahtar kelimeler: üreteroscopi, retrograd intrarenal cerrahi, taş dansitesi, taş boyutu, taş hacmi

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Introduction

Urinary system stone disease is one of the oldest diseases affecting human health. The prevalence rate of stone disease varies between 1 and 20%, depending on climate, ethnic characteristics, genetics, and dietary habits. Among individuals with stone disease experiencing at least one episode in their lifetime, the recurrence rate has been reported to be approximately 50% [1]. The prevalence of stone disease is 3-11% in Europe; however, in regions with hot climates, such as Africa and the Middle East, it can reach 20% [2,3]. In Türkiye, this rate was found to be 14.8% according to a study conducted by Akinci et al. [4].

Non-contrast computed tomography (CT) has now replaced urography as the gold standard due to its high sensitivity and accuracy in diagnosing urolithiasis and the incorporation of new techniques to reduce radiation doses [5,6]. In addition to the diagnosis of urolithiasis, CT also provides important information concerning stone location, stone density, stone size, stone volume, stone-to-skin distance, hydronephrosis, and perinephric stranding. Stone density is determined by measuring the Hounsfield unit (HU) of the stone on CT. Through these measurements, the hardness, composition, heterogeneity, or homogeneity of the stone can be calculated. This information is important for clinicians to determine the fragility of the stone [7-9]. Evaluation of stone density has been integrated into daily medical practice to decide on the best treatment option for urinary tract stone disease. It has been suggested that HU affects the success of lithotripsy in treatment methods such as extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS), and percutaneous nephrolithotomy (PCNL) [10-12].

We hypothesized that stone density would affect the duration of lithotripsy performed with a Holmium laser as well as the postoperative stone-free outcome. Thus, large-volume kidney and ureteral stones with low stone density can be treated with URS and RIRS, and stone density can be an important determinant in case selection. In this study, we aimed to investigate the effect of stone density on the success of URS and RIRS in the treatment of kidney and ureteral stones.

Materials and Methods

After obtaining approval from the Ethics Committee of Bozok University Faculty of Medicine (approval number: 2018-KAEK-189_2018.02.27_13), the data of patients who underwent URS or RIRS due to kidney and ureteral stones from January 1, 2013, to March 31, 2018, were retrospectively screened. Patients who had undergone CT as an imaging modality and whose stone follow-up forms were completed were included in the study. Excluded from the sample were patients aged under 18 years, pregnant women, patients using anticoagulants, those with preoperative urinary tract infections, and those who had a double-J (DJ) stent placed due to reasons such as ureteral stenosis, surgical complications, inability to reach the stone, and pus discharge.

For all patients, age, gender, comorbidities, the American Society of Anesthesiologists (ASA) score, the preoperative presence of a DJ stent and an ESWL history, ipsilateral stone surgery history, the presence of renal anomalies, stone laterality,

stone opacity, stone density, stone size, stone volume, operative time, stone-free status, and the presence of and size residual stones were recorded. Taking the length and width obtained from the transverse section and the depth obtained from the coronal plane on CT images, the longest measured diameter was determined as the stone size and recorded in mm. In the presence of multiple stones, stone size was determined by summing the longest diameters of each stone. Stone volume was calculated with the following formula: length x width x depth x 0.52. In the presence of multiple stones, stone volume was determined by calculating the stone volume of each stone and taking their total. In the measurement of stone density, the level where the stone had the largest diameter in transverse sections was determined. Using the circular drawing tool, the largest ellipse that remained in the stone was drawn. The average density of the area within the drawn ellipse was determined in HU. Postoperative DJ stent requirements were recorded. Postoperative DJ stenting was performed according to the surgeon's preference, taking into account factors such as operation time, ureteral calibration-edema, and complete fragmentation of the stone. Plain radiography or urinary ultrasonography was performed the third week after surgery to evaluate whether there was any residual stone. Stones below 2 mm were considered clinically insignificant residual fragments. The size of residual stones was also recorded.

Statistical Analysis

The obtained data were evaluated using the IBM-SPSS software package. Number, percentage, mean \pm standard deviation, median, minimum, maximum, and 25-75th percentile values were used as descriptive statistics. The Shapiro-Wilk test was conducted to compare continuous data. Since the normality test result revealed that the data did not comply with a normal distribution, non-parametric methods were employed. The Mann-Whitney U and Kruskal-Wallis tests were used to compare categorical groups, and Spearman correlation analysis was used to compare continuous data. $P \leq 0.05$ was accepted as the statistical significance level.

Results

The study included a total of 566 patients, of whom 186 (32.9%) were women and 380 (67.1%) were men. The mean age of the patients was 47 years. Of all patients, 108 (19.1%) had a history of RIRS, 58 (10.2%) had a history of URS, 28 (4.9%) had a history of PCNL, 16 (2.8%) had a history of open surgery, one (0.2%) had a history of pyeloplasty, and 21 (3.7%) had a history of other genitourinary operations. Preoperatively, DJ stents were present in 54 (9.5%) of the patients. The mean stone size was 10 mm, and the mean stone density was 886 HU. The mean stone volume was 426.13 mm³. Of the stones, 28.6% were in the distal ureter, 25.6% in the proximal ureter, 18.4% in the renal pelvis, 12.7% in the lower calyx, 3.2% in the upper calyx, 3% in the middle calyx, and 2.7% in the ureteropelvic junction, while the remaining 5.6% were multicalyceal. RIRS was performed in 265 (46.8%) of the patients, and URS in 301 (53.2%). The mean operative time was 31 minutes. The stone-free rate was 89.4%. Of all stones, 387 (68.4%) were opaque, and 179 (31.6%) were non-opaque. No DJ stent was required in

Table 1. Correlation analysis of stone density, stone size, stone volume, residual stone size, and operative time

	Stone density (HU)	Stone size (mm)	Stone volume (mm ³)	Residual stone size (mm)	Operative time (min)
Stone density	-	<0.001	<0.001	<0.001	<0.001
Stone size	<0.001	-	<0.001	<0.001	<0.001
Stone volume	<0.001	<0.001	-	<0.001	<0.001
Residual stone size	<0.001	<0.001	<0.001	-	<0.001
Operative time	<0.001	<0.001	<0.001	<0.001	-

HU: Hounsfield unit

Table 2. Statistical comparison of stone density with other parameters

		Stone density (HU)							
		Count	Column n %	Mean	SD	Median	Min	Max	P
Stone localization	Upper calyx	18	3.20%	1016	350	1165	404	1400	<0.001
	Middle calyx	17	3.00%	889	386	1002	283	1388	
	Lower calyx	72	12.70%	943	382	960	322	1601	
	Pelvis	104	18.40%	1016	366	1100	330	1605	
	UPJ	15	2.70%	893	384	841	337	1522	
	Proximal ureter	145	25.60%	851	392	911	208	1674	
	Distal ureter	162	28.60%	760	367	737	108	1506	
	Multiple calyces	33	5.80%	1054	314	1110	305	1518	
Opacity	Non-opaque	179	31.60%	469	210	414	108	1450	<0.001
	Opaque	387	68.40%	1079	280	1110	309	1674	
DJ stent requirement	Absent	28	4.90%	529	267	441	108	1303	<0.001
	Present	538	95.10%	905	381	938	119	1674	
Surgical technique	RIRS	265	46.80%	994	364	1056	283	1632	<0.001
	URS	301	53.20%	791	378	789	108	1674	

HU: Hounsfield unit; SD: standard deviation; UPJ: ureteropelvic junction; DJ: double-J; RIRS: retrograde intrarenal surgery; URS: ureterorenoscopy

28 (4.9%) of the patients after surgery. DJ stents were placed in 538 (95.1%) patients after the operation.

Correlation analysis revealed that as stone density increased, stone size ($p<0.001$), stone volume ($p<0.001$), residual stone size ($p<0.001$), and operative time ($p<0.001$) increased. In addition, as stone volume increased, residual stone size ($p<0.001$) and operative time ($p<0.001$) also increased (**Table 1**). There was a statistically significant relationship between stone density and stone localization ($p<0.001$). The highest stone density was detected in the upper calyx and the lowest stone density in the

distal ureter. The stone density of opaque stones was found to be significantly higher than that of non-opaque stones ($p<0.001$). Furthermore, stone density was significantly higher in patients with a postoperative DJ stent requirement than in the remaining patients ($p<0.001$) (**Table 2**). Among patients who were not stone-free, there was a significant positive correlation between stone density and residual stone size ($p=0.003$). In the stone-free group, stone density was significantly positively correlated with stone size ($p<0.001$), stone volume ($p<0.001$), and operative time ($p<0.001$) (**Table 3**).

Table 3. Correlation analysis of stone density, stone size, stone volume, residual stone size, and operative time according to stone-free status

Stone-free status		Stone density (HU)	Stone size (mm)	Stone volume (mm ³)	Operative time (min)	Residual stone size (mm)
Absent	Stone density (HU)	-	0.310	0.232	0.455	0.003
	Stone size (mm)	0.310	-	<0.001	<0.001	<0.001
	Stone volume (mm ³)	0.232	<0.001	-	<0.001	<0.001
	Operative time (min)	0.455	<0.001	<0.001	-	=0.001
	Residual stone size (mm)	=0.003	<0.001	<0.001	=0.001	-
Present	Stone density (HU)	-	<0.001	<0.001	<0.001	0.894
	Stone size (mm)	<0.001	-	<0.001	<0.001	0.372
	Stone volume (mm ³)	<0.001	<0.001	-	<0.001	0.043
	Operative time (min)	<0.001	<0.001	<0.001	-	0.117
	Residual stone size (mm)	0.894	0.372	0.043	0.117	-

HU: Hounsfield unit

Discussion

With the developments in technology, treatment of urinary system stone disease has become more non-invasive and comfortable. When determining the treatment method, factors such as stone size, stone volume, stone localization, and stone density are taken into account. The main objective is to achieve stone-free status. However, residual stone fragments after treatment may cause new stone formation and lead to the need for repeated operations. In the current study, we investigated the effect of stone density on the success of URS and RIRS. Our results revealed that stone density was significantly positively correlated with operative time and residual stone size. In addition, we found that stone density was significantly correlated with residual stone size among patients that did not achieve stone-free status after treatment and with operative time among stone-free patients. These findings demonstrate the importance of the preoperative evaluation of stone density.

There was a significant relationship between stone localization and stone density. The highest stone density was found in the upper calyx, and the lowest stone density in the distal ureter. To the best of our knowledge, the literature contains no study comparing stone density according to stone localization. Our finding may indicate that high stone density negatively affects spontaneous stone passage. In two studies conducted in the literature on this subject, although the stone density of stones with spontaneous passage was lower than that of those without spontaneous passage, there was no statistically significant difference [13,14]. This may be due to the small number of patients. Based on the results of our study, we consider that there is a need for further studies with a higher volume to investigate

the impact of stone density on the occurrence of spontaneous stone passage.

In this study, stone density was significantly higher in patients who required postoperative DJ stent placement than in those without this requirement. This can be attributed to the more effective fragmentation of low-density stones by laser and the shorter time of the procedure. The endourologist's decision may have been influenced by the expectation that effective fragmentation in a short time would reduce postoperative edema and pain. In the literature, the only study evaluating postoperative DJ stent requirements reported that a low stone burden, the presence of a ureteral stent, the absence of an access sheath, and a short operative time were associated with postoperative stent-free status [15]. Based on the results obtained from our study and the limited existing literature on this topic, further research is warranted to explore the use of postoperative DJ stents in patients undergoing URS or RIRS.

Stone density has been the subject of many investigations in the literature since it is a parameter that can be easily calculated on CT. Studies have reported that stone density is an important criterion in predicting the success of ESWL [16,17]. It is also a parameter included in the R.I.R.S. scoring system to predict the success of RIRS, and in an external validation study, this scoring system was determined to be an independent predictor of stone-free status [18,19]. Similarly, stone density is among the parameters included in the T.O.H.O score (Tallness, Occupied lesion, Hounsfield unit evaluation) scoring system used to predict RIRS success, and an external validation study reported this score to be an independent predictor of stone-free status [20,21]. In the current study, we observed a positive correlation between stone density, operative time, and residual stone size,

consistent with the literature. Additionally, we found a positive correlation between stone density and residual stone size among patients who did not achieve stone-free status after surgery.

One of the important parameters affecting stone-free status in URS is stone diameter or volume. Scoring systems and external validation studies used to predict the success of RIRS have also found that stone size is one of the important parameters [18-22]. In our study, we detected a positive correlation between stone size, operative time, and residual stone size, consistent with the literature. Furthermore, we observed that among patients who were not stone-free after surgery, stone size was positively correlated with operative time and residual stone size.

Although URS and RIRS are safe procedures, infectious complications are frequently encountered. In previous studies, one of the important parameters that increased the risk of infectious complications was reported to be operative time [23,24]. In a study conducted with 219 patients who underwent RIRS, Ito et al. found that high stone density negatively affected fragmentation efficiency and reduced the efficiency of operative and fragmentation times in stones smaller than 20 mm [11]. In our study, there was a positive correlation between stone density and operative time, which is in agreement with the literature.

Concerning the limitations of our study, the major drawbacks are related to the retrospective design and the absence of stone analysis. Another limitation is that multivariate analysis was not performed to evaluate independent factors predicting stone-free status. The lack of complication evaluation can also be considered an important limitation. The notable findings of our study are that a statistically significant difference was detected between stone localization and stone density and that stone density was significantly higher in patients who required postoperative DJ stent placement than in those without this requirement.

Conclusion

In this study, it was determined that stone density, stone size, and stone volume were positively correlated with residual stone size and operative time. In addition, stone density was positively correlated with residual stone size in patients who did not achieve stone-free status, indicating that high stone density negatively affects stone-free status even in cases presenting with small stone size and volume preoperatively. That is, as the stone density increases, more time and energy must be spent to achieve the stone-free status. Preoperative determination of these parameters, which can be easily performed on CT, can facilitate the prediction of treatment success, and provide more patient information before surgery. We consider that this study will significantly contribute to the decision-making process of urologists when selecting the appropriate treatment in their daily clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bozok University Faculty of Medicine (approval number: 2018-KAEK-189_2018.02.27_13).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – M.A., S.S., A.G.; Design – M.A., A.H.Y., S.S., A.G.; Supervision – F.K.Y., I.K., S.S., A.G.; Resources – M.A., A.T., A.H.Y.; Materials – M.A., A.T., A.H.Y.; Data Collection and/or Processing – M.A., S.S.; Analysis and/or Interpretation – A.T., F.K.Y., I.K.; Literature Search – M.A., A.T., A.H.Y., F.K.Y.; Writing Manuscript – M.A., A.T., I.K.; Critical Review – M.A., I.K., S.S., A.G.

Conflict of Interest: The authors declare no conflict of interest.

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


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Partial Nephrectomy in Wilms Tumor: A Rarely Implemented Surgical Method

Wilms Tümöründe Parsiyel Nefrektomi: Çok Nadir Uygulanan Bir Cerrahi Yöntem

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Cite as: Yalçın K. Partial nephrectomy in Wilms tumor: A rarely implemented surgical method. Grand J Urol 2024;4(1):25-7

Submission date: 21 November 2023 **Acceptance date:** 26 December 2023 **Online first:** 02 January 2024 **Publication date:** 19 January 2024

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Abstract

Nephroblastoma (Wilms Tumor/WT) is the rare but the most common primary kidney tumor in children. The WT is generally diagnosed between ages of 1 and 5 and the most common diagnosis is the age of 3. Up to 95% of WTs are diagnosed correctly with imaging (ultrasound, computed tomography and magnetic resonance). Histopathologically tissue examination is implemented and subtypes are determined. Surgery is one of the key factors in WT treatment. Transperitoneal radical nephrectomy is the standard operation for unilateral WTs. Nephron sparing surgery (partial nephrectomy) is suggested only in selected cases with a single kidney or bilateral WT. Other treatment combination for Wilms tumor involves chemotherapy and radiation treatment. A patient who was diagnosed with Wilms tumor in the right kidney and underwent partial nephrectomy which is rarely implemented or recommended in selected cases is represented in this article.

Keywords: Wilms tumor, child, partial nephrectomy

Özet

Nefroblastoma (Wilms tümörü/WT) çocuklarda nadir fakat en sık görülen primer böbrek tümürüdür. WT tanısı genellikle 1 ile 5 yaş arasında konur ve en sık tanı 3 yaştır. WT'lerin %95'e kadarı görüntüleme (ultrason, bilgisayarlı tomografi ve manyetik rezonans) yöntemleri ile doğru şekilde teşhis edilir. Histopatolojik olarak ise doku incelemesi yapılır ve alt tipleri belirlenmektedir. Cerrahi WT tedavisinin temel taşlarından biridir. Tek taraflı WT'ler için transperitoneal radikal nefrektomi standart operasyondur. Nefron koruyucu cerrahi (parsiyel nefrektomi) yalnızca tek böbrekli veya iki taraflı WT'li seçilmiş hasta vakalarında uygulanması önerilmektedir. Wilms tümörünün diğer tedavi kombinasyonu ise kemoterapi ve radyasyon tedavisini içermektedir. Bu yazıda sağ böbrekte Wilms tümörü tanısı alan, çok nadiren yapılan veya seçilmiş vakalarda yapılması önerilen parsiyel nefrektomi yapılmış hasta sunulmaktadır.

Anahtar kelimeler: Wilms tümörü, çocuk, parsiyel nefrektomi

Introduction

Wilms tumor (WT) is the most common renal tumor in childhood period, affecting one in 10,000 children [1–3]. It is mostly seen between the ages of 2-4. WT is an embryological tumor that classically shows a triphasic histological complex structure originating from blastem, epithelial and stroma components. Besides that it may also includes cartilage, osteoid and neuronal elements [4].

The WT treatment is implemented with two distinctive methods: The Europe's International Society of Pediatric Oncology (SIOP) method which adopts the principle of initiating chemotherapy (CT) without tissue diagnosis and then surgical application and North America's National Wilms Tumor Study (NWTs), now known as the Children's Oncology Group method (COG) which carries out a treatment plan with tissue diagnosis. Primarily providing CT contributes to prevention of phase escalation due to tumor cells being shed during surgery and surgical complications that may occur in the presence of large-sized or thrombus but besides that has a disadvantage of providing unnecessary CT to the cases diagnosed histopathologically other than WT. In NWTs/COG method, although tissue diagnosis is the main criterion, the principle of providing CT first is adopted in very large tumors, bilateral cases and the presence of thrombus extending into the IVC or atrium. However, the most important factor determining the prognosis in both methods is the phase of tumor, whether it contains anaplasia and the positivity of biological indicators such as 1p, 16q LOH veya 11p15q LOH [2,3,5].

Surgery is one of the key factors in WT treatment. Transperitoneal radical nephrectomy is standard operation for unilateral WTs. Nephron sparing surgery is suggested to be implemented in selected patient cases with single kidneys or bilateral WT. In this case report, a patient who diagnosed with Wilms tumor in right kidney at the age of 4 and underwent partial nephrectomy which is rarely implemented or suggested to be implemented in selected cases is represented.

Case

Our case is a 4-years old male patient who was brought to our clinic by his parents with the complaint of bleeding in the urine which had been going on for 1 month. Full blood cell count and biochemical values of the patient were within normal limit, there was 3+ hematuria in the urinalysis. In the urinary track ultrasound examination a 4 cm suspicious mass was seen in the lower pole of right kidney. Whole abdominal magnetic resonance imaging performed on the patient was reported as 'a mass lesion approximately 42x37 mm in size in the lower pole of the right kidney, with a smoothly circumscribed, encapsulated appearance, containing cystic areas, extending towards the renal pelvis, but not creating an appearance in favor of significant invasion findings and showing lower but heterogeneous contrast uptake compared to the renal parenchyma and other organs in the abdomen are normal (Figure 1). Partial nephrectomy decision was made due to the fact that the tumor was located in a single pole, infiltrated less than 1/3 of the kidney, there was no renal vein invasion, and there was surgical experience in this regard. The patient underwent right partial nephrectomy with the

provisional diagnosis of renal mass. Partial nephrectomy was 4,5x3,5x3 cm in size and in the form of yellowish brown tumor tissue with a diameter of 3,5 cm at a distance of 0,2 cm from the nearest surgical margin in cross sections. Microscopically, in the examination of the sections, a partially cystic tumor tissue with a generally solid pattern that is separated from the kidney tissue with a distinct but irregular border line is seen. The tumor is comprised of 3 different components; epithelial component which is differentiated to generally tubular, partially glomerulus structures, blastomatous component characterized with primitive fusiform cells surrounding them and stromal component which formed bundles between them and partly showed prominent rhabdoid differentiation. In immunohistochemical studies, it was reported that positive colouration was detected in epithelial component with Pan-CK, in both the stromal and partly blastomatous components with vimentin, in rhabdomyoblastic cells with desmin. As a result of these histopathological findings, tumor was reported as WT with classical, triphasic features and appropriate histology (Figure 2). The patient then underwent chemotherapy and radiotherapy. No relapse was observed during patient's 8-years follow-up. No problems occurred in the kidney that underwent partial nephrectomy within years (Figure 3).

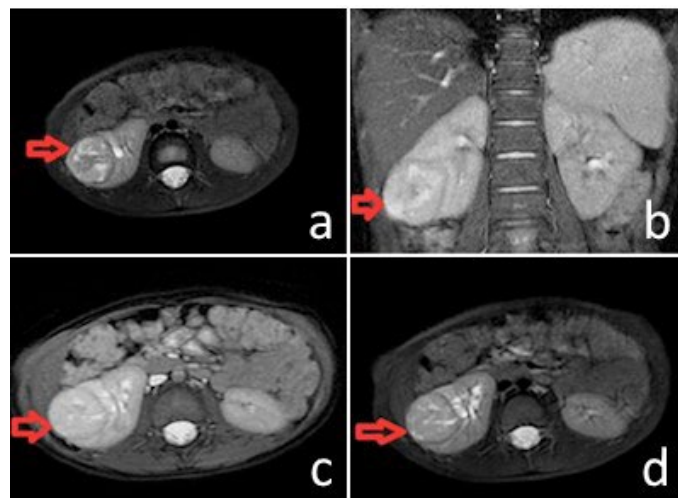


Figure 1. Mass lesion approximately 42x37 mm in size in the lower pole of the right kidney, with a smoothly circumscribed, encapsulating appearance, containing cystic areas, extending toward the renal pelvis, but not creating appearance in favor of significant invasion findings and showing lower but heterogeneous contrast uptake compared to the renal parenchyma

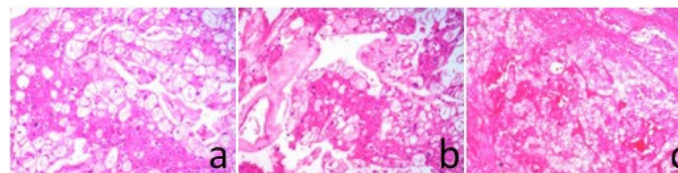


Figure 2. H&EX20 epithelial component which is differentiated to generally tubular, partially glomerulus structures, blastomatous component characterized with primitive fusiform cells surrounding them and stromal component which formed bundles between them and partly showed prominent rhabdoid differentiation

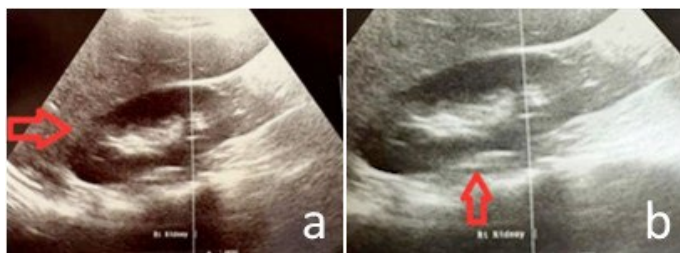


Figure 3. View of the kidney that underwent partial nephrectomy at the last check-up

Discussion

Surgery is one of the key factors in WT treatment. The SIOP method in Europe suggests chemotherapy before surgery while COG in North America suggests operation before chemotherapy [6]. The direction of WT requires a multidisciplinary approach with the participation of pediatric radiologist, oncologist, surgeon and radiotherapist. Firstly, in order to determine the origin of tumor, its position as regards to surrounding tissue and vascular uptake the patient should be carefully evaluated in pre-operative period by using appropriate imaging techniques.

Transperitoneal radical nephrectomy is standard operation for unilateral WTs. Nephron sparing surgery is suggested only in selected patient cases with single kidney or bilateral WT [7]. It is discussed in unilateral cases whether it should be implemented by partial nephrectomy or enucleation [8,9]. This approach is suggested only in synchronous or metachronous bilateral cases or single kidneys. Only less than 5% of unilateral WTs are appropriate for partial nephrectomy because most of the kidneys are locally progressed during diagnosis [8,10]. For partial resection surgical criteria are as follows: tumor is placed in a single pole and infiltrated less than 1/3 of the kidney; there is no renal vein invasion, surgeon has experience in pediatric oncology [8,11]. We think that our case will contribute to literature in a way that it is a case presentation diagnosed with Wilms tumor in the right kidney and underwent partial nephrectomy that is rarely implemented or suggested to implemented in selected cases.

Conclusion

Although radical nephrectomy was standard in cases which Wilms tumor was detected we would like to specify that partial nephrectomy operation may give successful results in selected cases.

Ethics Committee Approval: N / A.

Informed Consent: An informed consent was obtained from the patient's parents.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – K.Y.; Design – K.Y.; Supervision – K.Y.; Resources – K.Y.; Materials – K.Y.; Data Collection and/or Processing – K.Y.; Analysis and/or Interpretation – K.Y.; Literature Search – K.Y.; Writing Manuscript – K.Y.; Critical Review – K.Y.

Conflict of Interest: The author declares that there was no conflict of interest.

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

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Prostate Cancer with Osteolytic Sternal Metastasis: A Rare Clinical Presentation

Osteolitik Sternal Metastazlı Prostat Kanseri: Nadir Bir Klinik Sunum

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Cite as: Sharma S, Ac KR, Sharma SR. Prostate cancer with osteolytic sternal metastasis: A rare clinical presentation. Grand J Urol 2024;4(1):28-31

Submission date: 26 December 2023 **Acceptance date:** 10 January 2024 **Online first:** 12 January 2024 **Publication date:** 19 January 2024

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Abstract

Chest wall malignancies are rare, constituting only 1% of all cancers. Prostate cancer, the second most common in men, typically metastasizes to bones, lymph nodes, and organs. However, sternum involvement is exceptionally rare, particularly with osteolytic metastasis. We report a 75-year-old man, clinically presenting with large anterior chest wall mass, which on further investigation revealed an expansile osteolytic sternal body metastasis from prostate cancer. This rarity poses diagnostic and therapeutic challenges, as documented cases of osteolytic secondaries to the sternum are scarce in medical literature. Diagnostic efforts involved comprehensive imaging and biopsy, confirming prostate cancer metastasis. Management requires a multidisciplinary approach, balancing effective cancer control with preserving the patient's quality of life through systemic therapies, radiation, and surgery. The scarcity of osteolytic sternal body metastasis in reported cases highlights the atypical pattern of metastasis in prostate cancer emphasizing the need for a deeper understanding and contributing to the knowledge of this uncommon manifestation.

Keywords: prostate cancer, sternal metastasis, osteolytic presentation, chest wall tumors, positron emission tomography, multidisciplinary approach

Özet

Göğüs duvarı maligniteleri nadirdir ve tüm kanserlerin yalnızca %1'ini oluşturur. Erkeklerde ikinci sıklıkta görülen prostat kanseri, genellikle kemiklere, lenf nodlarına ve organlara metastaz yapar. Bununla birlikte, özellikle osteolitik metastazlarda sternum tutulumu son derece nadirdir. Klinik olarak göğüs ön duvarında büyük bir kitle ile başvuran ve daha ileri incelemelerde prostat kanserinden kaynaklanan ekspansil osteolitik sternal vücut metastazını ortaya çıkaran 75 yaşında bir erkeği sunuyoruz. Bu nadirlik, tıbbi literatürde sternuma sekonder osteolitik sekonder vakaların az olması nedeniyle teşhis ve tedavi açısından zorluklar doğurmaktadır. Teşhis çabaları, prostat kanseri metastazını doğrulayan kapsamlı görüntüleme ve biyopsiyi içeriyordu. Yönetim, sistemik tedaviler, radyasyon ve cerrahi yoluyla hastanın yaşam kalitesinin korunmasıyla dengeleyen multidisipliner bir yaklaşımla etkili kanser kontrolünü gerektirir. Bildirilen vakalarda osteolitik sternal vücut metastazının azlığı, prostat kanserindeki atipik metastaz paterninin daha derin bir anlayışa ihtiyaç duyulduğunu vurgulayarak, bu nadir görülen tezahürün bilgisine katkıda bulunmaktadır.

Anahtar kelimeler: prostat kanseri, sternal metastaz, osteolitik başvuru, göğüs duvarı tümörleri, pozitron emisyon tomografisi, multidisipliner yaklaşım

Introduction

Chest wall malignancies are considered rare, constituting approximately 1% of all malignancies. These malignancies may originate primarily from bone or soft tissue, result from the infiltration of adjacent organ malignancies, or occur secondary to distant metastasis, with the latter being the predominant cause [1]. Prostate cancer, ranking as the second most diagnosed cancer in men and the fourth most common overall, typically exhibits metastasis to various sites, including bone, lymph nodes, lung, bladder, liver, and adrenal glands [2].

While the literature reports prostatic metastases to almost every organ in the body, involvement of the sternum is notably infrequent in prostate cancer cases [3]. Within sternum involvement, osteosclerotic metastasis have been documented, yet osteolytic metastasis in the sternum due to prostate cancer remains an exceedingly rare occurrence, lacking documented cases in medical literature [4].

This article presents a noteworthy case of metastatic prostate cancer, wherein the clinical presentation manifested as a sizable sternal mass. Further evaluation revealed an expansile osteolytic sternal body metastasis in a 75-year-old gentleman. The peculiarity of this manifestation, along with its diagnostic and therapeutic challenges, underscores the need for a detailed examination of such atypical cases.

Case

A 75-year-old male presented with a painful swelling on the chest wall that gradually increased in size. Upon clinical examination, an 11 cm x 8 cm bony hard, non-mobile, and non-tender mass was identified (**Figure 1**). Vital signs were within normal limits. Computed Tomography of the chest identified an expansile osteolytic lesion in the body of the sternum without any abnormal lesions in the mediastinum or lung parenchyma (**Figure 2**). An 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) was performed showing an expansile osteolytic metastatic lesion in the sternum and diffuse osteolytic skeletal metastasis with a non-homogeneously enlarged prostate (**Figure 3,4**). No history of lower urinary tract symptoms was reported, while a digital rectal examination indicated a hard prostate prompting serum prostate-specific antigen (PSA) level which was found to be elevated (1347 ng/mL).

Confirmation through CT-guided biopsy demonstrated metastatic deposits originating from the prostate, while a transrectal ultrasound-guided biopsy of the prostate revealed a primary adenocarcinoma with a Gleason score of 5+5. Initiation of treatment with a subcutaneous injection of degarelix (240 mg loading dose), a gonadotropin-releasing hormone (GnRH) receptor antagonist, resulted in a significant reduction in



Figure 1. The anterior (A) and lateral view (B) of a large anterior chest wall mass with bony-hard consistency showing the size and extent of the painful bone mass



Figure 2. Computed Tomography of the chest with a soft tissue window, revealing bony metastasis in the sternum, with no apparent lung or mediastinal lesions evident



Figure 3. A coronal view of a Positron Emission Tomography reveals widespread bony metastasis affecting both the axial and appendicular skeleton

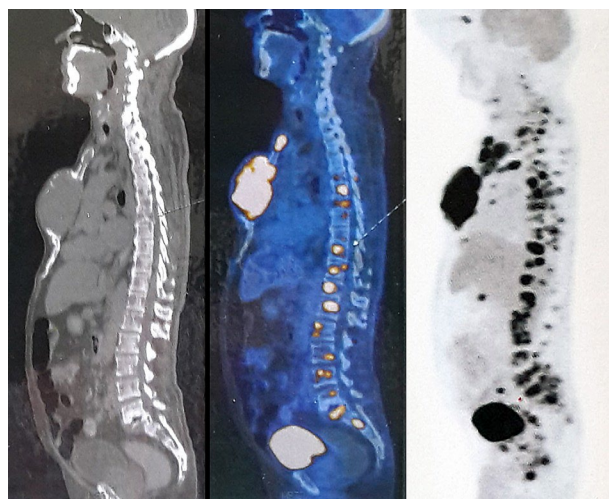


Figure 4. Sagittal view of Computed Tomography/ Positron Emission Tomography reveals an enlarged and non-homogeneously enhancing prostate with hypermetabolic activity noted in mediastinal nodes (retrosternal and both internal mammary regions), an expansile lytic lesion in the sternum (95.5 x 61.3 mm), and multiple lytic lesions in the axial and appendicular skeleton

pain. Following consultations with a multidisciplinary team comprising medical oncologists, radiation oncologists, and pathologists, a consensus was reached. The decision to commence hormonal therapy was made, and based on the treatment response, radiotherapy may or may not be considered for sternal metastasis. Currently, the patient is receiving injection leuprolide (11.25 mg), a gonadotropin-releasing hormone (GnRH) agonist, alendronate (bisphosphonate) and calcium with vitamin D 3. The patient is pain-free at the end of a one-month follow-up.

Discussion

Prostate cancer ranks as the second most frequently diagnosed cancer in men, registering an estimated 1.4 million global diagnoses in 2020 [5]. In the hierarchy of metastatic occurrences, the typical sites include the bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13%) [6]. While the spine, pelvis, and ribs are the most common sites of bone metastasis in prostate cancer, sternum involvement is rare [7].

The sternum, comprising the manubrium, corpus, and xiphoid process, exhibits distinct patterns of metastasis. Corpus sternum involvement is more prevalent in lung cancer, whereas prostate cancer may manifest in the manubrium and xiphoid [8]. Adenocarcinomas of prostate cancer demonstrate osteotropism, giving rise to both osteosclerotic and osteolytic lesions, with sclerotic metastasis being a predominant feature [9].

Chest wall tumors can be primary or metastatic with latter being the most common. Metastatic tumors to the chest wall commonly arise from primary cancers in nearby organs such as the breast, lung, kidney, and thyroid, among others. A significant portion, roughly twenty percent, is incidentally discovered through chest radiographs, with sarcomas like chondrosarcomas, osteosarcomas, rhabdomyosarcomas, plasmacytomas, malignant fibrous histiocytomas, and Ewing sarcomas forming the primary malignant chest wall tumors [10].

While there are case reports documenting the metastatic involvement of the chest wall, including the sternum, in the context of prostate cancer, it is noteworthy that there is a scarcity of data specifically addressing osteolytic sternal body metastasis in published literature.

In a comparative study by Wang et al., sternal metastasis in prostate cancer was reported at 1.72% in few bony metastases, 0.62% in moderate metastases, and 3.14% in extensive bony metastases, signifying its rarity in this context [11]. The utility of positron emission tomography in staging, treatment response evaluation, and recurrent disease detection in chest wall tumors is acknowledged [12].

Although an extensive meta-analysis by Carsote et al. reported a staggering 68% involvement of chest wall (ribs + sternum) metastasis in prostate cancer, the specific data on sternal metastasis remains elusive [13]. Noteworthy cases reported by Roxburgh et al. and Matei et al. were predominantly osteoblastic secondaries, setting this case apart as a unique instance of osteolytic sternal secondaries from prostate cancer, clinically presenting as a sternal mass without urinary symptoms [14,15].

The evaluation of serum prostate-specific antigen (PSA), an aspect not routinely included in pre-operative assessments

for chest wall tumors, played a pivotal role in confirming the diagnosis in this distinctive case. After the establishment of sternal metastases, comprehensive medical interventions involving radiotherapy, hormonal therapy, or chemotherapy become imperative, irrespective of the metastatic lesion's location and size.

When confronted with sternal metastases in isolation, a spectrum of therapeutic strategies comes into play. Established modes of treatment include surgical excision of the tumor, accompanied by sternum reconstruction using materials like titanium mesh, locking titanium plates, or allogenic transplants, along with stereotactic radiotherapy [16].

Conclusion

In conclusion, this case, presenting an exceedingly rare manifestation of osteolytic sternal metastasis from prostate cancer, underscores the complexity of metastatic involvement in the chest wall, particularly the sternum. The scarcity of similar cases in the literature calls for enhanced understanding and recognition of such atypical presentations. It underscores the importance of advanced diagnostic tools, like PET scans, for effective evaluation. The treatment of such metastases is characterized by consistent approaches, emphasizing the necessity of individualized and multidisciplinary management strategies. Notably, the positive response to GnRH injection in this case suggests the potential role of hormonal treatments, highlighting an area for further research. This report contributes significantly to the limited existing literature on this topic, underlining the need for continued research and comprehensive management of these unique clinical scenarios.

Ethics Committee Approval: N / A.

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

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – S.S., K.R.A., S.R.S.; Design – S.S., K.R.A., S.R.S.; Supervision – S.S., K.R.A., S.R.S.; Resources – S.S., K.R.A., S.R.S.; Materials – S.S., K.R.A., S.R.S.; Data Collection and/or Processing – S.S., K.R.A., S.R.S.; Analysis and/or Interpretation – S.S., K.R.A., S.R.S.; Literature Search – S.S., K.R.A., S.R.S.; Writing Manuscript – S.S., K.R.A., S.R.S.; Critical Review – S.S., K.R.A., S.R.S.

Conflict of Interest: The author declares that there was no conflict of interest.

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

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A Rare Clinical Condition That Can Mimic Bladder Malignancy: Primary Bladder Amyloidosis

Mesane Malignitesini Taklit Edebilen Nadir Bir Klinik Durum: Primer Mesane Amiloidozu

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Cite as: Negi SK, Desai S, Faujdar G, Sahu RD, Bansal S, Priyadarshi S. A rare clinical condition that can mimic bladder malignancy: Primary bladder amyloidosis. Grand J Urol 2024;4(1):32-4

Submission date: 02 January 2024 **Acceptance date:** 12 January 2024 **Online first:** 15 January 2024 **Publication date:** 19 January 2024

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Abstract

Amyloidosis is related to the extracellular deposition of abnormal protein fibrils in various tissues. It is clinically interesting that such cases' clinical, radiological, and even endoscopic presentation mimic urothelial carcinoma to a great extent. Here, we discuss a case of a 34-year-old gentleman who presented with frank painless hematuria. The patient was diagnosed with a bladder mass suspicious of malignancy depending on the clinical presentation aided by the cystoscopic and radiological evaluation. Histopathologic samples of the transurethral resection of the mass proved to be primary bladder amyloidosis. Further investigations of systemic illness excluded the secondary amyloidosis. The purpose of this case presentation is to create awareness among the urologists to think for the rare entity of urinary amyloidosis especially if the histopathology is negative for the malignant cells.

Keywords: amyloidosis, TUR, malignancy, Congo red

Özet

Amiloidoz, anormal protein fibrillerinin çeşitli dokularda hücre dışı birikmesiyle ilişkilidir. Bu tür vakaların klinik, radyolojik ve hatta endoskopik görünümlerinin ürotelyal karsinomu büyük ölçüde taklit etmesi klinik açıdan ilginçtir. Burada ağrısız hematüri şikayetiyle başvuran 34 yaşındaki erkek olguyu tartışıyoruz. Sistoskopik ve radyolojik değerlendirmenin yardımıyla hastaya klinik tabloya göre malignite şüphesi taşıyan mesane kitlesi tanısı konuldu. Kitlenin transüretal rezeksiyonunun histopatolojik örneklerinin primer mesane amiloidozu olduğu kanıtlandı. Sistemik hastalıkla ilgili daha ileri araştırmalar sekonder amiloidozu dışladı. Bu olgu sunumunun amacı ürologlar arasında nadir görülen bir durum olan üriner amiloidozun, özellikle de histopatolojinin malign hücreler için negatif olduğu durumlarda düşünülmesi konusunda farkındalık yaratmaktır.

Anahtar kelimeler: amiloidoz, TUR, malignite, Kongo kırmızısı

Introduction

Amyloidosis is a rare disease characterized by deposition of extracellular, hyaline and proteinaceous material in various organs. Amyloidosis can be primary, secondary, and hereditary. Localized amyloidosis of the urinary bladder is rare easily confused with an infiltrating tumor on imaging and cystoscopy [1]. Accurate diagnosis depends on biopsy showing negative malignant cells and presence of amyloid fibrils on cong red staining.

Case

34 yr male patient with gross hematuria. H/o smoking. Urinary ultrasonography showed that bladder mass of 3x2cm on left lateral wall. Urine for malignant cytology negative. Magnetic resonance imaging showed that 3x2.5 cm hyperintense mass in left lateral wall of urinary bladder s/o neoplastic etiology (**Figure 1**). Patient underwent cystoscopy and complete transurethral bladder tumour resection (TUR). Patient discharge on day 3 and follow up in outpatient department with histopathology report come to be amyloidosis (**Figure 2**). After that patient underwent investigations to rule out systemic amyloidosis which were normal. Patient also underwent cystoscopy at 3 month and found to be normal. Now on regular follow up.

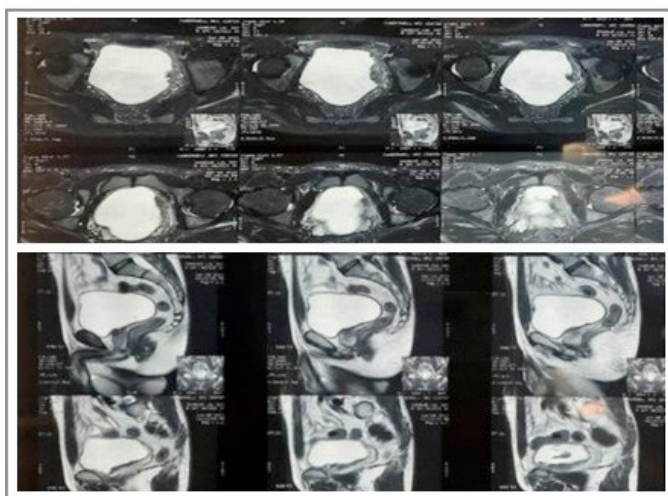


Figure 1. MRI images showing bladder mass on left lateral wall of UB

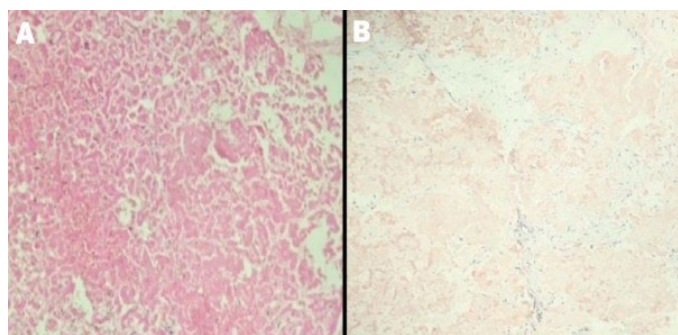


Figure 2. (A) Microscopy of tumour and (B) Congo red stain examined under polarized light shows characteristic apple-green birefringence appearance

Discussion

Amyloidosis can be either primary (AL) associated with immunocyte dyscrasia or secondary (AA) as a complication of chronic inflammation. The involvement of the kidney more common in secondary amyloidosis about 57% of all systemic disease, whereas in primary amyloidosis, the urinary bladder is more [2,3]. On imaging and cystoscopy poses diagnostic dilemma mimic malignancy. Biopsy will confirm diagnosis. TUR of lesion is successful treatment in most cases, medical therapy show only limited success. long- term follow-up with cystoscopy is indicated for recurrent amyloidosis [4].

Amyloidosis is a rare disease that occurs when an abnormal protein (amyloid) builds up in organs and interferes with their normal function. A very similar to that of bladder malignancy in regards to its presentation. A recently published systematic review by Pyrgidis et al (2021), 184 cases were reported, among 184 cases, 21.7% were asian [4]. Depending on the degree of disease involvement, patients may present with painless hematuria, irritative urinary symptoms, and obstructive symptoms. Urine cytology cannot distinguish amyloidosis from carcinoma because of the subendothelial location of most amyloid deposits and limited sensitivity for urothelial carcinoma. Definitive diagnosis of amyloidosis is achieved with biopsy. Like in our case, congo red staining of amyloid under light microscopy with polarized light produced the appearance of apple green birefringence. Although amyloidosis and bladder cancer's gross picture can look similar, it is easy to differentiate amyloidosis from urothelial carcinoma by light microscopy. On the one hand, amyloidosis is an acellular process, but on the other hand, urothelial carcinoma is a very cellular process. Another differential diagnosis besides urothelial carcinoma is chronic cystitis with fibrosis. Amyloidosis and cystitis can be associated with severe inflammation and deposition of proteinaceous material.

Conclusion

Adiagnosis of bladder amyloidosis is challenging, particularly when primary bladder malignancy has been suspected surgical pathologists and urologist to be aware of the unusual findings of urinary bladder amyloidosis for accurate diagnosis and workup.

Ethics Committee Approval: N / A.

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

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – S.K.N., S.D.; Design – S.K.N., S.D.; Supervision – S.K.N., S.P.; Resources – G.F., R.D.S., S.B.; Materials – G.F., S.B.; Data Collection and/or Processing – S.K.N., G.F., R.D.S., S.B.; Analysis and/or Interpretation – S.K.N., G.F., S.B.; Literature Search – G.F., R.D.S., S.B.; Writing – S.K.N., S.D.; Critical Review – S.K.N., S.P

Conflict of Interest: The author declares that there was no conflict of interest.

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

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