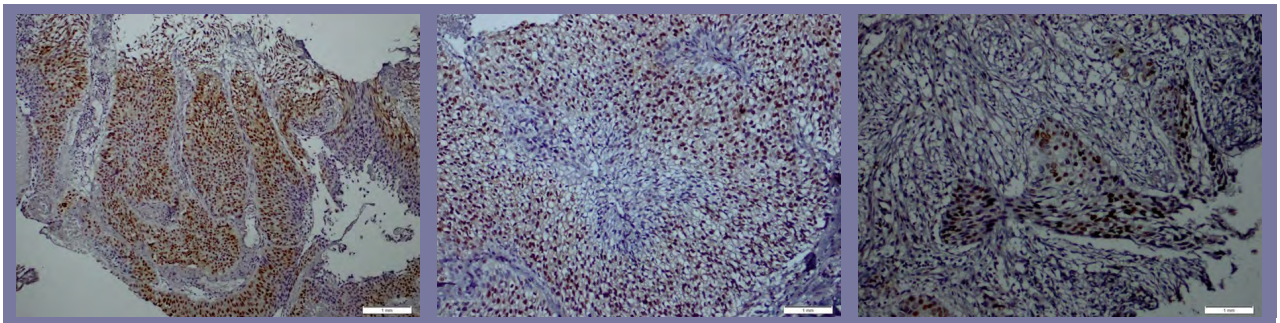
ISSN 1305-2489
eISSN 2687-1955

YENİ ÜROLOJİ DERGİSİ

The New Journal of Urology



Ezer M, Ertürk F, Beşeren H, Adalı Y. Investigation of Cyclin-D1 immunohistochemical expression in bladder urethelial carcinoma. The New Journal of Urology. 2023;18(2):115-123.

EURASIAN URO-ONCOLOGICAL ASSOCIATION

YENİ ÜROLOJİ DERGİSİ

The New Journal of Urology
New J Urol

• Volume **18** • Number **2** • June **2023**

EURASIAN
URO-ONCOLOGICAL
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YENİ
ÜROLOJİ
DERGİSİ

The New Journal of Urology
New J Urol

p-ISSN:1305-2489 e-ISSN:2687-1955

Volume 18 / Number 2 - June 2023

Publisher
Pera Publishing
https://www.perayayincilik.com/

Corporate Communication Director
Fatma Taşçı

Publishing Coordinator
Seda Karlıdağ

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Istanbul St. Yenimahalle Mah. Kosk Apt.
N:113/A Bakırkoy / Istanbul
0533 726 72 55
www.yeniurolojidergisi.org
yeniuroloji@yeniurolojidergisi.org

Printing–Binding
Pınarbaş Matbaacılık Ltd. Şti.
0212 544 58 77

The New Journal of Urology is an international peer-reviewed journal, published triannually (in February, June, October). Publication languages is English. All responsibility for the submitted and published content rests solely with the author(s).

Indexed by
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This journal is the publication of the Eurasian Urooncological Association

Dear Colleagues,

We are pleased to have published the second issue of The New Journal of Urology for 2023. This issue includes 8 original articles and 1 case report. Published articles consist of general urology, urooncology, endourology, transplantation and andrology. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

I am handing over my duty as the editor of the New Journal of Urology, which I have been fulfilling for 3 years, to the esteemed Yavuz Onur Danacıoğlu with this issue. It has been an honor and a privilege to serve as the editor of this esteemed journal. Together, we have witnessed remarkable advancements in the field of urology, and our journal has played a significant role in disseminating cutting-edge research, promoting innovative ideas, and fostering collaboration among urologists. I am proud of what we have accomplished together.

I would like to express my gratitude to Prof. Ali İhsan Taşçı for granting me the privilege of serving as Editor. It has been an honor, and I am grateful for the trust you have placed in me. I want to extend my heartfelt gratitude to you, not only for your leadership as the Editor-in-Chief but also for your guidance and support.

I also want to express my appreciation to the entire editorial team and staff of the New Journal of Urology. Their hard work, dedication, and passion for excellence have been pivotal in maintaining the journal's high standards and ensuring the timely publication of quality research. I am grateful for their support and the camaraderie we have built over the years.

I am confident that Mr. Danacıoğlu's expertise and dedication will further enhance the journal's reputation as a leading publication in the field of urology. I have full confidence that the New Journal of Urology will continue to thrive under the new editorial team.

I encourage all academicians to extend their support and cooperation to the journal.

Respectfully yours.

Fatih YANARAL

CONTENTS

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):108-114. doi: 10.33719/yud.2023;18-2-1187893**

Original Research / Özgün Araştırma

The effect of an herbal agent "Tutukon®" on the spontaneous passage rates of ureteric stones

Bitkisel bir ajan "Tutukon®"un üreter taşlarının spontan pasaj oranlarına etkisi

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Geliş tarihi (Submitted): 2022-10-20
Kabul tarihi (Accepted): 2023-03-30

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Özet

Amaç: Bu çalışmanın amacı, bir bitkisel ajan olan Tutukon®' un 5-10 mm üreter taşlarının spontan geçiş oranları üzerindeki etkinliğini değerlendirmektir.

Gereç ve Yöntemler: 5-10 mm çapında, tek radyoopak üreter taşı olan 96 hasta randomize olarak iki gruba ayrıldı. Grup 1'e (n=51) konservatif yaklaşıma ek olarak 45 mg/gün (üç kez) Tutukon®, Grup 2' deki hastalar (n=45) ise 4 haftalık takip süresince klasik konservatif yaklaşımla takip edildi. Taş geçiş oranları, taş çıkarma süreleri, haftalık kolik ataklarındaki değişim ve kolik ağrısı nedeniyle hastaneye yeniden başvuru oranları karşılaştırıldı.

Bulgular: Taş çıkarma oranları iki grup arasında istatistiksel olarak anlamlı farklılık gösterdi (%66.7'ye karşı %46.7, p = 0.048). Ek olarak, Tutukon® alan vakalarda, sadece konservatif önlemler alan Grup 2 hastaları ile karşılaştırıldığında, taşların spontan geçişi için gereken ortalama süre anlamlı olarak kısaydı (sırasıyla 5,79 ± 2,39 ve 8,82 ± 3,48 gün) (p = 0,001). Benzer şekilde, takip süresi boyunca ortalama renal kolik atakları Grup 1 hastalarında önemli ölçüde azaldı (sırasıyla %66,6'ya karşı %36, p = 0,001). Son olarak Grup 1'de kolik ağrı ataklarının daha az olduğu görüldü ve "Tutukon®"un bir diğer avantajı da taşların üreterin daha distal kısmına yer değiştirmesiydi (%35.2'ye karşı %4).

Sonuç: Üreter taşlarının medikal tedavisinde Tutukon® kullanımı, taşların spontan düşüş oranlarını hızlandırabilir ve aynı zamanda üreterin daha alt seviyelerine geçişini hızlandırabilir.

Anahtar Kelimeler: bitkisel ajanlar; medikal terapi; spontan pasaj; üreter taşları

Abstract

Objective: The objective of this study is to assess the efficacy of an herbal agent (Tutukon®) on the spontaneous passage rates of ureteral calculi 5-10 mm.

Material and Methods: 96 patients having a single radio-opaque ureteral stone 5-10 mm were randomized into two groups. Group 1 (n = 51) received Tutukon®, 45 mg/day (three times) in addition to the conservative approach and Group 2 patients (n = 45) were followed with the classical conservative approach during 4 weeks of follow-up. The stone passage rates, stone expulsion time, change in weekly colic episodes and hospital readmission rates for colicky pain were compared.

Results: Stone expulsion rates showed a statistically significant difference between the two groups (66.7 % vs 46.7 %, p = 0.048). Additionally mean time period required for the spontaneous passage of the calculi was meaningfully short in those cases receiving Tutukon® when compared with Group 2 patients undergoing conservative measures only (5.79 ± 2.39 vs 8.82 ± 3.48 days, respectively) (p = 0.001). Similarly, the mean renal colic episodes during the follow-up period were significantly diminished in Group 1 patients (66.6 vs 36%, p = 0.001, respectively). Lastly, colic pain attacks were noted to be less in Group 1, and another advantage of "Tutukon®" was the relocation of the stones to a more distal part of the ureter (35.2 vs 4 %).

Conclusion: Use of Tutukon® in the medical management of ureteral calculi can accelerate the spontaneous passage rates and also relocate them into the lower portion of the ureter.

Keywords: Herbal agents; medical therapy; spontaneous passage; ureteral stones

The study was approved by Ethics Committee of Clinica Endourologica Timisoara (Approval number: 02.05.2018/137). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

7 - 10 % of the population suffers from urolithiasis and related problems[1,2]. Ureteric stones should be detected and removed as quickly as possible to prevent obstruction and the associated discomfort of colic. This is the case regardless of where the calculus is located in the urinary system (3,4).

Although the likelihood of spontaneous passage of larger ureteral stones (> 10 mm) is decreased, in asymptomatic cases without obstruction, a conservative approach with pain management and medical expulsive therapy (MET) are reasonable options. Also, compared to minimally invasive surgical procedures, these approaches are safer and less expensive (2). Conservative management, including the use of MET when there is adequate evidence (5,6) is recommended by both the EAU and the AUA guidelines.

As a herbal agent, Tutukon® (Laboratorio Miguel&Garriga, S.A. Barcelona, Spain) is composed of eight different plants. Components of the medication individually show anti-apoptotic, nephroprotective, antioxidant, anti-apoptotic, and spasmolytic effects(7,8). The diuretic, spasmolytic, and anti-inflammatory actions of plant extracts from Opuntia ficus indica (9), Rosmarinus officinales (10), and Cynodon dactylon[11] have all been studied for their potential effects on stone formation.

The present study aimed to investigate the possible effects of an herbal agent, "Tutukon®" on the spontaneous passage rates of ureteral stones and related factors.

MATERIAL AND METHODS

From December 2017 to December 2018, 96 patients were enrolled (58 men, 38 females, M/F: 1.52) with a single radio-opaque ureteral stone (5-10 mm). Patients with multiple ureteral stones, bilateral stones, renal stones, severe hydronephrosis, a solitary kidney, a surgical history, diabetes, hypertension, pregnancy, or renal failure were excluded from this study. The protocol for the study was approved by the institution's Ethical Committee, and all participants supplied written informed consent after being given thorough information regarding the herbal substance.

X-ray, abdominal sonography, and plain X-ray (KUB) are all examples of imaging modalities that can be used to examine the urinary system (NCCT).

As a result of these assessments, the 96 patients were split into two groups: Group 2 (n = 45) received the standard conservative treatment (adequate hydration, increased physical activity, and routine pain management with nonsteroidal anti-inflammatory drugs), while Group 1 (n = 51) received a herbal agent (Tutukon®, 45 ml/day) for the same 4-week follow-up period.

If a patient's radiographic evidence of kidney stone passage occurred during this time period, treatment was stopped. In case there was any doubt about the stone's purported spontaneous transit, an NCCT was carried out in addition to the standard video evidence (KUB). Shock wave lithotripsy (SWL) and ureteroscopy will be used to remove a stone if the patient is unable to pass it on their own or if removal of the stone is deemed required due to severe colic pain, the development of hydronephrosis, infection, or hematuria.

Success rates in passing stones, the average time to expel stones, number of weekly colic episodes, and adverse effects were measured in both patient groups.

Herbal Agent

Tutukon® Neo, a herbal supplement produced by the Spanish company Laboratorio Miquel Y Garriga, SA in Barcelona, is always made using the same exact ingredients. Essential fatty acids, flavonoids, polysaccharides, the flavonoid quercetin, and boldin are all present. The components have been studied extensively and found to provide a wide variety of health benefits, including nephroprotective, diuretic, anti-inflammatory, antioxidant, antibacterial, and spasmolytic actions. The drug is available in a hidrolate form and comes in bottles of 250 milliliters. Ideally, adults should take three 7-ml doses daily. Components include 1.413 milligrams of flowers from Sideritis angustifolia, 1.413 milligrams of Melissa officinalis, 1.413 milligrams of flowers from Opuntia ficus-indica, 2.327 milligrams of flowers from Rosmarinus officinalis, and 4.738 milligrams of the aqueous distillate of the dried parts of an Enguisetum arvensis

stem.

Statistical evaluation: SPSS version 22.0 was used for the statistical evaluation (SPSS Inc., Chicago, IL, USA). The presentation of continuous variables was as mean and standard deviation. When a normal distribution was not seen in these variables, the median and IQR were used to present the data. These variables were compared using either a Mann-Whitney U-test or an independent T-test. Categorical variables were expressed using numbers and percentages (%). The Fisher's exact or Chi-square test was used to compare these variables. For all statistical studies, a p-value of <0.05 was used.

RESULTS

A total of 96 people took part in the study (Group 1: 51; Group 2: 45). There were 58 men and 38 women in Group 1 (M/F = 1.52), with a mean age of 36.9±11.3 and 33.2±7.2 in Group 2. Table 1 displays that there was no significant difference between the two groups with regard to the patient (age, gender), stone (size, position), and data. Although few patients experienced mild side effects during the follow-up period, no one stopped taking the medication due to these problems.

The following are the findings from our examination of data collected from both sets of participants: Patients who were given "Tutukon®" (66.7% expulsion rate) had a significantly better outcome than those who were given conservative therapy without medication (46.7% expulsion rate; p = 0.048) in the analysis of the most relevant parameter. Furthermore, it indicated that those in Group 2 who did not get "Tutukon®" passed their ureteric stones more quickly than those in Group 1. Tutukon® significantly accelerated the average time needed for spontaneous transit of calculi compared to Group 2 patients who were treated with just conservative measures (p=0.001). As a result, "Tutukon®" medication facilitated the transit of ureteric stones at a higher rate than conservative treatment alone, resulting in the cases becoming stone-free in a short period (Figure 1).

No statistically significant difference in the mean number of colic attacks was found between the two groups after diligent follow-up for four weeks using only conservative strategies for treating the discomfort (Table 1).

However, when comparing patients in Group 2 who received no specific medication other than conservative management measures with those in Group 1, those who received "Tutukon®" had a significantly higher rate of improvement in the degree of hydronephrosis (delta grade changes), indicating that the dilatation of the upper tract resolved more quickly and effectively in the former group. This finding once again revealed the patent spasmolytic advantages of "Tutukon®" which, throughout the 4-week follow-up period, normalized the urine flow in most cases [1.47 (0.82-2.74) vs. 1.31 (0.73-1.94), p: 0.210].

Stones migrated and relocated from the proximal ureter to the lower ureter in 6 of 17 cases (35.2%), compared to the extremely limited cases in Group two (1 of 24 cases, 4%), suggesting that "Tutukon® application" has additional benefits beyond simply increasing the rate of spontaneous stone passage. The use of "Tutukon®" appears to aid in the migration of stones from the upper to the lower ureter, offering urologists a major advantage in the event of no spontaneous passage and making stone removal more feasible.

When medication and conservative care failed to get the stone to pass on its own, doctors in both groups turned to SWL (in 5 cases) and URS (in 28 cases) to break up the obstruction (3 SWL in Group 1 and 2 in Group 2, 17 URS procedure applied in Group 1 and 11 in Group 2 cases). The classification of Spontaneous Passage rates according to stone localization is given in Table 2.

Modest and transient side effects were reported by patients taking "Tutukon®" including nausea in 9 patients, vomiting in 1 patient, an inability to taste in 3 patients, dysuria in 5 patients, and headache in 5 patients, according to follow-up evaluations of adverse effects. At the end of the follow-up period, seven patients in Group 2 reported only dysuria. These modest and transient side effects did not cause any patients to withdraw from the research and stop treatment.

Table 1. Evaluation of patient and stone related parameters along with the treatment outcomes in both groups

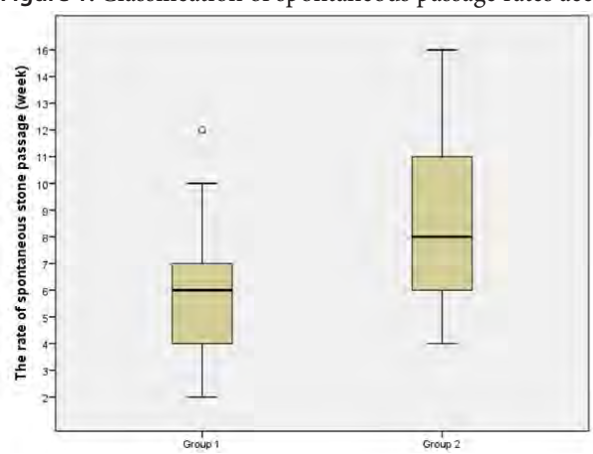
		Group 1 (n: 51)	Group 2 (n:45)	P Value
Gender (Male/ Female)		32(62%)/19(38%)	26(57%)/19(43%)	0.619
Age (mean; year ± SD)		36.9 ± 11.3	33.2 ±7.2	0.067
Stone size (mm± SD)		0.73±0.15	0.70 ± 0.14	0.423
Stone localization	Proximal ureter	21 (41.2 %)	20(44.4 %)	0.945
	Distal ureter	16 (31.4 %)	13 (28.9 %)	
	Vesicoureteral junction	14 (27.5 %)	12 (26.7 %)	
The rate of spontaneous stone passage n (%)		34 (66.7 %)	21 (46.7 %)	**0.048**
Mean number of colic pain/weeks during follow-up period	1. Week	1.69 ± 0.78	1.36 ±0.57	0.220
	2. Weeks (median-IQR)	0.52 (0.31-0.83)	0.39 (0.261.08)	0.756
	3. Weeks	1.49 ± 0.61	1.69 ± 0.46	0.802
	4. Weeks	1.45 ±0.67	1.56 ± 0.54	0.490
	Total	5.24 ± 0.95	5.15 ±1.24	0.710
Improvement of the degree of hydronephrosis (Delta grade) (median-IQR)		1.47 (0.82-2.74)	1.31 (0.73-1.94)	0.210
Need for JJ insertion or ureteroscopy		8 (15.7 %)	8(17.8 %)	0.784
Mean time to spontaneous stone passage(week ± SD)		5.79 ± 2.39	8.82 ± 3.48	**0.001**

Abbreviations: *SD, Standart Deviation*

Table 2. Classification of spontaneous passage rates according to stone localization

	Group 1	Group 2
Proximal Ureter	47.6 % (10/21)	25.0 % (5/20)
Distal Ureter	75.0 % (13/16)	53.8 % (7/13)
Vesicoureteral	85,7% (11/14)	75.0 % (9/12)

Figure 1. Classification of spontaneous passage rates according to stone localization



Group 1: Patient receiving "Tutukon" medication addition to conservative measures

Group 2: Patients receiving only conservative measures

DISCUSSION

Ureteral stone disease, or urolithiasis, affects 2-3% of the population and has a high recurrence rate of around 50%[1]. In order to prevent functional and morphological problems in the kidney, prompt decompression is required in patients with ureteric stones referring to emergency rooms with varying degrees of obstruction in the renal collecting system. Patients for whom conservative treatment does not provide adequate symptom relief or fail to result in the spontaneous passage of the stone(s) may also require stone removal (12). With respect to the likelihood of spontaneous passage in patients treated with conservative treatment, a meta-analysis found that stones 5 mm and 5-10 mm had spontaneous passage rates of 68 and 47%, respectively, with a 95% confidence interval of 46-85% (13). Available data show that the size and location of the ureteral stone have a significant impact on both the success rate of expulsion and the length of time for spontaneous passage. It was shown that the size of the stone is a strong indicator of spontaneous passage rates. Although spontaneous passage is documented in 71%-98% of distal ureteral stones 5 mm, only 25%-51% of stones 5 mm pass without intervention (14).

When considering the risks of traditional treatment methods (such as open surgery, extracorporeal shock wave lithotripsy, and ureteroscopy), physicians looked for less invasive options like "medical expulsive therapy" (MET) to increase the proportion of patients with asymptomatic ureteral calculi who pass the stone on their own during a monitored observation period[15]. Numerous medications have been used, but only alpha-1 blockers were the most commonly used ones for this purpose (15,16). These medications include calcium channel blockers, prostaglandins production inhibitors, glyceryl trinitrate, and steroids. These medications were shown to inhibit ureteral spasms by decreasing the peristaltic frequency and blocking ureteral wall basal tone (7). Alpha-1 blockers have been shown in multiple studies (9,10,17) to be an effective and safe treatment for ureteral stones. While the European Association of Urology (EAU) guidelines advocate MET for all ureteral stones, the current AUA guidelines announced in May 2016 only prescribe treatment for patients with distal ureteral stones 10 mm (6,18).

Other benefits of MET described by the number of well-conducted studies include increased rates of spontaneous passage; a shorter stone passage duration was observed (9,19,20) a considerable reduction in the need for minimally invasive procedures, less unpleasant pain episodes with lower VAS scores, and reduced demand for analgesics (2,21,22).

Reviewing the relevant literature, we find that herbal medicine has been increasingly important in treating and preventing urinary stones during the past few decades in relation to the medical management of stones with an emphasis on medical expulsive therapy. Phytotherapy has been shown in multiple studies to significantly enhance the effects of lithotripsy, increase spontaneous passage rates, and improve the efficacy of urinary tract stone prevention in the conservative treatment of urolithiasis (17). Several of these herbal components show therapeutic potential for the facilitation of spontaneous passage and the treatment of colic discomfort (23), in addition to avoiding crystallization and the formation of new stones. Because of the beneficial effects observed when using these medicines, they are widely employed for the treatment, prevention, and prophylaxis of urolithiasis. These agents were deemed beneficial due to the fact that their active components allowed them to perform multiple functions while posing a minimal danger of unwanted side effects. Recent publications on animal models have investigated the unique antioxidant, anti-inflammatory, spasmolytic, diuretic, and renoprotective effects of "Tutukon®" which is comprised of eight different components (8). As a result of their diuretic, spasmolytic, and anti-inflammatory properties, plant extracts such as those from the Opuntia ficus-indica (9), Rosmarinus officinalis (10), and Cynodon dactylon (11) have been demonstrated to have significant benefits on infection prophylaxis and stone formation (8,24,25).

The goal of this study was to assess the effects of the herbal agent "Tutukon®" on spontaneous passage

rates, time to stone expulsion, and colic attacks during the conservative follow-up of ureteral stones (5-10 mm) without evident blockage or infection. Our data analysis clearly indicated the evident benefits of this agent on these parameters, where a sizeable proportion of patients treated with this therapy passed their calculi in a shorter period of time compared to patients treated with only a conservative medical strategy. There was a decrease in the number of colics observed during weekly follow-up, and in some patients with proximal ureteral stones (who were unable to pass them during 4 weeks of follow-up), the stones migrated from the upper to the lower portion of the ureter, allowing the responsible urologists to more easily and quickly treat them via endoscopic means. Tutukonunique®'s constituents demonstrate the aforementioned various effects (spasmolytic, diuretic, and anti-inflammatory), therefore its administration will aid in expediting the spontaneous passing of ureteric stones in a shorter amount of time before any endoscopic intervention may be necessary.

Increased spontaneous passing rates and decreased colic attacks requiring pain medication are two ways in which "Tutukon®" might improve the quality of life for patients undergoing conservative treatment for ureteral stones (rapid return to daily activities and work, fewer emergency department visits, and fewer surgical procedures). Our previous study addressed the "displacement issue," or the distal migration of proximal ureteral stones during MET treatment. This is a huge plus since it will allow the urologist to do ureteroscopy to remove calculi in a less invasive and risky way. We believe that our findings can help clinicians determine whether or not such herbal drugs are useful in the conservative therapy of ureteral calculi as patients wait for possible spontaneous passage, despite the fact that our trial's small sample size could be a major restriction.

CONCLUSIONS

Our results suggest that patients with medium-sized (10-15 mm) ureteral stones may benefit from the use of the herbal agent "Tutukon®" during the watchful waiting follow-up period to assist and accelerate the spontaneous passage and minimize the number of colic attacks caused by these stones. Additionally distal migration of the stones after Tutukon® application, may maket he subsequent treatment easier and safer.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethics Committee of Clinica Endourologica Timisoara (Approval number: 02.05.2018/137) The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

All authors contributed equally to this work.

REFERENCES

1. Scales CD, Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. Eur Urol 2012;62(1):160–165. https://doi.org/10.1016/J.EURURO.2012.03.052
2. Hubner WA, Irby P, Stoller ML. Natural history and current concepts for the treatment of small ureteral calculi. Eur Urol 1993;24(2):172–176. https://doi.org/10.1159/000474289
3. Bierkens AF, Hendrikx AJM, de La Rosette JJMCH, et al. Treatment of mid- and lower ureteric calculi: extracorporeal shock-wave lithotripsy vs laser ureteroscopy. A comparison of costs, morbidity and effectiveness. Br J Urol 1998;81(1):31–35. https://doi.org/10.1046/J.1464-410X.1998.00510.X
4. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. J Urol 2005;174(1):167–172. https://doi.org/10.1097/01.JU.0000161600.54732.86
5. Pradère B, Doizi S, Proietti S, et al. Evaluation of Guidelines for Surgical Management of Urolithiasis. J Urol 2018;199(5):1267–1271. https://doi.org/10.1016/J.JURO.2017.11.111

6. Türk C, Petřík A, Sarica K, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol 2016;69(3):468–474. https://doi.org/10.1016/J.EURURO.2015.07.040
7. Nakada SY, Coyle TLC, Ankem MK, et al. Doxazosin relaxes ureteral smooth muscle and inhibits epinephrine-induced ureteral contractility in vitro. Urology 2007;70(4):817–821. https://doi.org/10.1016/J.UROLOGY.2007.06.002
8. Sahin C, Sarikaya S, Basak K, et al. Limitation of apoptotic changes and crystal deposition by Tutukon following hyperoxaluria-induced tubular cell injury in rat model. Urolithiasis 2015;43(4):313–322. https://doi.org/10.1007/S00240-015-0777-1
9. Meiouet F, el Kabbaj S, Daudon M. [In vitro study of the litholytic effects of herbal extracts on cystine urinary calculi]. Prog Urol 2011;21(1):40–47. https://doi.org/10.1016/J.PUROL.2010.05.009
10. Naber KG. Efficacy and safety of the phytotherapeutic drug Canephron® N in prevention and treatment of urogenital and gestational disease: review of clinical experience in Eastern Europe and Central Asia. Res Rep Urol 2013;5(1):39–46. https://doi.org/10.2147/RRU.S39288
11. Rad AK, Hadjzadeh M-A-R, Rajaei Z, et al. The beneficial effect of Cynodon dactylon fractions on ethylene glycol-induced kidney calculi in rats. journals.sbmu.ac.ir 2011;8(3):179–84
12. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27(1):117–126. https://doi.org/10.1016/0304-3959(86)90228-9
13. Segura JW, Preminger GM, Assimos DG, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol 1997;158(5):1915–1921. https://doi.org/10.1016/S0022-5347(01)64173-9
14. Al-Ansari A, Al-Naimi A, Alobaidy A, et al. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology 2010;75(1):4–7. https://doi.org/10.1016/J.UROLOGY.2009.09.073
15. Johnson DB, Pearle MS. Complications of ureteroscopy. Urologic Clinics of North America 2004;31(1):157–171. https://doi.org/10.1016/S0094-0143(03)00089-2
16. Borghi L, Meschi T, Amato F, et al. Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. J Urol 1994;152(4):1095–1098. https://doi.org/10.1016/S0022-5347(17)32511-9
17. Patle A, Hatware KV, Patil K, et al. Role of Herbal Medicine in the Management of Urolithiasis- A Review for Future Perspectives. J Environ Pathol Toxicol Oncol 2019;38(2):97–118. https://doi.org/10.1615/JENVIRONPATHOLTOXICOLONCOL.2019029075
18. Assimos D, Krambeck A, Miller NL, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol 2016;196(4):1161–1169. https://doi.org/10.1016/J.JURO.2016.05.091
19. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. J Urol 2003;170(6 Pt 1):2202–2205. https://doi.org/10.1097/01.JU.0000096050.22281.A7
20. Autorino R, de Sio M, Damiano R, et al. The use of tamsulosin in the medical treatment of ureteral calculi: where do we stand? Urol Res 2005;33(6):460–464. https://doi.org/10.1007/S00240-005-0508-0
21. Ye Z, Zeng G, Yang H, et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. Eur Urol 2018;73(3):385–391. https://doi.org/10.1016/J.EURURO.2017.10.033
22. Resim S, Ekerbicer H, Ciftci A. Effect of tamsulosin on the number and intensity of ureteral colic in patients with lower ureteral calculus. Int J Urol 2005;12(7):615–620. https://doi.org/10.1111/J.1442-2042.2005.01116.X
23. Monti E, Trinchieri A, Magri V, et al. Herbal medicines for urinary stone treatment. A systematic review. Arch Ital Urol Androl 2016;88(1):38. https://doi.org/10.4081/AIUA.2016.1.38
24. Yuruk E, Tuken M, Sahin C, et al. The protective effects of an herbal agent tutukon on ethylene glycol and zinc disk induced urolithiasis model in a rat model. Urolithiasis 2016;44(6):501–507. https://doi.org/10.1007/S00240-016-0889-2
25. Tuken M, Temiz MZ, Yuruk E, et al. The role of an herbal agent in treatment for Escherichia coli induced bacterial cyctitis in rats. Arch Ital Urol Androl 2017;89(2):134–138. https://doi.org/10.4081/AIUA.2017.2.134

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):115-123. doi: 10.33719/yud.2023;18-2-1150164**

Original Research / Özgün Araştırma

Investigation of Cyclin-D1 immunohistochemical expression in bladder urethelial carcinoma

Mesane ürotelyal karsinomlarında Cyclin-D1 immünohistokimyasal ekspresyonunun araştırılması

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Geliş tarihi (Submitted): *2022-07-28*
Kabul tarihi (Accepted): *2023-03-30*

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Özet

Amaç: Cyclin D1 hücre siklusunun düzenlenmesinde görev alan ve CCND1 geni tarafından kodlanan bir proteindir. Liteatürde Cyclin D1 ile ilgili az sayıda çalışma mevcut olup çalışmalarda sonuçlar farklılık göstermektedir. Bu çalışmada mesane ürotelyal karsinomlarda Cyclin D1ekspresyonunun prognostik faktörler ile ilişkisi araştırıldı.

Gereç ve Yöntemler: Çalışmaya Kafkas Üniversitesi Sağlık Araştırma ve Uygulama Hastanesi'nde TUR-M yapılmış 46 olgu dahil edildi. Olgulara dair genel bilgiler ve patoloji raporları hastane otomasyon sisteminden elde edildi. Hematoksilen&Eozin boyalı patoloji preparatlarından tümör içeren kesitler seçilip seçilen kesitlere ait bloklara Cyclin D1 primer antikoru ile immünohistokimyasal boyama manuel yöntem ile yapılmıştır.Boyanan kesitler ışık mikroskobunda nükleer ve sitoplazmik olarak ayrı ayrı 0-4 olarak skorlanarak değerlendirildi.

Bulgular: Olguların yaş aralığı 51-93 olup ortalama yaş 69.2±11.7'dir. Olguların 12'si (%26.1) kadın, 34'ü (%73.9) erkektir. Histopatolojik bulgular incelendiğinde olguların 29'unun (%63.0) düşük dereceli 17'sinin (%37.0) yüksek dereceli olduğu gözlenmiştir. Olguların 18'i (%39.1) invaziv, 28'i (%60.9) noninvaziv niteliktedir. Yapılan istatistiksel analizlerde invazyon gösteren tümörlerin non-invaziv tümörlere göre (pTa) anlamlı düzeyde yüksek dereceli olduğu dikkati çekmiştir (p= 0.007). Benzer şekilde ve invaziv tümörlerde lenfovasküler invazyon varlığı non-invaziv tümörlere göre anlamlı derecede daha fazla saptanmıştır (p=0.001). Nükleer cyclin

Abstract

Objective: Cyclin D1 is a protein that is involved in the regulation of the cell cycle and is encoded by the CCND1 gene. There are few studies on Cyclin D1 in the literature, and the results differ in the studies. In this study, the relationship between Cyclin D1 expression and prognostic factors in bladder urothelial carcinomas was investigated.

Materials and Methods: Forty-six patients who underwent TUR-M at the Kafkas University Health Research and Application Hospital were included in the study. General information about the cases and pathology reports were obtained from the hospital automation system. Tumor-containing sections were selected from the Hematoxylin and Eosin stained pathology slides, and immunohistochemical staining was performed manually with Cyclin D1 primary antibody on the blocks of the selected slides. Immunostained pathology slides were evaluated under light microscope by scoring 0-4 separately as nuclear and cytoplasmic scores.

Results: The age range of the cases was 51-93, and the mean age was 69.2±11.7. Twelve (26.1%) cases were female and 34 (73.9%) were male. It was observed that 29 (63.0%) of the cases were low-grade and 17 (37.0%) were high-grade. Eighteen (39.1%) of the cases were invasive and 28 (60.9%) were noninvasive. In the statistical analyzes, it was noted that invasive tumors had a significantly higher grade compared to non-invasive tumors (pTa) (p= 0.007). Similarly, the presence of lymphovascular invasion in invasive tumors was statistically <0.005 higher than that of in non-invasive tumors. (p=0.001). It was observed that

The study was approved by Ethics Committee of Kafkas University (Approval number: 2021.07.01/29). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

D1 expresyonunun (p=0.003) invaziv olgularda anlamlı düzeyde daha yüksek olduğu izlenmiştir. Ayrıca düşük dereceli tümörlerde nükleer cyclinD1 ekspresyonu anlamlı düzeyde yüksek bulunduğu saptanmıştır (p=0.044).

Sonuç: Çalışma sonucunda mesane ürotelyal karsinomlu hastalarda Cyclin D1 ekspresyonun tümör derecesi ve invazyon durumu ile ilişkisi gözlenmiştir ancak Cyclin D1'in biyobelirteç olarak kullanılabilmesi için daha geniş olgu serilerinde çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimler: mesane, Cyclin D1, üretelyal karsinom, immünohistokimya

nuclear cyclin D1 expression (p=0.003) was significantly higher in invasive cases. In addition, nuclear cyclinD1 expression was found to be statistically significantly higher in low-grade tumors (p=0.044).

Conclusion: As a result of the study, a relationship between Cyclin D1 expression and tumor grade and invasion status was observed in patients with bladder urothelial carcinoma, but studies with larger case series are needed to use Cyclin D1 as a biomarker.

Keywords: bladder, Cyclin D1, urothelial carcinoma, immunohistochemistry

INTRODUCTION

Bladder carcinoma is the fourth most common cancer in men and the seventh most common cancer in women (1). Despite advances in treatment, its prognosis still remains poor (2). In bladder carcinomas, mortality and recurrence rates increase as urothelial carcinomas progress from the superficial form to the invasive form (3). In 70% of patients, the tumor is limited to the lamina propria (4) Recurrence may occur in at least one of 50% of bladder tumors after treatment. Recurrence after treatment is partially related to the histological grade and depth of invasion (5). Although factors such as tumor diameter, grade and stage are routinely used to determine recurrence and prognosis, these factors are often not sufficient to determine the course of the tumor (6). Therefore, studies are continuing to understand the effectiveness of treatment methods by determining the recurrence

and prognosis in these tumors (6). The way to do this is through the use of effective markers showing recurrence and prognosis. One of these markers is Cyclin D1, that has been reported to be a marker that plays a very important role in the emergence, development and spread of bladder cancer (7).

Cyclins are the regulatory subunit of "Cyclins are the regulatory subunit of cyclin dependent kinases (CDK)" and provide control in the transition from one phase to another in different phases of the cell cycle (8). The transient emergence of cyclins controls the enzymatic activity of CDKs resulting in the formation of a cyclin/CDK complex. Cyclin AS is required for transition to S phase and G2 phase in mammalian somatic cells (9). While Cyclin D and E control the transition to G1, Cyclin B has assumed the role of an important controller of all mitosis (10). Their mutations cause the cell to get stuck in G2 phase. It plays a role in all stages of the disease in renal cell carcinomas and various soft tissue tumors (11).

The cell cycle consists of G1 (presentetic), S (DNA synthesis), G2 (premitotic) and M (mitotic) stages. The transition from G1 to S is believed to be the most important control point in the cell cycle (12). The progression of the cell from phase to phase during the cycle is controlled by cyclins, cyclin-dependent kinases (CDK) and their inhibitors (13). Cyclins are among the positive regulators of this cycle (14). Cyclins, together with their catalytic subunit, cyclin-dependent kinase (CDK), play an important role in the cell cycle (15). CDK inhibitors, which are negative regulators, regulate the activity of the Cylin-CDK complex (17). Disruption of cell cycle regulation plays a key role in the development and progression of malignant tumors (16). In normal tissues, cyclins are positive regulators of the cell cycle and are associated with cell proliferation (16). However, their expression in tumors is deregulated depending on the proliferation status of the tumor (17). Cyclin D1 overexpression is observed in many tumors including liver, breast, lung, head and neck tumors (18). Recent studies have shown that CylinD1 overexpression is also found in bladder urothelial carcinomas, and this is associated with low grade in many studies

Neoplastic expression can be detected in a wide variety of Cyclin D1/bcl-1 (=G2 M phase Cyclin) processes, including bladder urothelial cancers (19). For example, 50-70% of Mantle cell lymphomas have been demonstrated to overproduce this protein (19). In the G1-S phase transition, an increase in the amount

of cyclin D1 is observed. In a study conducted in lung cancer patients other than small cell lung cancers, it was determined that p53 protein and CyclinD1 have a very significant interaction(20). It has been reported that Cyclin D1 is effectively used in the follow-up of pathogenesis and prognosis in these tumors and in cases with diffuse alveolar destruction (21). The increase in this protein is an important marker indicating poor prognosis (22). Tumor grade and stage are important prognostic indicators in urothelial tumors of the bladder. Molecular changes associated with bladder carcinoma contribute to the determination of prognosis. Therefore, in this study, we aimed to evaluate the relationship of Cyclin D1 marker with tumor stage, grade and lymphovascular invasion in patients who underwent transurethral resection (TUR) for bladder urothelial carcinoma.

MATERIAL AND METHODS

Prior to the study, approval was obtained from the Non-Invasive Studies Ethics Committee of the Faculty of Medicine of Kafkas University, dated 01.07.2021 and numbered 07. Forty-six patients who underwent TUR-M at the Kafkas University Health Research and Application Hospital were included in the study. General information about the cases and pathology reports were obtained from the hospital automation system. Tumor-containing sections were selected from the H&E stained pathology slides, and the blocks of the selected slides were immunohistochemically stained with Cyclin D1 by a manual method (Clone SP4, ThermoScientific, USA) primary antibody as indicated below.

Sections were taken from paraffin blocks on a 3-4 micron thick adhesive slide. Sections were kept in an oven at 56 degrees overnight. The next day, the sections were kept in three separate xylenes for 5 minutes. Then, they were kept in graded alcohols for 5 minutes and washed in distilled water for 1 minute. They were boiled in 10% citrate buffer (Sigma-Aldrich, USA, Ph6.0) solution for 10 minutes. The lid of the vessel containing the boiled slides was opened and kept at room temperature for 20 minutes. The sections were rinsed with distilled water and kept in 10% hydrogen peroxide solution for 10 minutes, then washed again in distilled water and kept in a W block (ThermoScientific, USA) for 5 minutes. At the end of the period, the primary antibodies diluted at a ratio of 1:50 were dropped by shaking the W block on the sections without washing. Antibodies were incubated for 60 minutes. After incubation, washing was done in distilled water for 10 minutes. Then, it was passed to the secondary antibody stage and kept in biotin (ThermoScientific, USA) solution for 20 minutes, washed in distilled water for 5 minutes and kept in streptavidin (ThermoScientific, USA) solution for 20 minutes. After washing in distilled water for 5 minutes, it was incubated in DAB chromogen (ThermoScientific, USA) for 7 minutes and washed. Finally, after 5 minutes of staining in Mayer's hematoxylin (Bio-Optica, Italy), it was passed through alcohol and xylene and closed with a mount.

Immunohistochemically stained sections were evaluated nuclear and cytoplasmic separately under the light microscope (Olympus BX51 BF/DF) by scoring "0: no staining, 1: mild staining, 2: moderate staining, 3: strong staining". SPSS 15.0 package program was used for statistical analysis (SPSS Inc. Released 2006. SPSS for Windows, Version15.0. Chicago, SPSS Inc.). The conformity of the immunohistochemical staining scores to the normal distribution was evaluated with the Kolmogorov Smirnov and Shapiro Wilk tests. Immunohistochemical staining scores and tumors were compared according to their pT stage and categorized as invasive/noninvasive in analyzes performed using Mann Whitney U, Kruskal Wallis tests and T test for independent samples in the 95% confidence interval. In addition, low/high tumor grade and presence of lymphovascular invasion were also compared with the staining scores.

RESULTS

The mean age of cases was 69.2±11.7. Twelve (26.1%) cases were female and 34 (73.9%) were male. It was observed that, 29 (63.0%) of the cases were low-grade and 17 (37.0%) were high-grade. Eighteen (39.1%) of the cases were invasive and 28 (60.9%) were noninvasive. In the pathological stage evaluation, it was noted that 28 (60.9%) cases were pTa, 11 (23.9%) cases were pT1 and 7 (15.2%) cases were pT2. While lymphovascular invasion was detected in 6 (13.0%)

cases; it was not observed in 40 (87.0%) cases. In the statistical analyzes performed, it was noted that invasive tumors had a significantly higher grade compared to non-invasive tumors (pTa) (p= 0.010). Similarly, the presence of lymphovascular invasion in invasive tumors was significantly higher than in non-invasive tumors (p=0.009) (Table-1).

Table 1. Patient and tumor characteristics

Variable	n (%)
Age	69.2±11.7
Gender	
Woman	12 (26.1)
Male	34 (73.9)
Invasive	18 (39.1)
Noninvasive	28 (60.9)
Grade	
Low grade	29 (63.0)
High grade	17 (37.0)
Tumor Classification	
pTa	28 (60.9)
pT1	11 (23.9)
pT2	7 (15.2)
pT3	0 (0)
pT4	0 (0)
Presence of lymphovascular Invasion	6 (13)

Table 2. Nuclear and cytoplasmic cyclin D1 expression scores

Variable	n (%)
Nuclear cyclin D1 expression	
0 (no staining)	9 (19.6)
1 (mild staining)	15 (32.6)
2 (moderate staining)	11 (23.9)
3 (strong staining)	11 (23.9)
Cytoplasmic cyclin D1 expression	
0 (no staining)	30 (65.2)
1 (mild staining)	16 (34.8)
2 (moderate staining)	0 (0)
3 (strong staining)	0 (0)

Nuclear and cytoplasmic cyclin D1 expression is demonstrated in figures 1-3 and scores are presented in Table 2. The staining scores were not distributed normally (p=0.000 on both Kolmogorov Smirnov and Shapiro Wilk tests). The interquartile range for nuclear cyclin D1 scores were calculated as 1 as well as cytoplasmic cyclin D1 scores. It was detected that neither age nor gender showed statistical significance with nuclear cyclin D1 expression (p=0.909, p=0.458 respectively) and cytoplasmic cyclin expression (p= 0.928, p=0.905 respectively). In the analyzes, it was observed that nuclear cyclin D1 expression (p=0.002) was statistically significantly higher in invasive cases. However, the same significance could not be demonstrated between cytoplasmic cyclinD1 (p=0.428) expression and invasion. There was also a statistical significance between pT stage and nuclear cyclin D1 expression (p=0.011). In addition, as in invasion, no correlation was found with cytoplasmic expressions (p= 0.730). With the Mann Whitney U test, nuclear cyclinD1 (p=0.044) expression was found to be statistically significantly higher in low-grade tumors, but the same relationship could not be shown in cytoplasmic expression (p= 0.562). It was noted that the nuclear (p=0.112) and cytoplasmic cyclin D1 (p=0.937) expression in the mannWhitney U test for lymphovascular invasion did not show a statistically significant difference.

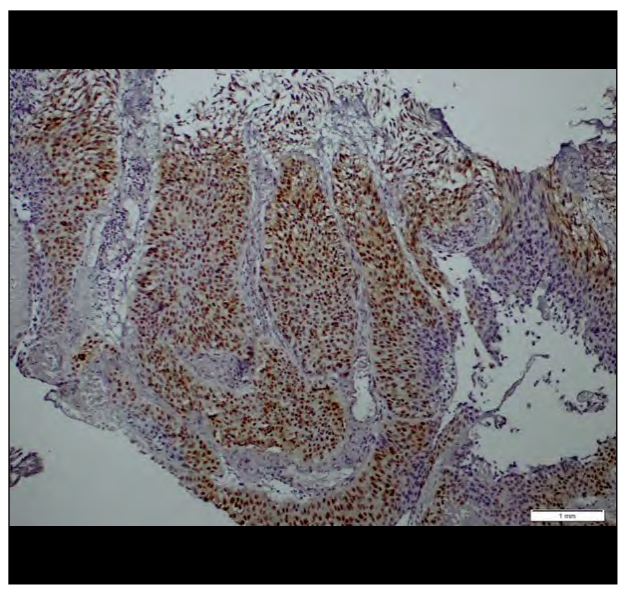

Figure 1. Moderate cytoplasmic and nuclear cyclin D1 staining, 100x

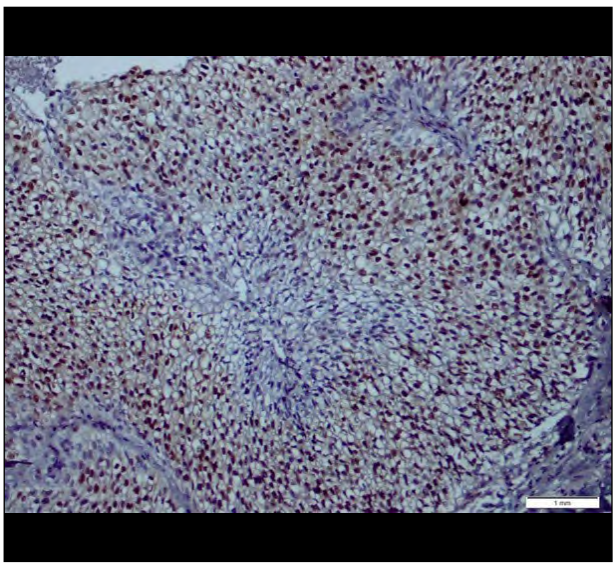

Figure 2. Mild cytoplasmic and strong nuclear cyclin D1 staining, 200x

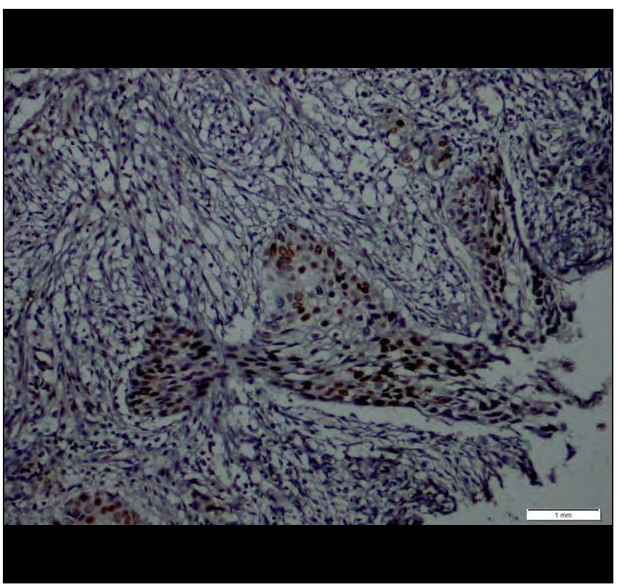

Figure 3. No cytoplasmic cyclin D1 staining and moderate-strong nuclear cyclin D1 staining, 400x

DISCUSSION

Conventional prognostic factors provide important information in evaluating the prognosis of bladder cancer (23). However recently, new markers related to cell cycle and apoptosis mechanisms, which are thought to provide more objective data in evaluating the prognosis and clinical course of bladder tumors, have been studied. Among the conventional prognostic factors, staging is the most important prognostic factor in bladder cancer (24). While 5-year survival is more than 75% in tumors with only lamina propria invasion, it decreases to 40% in muscularis propria invasion and 20% in perivesical adipose tissue invasion (25). While recurrence rate and rate in progression in low grade urothelial carcinoma are is 64% and 10.5%, respectively; recurrence rate in high grade urothelial carcinoma is 56.4% and risk of progression is 27% (26).

In some studies, no relationship was found between cyclin D1 and stage and grade, but it was reported that patients with high Cyclin D1 expression had a long disease-free survival and recurrence was higher in those with low Cyclin D1 expression (26). When cell cycle-related genes are altered, they can cause neoplastic transformation. Cyclin D1 is one of them that plays a role as an oncogene for various neoplasms (27). This is generally said to occur with increased expression and amplification of mRNA (27). In recent studies, it has been determined that high expression of exogenous Cyclin D1 in breast cancer cells inhibits rather than increases the growth of breast cancer cells. These also support the double-acting role of Cyclin D1 in the cell cycle (28).

By defining the signal transmission pathways of molecules, it has facilitated our understanding of processes such as cellular life, metastasis, and invasion in tumors (29). Apoptosis, which occurs as a result of mutation, plays an important role in carcinogenesis, metastasis and invasion of the disease (29). Many studies are carried out to determine the relationship of genes with epithelial mesenchymal transition, apoptosis and angiogenesis in bladder tumors. Cyclin D1 is one of these studies. It has been reported that staining with a good prognosis is high, especially in studies performed to determine prognosis (29). In the staining performed by Sayar (2016) on 149 cases, the pT stage of Cyclin D1 was found to be significantly higher in TaT1, low grade, cases without recurrence and progression, and the first pT stage T2-T4 in high grade cases (1).

Khabaz et al. (2016); found a significant correlation with the stage and invasion of the tumor with Cyclin

D1 staining performed on 128 bladder tumor cases. They reported that there was a high degree of staining in low-stage bladder tumors (30). Amer et al. (2019); In a study of Amer et al, the authoprs examined the correlation of CyclinD1 and p53 expression in bladder tumors in 90 cases. According to the staining results, weak expression was observed in high-grade bladder tumors (31).

Regarding Cyclin D1, it was expressed in 85% of the non-neoplastic urothelium and 76.2% (P>0.05) of the malignant group in the current study. Our results are in line with Khabaz et al., 2016, who reported similar frequency of Cyclin D1 immunoreactivity in bladder tumors (51.6%) and normal bladder tissue (50%) (30). A study by in 2007 reported equal intensity of Cyclin D1 expression in the non-neoplastic group. However, in other studies (31), higher Cyclin D1 protein expression was reported in UBC and endometrial carcinoma compared to adjacent normal tissue. In other studies (30), complete absence of Cyclin D1 has been reported in normal urothelium and other tissues such as colonic and gastric mucosa (32) expressed in the carcinoma group.

In the current study, high expression of Cyclin D1 is associated with the early-stage group (P=0.031), which is consistent with several studies (33), as well as lymph node involvement and MIBC. The present signs showed no bilharzial invasion (P=0.001), consistent with a study by (34) that showed a more advanced occurrence of UBC disseminated with schistosomiasis in all elevated IRS Cyclin D1 cases (20/20). Positive prognostic uses of Cyclin D1 UBC (33).

The favorable prognostic effect inferred from Cyclin D1 overexpression is attributed to early-stage evidence that cell proliferation with no tumor invasion or metastasis is a necessary step and low Cyclin D1 expression may be, as suggested by Guang and Tian (2015). A surrogate for other genetic events in the same cells ultimately drives cell growth and leads to a worse prognosis (35). In addition, the phenotype of Cyclin D1 was associated with the extent of cancer progression and the degree of invasiveness. Altered expression of Cyclin D1 can lead to changes in the biological behavior of transformed cells, such as growth, proliferation, invasion and metastasis (36). The inverse correlation between Cyclin D1 expression and poor prognostic parameters has not been reported only in urothelial carcinoma; it is also found in gastric carcinoma, laryngeal squamous cell carcinoma and invasive breast carcinoma among other tumors (37).

Limitations

Due to the fact that the patients were treated in different centers and/or lacked follow- up, recurrence and survival could not be evaluated with data.

CONCLUSION

In our study, recurrence was observed to be higher in T1 stage compared to Ta stage tumors but it was not found to be statistically significant. Consistent with the general information, it was observed that the recurrence rate increased significantly in the T2 stage. Low-grade carcinomas were found to recur significantly more than high-grade carcinomas. It was observed that high-grade carcinomas also recurred more than low-grade carcinomas, but it was not statistically significant.

New potential prognostic markers are being identified that will provide important information in detecting the clinical course of bladder cancer and in determining the recurrence or progression of patients. We know that some molecules play very important roles in cell regulation disorders and that altered expressions of these molecules may be effective in tumor progression. In this study, a relationship between Cyclin D1 expression and tumor grade and invasion status was observed in patients with bladder urothelial carcinoma, but studies with larger case series are needed to use Cyclin D1 as a biomarker.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethics Committee of Kafkas University (Approval number: 01.07.2021/29).

The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design: Beşeren H, Adalı Y, Data acquisition: Ezer M, Data analysis and interpretation: Ertürk F, Drafting the manuscript: Beşeren H, Critical revision of the manuscript for scientific and factual content: Beşeren H, Statistical analysis: Beşeren H, Supervision: Beşeren H, Adalı Y.

REFERENCES

1. Sayar İ. The Prognostic significance of the Cyclin D1/ p16/Ki-67 markers in bladder urothelial carcinomas. Middle East Journal of Medicine. 2017;9(2):73-8. doi:10.21601/ortadogutipdergisi.265416.
2. Siegel R, Naishadham D, Jemal A. Cancerstatistics, CA Cancer J Clin 2012;62(1):10-29. doi: 10.3322/ caac.20138.
3. Ren B, Li W, Yang Y, Wu, S. Theimpact of cyclin D1 overexpression on theprognosis of bladdercancer: a meta-analysis. World Journal of SurgicalOncology 2014;1:1. doi: 10.1186/1477-7819-12-55.
4. Santos LL, Amaro T, Pereira SA, Lameiras CR, Lopes P, Bento MJ, et al. Expression of cell- cycleregulatory proteins and their prognostic value in superficiallow-grade urothelial cell carcinoma of the bladder. Eur J SurgOncol 2003;29:74-80. doi: 10.1053/ejso.2002.1371.
5. Yurakh AO, Ramos D, Calabuig-Fariñas S, López-Guerrero JA, Rubio J, Solsona E, et al. Molecular and immunohistochemical analysis of the prognostic value of cell-cycleregulators in urothelial neoplasms of the bladder. EurUrol 2006;50:506-515. doi: 10.21601/ ortadogutipdergisi.265416.
6. Eble JN, Young RH. Carcinoma of the urinary bladder: a review of its diver semorphology.Semin Diagn Pathol 1997;14:98–108. PMID: 9179971.
7. Eble JN, Sauter G, Sesterhenn IA. Tumours of theUrinarySystem. In: KleihuesP, SobinLH. World Health Organization Classification of Tumours Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. France: Lyon, IARC press, 2004: 89-158.
8. Tiguert R, Lessard A, So A, Fradet Y. Prognostic markers in muscle invasive bladder cancer. World J Urol 2002;20:190–195. doi: 10.1007/s00345-002-0279-y.
9. Ren B, Li W, Yang Y, Wu, S. The impact of cyclin D1 overexpression on the prognosis of bladder cancer: a meta analysis. World Journal of SurgicalOncology 2014;1:1. doi:10.21601/ortadogutipdergisi.265416.
10. Krüger S, Mahnken A, Kausch I, Feller AC. P16 immunoreactivity is an in dependent predictor of tumor progression in minimally invasive urothelial bladder carcinoma. Eur Urol 2005;47:463-7. doi:10.1016/j. eururo.2004.12.018.
11. Yurakh AO, Ramos D, Calabuig-Fariñas S, López-Guerrero JA, Rubio J, Solsona E, et al. Molecular and immunohistochemical analysis of the prognostic value of cell-cycle regulators in urothelial neoplasms of the bladder. Eur Urol 2006;50:506-15. doi:10.1371/journal. pone.0158891.
12. Sgambato A, Migaldi M, Faraglia B, De Aloysio G, Ferrari P, Ardito R, De Gaetani C, Capelli G, Cittadini A, Trentini GP: Cyclin D1 expression in papillary superficial bladder cancer: it sassociation with other cell cycle-associated proteins, cell proliferation and clinical out come. Int J Cancer 2002, 97:671–678. doi:10.1159/000078807.
13. Tut VM, Braithwaite KL, Angus B, Neal DE, Lunec J, Mellon JK: Cyclin D1 expression in transitional cellc arcinoma of the bladder: correlation with p53, waf1, pRband Ki67. Br J Cancer 2001, 84:270–275. doi:10.1054/bjoc.2000.1557.
14. Takagi Y, Takashi M, Koshikawa T, Sakata T, Ohshima S: Immunohistochemical demonstration of cyclin D1 in bladder cancers as an inverseindicator of invasiveness but not an independent prognostic factor. Int J Urol 2000, 7:366–372. doi:10.1046/j.1442- 2042.2000.00212.x.
15. Shin KY, Kong G, Kim WS, Lee TY, Woo YN, Lee JD: Overexpression of cyclin D1 correlates with early recurrence in superficial bladder cancers. Br J Cancer 1997, 75:1788–1792. doi:10.1136/mp.51.1.1.
16. Niehans GA, Kratzke RA, Froberg MK, Aeppli DM, Nguyen PL, Geradts J: G1 check point protein and p53 abnormal it iesoccur in most invasive transitional cell carcinomas of the urinary bladder. Br J Cancer 1999, 80:1175–1184. doi:10.1038/sj.bjc.6990483.
17. Ploeg M, Aben KK, Kiemeney LA: The present and future burden of urinary bladder cancer in the world. World J Urol 2009, 27:289–293. doi:10.1007/s00345-009-0383-3.

18. Lee K, Jung ES, Choi YJ, Lee KY, Lee A. Expression of pRb, p53, p16 andcyclin D1 and their clinical implications in urothelial carcinoma. J Korean Med Sci 2010; 25: 1449-55. doi:10.3346/jkms.2010.25.10.1449.

19. Kamalati T, Davies D, Titley J, Crompton MR. Functionalconsequence of cyclin D1 overexpression in human mammary luminal epithelial cells. Clin Exp Metastasis 1998:16;415- 426. doi:10.1023/a:1006529407652.

20. Xu XL, Chen SZ, Chen W, Zheng WH, Xia XH, Yang HJ, Li B, Mao WM: The impact of cyclin D1 over expression on the prognosis of ER-positive breast cancers: a meta-analysis. Breast Cancer Res Treat 2013, 139:329–339. doi:10.1186/1477-7819-12-55.

21. Alao JP: The regulation f cyclin D1 degradation: roles in cancer developmentand the potential for ther apeuticinvention. Mol Cancer 2007, 6:24. doi:10.1186/1476-4598-6-24.

22. Fristrup N, Birkenkamp-Demtroder K, Reinert T, Sanchez-Carbayo M, Segersten U, Malmstrom PU, Palou J, Alvarez-Mugica M, Pan CC, Ulhoi BP, Borre M, Ørntoft TF, Dyrskjøt L: Multicentervalidation of cyclin D1, MCM7, TRIM29, and UBE2C as prognostic protein markers in non-muscle invasive bladder cancer. Am J Pathol. 2013,182:339–349. doi:10.18632/oncotarget.11277.

23. Olsson H, Hultman P, Monsef N, Rosell J, Jahnson S: Immunohistochemical evaluation of cell cycle regulators: impact on predicting prognosis in stage t1 urinary bladder cancer. ISRN Urol 2012, 2012:379081. doi:10.5402/2012/379081.

24. Behnsawy HM, Miyake H, Abdalla MA, Sayed MA, AhmedAel F, Fujisawa M: Expression of cellcycle-associated proteins in non-muscle-invasive bladder cancer: correlation with intravesical recurrence following transurethral resection. Urol Oncol 2011, 29:495–501. doi:10.1016/j.urolonc.2009.08.002.

25. Lee K, Jung ES, Choi YJ, Lee KY, Lee A: Expression of pRb, p53, p16 andcyclin D1 and the clinical implications in urothelial carcinoma. J Korean Med Sci 2010, 25:1449–1455. doi:10.3346/jkms.2010.25.10.1449.

26. Shariat SF, Ashfaq R, Sagalowsky AI, Lotan Y: Association of cyclin D1 and E1 expression with disease progression and biomarkers in patients with non muscle invasive urothelial cell carcinoma of the bladder. Urol Oncol 2007, 25:468–475. doi:10.1016/j.urolonc.2006.09.011.

27. Lee, Eun Ju, et al. Aberrant methylation of Fragile Histidine Triad gene is associated with poor prognosis in early stage esophageal squamous cell carcinoma. European journal of cancer, 2006, 42.7: 972-980. doi:10.1016/j.ejca.2006.01.021

28. Kopparapu, Pradeep Kumar, et al. Expression of cyclin d1 and its association with disease characteristics in bladder cancer. Anticancer research, 2013, 33.12: 5235-5242. doi:24324055

29. Russell A, Thompson MA, Hendley J, Trute L, Armes J, Germain D. Cyclin D1 and D3 associate with the SCF complex and are coordinately elevated in breast cancer. Oncogene 1999; 18: 1983-91. doi: 10.1038/sj.onc.1202511

30. Khabaz M.N., Buhmeida A., Ghabrah T., Qureshi I.A., Butt N.S., Al-Maghrabi B., Nedjadi T., AlQahtani M., Al-Maghrabi J. Cyclin D1 expression is associated with stage, grade and survival in urinary bladder carcinoma. Int J Clin Exp Med 2016;9, 23482-23490. doi:1087/328295.

31. Sharıat, Shahrokh F., et al. Association of cyclin D1 and E1 expression with disease progression and biomarkers in patients with nonmuscle-invasive urothelial cell carcinoma of the bladder. In: Urologic Oncology: Seminars and Original Investigations. Elsevier 2007; p. 468-475. doi: 10.1016/j.urolonc.2006.09.011

32. Amer, Alaa Ibrahim; EID, Asmaa Mustafa. Prognostic significance of Cyclin D1 in urothelial carcinoma; correlation with p53 and clinicopathological parameters. J Am Sci, 2019, 15: 86- 91. doi:10.13668/sc.am.125448

33. Kopparapu, Pradeep Kumar, et al. Expression of cyclin d1 and its association with disease characteristics in bladder cancer. Anticancer research 2013; 33.12: 5235-5242. doi:10.1371/0158891.

34. Yan, Rongrong, et al. Overexpression of peptidyl-prolyl isomerase 1 (Pin1) and cyclin D1 in endometrial cancer. Int J Clin Exp Patho 2017;10: 3335-3343. doi: PMC4122540

35. Yan, Rongrong, et al. Overexpression of peptidyl-prolyl isomerase 1 (Pin1) and cyclin D1 in endometrial cancer. Int J Clin Exp Patho, 2017, 10: 3335-3343. doi:10.1158/14785-240X-2

36. Frıstrup, Niels, et al. Multicenter validation of Cyclin D1, MCM7, TRIM29, and UBE2C as prognostic protein markers in non-muscle–invasive bladder cancer. The American journal of pathology 2013;182.2: 339-349. doi: 10.1016/j.ajpath.2012.10.017

37. Bahnassy, Abeer A., et al. Cyclin A and cyclin D1 as significant prognostic markers in colorectal cancer patients. BMC gastroenterology 2004; 4.1: 1-12. doi: 10.1186/1471-230X- 4-22

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):124-134. doi: 10.33719/yud.2023;18-2-1185919**

Original Research / Özgün Araştırma

Safety and effectivity of open simple prostatectomy in octogenarians: A single center experience

Açık basit prostatektominin seksenliklerde güvenilirlik ve etkinliği: Tek merkez deneyimi

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Geliş tarihi (Submitted): 2022-10-07

Kabul tarihi (Accepted): 2023-03-30

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Özet

Amaç: Bu çalışma ile 80 yaşından büyük hastalarda açık simple prostatektominin (ASP) güvenilirliğinin ve etkinliğinin araştırılması amaçlandı.

Gereç ve Yöntemler: Ocak 2012-Ocak 2018 tarihleri arasında merkezimizde ASP uygulanan hastalar bu çalışmanın hedef kitlesini oluşturmuştur. Hastalar, tüm kohort üç yaş grubuna bölünerek değerlendirilmiştir: 50-64, 65-79 ve ≥80. Çalışma grupları demografik özellikler, ameliyat öncesi klinik veriler, operasyonel parametreler, ameliyat sonrası birinci ay ve üçüncü ay üroflowmetrik veriler ve kısa dönem komplikasyon oranları açısından karşılaştırıldı.

Bulgular: Ameliyat öncesi dirençli akut üriner retansiyon ve üretral kateterizasyon oranları, ≥80 yaş grubunda olanlarda diğer hasta gruplarına göre anlamlı derecede yüksekti. Gruplar intraoperatif tahmini kan kaybı, kan transfüzyonu, Clavien-Dindo Class≥3 komplikasyon oranları ve genel komplikasyon oranı açısından istatistiksel olarak benzerdi. Karşılaştırmalı analiz, kateterizasyon süresinin Grup 2 ve 3'te Grup 1'e göre anlamlı olarak daha uzun olduğunu gösterdi (p=<0,001). Hastanede kalış süresi de Grup 3'teki hastalarda Grup 1'deki hastalara göre anlamlı olarak daha yüksekti (p=0,003). Postoperatif 3. ay IPSS değeri Grup 3'de diğer gruplara göre daha yüksek izlenmiştir (p=0.042).

Sonuç: ASP, ≥80 yaş grubunda olanlarda etkili ve güvenli bir cerrahi tedavi yöntemi olmasına rağmen, kateterizasyon süresi, hastanede kalış süresi ve IPSS skorları açısından etkinliği diğer gruplara göre sınırlıdır. ASP öncesinde işleme

Abstract

Objective: This study aimed to investigate the safety and effectiveness of open simple prostatectomy (OSP) in patients older than 80 (i.e., octogenarians).

Material and Methods: Patients who underwent OSP in our center between January 2012 and January 2018 constituted this study's target population. The patients were evaluated by dividing the entire cohort into three age groups: 50-64, 65-79, and ≥80. The study groups were compared regarding demographic features, preoperative clinical data, operative parameters, postoperative first-month and third-month uroflowmetric data, and short-term complication rates.

Results: Preoperative persistent acute urinary retention and urethral catheterization rates were significantly higher in octogenarians than in the other patients. The groups were similar concerning intraoperative estimated blood loss, blood transfusion rates, Clavien-Dindo Class≥3 complication rates and the general complication rate statistically. The comparative analysis revealed that the duration of catheterization was significantly longer in Group 2 and 3 than Group 1 (p=<0.001). The length of hospital stay was also significantly higher in octogenarians than the patients in Group 1 (p=0.003). Postoperative third-month IPSS valuee were significantly higher in octogenarians compared to the other groups (p=0.042).

Conclusion: Although OSP is an effective and safe surgical treatment method in octogenarians, its effectiveness is limited compared to other

The study was approved by University of Health Sciences Ethics Committee (Approval number: 2020-22-23, Date: 2020/11/02). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

bağlı morbidite ve mortalite oranlarını azaltmak için her hasta bireyselleştirilmiş bir yaklaşımla yönetilmelidir.

Anahtar Kelimeler: Benign prostat hiperplazisi, Açık simple prostatektomi, Seksenlikler

groups in terms of urethral catheter duration, length of hospital stay and IPSS scores. Before OSP, each patient should be managed by an individualized approach for lowering the procedure-related morbidity and mortality rates.

Keywords: Benign prostatic hyperplasia, Open simple prostatectomy, Octogenarians

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptoms (LUTS) in male patients older than 50(1). Among the patients with BPH, approximately 30% necessitate surgical interventions due either to BPH-related complications or its impact on the patient's quality of life (2). The European Association of Urology (EAU) guidelines recommend open simple prostatectomy (OSP) as a surgical treatment option in patients suffering from LUTS who has a prostate volume of higher than 80 ml (3).

Open simple prostatectomy has gained popularity since it gives the surgeon the chance to remove a considerable amount of adenomatous tissue with favorable post-surgical outcomes in both short and long terms (4-7). It was also reported that the reoperation rates were relatively lower. However, it is widely accepted that OSP can cause significant blood loss, require a blood transfusion and relatively long duration of hospital stay and recovery period (8,9). Since elderly patients are vulnerable to postoperative adverse events, they should be given special attention during and after the OSP procedure (10).

Although it is known that the incidence of BPH increases with aging, the potential impact of aging on the efficacy and safety of OSP has not been widely investigated (11,12). Since average life expectancy is increasing worldwide, the possibility of encountering an octogenarian patient afflicted by medical treatment-resistant LUTS with a high prostate volume is also increasing. Thus, this study aimed to compare the success and safety of OSP between patients who are older than 80 (i.e., octogenarians) and those who are relatively younger.

MATERIAL AND METHODS

This study was approved by the Ethical Review Committee of our institution (2020/467). Data of the patients who underwent OSP in our center between January 2012 and January 2018 were retrospectively reviewed. Patient using anticoagulants and antiaggregants, patients who had a history of prostate or urethra surgeries, those who had an urodynamically-approved diagnosis of neurogenic voiding dysfunction, and those with prostate cancer were excluded. Patients with incomplete follow-up data were also omitted.

All patients underwent a general medical and standard urological evaluation preoperatively. The latter included a digital rectal examination (DRE), urinalysis, transrectal ultrasonography (TRUS) and prostate volume (PV) measurement, analysis of prostate-specific antigen (PSA), maximum flow rate (Qmax), post-voiding residual urine volume (PVR) and IPSS (International Prostate Symptom Score) assessments. The prostate volumes were measured by TRUS, and Qmax values were analyzed by uroflowmetry. Since we believed that the measurements performed immediately after voiding in the toilet would give more accurate results than the measurements performed after uroflowmetry, we preferred the former approach for PVR assessments. A portable bladder scanner was used in order to calculate the residual urine volume.

Recurrent acute urinary retention (AUR) or urinary tract infections, prostate-related macroscopic hematuria, medical treatment-resistant LUTS, renal functional deterioration due to BPH were considered indications of OSP in the presence of a PV higher than 80 ml.

All OSP procedures were performed using the transvesical (i.e., Freyer's) technique by postgraduate year 4 and 5 urology residents under urology specialists' supervision (13). Continuous bladder irrigation was initiated immediately after insertion

of a 22F 3-way Foley catheter following enucleation of the prostate and bleeding control. A non-suction drain was inserted before closure. The drain was removed once the daily discharge was less than 100 cc per day. Duration of surgery and estimated blood loss (EBL) were obtained from recorded in patient folders. Hemoglobin (Hgb) and hematocrit (Hct) drops were calculated as taking the difference between the pre-operative levels and postoperative lowest levels. The decision regarding blood transfusion was given based on EBL and Hgb or Hct drops. Patients who developed anemia symptoms or hemodynamic instability were given blood transfusions regardless of the laboratory parameters. EBL, Hgb and Hct levels. The Foley catheters were removed at post-operative fifth day once the urine output was clear, and patients were discharged after ensuring that the patient could void spontaneously. The complications were categorized based on Clavien-Dindo classification. Histopathological assessment reports of all patients were obtained from recorded in patient folders. The Qmax and PVR were measured during the first month, and the IPSS questionnaire was performed during the third-month outpatient clinic encounter.

Patients were grouped based on their age: Group 1 included patients older than 50 and younger than 65, Group 2 consisted of patients between the ages of 65 and 80, while Group 3 included those aged ≥80 (i.e., octogenarians). Study groups were compared regarding demographic and clinical preoperative features, duration of the procedure, EBL, the weight of the specimen, Hgb drop, Hct drop, blood transfusion rate, overall complication rate, Clavien-Dindo Class 3 or higher complication rate, duration of drain output, catheterization and hospital stay, postoperative Qmax, PVR and IPSS.

Statistical Analysis

Categorical variables were presented as numbers and percentages, while continuous variables were given as means and standard deviations. The normal distribution of the continuous variables was tested by the Kolmogorov-Smirnov Shapiro-Wilk test. Means of the multiple groups with normal and non-normal distributions were compared using Analysis of Variance (ANOVA) and Kruskal-Wallis tests. The Tukey HSD test was performed for post-hoc analysis when the ANOVA revealed a significant difference. The Tamhane's T2 test was used when the Kruskal-Wallis test gave significant results. The rates of categorical variables were compared using Pearson chi-square and Fisher's exact tests. The statistical analyses were performed by Statistical Package for Social Sciences (SPSS v21, IBM SPSS Statistics; IBM Corp., Armonk, NY).

RESULTS

Our retrospective review revealed that 255 patients underwent OSP during the study period. After the application of inclusion and exclusion criteria, 178 patients were included. Among these patients, 42 were in Group 1 (i.e., aged between 50 and 65), 96 in Group 2 (i.e., aged between 65 and 80), and 40 in Group 3 (i.e., age≥80). Demographic and clinical data of the study patients are displayed in Table 1.

The rate of patients with ASA score of 3 was 7,1%, 18,8% and 27,5% in Group 1, 2 and 3, respectively (p=0.054). The rate of hypertension was significantly higher in Group 2 and Group 3 (i.e., octogenarians) than compared to Group 1 (p=0.014; Table 2). Although there was no difference between the groups regarding preoperative serum PSA levels, the rate of prostate biopsy rate was significantly higher in Group 1 and Group 2 than in compared to octogenarians. On the other hand, preoperative persistent AUR frequencies were significantly higher in octogenarians compared to others. Mean preoperative Qmax values were 5.57 ± 1.51, 6.84 ± 3.93 and 5.95 ± 2.04 ml/s in Group 1, Group 2 and Group 3, respectively. The mean PVR values were calculated as 136 ± 34, 137 ± 34, and 156 ± 29 in Group 1, Group 2, and Group 3, while the mean IPSS scores were 21.8 ± 4.37 in Group 1, 21.0 ± 6.41 in Group 2, and 22.5 ± 4.43 in Group 3 (Table 2).

There was no significant difference between the groups concerning the duration of the procedure, EBL and specimen weight. The overall blood transfusion, complication and Clavien-Dindo Class≥3 complication rates were calculated as 13.5% (24/178), 24.1%, and

Table 1. Demographic data and clinical characteristics of the whole study population

Number of patients	178
Mean age ± SD, (yrs)	65.8 ± 7.53
Mean BMI ± SD, (kg/m^2)	27.1 ± 3.73
ASA score, n(%)	
ASA 1	58 (32.6)
ASA 2	88 (49.4)
ASA 3	32 (18.0)
HT, n(%)	37 (20.8)
DM, n(%)	20 (11.2)
Mean PSA ± SD, (ng/ml)	8.33 ± 5.84 7.9 ± 3.1
Mean TRUS PV ± SD, (cm^3)	140 ± 45
Median lob, n(%)	69 (38.8)
Preop prostate biopsy, n(%)	105 (59.3)
Bladder diverticulum, n(%)	9 (5.1)
Bladder stone, n(%)	59 (33.1)
Preop urethral catheter dependency, n(%)	75 (42.1)
History of AUR, n(%)	106 (59.6)
Mean preop Qmax ± SD, (ml/s)	6.41 ± 3.30
Mean preop PMRV ± SD, (ml)	146 ± 135 141 ± 33
Mean preop IPSS ± SD	21.9 ± 5.74
Mean OT ± SD, (min)	120 ± 44
Mean EBL ± SD, (ml)	553 ± 334
Mean specimen weight ± SD, (g)	106 ± 58
Transfusion, n(%)	24 (13.5)
Overall complication, n(%)	43 (23.9)
Clavien ≥ 3 complication, n(%)	12 (6.7)
Mean catheterization time ± SD, (days)	5.67 ± 1.10
Mean LOS ± SD, (days)	5.67 ± 1.48
Mean postop Qmax ± SD, (ml/s)	22.3 ± 7.95
Mean postop PVR ± SD, (ml)	6.75 ± 2.38
Mean postop IPSS ± SD	18.8 ± 13.8

SD, standart deviation; ***BMI,*** body massindex; ***ASA***, American Society of Anaesthesiology score; ***HT,*** hypertension; ***DM***, diabetes mellitus; ***PSA,*** prostate specific antigen; ***TRUS***, transrectal ultrasonography; ***PV***, prostate volume; ***AUR***, acute urinary retention; ***PVR***, post-voiding residual urine; ***IPSS,*** International prostate symptom score; ***OT,*** operative time; ***EBL***, estimated blood loss; ***LOS***, lenght of hospital stay

Table 2. Comparison of preoperative patient characteristics between the age groups

Variables	Groups			P value
	Group 1 (50-65)	Group 2 (65-79)	Group 3 (≥80 yrs)	
Number of patients	42	96	40	
Mean BMI, (kg/m²)	26.2 ± 3.45	27.2 ± 3.64	27.6 ± 4.17	0.211*
Mean ASA score ± SD	1.59 ± 0.62	1.87 ± 0.69	2.07 ± 0.69	0.007* 1 vs 3 0.005
ASA 3 score, n(%)	3 (7.1)	18 (18.8)	11 (27.5)	0.054 ¥
HT, n(%)	2 (4.8)	25 (26.0)	10 (25.0)	0.014 ¥ 1 vs 2 0.004 1 vs 3 0.01
DM, n(%)	4 (9.5)	13 (13.5)	10 (25.0)	0.120 ¥
Mean PSA ± SD, (ng/ml)	8.81 ± 6.29 8.2 ± 2.7	8.13 ± 6.22 8.0 ± 3.4	8.33 ± 4.29 7.47 ± 2.84	0.822* 0.532*
Mean TRUS PV ± SD, (cm³)	125 ± 30	141 ± 43	152 ± 57	0.141**
Median lob, n(%)	18 (42.9)	40 (41.7)	30 (44.8)	0.925 ¥
Preop prostate biopsy, n(%)	30 (71.4)	60 (63.2)	15 (37.5)	0.004 ¥ 1 vs 3 0.002 2 vs 3 0.006
Bladder diverticulum, n(%)	2 (4.8)	5 (5.2)	2 (5.0)	0.994 ¥
Bladder stone, n(%)	10 (23.8)	32 (33.3)	17 (42.5)	0.199 ¥
Preop urethral catheter dependency, n(%)	16 (38.1)	32 (33.3)	27 (65.5)	0.001 ¥ 1 vs 3 0.008 2 vs 3 <0.001
History of AUR, n(%)	22 (52.4)	51 (53.1)	33 (82.5)	0.004¥ 1 vs 3 0.008 2 vs 3 <0.001
Mean preop Qmax ± SD, (ml/s)	5.57 ± 1.51	6.84 ± 3.93	5.95 ± 2.04	0.698**
Mean preop PVR ± SD, (ml)	136 ± 34	137 ± 34	156 ± 29	0.558*
Mean IPSS ± SD	21.8 ± 4.37	21.0 ± 6.41	22.5 ± 4.43	0.609*
Mean hemoglobin ± SD, (g/dl)	14.2 ± 1.05	14.3 ± 1.34	14.1 ± 1.48	0.339**
Mean hematocrit ± SD, (%)	43.2 ± 2.82	43.1 ± 3.62	43.0 ± 3.88	0.959*

SD, standart deviation; **BMI**, body massindex; **ASA**, American Society of Anaesthesiology score; **HT**, hypertension; **DM**, diabetes mellitus; **PSA**, prostate specific antigen; **TRUS**, transrectal ultrasonography; **PV**, prostate volume; **AUR**, acute urinary retention; **PVR**, post-voiding residual urine; **IPSS**, international prostate symptom score
*One way **ANOVA**; ¥ Pearson Chi-Square; **Kruskal Wallis Test; &Fisher's Exact Test

6.7%, respectively. The groups were similar regarding blood transfusion rates, overall complication rates, the Clavien-Dindo Class≥3 complication rate, statistically (Table 3). The comparative analysis revealed that the duration of catheterization was significantly longer in Group 3 compared to groups 1 and 2 and 3 (p=<0.001). The length of hospital stay was also significantly higher in octogenarians compared to the patients in Group 1 (p=0.003). The mean postoperative first-month Qmax values were 21.3 ± 8.95 in Group 1, 23 ± 7.62 in Group 2, and 21.9 ± 7.66 in Group 3. The mean postoperative PVR values were 17.1 ± 13.3 in Group 1, 18.1 ± 8.78 in Group 2, and 22.3 ± 21.7 in Group 3. On the other hand, the mean postoperative third-month IPSS scores

Table 3. Intraoperative and postoperative outcomes of the patients stratified by age category

Variables	Groups			P value
	Group 1 (50-65)	Group 2 (65-79)	Group 3 (≥80 yrs)	
Number of patients	42	96	40	
Perioperative data				
Mean OT ± SD, (min)	123 ± 47	120 ± 45	116 ± 40	0.771*
Mean EBL ± SD, (ml)	496 ± 367	560 ± 345	596 ± 261	0.385*
Mean specimen weight ± SD, (g)	97.9 ± 29.6	109 ± 67.5	110 ± 59.7	0.834**
Postoperative data				
Mean hemoglobin drop ± SD	2.69 ± 1.63	2.57 ± 1.47	2.35 ± 1.24	0.570*
Mean hematocrit drop ± SD	8.49 ± 5.12	7.77 ± 4.49	7.33 ± 3.98	0.502*
Transfusion rate, n(%)	7 (16.7)	11 (11.5)	6 (15.0)	0.677¥
Overall complication, n(%)	9 (21.4)	23 (24.0)	11 (27.5)	0.812¥
Clavien ≥ 3 complication, n(%)	2 (4.8)	5 (5.2)	5 (12.5)	0.287¥
Mean drainage time ± SD, (days)	3.23 ± 1.58	3.64 ± 1.56	3.55 ± 1.43	0.360*
Mean catheterization time ± SD, (days)	5.21 ± 0.68	5.47 ± 1.08	6.25 ± 1.13	<0.001* 1 vs 2 0.235 1 vs 3 <0.001 2 vs 3 <0.001
Mean LOS ± SD, (days)	5.09 ± 1.20	5.70 ± 1.47	6.20 ± 1.60	0.003* 1 vs 3 0.002
Mean Qmax ± SD, (ml/s)	21.3 ± 8.95	23.0 ± 7.62	21.9 ± 7.66	0.459*
Mean PVR ± SD, (ml)	17.1 ± 13.3	18.1 ± 8.78	22.3 ± 21.7	0.177*
Mean IPSS ± SD	6.38 ± 2.44	6.57 ± 2.28	7.57 ± 2.42	0.042* 1 vs 3 0.069 2 vs 3 0.075

Figure 1. Preoperative and postoperative third-month Qmax, PVR and IPSS of the patients stratified by age category

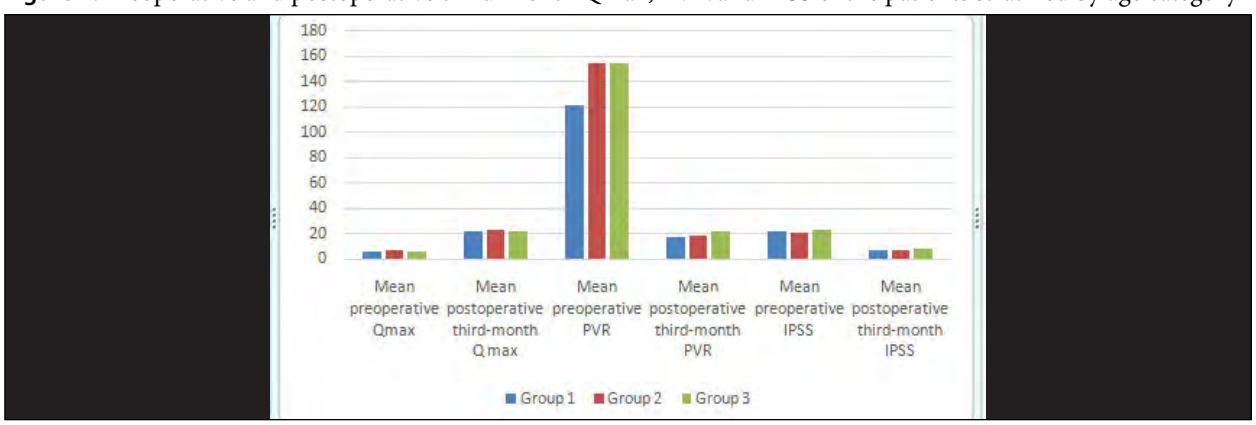

Table 4. Comparison of transfusion rates and complication rates between age groups, summary of complications and complication management

Variables	Group 1 (50-65)	Group 2 (65-79)	Group 3 (≥80 yrs)	P value
Transfusion rate, n(%)	7 (16.7)	11 (11.5)	6 (15.0)	0.677¥
Overall complication, n(%)	9 (21.4)	23 (24.0)	11 (27.5)	0.812¥
Clavien ≥ 3 complication, n(%)	2 (4.8)	5 (5.2)	5 (12.5)	0.287¥
Complication	**n(%)**	**Classification according to CDCS**	**Management**	
Fever	2 (1.1)	I	Antipyretics	
Transient elevation of serum creatinine	1 (0.5)	I	Hydration	
Urge incontinence	2 (1.1)	I	Antimuscarinic	
UTI	2 (1.1)	II	Antibiotics	
Hemorrhage requiring blood transfusion	24 (13.4)	II	Blood transfusion	
Organised haematoma in bladder	2 (1.1)	IIIb	Endoscopic intervention	
Bladder neck stenosis	3 (1.6)	IIIb	Bladder neck resection	
Urethral stenosis	6 (3.3)	IIIb	Internal urethrotomy, Urethroplasty	
Pulmonary embolism	1 (0.5)	IVa	ICU admission	

CDCS, Clavien Dindo classification system; ***UTI,*** urinary tract infection; ***ICU,*** intensive care unit

SD, standart deviation; ***OT***, operative time; ***EBL***, estimated blood loss; ***LOS***, lenght of hospital stay; ***PVR***, post-voiding residual urine; ***IPSS***, international prostate symptom score

*One way ANOVA; ¥ Pearson Chi-Square; ** Kruskal Wallis Test; &Fisher's Exact Test

were calculated as 6.38 ± 2.44 in Group 1, 6.57 ± 2.28 in Group 2, and 7.57 ± 2.42 in Group 3 (Table 3). The values of Qmax, PVR, and IPSS values in all groups before and after OSP are shown in Figure 1.

The complications, classification of complications according to the Clavien Dindo system and management of complications are presented in Table 4.

DISCUSSION

The OSP procedure became popular due to its favorable short and long-term outcomes by excising a considerable amount of adenomatous prostate tissue (4-6). On the other hand, the popularity of the minimally invasive methods such as laser prostatectomy techniques and robotic surgery has also increased during the last two decades because of similar success rates and low morbidity rates related with these techniques and relatively high blood transfusion rates and long recovery times associated with OSP (14). Some of these minimally invasive procedures including Holmium laser enucleation and thulium laser enucleation are considered current methods that can be performed in patients with high prostate volumes. In a review study comparing transurethral laser prostatectomy procedures compared to OSP, those who underwent laser prostatectomy showed less hemoglobin reduction, shorter catheterization time, shorter hospital stay and less blood transfusion rate (15). Some studies reported that blood transfusion rates were observed more frequently in octogenarians, probably because the frequency of use of anticoagulants is higher than in other age groups (16). One of the advantages of laser technologies over other prostatectomy techniques is that surgery can be performed without the necessity of interruption of blood thinning agents (17). However most health centers do not have the equipment or trained and experienced staff to perform these procedures.

In studies comparing laparoscopic simple prostatectomy and OSP, the overall complication rates and blood transfusion rates were found to be similar, the operation time was found to be longer in the laparoscopic technique.(18,19) When comparing robotic simple prostatectomy with laparoscopic simple

prostatectomy and OSP, blood transfusion rate was observed less in robotic simple prostatectomy compared to both surgical techniques. There was no difference was observed between the three methods in terms of improvement in long-term functional results (20,21). Considering all these, OSP is still commonly performed worldwide. In cases with PV>80 ml with large bladder stones or urethral stenosis, OSP may offer excellent postoperative results in suitable patient groups (18).

Average life expectancy is increasing worldwide. Since, it is not uncommon to encounter patients older than 80 with relatively high prostate volumes and LUTS, we investigated the efficacy and safety of OSP in this patient population. It is known that the elderly male patient population with urological diseases also has relatively high risk of systemic comorbidities (14). These comorbidities, including cardiovascular diseases, pulmonary disorders, and aging-related metabolic changes, can pave the way for post-surgical complications and unfavorable outcomes (15-17). Since OSP leads to a challenging postoperative recovery period even for relatively young patients, it is evident that octogenarians undergoing this procedure necessitate special attention. It is widely accepted that a thorough pre-operative assessment is crucial in these cases. Our analysis revealed that the rate of hypertension was significantly lower in patients younger than 65 than the others, while there was no difference between these patient groups concerning the rate of diabetes mellitus. Since it is accepted as a marker of high risk in elderly patients (18), an ASA score higher than two was used as the comparison parameter. In our cohort, the rate of patients with an ASA score of 3 increased with increasing patient age. However there was no statistically significant difference between the groups in this regard.

On the other hand, a comparison of the mean ASA scores elucidated significant differences between the octogenarians and the patients younger than 65. The pre-OSP prostate biopsy rate was significantly higher in Group 1 and Group 2 compared to than in octogenarians. The relatively lower prostate biopsy rate in octogenarians can be because these patients had a shorter life expectancy, and this fact was considered while making biopsy decisions (19). In our cohort, the rate of preoperative persistent urethral catheterization and acute urinary retention was significantly higher in octogenarians than the other patients, as reported in the literature (20).

As such, the overall blood transfusion rate of 13,5% was also consistent with the previously published literature (21,22). The three groups were similar regarding blood transfusion rate, Clavien-Dindo Class 3 or higher complication rate and the overall complication rate. This latter finding is not consistent with the literature (20). This finding can be attributed to the exclusion of patients using anticoagulant and antiaggregant therapy in our study, and to the fact that more patients in the octogenarian group in the related study. The general complication rate of 27,5% in our octogenarian patients is lower than the rates reported in previous studies (20,23). This difference can be explained by the evolvement of preoperative assessment tools, anesthesia methods, and postoperative care protocols. Our comparative analysis revealed that the mean duration of catheterization was significantly higher in older patients than younger patients. Since we usually remove the urethral catheters on the day of discharge, this approach might have led to a relatively longer length of hospital stay in these patients. Also, a relatively longer postoperative recovery period and a higher general complication rate in octogenarians might have contributed to more extended hospital stays. It should also be considered that studies investigating the length of hospital stay in patients undergoing transurethral resection of the prostate (TURP) or radical prostatectomy revealed that advanced patient age was significantly associated with prolonged hospital stay (24).

One of our significant findings was that the postoperative third-month IPSS score was significantly higher in octogenarians than the other patients. Gormley et al. reported that LUTS persisted after TURP in most patients with advanced age due to aging-related detrusor instability that was present preoperatively (25). Jeong Kim et al. hypothesized that this finding was due to the changes in the urinary bladder wall's ultrastructure due to chronic obstruction (26). They also noted that these changes included collagen deposition and increased receptor

sensitivity. The fact that the rates of persistent AUR and preoperative urethral catheterization were higher in our octogenarian patients than the younger patients supports the hypothesis of Jeong Kim et al.(26). Although the length of hospital stay, general complication rate, and postoperative IPSS scores of our octogenarian patients was higher than the other patients, the value of OSP in patients with medical treatment-resistant LUTS and high prostate volumes should not be underestimated. In our study, none of our patients -including octogenarians- died, and there was no difference between the patient groups regarding Clavien-Dindo Class 3 or higher complication rates which can potentially contribute to procedure-related morbidity and mortality. We postulate that improvements in preoperative patient assessment, regional anesthesia techniques, and intensive care unit patient management protocols led to this result.

Our study has some limitations that need to be considered while evaluating its findings. First, it is a retrospective study. Second, it is a single-center study, and it does not include long-term outcomes. Third, OSP procedures were performed by different urologists and senior urology residents. Therefore, there may be an operator-dependent bias.

CONCLUSIONS

Despite the limitations mentioned above, we conclude that OSP is a safe procedure, and its effectiveness is limited compared to the other groups in terms of urethral catheter duration, length of hospital stay and IPSS scores. Before OSP However, perioperative management should be individualized for each patient.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by University of Health and Sciences Ethics Committee (Approval number: 2020-22-23). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design: Şam E, Data acquisition: Şeker KG, Data analysis and interpretation: Kalfazade N, Drafting the manuscript: Kalfazade N, Critical revision of the manuscript for scientific and factual content: Güner E, Şahin S, Tuğcu T, Statistical analysis: Kalfazade N, Supervision: Güner E, Şahin S, Tuğcu T.

REFERENCES

1. McCullough TC, Heldwein FL, Soon SJ, et al. Laparoscopic versus open simple prostatectomy: An evaluation of morbidity. Journal of Endourology. 2009;23(1):129–33. doi:10.1089/end.2008.0401
2. Kim JH, Park JY, Shim JS, et al. Comparison of outpatient versus inpatient transurethral prostate resection for benign prostatic hyperplasia: Comparative, prospective bi-centre study. Journal of the Canadian Urological Association. 2013;8:1–6. doi:10.5489/cuaj.1370
3. Gratzke C, Bachmann A, Descazeaud A, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. 2022European Urology. 2015;67:1099–109. doi:10.1016/j.eururo.2014.12.038 Gravas S, Cornu JN, Gacci M, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. 2022
4. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. Journal of Urology. 2011;185:1793–803. doi:10.1016/j.juro.2011.01.074
5. Suer E, Gokce I, Yaman O, et al. Open Prostatectomy Is Still a Valid Option for Large Prostates: A High-Volume, Single-Center Experience. Urology. 2008;72(1):90–4. doi:10.1016/j.urology.2008.03.015
6. Varkarakis I, Kyriakakis Z, Delis A, et al. Long-term results of open transvesical prostatectomy from a contemporary series of patients. Urology.

2004;64(2):306–10. doi:10.1016/j.urology.2004.03.033

7. Tubaro A, Carter S, Hind A, et al. A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. Journal of Urology. 2001;166(1):172–6. doi:10.1016/S0022-5347(05)66102-2
8. Hoy NY, Zyl S Van, Martin BAS. Initial Canadian experience with robotic simple prostatectomy: Case series and literature review. Canadian Urological Association Journal. 2015;9:E626–30. doi:10.5489/cuaj.2750
9. Banapour P, Patel N, Kane CJ, et al. Robotic-assisted simple prostatectomy: A systematic review and report of a single institution case series. Prostate Cancer and Prostatic Diseases. 2014;17(1):1–5. doi:10.1038/pcan.2013.52
10. Dal Moro F, Morlacco A, Motterle G, et al. Frailty and elderly in urology: Is there an impact on post-operative complications? Central European Journal of Urology. 2017;70(2):197–205. doi:10.5173/ceju.2017.1321
11. Tubaro A, Montanari E. Management of symptomatic BPH in Italy: Who is treated and how? European Urology. 1999;36:28–32. doi:10.1159/000052346
12. Serretta V, Morgia G, Fondacaro L, et al. Open prostatectomy for benign prostatic enlargement in southern Europe in the late 1990s: A contemporary series of 1800 interventions. Urology. 2002;60(4):623–7. doi:10.1016/s0090-4295(02)01860-5
13. Freyer PJ. A new method of performing perineal prostatectomy. Br Med J. 1900;1(2047):698-9. doi:10.1136/bmj.1.2047.698-a.
14. Burney TL, Badlani GH. Anesthetic considerations in the geriatric patient. Urologic Clinics of North America. 1996;23(1):19–26. doi:10.1016/s0094-0143(05)70290-1
15. Tonner PH, Kampen J, Scholz J. Pathophysiological changes in the elderly. Best Practice and Research: Clinical Anaesthesiology. 2003;17(2):163–77. doi:10.1016/s1521-6896(03)00010-7
16. Priebe HJ. The aged cardiovascular risk patient. British Journal of Anaesthesia. 2000;85(5):763–78. doi:10.1093/bja/85.5.763
17. Sieber FE. Postoperative Delirium in the Elderly Surgical Patient. Anesthesiology Clinics. 2009;27(3):451–64. doi:10.1016/j.anclin.2009.07.009
18. Pope D, Ramesh H, Gennari R, et al. Pre-operative assessment of cancer in the elderly (PACE): A comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery. Surgical Oncology. 2006;15(4):189–97. doi:10.1016/j.suronc.2007.04.009
19. Lee DJ, Mallin K, Graves AJ, et al. Recent Changes in Prostate Cancer Screening Practices and Epidemiology. Journal of Urology. 2017;198(6):1230-1240. doi:10.1016/j.juro.2017.05.074
20. Nadu A, Mabjeesh NJ, Ben-Chaim J, et al. Are indications for prostatectomy in octogenarians the same as for younger men? International Urology and Nephrology. 2003;36(1):47–50. doi:10.1023/b:urol.0000032683.36827.63
21. Alivizatos G, Skolarikos A, Chalikopoulos D, et al. Transurethral Photoselective Vaporization versus Transvesical Open Enucleation for Prostatic Adenomas >80 ml: 12-mo Results of a Randomized Prospective Study. European Urology. 2008;54(2):427–37. doi:10.1016/j.eururo.2007.11.044
22. Kuntz RM, Lehrich K. Transurethral holmium laser enucleation versus transvesical open enucleation for prostate adenoma greater than 100 gm.: A randomized prospective trial of 120 patients. Journal of Urology. 2002;168:1465–9. doi:10.1097/01.ju.0000027901.47718.fc
23. Luttwak Z, Lask D, Abarbanel J, et al. Transvesical prostatectomy in elderly patients. Journal of Urology. 1997;157(6):2210–1. doi:10.1016/S0022-5347(01)64720-7
24. Gardner TA, Bissonette EA, Petroni GR, et al. Surgical postoperative factors affecting length of hospital stay after radical prostatectomy. Cancer. 2000;89(2):424–30. doi:10.1002/1097-0142(20000715)89:2<424::aid-cncr30>3.0.co;2-6
25. Gormley EA, Griffiths DJ, McCracken PN, et al. Effect of transurethral resection of the prostate on detrusor instability and urge incontinence in elderly males. Neurourology and Urodynamics. 1993;12(5):445–53. doi:10.1002/nau.1930120502
26. Kim SJ, Al Hussein Alawamlh O, Chughtai B, et al. Lower Urinary Tract Symptoms Following Transurethral Resection of Prostate. Current Urology Reports. 2018;19(10):85. doi: 10.1007/s11934-021-01071-9
27. Shah AA, Gahan JC, Sorokin I. Comparison of Robot-

Assisted Versus Open Simple Prostatectomy for Benign Prostatic Hyperplasia. Current Urology Reports. 2018;19(9):1–8. doi:10.1007/s11934-018-0820-1

28. Cho JM, Moon KT, Lee JH, et al. Open simple prostatectomy and robotic simple prostatectomy for large benign prostatic hyperplasia: Comparison of safety and efficacy. Prostate International. 2021; 9(2):101-106. doi:10.1016/j.prnil.202.11.004
29. Autorino R, Zargar H, Mariano MB, et al. Perioperative Outcomes of Robotic and Laparoscopic Simple Prostatectomy: A European-American Multi-institutional Analysis. European Urology. 2015; 68(1):86-94. doi:10.1016/j.eururo.2014.11.044

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):135-144. doi: 10.33719/yud.2023;18-2-1193464**

Original Research / Özgün Araştırma

Norepinephrine infusion in brain dead organ donor: A retrospective study on its effects on graft function after renal transplant

Beyin ölümü organ donörlerinde norepinefrin infüzyonunun greft fonksiyonu üzerine etkileri: Retrospektif bir çalışma

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Geliş tarihi (Submitted): *2022-10-23*
Kabul tarihi (Accepted): *2023-05-30*

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Özet

Amaç: Beyin ölümü gerçekleşen organ donörlerinde vazoaktif ilaç kullanımının renal alıcı greft fonksiyonu üzerindeki etkisini araştırmak.

Gereç ve Yöntemler: Merkezimizde Temmuz 2017 ile Kasım 2021 arasında, beyin ölümü gerçekleşen 30 organ bağışçısından ve 30 alıcıdan alınan klinik veriler geriye dönük olarak analiz edilmiştir.

Bulgular: 30 kadavra donörünün hepsinde norepinefrin infüzyonu kullanılmıştı. 11 donörün inotrop ilaç kombinasyonuna sahip olduğu görüldü. Norepinefrin infüzyonlarının ortalama dozu 0.2 mcg/kg/dk idi. Donörlerde norepinefrin süresi ve dozları ile böbrek alıcılarında greft reddi, greft kaybı ve diyaliz gereksinimi arasında ilişki yoktu.

Sonuç: Beyin ölümü organ bağışçısında sıvı resüstasyonunun yeterli olduğu durumlarda .0.2 mcg/kg/dk'nın altındaki intravenöz norepinefrin infüzyonunun, renal greft fonksiyonu üzerine etkisi olmadığı görüldü.

Anahtar Kelimeler: Beyin ölümü, donör, vazoaktif ilaçlar, greft sağkalımı

Abstract

Objective: To investigate the effect of vasoactive drugs use in brain-dead organ donors in renal recipient graft function.

Material and Methods: Clinical data from 30 brain-dead organ donors, and 30 recipients in our center were analyzed retrospectively between July 2017 and November 2021.

Results: Norepinephrine infusion was used in all 30 cadaveric donors, where 11 donors had inotropic combinations. Norepinephrine was infused at a median dose of 0.2mcg/kg/min. There was no relationship between duration and doses of norepinephrine in donors and graft rejection, graft loss, and dialysis requirement in renal recipients.

Conclusion: Intravenous norepinephrine infusion below 0.2mcg/kg/min had no effect on graft function in the renal recipient, where fluid resuscitation was sufficient in the cadaveric donor.

Keywords: Brain dead, organ donors, vasoactive drugs, graft survival.

The study was approved by Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval Date15.12.2021 and Protocole Number: 2011-KAEK-25 2021/12-09). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

The mortality rate of the patients on the waiting list for organ transplants remains high (1). It was reported in 2021 that 17 individuals, who waited for a transplant, died each day in the United States (2). There are 23,955 patients on the transplant waiting list according to 2020 data in Turkey (3). Whereas, one individual dies every three hours and eight individuals every day while waiting for an organ transplant (4). Efforts were aimed at early brain death diagnosis and increase the number of donations in place to find a solution to waiting queues. Nevertheless, the fact that organs harvested from potential donors diagnosed with brain death are often rejected due to insufficient quality has an adverse impact on the situation. Further efforts should be in place to optimize the quality of organs from donors (5).

The hemodynamic responses upon brain death were identified. Hemodynamic instabilities during that period constitute the main difficulty in the management of brain-dead organ donors (BDDs) (6). Approximately 20% of the organs of brain-dead donors are lost due to hemodynamic instabilities. Therefore, hemodynamic management of donors plays a key role in the donation process (7).

Elevation in arterial blood pressure is the primary destructive response upon brain death and is induced by the activation of the sympathetic nervous system. This is followed by vasoplegia; the hypotensive phase requiring fluid and/or vasoactive therapy. Available information regarding the vasoactive agent that could be selected during that phase is unclear/insufficient (8). Furthermore, catecholamine preparations (Dopamine, Dobutamine, Adrenaline, Noradrenaline), which are used to maintain the target average arterial pressure at 60-100 mmHg may also have undesirable effects especially on the renal graft functions in the recipient (9-11).

The present study aims to investigate the effects of vasoactive agents and doses used in management of donor candidates who donated organs upon brain death, on graft rejection, graft loss, and dialysis requirement in renal recipients and to determine the appropriate agent and dose.

MATERIAL AND METHODS

The present study was commenced upon the approval of the Ethics Committee, Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (2011-KAEK-25-25 2021/12-21). Patient records were retrieved from the hospital archival system. The first kidney transplant in our hospital was performed on July 20, 2017.

The study therefore included donors aged above 18 years, diagnosed with brain death, whose kidneys were transplanted in our hospital between July 2017 and November 2021. Brain-dead individuals aged below 18 years or did not donate organs were not included in the study.

The information of the donors in the study on age, gender, co-morbidities, hemogram values before organ removal, kidney function tests, sodium level, blood gas analysis values, intravenous fluid therapy for the last 24 hours, urine output (per hour), length of stay in the intensive care unit, the cause of brain death and tests used for the diagnosis of brain death, vasoactive drugs used, and blood products consumption were recorded. The international guidelines for hemodynamic management of donor care were taken as a basis in our clinic and doses of 0.5μg/kg/min and below were accepted as low doses as regards the norepinephrine dose (8,12).

Recipient information in the study on age, gender, co-morbidities, cause of renal failure, duration of transplantation operation, serum creatinine (CRE), blood urea nitrogen (BUN), glomerular filtration rate (GFR), and other laboratory values at Day 1, Month 1, and Month 3, duration of cold ischemia, delayed graft function (DGF), graft rejection, and graft loss and renal replacement therapy (requirement for dialysis), were recorded.

The acute rejection episode in the recipient was diagnosed by renal cortex biopsy in our hospital and each patient was treated with immunosuppressive treatment pursuant to hospital protocols (13). The primary endpoint was taken as the relationship of vasoactive drugs used in donor management with the requirement for dialysis in the first three months following transplant, where the relationship with graft

rejection and graft loss were taken as the secondary endpoint.

Statistical Method

The IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, USA) for Windows 23.0 software was used to analyze the patient data collected within the scope of the study. Descriptive values for categorical data were presented in frequency and percentage and in median, minimum, and maximum for continuous values. The Friedman test was used to review the difference between laboratory parameters measured over time.

Spearman's Correlation Analysis was used to test the relationship between treatment duration and treatment doses and laboratory parameters of donors. The logistic regression analysis was used to test whether the treatment used in donor patients posed a risk for graft rejection and graft loss in the recipients. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

There were 149 cases of brain death in our hospital within the study interval. A total of 68 of those cases had organ donation approvals from families, where the organs of 10 cadavers in the foregoing group were not medically suitable for transplantation, and the cadaveric kidneys harvested from 28 cases were transferred to other centers. Therefore, 30 brain-dead donors and 30 recipients of renal transplant in our center were included in the present study.

Male cadaveric donors accounted for 56.7% (17 individuals) and 43.3% (13 individuals) were female. The most prevalent cause of death was primary cerebrovascular lesions (96.7%), where the most prevalent concomitant disease was hypertension (33.3%). Computed tomography (CT) angiography was used in the diagnosis of brain death in 76.6% (23 individuals), mean duration of cold ischemia was 819 (515-1047) minutes, mean daily intravenous fluid treatment for donors during the last 24 hours was 4525 (2050-9360) cc/day, and mean urine output was 152.9 cc/h (0-400). Clinical and demographic characteristics of cadaveric donors are presented in Table 1. All the donors received at least one vasopressor during their intensive care unit stay.

Table 1. A Distribution of Clinical and Demographic Characteristics of Organ Donor Patients

Variables (n=30)*	n (%) or Mean±SD
Gender	
Male	17 (56.7)
Female	13 (43.3)
Age (years)	51±14.1
Hospitalization reason	
Primary cerebrovascular disease	29 (96.7)
Meningitis	1 (3.3)
Smoking	4 (13.3)
Comorbidities	12 (40.0)
Hypertension	10 (33.3)
Diabetes Mellitus	4 (13.3)
Coronary artery disease	1 (3.3)
Others	3 (9.9)
Brain death diagnosis	
CT angiography	23 (76.7)
Apnea	7 (23.3)
Length of stay intensive care unit (days)	3.5±1.9
pH	7.4±0.08
pCO_2 (mmHg)	39.5±6.3
pO_2 (mmHg)	134.2±50.1
HCO3 (mg/dl)	24.7±3.1
Osmolarity	318.1±24.0
Total fluid intake (ml/day)	5144.1±1773.6
Last 24 hours balance (ml)	1517.8±1773.9
Urine output (ml/h)	158.7±90.8
Na (mmol/L)	155.7±11.5
Urea (mg/dl)	19±18.8
Creatinine (mg/dl)	1.0±0.45
Hgb (g/dl)	11.6±2.8
GFR	92.3±33.1
Duration of cold ischemia (minute)	828.6±125.8

***SD:** Standard deviation; **HCO3:** Bicarbonate, **GFR:** Glomerular filtration rate; **Hgb:** Hemoglobulin, **pO2:** Partial oxygen pressure, **pCO2:** Partial carbon dioxide pressure

Norepinephrine was used in the treatment of all the donors (100%), 11 (36.6%) had combination therapy. The median treatment dose of norepinephrine, epinephrine, dopamine and dobutamine used in the patients was 0.2mcg/kg/min (min: 0.02, max: 0.55 mcg/kg/min), 0.28mcg/kg/min (min: 0.11, max: 0.44 mcg/kg/min), 11.3 mcg/kg/min (min:8, max: 22 mcg/kg/min), and 20 mcg/kg/min (min: 20, max: 20 mcg/kg/min), respectively. Treatments specific to clinical symptoms of brain death and the durations thereof in cadaveric donor treatment are presented in Table 2. A distribution of the clinical and demographic characteristics of the patients, who received renal transplant within the scope of the study, is provided in Table 3. The mean age of the organ transplant patients was 46 (Min: 26, Max: 68), and hypertension was the most prevalent reason for transplantation. The median postoperative dialysis requirement was 2(Min: 1-Max: 6). There were five (16.6 %) renal recipients with graft rejection and three (10%) with graft loss. Reasons for rejection were immunological in two patients, vascular thrombosis in two patients and hematoma at the surgical site in one patient. Also the causes of graft loss were immunological in one patient and thrombosis in two patients.

Spearman correlation analysis was performed separately to investigate the relationship between the dose and duration of norepinephrine treatment in donor patients, and the renal function parameters of the renal transplant recipients (Table 4). There was no statistically significant relationship between the dose and duration of norepinephrine treatment and the renal function parameters measured at all times ($p>0.05$). A review of the relationship between the duration and dose of norepinephrine treatment in BDDs and the number of dialysis requirement of renal transplant recipients indicated that there was no statistically significant relationship ($p>0.05$) (Table 5). There was no significant relation between the duration and dose of norepinephrine treatment in BDDs and graft rejection and graft loss in the renal transplant recipients ($p>0.05$) upon risk analysis (Table 6).

Table 2. A Distribution of Treatment of Organ Donor Patients

Variables (n=30) *	**n (%) or Mean±SD**
Steroid Use	14 (46.7)
Blood product	5 (16.7)
Norepinephrine (number of donors)	30 (100)
Norepinephrine duration (hours)	33.2±18.0
Norepinephrine dose, (mcg/kg/min)	0.23± 0.14
Epinephrine (number of donors)	6 (20)
Epinephrine duration, (hours)	30.2±25.8
Epinephrine dose (mcg/kg/min)	0.28 ± 0,13
Dopamine (number of donors)	11 (36.6)
Dopamine duration (hours)	38.6±21.6
Dopamine dose (mcg/kg/min)	11.3 ± 4,69
Dobutamine (number of donors)	1 (3.3)
Dobutamine duration (hours)	4±0
Dobutamine dose (mcg/kg/min)	20

*mcg/kg/min: microgram/kilogram/minuet; SD: Standart deviation

Table 3. A Distribution of Clinical and Demographic Characteristics of Renal Transplant Recipients

Variables (n=30)	**n (%) or Mean±SD**
Age (years)	46±13
Reason for transplantation	
Unknown	4 (13.3)
Diabetes Mellitus	1 (3.3)
Hypertension	13 (43.3)
Hypertension-PCB	5 (16.7)
Hypertension+ Diabetes Mellitus	4 (13.3)
Hypertension+ Diabetes Mellitus -PCB	1 (3.3)
PCB	2 (6.7)
Operation time (hours)	5.2±0.9
Recipient's postoperative dialysis requirement	15 (50)
Number of dialysis requirement of patients	1±2
Delayed Graft Function	1 (3.3)
Graft rejection	5 (16.6)
Graft loss	3 (10)

Table 4. An Assessment of the Relationship between Dose and Duration of Norepinephrine Treatment in Donor and Renal Function Parameters in Recipient

Norepinephrine dose (n=30) *	**Day 1** **r*/ p-value**	**Month 1** **r*/ p-value**	**Month 3** **r*/ p-value**
BUN	-0.069 / 0.721	0.138 / 0.477	0.039 / 0.842
Creatinine	0.028 / 0.886	-0.050 / 0.797	0.295 / 0.121
GFR	-0.099 / 0.610	-0.063 / 0.745	0.256 / 0.181
Norepinephrine duration (N=30)			
BUN	0.022 / 0.910	0.081 / 0.676	0.157 / 0.417
Creatinine	0.075 / 0.699	-0.067 / 0.731	-0.185 / 0.338
GFR	0.076 / 0.695	0.001 / 0.997	0.173 / 0.369

***BUN:** Blood urea nitrogen, **GFR:** Glomerular filtration Rate * **r:** Correlation coefficient

Table 5. As Assessment of Recipients' Requirement for Dialysis by Duration and Dose of Treatment in Donor

	Number of dialysis requirement	
	Correlation coefficient	**p-value**
Norepinephrine duration	0.146	0.451
Norepinephrine dose	-0.182	0.345

Table 6. An Assessment of Graft Rejection and Graft Loss Risk in Recipients by Treatment in Donor

	Graft rejection		Graft loss	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Norepinephrine duration	0.997 (0.947-1.049)	0.908	0.989 (0.923-1.060)	0.764
Norepinephrine dose	1.000 (0.998-1.002)	0.932	1.000 (0.996-1.002)	0.470

DISCUSSION

There was hypotension in all the donors and norepinephrine was used as the first choice in hemodynamic management in the present study. There was no relationship between the dose and duration of norepinephrine used in the BDDs and the graft function.

Dysfunction of the sympathetic and parasympathetic nerves upon brain death led to vascular tone instability, and a decrease in blood pressure, causing hot ischemia of the organ. Hemodynamic instability upon brain death in donors can lead to donation failure in 25% of potential donors, and more than 80% of potential donors need vasoactive drugs to restore hemodynamic stability on the grounds that prolonged hypotension would increases the risk of primary dysfunction (14,15). Improved donor care and vasoactive drug use are therefore important factors for improved graft function and long-term graft survival. The role of vasoactive drugs in organ preservation is still controversial despite the said critical need (16-18).

Norepinephrine is the vasoactive drug of choice in a number of countries, including Europe, with increased use in recent years (19). Birtan et al. (11) reported in their study of 270 kidney recipients that norepinephrine use might have a beneficial effect in donor management due to reduced rates of graft rejection and loss upon norepinephrine treatment. Schnuelle et al. (16) showed that dopamine pretreatment reduced the risk of hemodialysis upon renal transplantation, despite the fact that there was no significant difference by long-term survival rate of the grafts between the dopamine and dopamine-free groups ($p>0.05$). A study of 152 renal transplant recipients suggested that dopamine use in donors reduced graft rejection and increased the long-term survival of transplanted kidneys (16).

There are also contrary opinions, which suggested that vasoactive drugs inflicted harm to graft function. O'Brien et al. (20) found that vasoactive drugs increased the incidence of acute tubular necrosis upon renal transplantation. Shao et al. (21) investigated the risk factors for graft dysfunction in 2012 upon renal transplantation and reported that 72.2% of the donors in the delayed graft function (DGF) group used norepinephrine, while only 10% of the donors in the fast-healing graft function group used norepinephrine.

Vasoactive drugs, especially norepinephrine, were used in all the donors in the present study. The present study focused on the effect of the said agent on the recipient's kidney since norepinephrine was the most frequently used vasoactive agent in patients. The dose of norepinephrine used for the purposes of donor management was lower (mean 0.2 mcg/kg/min) in our study population (22). Half of the recipients required dialysis following transplantation and three patients had graft loss. This loss was not directly attributed to the recipients use of vasopressors. There was no statistically significant relationship between the dose and duration of norepinephrine treatment, and the recipients BUN, creatinine, and GFR parameters in our analysis ($p>0.05$). The rate of delayed graft function in recipients of renal transplant from brain-dead donors ranged from 5% to 70% (23,24). It may develop due to a number of factors related to donor, recipient, and transplantation procedures. In the present study, there was one (3.3%) renal transplant recipient with delayed graft function despite vasoactive

agents were used in all the brain-dead donors. The fact that hemodynamic stability was achieved by low-dose norepinephrine treatment in BDDs might have been effective in protecting renal function regarding the lower rates in the present study. Birtan et al.(11) reported norepinephrine used in the management of brain death that 46.3% of the renal transplant recipients required hemodialysis after transplantation, where 53.7% did not need any support, and that vasoactive agents reduced the number of recipients, who required dialysis. The vasoactive drug use rate in their study population was 85.8%. Birtan et al. (11) did not record the number of dialysis sessions following transplantation. All the patients were on vasoactive medications in our donor population, and therefore we were not able to determine the need for dialysis in treatment-naive recipients. Nevertheless, there was no relationship between the norepinephrine doses and the number of patients, who needed dialysis after transplantation, and the number of dialysis sessions. In our study, vasoconstrictors were used to achieve a mean arterial pressure of 60 mmHg in all brain-dead donors, according to general recommendations (8). This suggested that maintaining hemodynamic stability in BDDs had a more dominant effect on renal function in the recipients rather than norepinephrine support.

In the present study, there was graft rejection in 16.6% recipients, while 10% recipients had graft loss and dose and duration of norepinephrine treatment were not significantly related to graft rejection and loss. Thereported rates of graft rejection (17.4%) and graft loss (10.3%) were higher than the results of the present study, despite the fact that 14.15% of donors had no vasoactive drug infusion although the sample size of Birtan et al. (11) study was larger compared to the present study. There was a graft rejection rate of 29.8% in recipients of renal transplants from donors, who used low-dose norepinephrine in a study by Zhang et al. (12). In the said study, the procedure of removing organs after cardiac death might have been effective in higher rates of graft dysfunction and rejection by noradrenaline use. Upon a comparison with the groups that received higher doses of norepinephrine and no norepinephrine, they did not find a relationship between graft rejection and norepinephrine administration although the above rate was higher than that the rejection rate of the present study.

The donor management guidelines emphasize the importance of prevention or immediate correction of hypovolemia to maintain perfusion in potentially transplantable organs. It is adopted to start vasopressor treatment in case of non-response to bolus fluid therapy in our clinic. It is still the primary therapeutic goal although euvolemic volume status is a concept that has not yet been completely defined (25). Euvolemic volume status was targeted during intravenous fluid treatment in the donor care period at the intensive care unit, and the mean urine output was 152.9 (0-400) cc/h.

Zhang et al. (12) investigated in their retrospective evaluation of cardiac post-mortem kidney transplants, the relationship between high-dose norepinephrine (≥1.3 μg/kg/min) infusions in donors, and the postoperative renal function and complications in recipients. Creatinine was significantly higher in the high-dose group compared to the low-dose and drug-free group ($p<0.05$) on postoperative Day 1 and 7. They reported that blood urea nitrogen values were also significantly higher in the high-dose group compared to the lowdose and drug-free group ($p<0.05$). Whereas in our study population, there was no significant relationship between the dose and duration of norepinephrine used in donor management at day one, first and third month after transplantation ($p>0.05$). In addition, we were not able to comment due to the fact that there was no vasopressor-free group in the present study. Furthermore, direct comparison was not available since the donors were brain-dead patients.

Limitations

The retrospective nature of our research, and the relatively smaller sample size are the limitations of the present study. In addition, the likelihood of differences by practitioners cannot be excluded although donor

care was based on guidelines. Moreover, the lack of vasopressor-free patients among the study groups prevented the investigation of the direct effect of vasopressors. Nevertheless, due to the impossibilities in conducting a study in which the direct effect is investigated, we still consider that our study will contribute to the literature.

Furthermore, there is no certainty regarding determination of high and low doses of vasopressors used in transplant patients. The cutoff value for the doses was calculated on the basis of Bassi et al. (26) study and further studies should definitely investigate the use of different cutoff values. The first agent to consider in case of hypotension is not norepinephrine in the legacy organ transplantation guidelines, where it has recently become the agent of choice. Therefore, dopamine and epinephrine was started in addition to norepinephrine in some of our patients, especially who were included in the early period of the study. In our study, dopamine was used together with norepinephrine in %36.6 of the patients. We determined the average dopamine doses in our donors were over 10 mcg/kg/min. Although we think that this effect can be determined in the presence of a larger sample, clinically, we determined that it had no effect on the number of dialysis needs and graft survival in recipients. Thus, there is a need for further studies, which would investigate and differentiate the effects of only a single agent.

CONCLUSIONS

The use of vasoactive drugs in BDDs may positively contribute to the improvement of renal function in renal transplant recipients. We believe that the low-dose norepinephrine used in the management of donors in intensive care unit has minimal or no effect on graft rejection, graft loss, and dialysis need in the renal recipient. We suggest, on the contrary, that hemodynamic stability may prevent delayed graft function in recipients if achieved at low vasopressor norepinephrine doses.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval Date15.12.2021 and Protocole Number: 2011-KAEK-25 2021/12-09). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

All authors contributed equally to this work.

REFERENCES

1. Citerio G, Cypel M, Dobb GJ, et al. Organ donation in adults: a critical care perspective. Intensive Care Med.2016;42 (3): 305–315. https://doi.org/10.1007/s00134-015-4191-5
2. Organ Donation Statistics. https://www.organdonor.gov/learn/organ-donation-statistics
3. TDIS KDS Public Information Pages https://organkds.saglik.gov.tr/dss/PUBLIC/PublicDefault2.aspx
4. Person-organ-transplant-waiting-lives. https://www.tonv.org.tr/en/
5. Lazzeri C, Bonizzoli M, Guetti C, Fulceri GE, and Peris A. Hemodynamic management in brain dead donors. World J Transplant. 2021;11(10): 410–420. https://doi.org/10.5500/wjt.v11.i10.410
6. Smith M. Physiologic changes during brainstem death-lessons for management of the organ donor. J Heart Lung Transplant. 2004;23(9):217–222. doi:10.1016/j.healun.2004.06.017
7. Ignacio Martin-Loeches ,Sandiumenge A , Charpentier J, et al. Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next? Intensive Care Med. 2019;45(3):322-330. https://doi.org/10.1007/s00134-019-05574-5

8. Kotloff RM, Blosser S, Fulda GJ, et al. Management of the potential organ donor in the ICU: society of critical care medicine/American college of chest physicians/association of organ procurement organizations consensus statement. Crit Care Med. 2015;43(6):1291–1325. https://doi.org/10.1097/CCM.0000000000000958
9. Stoica SC, Satchithananda DK, White PA, et al. Noradrenaline use in the human donor and relationship with load-independent right ventricular contractility. Transplantation. 2004;78(8):1193–1197. https://doi.org/10.1097/01.tp.0000137792.74940.4f
10. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation : a randomized controlled trial. JAMA. 2009;302(10):1067– 1075. https://doi.org/10.1001/jama.2009.1310
11. Birtan D, Arslantas MK, Altun GT, et al. Effect of vasoactive therapy used for braindead donors on graft survival after kidney transplantation. Transplant Proc.2018;50(5):1289–1291. https://doi.org/10.1016/j.transproceed.2018.02.058
12. Maciel CB, Greer DM. ICU Management of the Potential Organ Donor: State of the Art. Curr Neurol and Neurosci Rep. 2016;16(9):86. https://doi.org/10.1007/s11910-016-0682-1
13. Moreno-Camacho C A, Montoya-Torres JR, Jaegler A and Gondran N. Sustainability metrics for real case applications of the supply chain network design problem: A systematic literature review. Journal of Cleaner Production. 2019; 231:600-618. https://doi.org/10.1016/j.jclepro.2019.05.278
14. Lesieur O, Genteuil L and Leloup M. A few realistic questions raised by organ retrieval in the intensive care unit. Ann Transl Med. 2017; 5(4):44. https://doi.org/10.21037/atm.2017.05.08
15. Sawinski D, Forde K A, Re VL, et al. Mortality and Kidney Transplantation Outcomes Among Hepatitis C Virus–Seropositive Maintenance Dialysis Patients: A Retrospective Cohort Study. Am J KidneyDis. 2019;73(6):815–826. https://doi.org/10.1053/j.ajkd.2018.11.009
16. Schnuelle P, Schmitt W H, Weiss C, et al. Effects of dopamine donor pretreatment on graft survival after kidney transplantation: a randomized trial. Clin J Am Soc Nephrol. 2017; 12(3): 493-501. https://doi.org/10.2215/CJN.07600716
17. Benck U, Jung M, Krüger B, et al. Donor Dopamine Does Not Affect Liver Graft Survival: Evidence of Safety From a Randomized Controlled Trial. Liver Transplantation, 24(10), 1336-1345. https://doi.org/10.1002/lt.25301
18. Sun Q, Huang Z, Zhou H, et al. New Factors Predicting Delayed Graft Function: aMulti-Center Cohort Study of Kidney Donation After Brain Death Followed by Circulatory Death. Kidney Blood Press Res 2018;43(3):893–903. https://doi.org/10.1159/000490337
19. Peris A, Lazzeri C, D'Antonio L, et al. Epidemiological changes in potential heart donors after brain death: a retrospective 15 year cohort study. Internal and Emergency Medicine. 2019;14(3): 371-375. https://doi.org/10.1007/s11739-018-1897-8
20. O'Brien EA, Bour SA, Marshall RL, Ahsan N, Yang HC .Effect of use of vasopressors in organ donors on immediate function of renal allografts. Journal of Transplant Coordination. 1996; 6(4):215-216. https://doi.org/10.7182/prtr.1.6.4.e1g711321k55563r
21. Shao M, Ye O, Ming Y, et al. Delayed graft function after DCD kidney transplantation: risk factors for and impact on transplantation. Zhong nan da xue xue bao. Yi xue ban= Journal of Central South University. Medical Sciences, 37(10), 1045-1049. https://doi.org/10.3969/j.issn.1672-7347.2012.10.013
22. Maciel CB, Greer DM. ICU management of the potential organ donor: state of the art. Current neurology and neuroscience reports. 2016;16(9):1-12. https://doi.org/10.1007/s11910-016-0682-1
23. Yarlagadda SG, Coca SG, Formica Jr RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrology dialysis transplantation. 2009; 24(3), 1039-1047. doi:10.1093/ndt/gfn667
24. Helfer MS, Vicari AR, Spuldaro F, Gonçalves LFS, Manfro RC. Incidence, risk factors, and outcomes of delayed graft function in deceased donor kidney transplantation in a Brazilian center. In

Transplantation proceedings. 2014;46(6):1727-1729. https://doi.org/10.1016/j.transproceed.2014.05.026

25. Kotloff RM, Blosser S, Fulda G J, et al. Management of the potential organ donor in the ICU: society of critical care medicine/American college of chest physicians/association of organ procurement organizations consensus statement. Critical care medicine. 2015;43(6):1291-1325. https://doi.org/10.1097/CCM.0000000000000958
26. Bassi E, Park M and Azevedo LCP. Therapeutic Strategies for High-Dose Vasopressor-Dependent Shock. Crit Care Res Pract. 2013;2013:654708. https://doi.org/10.1155/2013/654708

Yeni Üroloji Dergisi - *The New Journal of Urology* 2023;18(2):145-155. doi: 10.33719/yud.2023;18-2-1196628

Original Research / Özgün Araştırma

The validity and reliability study of the Turkish version of the Sexual Satisfaction Scale for Men (SSS-M)

Erkekler için Cinsel Memnuniyet Ölçeği'nin (CMÖ-E) Türkçe formunun geçerlik güvenirlik çalışması

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Geliş tarihi (Submitted): *2022-10-30*
Kabul tarihi (Accepted): *2023-04-25*

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Özet

Amaç: Bu çalışma, Meston ve arkadaşları tarafından geliştirilen Kadın Cinsel Memnuniyet Ölçeği'nin (CMÖ-K) değiştirilmiş versiyonunu olan Erkekler İçin Cinsel Memnuniyet Ölçeği (CMÖ-E) Türkçe formunun geçerli güvenilir bir araç olup olmadığını belirlemek amacıyla yapıldı. **Gereç ve Yöntemler:** Metodolojik bir çalışma olup, Mart – Temmuz 2021 tarihleri arasında gerçekleştirildi. 30 maddeli, beş alt boyutlu ve likert tipindeki ölçeğin, dil çeviri ve kapsam geçerliliği çalışmalarından sonra 30 kişilik bir gruba ön uygulaması yapıldı. Veriler, etik onay alındıktan sonra çevrimiçi ortamda 193 erkek bireyden elde edildi. Ölçeğin kapsam/içerik geçerliliği için Content Validity Index, geçerliliğini test etmek için Confirmatory Factor Analysis yapıldı. Güvenirliğini test etmek için, Cronbach Alfa ve madde-toplam puan korelasyonu test edildi. Ölçeğin zamana göre değişmezliğini test-retest ile değerlendirildi. **Bulgular:** Ölçek, kapsam geçerliliği sekiz uzman tarafından gözden geçirildi. Ölçeğin yapı geçerliği, doğrulayıcı ve açımlayıcı faktör analizi kullanılarak yapıldı. Doğrulayıcı faktör yükleri .55 ile .87 ve açımlayıcı faktör yükleri 0.34 ile .83 arasında bulundu. Her bir maddenin puanı ile ölçek puanı arasındaki korelasyon katsayısı r=.35-.80 olarak belirlendi (p<.001). Cronbach Alfa iç tutarlık ve güvenirlik katsayısı ölçeğin toplamında .95 ve alt boyutlarının ise

Abstract

Objective: This study was carried out to determine whether the Turkish version of the Sexual Satisfaction Scale for Men (SSS-M), a modified version of the Women Sexual Satisfaction Scale (SSS-W) developed by Meston and his friends is a valid and reliable tool or not.

Material and Methods: This is a methodological study and was conducted between March and July 2021. After the language translation and content validity studies of the 30-item of which Likert-type scale and five sub-dimensions a preliminary application was carried out on a group of 30 people. Data were obtained from 193 male individuals on an online platform after ethical approval. Whereas for the scope\content validity of the scale Content Validity was used, to test for validity Confirmatory Factor Analysis was performed. To verify its dependableness, the Cronbach Alpha score and item-total correlation score were tested. The time invariance of the scale was evaluated with a test-retest.

Results: The scale and content validity was reviewed by eight experts. The construct validity of the scale was performed by using confirmatory and exploratory factor analyses. Confirmatory factor loads were determined between .55 and .87, and exploratory factor loads were determined between 0.34 and .83. The correlation coefficient between the score of each

*The study was presented as an oral presentation at the III.Başkent International Conference on Multidisciplinary Studies Congress between October 23-25.

The study was approved by Ethics Committee of İzmir Bakırçay University (Protocole Number: 2021/236). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

.82- .95'i olarak bulundu. Test-tekrar test güvenirlik analizinde anlamlı bir fark bulunmadı (p>.05). Maddelerin test-tekrar test korelasyonu ağırlıklı kappa değerleri 0.79-0.90.idi. **Sonuç:** Bu çalışmanın sonucunda, beş alt boyutlu "Erkekler İçin Cinsel Memnuniyet Ölçeği (CMÖ-E)" nin Türkçe versiyonunun dört boyutlu olarak geçerli ve güvenilir bir araç olduğu, araştırmalarda ve klinikte kullanılabileceğini belirlendi.

Anahtar Kelimeler: cinsel memnuniyet, erkekler, geçerlik, güvenirlik

item and the scale score was determined as r=.35-.80 (p<.001). The Cronbach Alpha internal consistency and reliability coefficients were found as .95 in the total of the scale and were found as.82-.95 in its sub-dimensions. No significant difference was found in the test-retest reliability analysis (p>.05). The weighted kappa values of test-retest correlation values of the items were 0.79-0.90.

Conclusion: As a result of this study, it was determined that the Turkish version of the five-dimension " SSS-M" is a valid and reliable four-dimensional instrument and can be used in research and clinic.

Keywords: Sexual satisfaction, men, validity, reliability

INTRODUCTION

Sexual satisfaction, a component of human sexuality, is considered the final stage of the sexual response cycle (1) and it's also an important factor that affects the quality of the individual's life. Thus, better physical and psychological health conditions (2,3), general well-being (1) and quality of life (4) are associated with high sexual satisfaction.

There are several definitions of sexual pleasure. One of the most accepted definitions is recommended by Lawrence and Byers (1995), who describe it as "an emotional response due to the subjective evaluation of positive and negative dimensions related to the person's sexual relationship" (5). Another sexual satisfaction is defined as the emotional response resulting from one's evaluation of one's sexual relationship, including the perception that one's sexual needs are met, fulfilment of self and partner's expectations, and a positive evaluation of the overall sexual relationship (1-4,6).

Despite the fact that satisfaction is defined as an emotional state that occurs when the expectations are met and/or exceeded (6), sexual satisfaction is defined as a situation that occurs with the fulfilment of individual wishes during sexual intercourse. Sexual satisfaction should not be confused with orgasm. It is associated with important variables such as relationship satisfaction and self-esteem and is indispensable for the continuity of the relationship for both men and women. Therefore, it is not surprising that sexual satisfaction is an important component of well-being for most individuals. Hence measuring sexual satisfaction for the individual is a very pivotal situation (3-6).

Although there are many male sexual satisfaction scales in the literature (4-7), there is no valid and reliable scale in Turkiye. Therefore, it is necessary to be developed or tailored suitable instruments for Turkish men. SSS-M is a modified version of SSS-W (8) for use in a male population. The Accurate Factor Analysis shows the consistency of the internal structure between the sexes. SSS-M can be considered a valid and reliable psychometric tool for measuring sexual satisfaction in men (9).

However, this is specific to the culture in which the scale is developed (9). Psychometric validation of the questionnaires related to sexual satisfaction, which is so culturally dependent, is required to be implemented in order to be applied in other cultures or languages. Therefore, in this study, it is determined whether the Sex Satisfaction Scale for Men (SSS-M) (9) Turkish version which is a modified version of SSS-W that is developed by Meston and her friends, is a valid and countable tool or not.

MATERIAL AND METHODS

This research was conducted online between March and July 2021 as a methodological study, since it examines whether the Turkish version of the Male Sexual Satisfaction Scale (SSS-M) is a valid and reliable tool. For this purpose, the universe of research was created by men over 18. To be able to analyse in reliability and validity of the scale, it is recommended that the number of scale items ought to be 5-10 times (10) and it is also stated that there must be at least 30 pairs of data to be performed of assessment (9). Therefore, in our planned research, the number of

substances (30 items) of the scale was based on the number of substances. The sample of study 18-65 consisted of 193 men who were members of social media groups and agreed to participate in the study, who were sexually active in the last four weeks, who had no chronic disease, who did not take continuous medication, who filled out the questionnaire form and provided a full return.

The application of the study was carried out in accordance with the steps mentioned in the international norms (10,11) to ensure the quality of an adapted scale as the adjustment is performed. For this, permission was attained via e-mail from Cindy Meston and Bridget Freihart, who first developed the scale. Accordingly, the following steps were followed to establish the scale for the Turkish version, to establish the content validity and to focus on pilot tests:

- The SSS-M was translated into Turkish and culturally adapted in accordance with stages recommended by Beaton et al. (2000)(12). Translation involved four steps: two native Turkish speakers-an English lecturer and nursing lecturer specializing in women's sexuality-independently translated the scales; the translated instrument was modified into a format better suited to the structure of the Turkish language; the translated scale was then back-translated into English by a bilingual native-English speaker who was not involved in the initial translation; subsequently, the equivalence of the back-translated and original scale was assessed by all translators and the primary investigator to ensure that the conceptual meaning of each item had been maintained.
- Six experts evaluated the translated instrument's content validity: four doctors and two nursing faculty members specializing in men's sexuality. They were asked to evaluate and rank the wording of each item as follows: 1 = not suitable; 2 = item needs revision; 3 = suitable, but requires minor changes; 4 = perfectly suitable. The content validity index (CVI) was calculated based on the experts' ratings. A CVI score of ≥ .85 indicates good content validity (13).
- The translated scale was first tested with 30 men with similar characteristics to the intended final sample. Participants were asked to comment on the items and make suggestions for the improvement of the tools. Since the pilot test results showed no perceptible language problem, the final version of the scale was created.
- For the validity and reliability of the scale, psychometric evaluation (factor analysis, reliability analysis; internal consistency, and test-retest) was performed.
- Test-retest analysis was performed to evaluate the test's invariance over time. In this test, it is recommended that there should be at least two weeks and a maximum of four weeks (10,11) between the first measurement and the second measurement, and the test should be carried out with at least 30 people (10).

Data Collection

In order to collect data, a 13-question survey form was prepared by the researchers in accordance with the literature (14,15) and the (SSS-M) form was used. The variables measured by the questionnaire form are age, education level, employment status, obtained income level, marital/relationship status, marriage/relationship duration and frequency of sexual intercourse.

Sexual Satisfaction Scale – Male consists of 30 subject scales and it was developed by Meston and Trampnell in 2005 (8). While the 29 items [5] of the scale are put in order as the five types of liquert: strongly disagree, [4] slightly disagree, [3] neither agree nor disagree [2] agree a little bit and [1] agree, another substance is put in order as [5] is completely satisfying, [4] very satisfying, [3] reasonably satisfying, [2] agree slightly and [1] absolutely agree. The five sub-dimensions of the scale include satisfaction, communication, accordance, personal concern and relational concern. The interpretation of the scale without a cut-off point is the higher the score obtained, the more sexual satisfaction. Taken scores from this measurement indicate that the individual has more sexual satisfaction. Average scores are calculated

for each lower scale. SSS-M reliably distinguishes men with or without sexual dysfunction. SSS-M measurement shows that among men with sexual dysfunction (r =0.62–.79) and men without sexual dysfunction (r =0.58–.79) can be accepted in terms of internal consistency (Cronbach's α ≥0.74) (9).

Statistical Analysis

For analysis of data SSPP dat. 20.0 (SPSS, Chicago, III) and LISREL programs were used. Descriptive statistics, averages, median, frequencies and percentages are used to demonstrate the distribution of male sociographic characteristics. Pearson multiplication moment correlation at α = 0.01 and two-way Paired Samples t-test at α = 0.01 were used to test the reliability and validity of the scale. Content validity refers to the extent to which a measure represents all aspects of a particular social construct (16). CVI was used to measure content validity with 8 experts evaluating the meaning of the substances. The adequacy of the SSS-M's five-factor model (satisfaction, communication, accordance, self-interest, and relational concern) was tested with confirmatory factor analysis and various indices of the model were estimated. (10,11,16,17) Reliability and Pearson Product Moments Correlation Coefficient was evaluated by using item-total correlation. In addition, Cronbach's alpha coefficients were determined and the internal consistency of the SSS-M was evaluated. The time invariance of the scale and its sub-dimensions was evaluated with the t-test (Paired-Samples t-test) and Pearson Product-Moment Multiplication Correlation Coefficient in dependent groups. (10,11)

RESULTS

Characteristics of Participants

In the study, a total of 193 men completed the survey. It was determined that the average age of men was 33.4±7.6 (Min:20, Max:58) and that they were married for an average of 10.4±9.05 years. It was determined that nearly half of the men (48%) were in the 30-39-year-old group, 34% were bachelors, more than half were employees (66.3%), most of them (77%) considered income states as 'medium', 40.7% were in 0-5 years of marriage and that the sex relationship frequency was once a week (32.3%) or 2-3 times a week (38.3%). The arithmetic means of the items in the 5-point Likert structure of the Sexual Satisfaction Scale for Men of the study participants ranged between X =3.13±1.01 and 3.84±0.84.

Internal Consistency; Analysis of Substances

In Table 1, the contribution of the scale items to the scale was given, and the contribution of the current item to the overall scale was shown in each row. Accordingly, the total correlation value of the scale of substance scale was found between 0.35 and 0.79 (Table 1).

Factor Analysis

The measurement of Keiser-Meyer-Olkin (KMO) sampling competency was used in the factor analysis of the scale. In this study, the value obtained for KMO was calculated as 0,928. In addition, Bartlett's sphericity test p-value, which is the measure of the significance of the correlation matrix of the items in the factor analysis, was found as <0.001.

The SSS-M of which consists 30 items, of the participants participating in the research was evaluated in terms of satisfaction (6 items), sub-dimension, Communication (6 items), sub-dimension of agreeableness (6 items) and anxiety (12 items). In this framework, a descriptive factor analysis was performed to reveal the factor pattern of the tool. For the purpose of revealing the factor pattern of SSS-M, principal component analysis as the factorization method and varimax which is one of the vertical rotation methods, as rotation was chosen. The numbers of the items in the satisfaction sub-dimension (6 items) of SSS-M are items 1, 2, 3, 4, 5 and 6.

Substance numbers are 7, 8, 9, 10,11, and 12 for the subdimensions of communication (6. substance). Substance numbers are 13, 14, 15, 16,17, and 18 for the coherance subdimensions (6.substance). Substance numbers are 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30 for subdimension of concern. The factors analysis was collected under a total of 4 factors as a result of the varimax rotation. The 4-factor structure which is consisted of 30 substances, describes 64.707% of the total variance. As it is seen in Table 2, 4 factors were

Table 1. Reliability: Total Correlation of matter

	Substance Analysis				
	Scale Average when the item is removed	**Scale variant when the item is removed**	**Material Scale Total Correlation**	**Multiple Annotation Coefficient ()**	**Scale Alpha when ıtem is removed**
M1	104.8342	405.285	0.350	0.507	0.956
M2	105.2073	395.457	0.538	0.544	0.954
M3	104.9223	390.791	0.697	0.707	0.953
M4	104.9171	401.233	0.454	0.448	0.955
M5	104.7772	397.966	0.528	0.448	0.954
M6	105.3109	397.195	0.527	0.533	0.955
M7	104.8964	395.687	0.642	0.625	0.954
M8	105.1036	395.343	0.555	0.550	0.954
M9	104.7409	403.183	0.392	0.690	0.956
M10	104.8705	400.363	0.464	0.710	0.955
M11	104.6010	404.272	0.429	0.731	0.955
M12	104.7876	402.908	0.456	0.694	0.955
M13	104.9896	387.292	0.697	0.661	0.953
M14	104.7617	391.943	0.668	0.586	0.953
M15	104.8756	387.630	0.703	0.610	0.953
M16	104.9119	388.695	0.744	0.733	0.953
M17	104.6373	395.170	0.619	0.586	0.954
M18	104.7617	389.557	0.682	0.636	0.953
M19	104.6477	390.511	0.706	0.653	0.953
M20	104.9585	386.915	0.712	0.643	0.953
M21	104.6062	391.115	0.597	0.634	0.954
M22	104.7513	386.782	0.796	0.778	0.952
M23	104.8135	386.653	0.720	0.709	0.953
M24	104.7565	386.841	0.746	0.749	0.953
M25	104.7409	387.620	0.718	0.779	0.953
M26	104.7927	385.738	0.728	0.780	0.953
M27	104.6062	389.917	0.644	0.635	0.954
M28	104.8031	384.680	0.765	0.832	0.952
M29	104.8497	383.358	0.753	0.853	0.953
M30	104.6891	383.924	0.748	0.785	0.953

Table 2. Factors Analysis Results for Size of Satisfaction Scale for Men]

	Gender Satisfaction Scale for Men Subdimensions	Frozen Factor loads *	Described as Variants
	Contentment (α=0.817)		
M1	I'm generally satisfied with my current sexual life.	0.816	4.515%
M2	I feel like something is missing in my sex life.	0.668	
M3	I feel like I haven't been emotionally close enough to my wife in my sex life.	0.350	
M4	I am satisfied with the frequency of sexual intimacy. such as kissing and having sexual intercourse.	0.551	
M5	I am not experiencing any major issues or concerns about stimulation. orgasms. frequency of sexual intercourse. harmony with my partner and communication.	0.617	
M6	How satisfying is your current sexual life for you?	0.655	
Communication (α=0.866)			
M7	When I want to talk about our sex life. my partner often has a defensive attitude.	0.337	6.646%
M8	My partner and I don't talk and share sufficiently our sexual lives.	0.435	
M9	When my partner wants to talk about our sex life. I speak freely.	0.824	
M10	When I want to talk about our sex life. my partner talks to me freely.	0.834	
M11	When my partner wants it. I can easily explain my deepest feelings and emotions to her.	0.826	
M12	When I want it. my partner can easily explain to me her deepest feelings and emotions	0.787	
Compatibility (α=0.881)			
M13	I don't think my partner is aware of or care sufficiently about my sexual desires and desires.	0.686	9.160%
M14	I don't think my partner and I are sexually compatible in general.	0.636	
M15	I think my partner's sexual beliefs and attitudes are very different from mine.	0.581	
M16	I think my partner and I are different in terms of need and desire for sexual intimacy.	0.649	
M17	I don't think we find each other physically attractive enough.	0.548	
M18	I don't think my partner and I have the same sexual style and preferences.	0.696	
Concern (α=0.951)			
M19	I'm worried that my sexual problems upset my partner.	0.556	44.386%
M20	I'm worried that my sexual problems adversely affect our relationship.	0.635	
M21	I'm worried about my partner can have an affair with someone else because of my sexual problems.	0.724	
M22	I'm worried my partner isn't sexually satisfied.	0.742	
M23	I'm worried that my wife might see me as a deficient man because of my sexual problems.	0.697	
M24	I think I let my wife down because of my sexual problems.	0.769	
M25	My sexual problems bother me.	0.778	
M26	My sexual problems are causing me have sexual dissatisfaction.	0.825	
M27	I'm worried about ı can have an affair with someone other than my wife because of my sexual problems.	0.717	
M28	My self-perception is affected by my sexual concerns.	0.721	
M29	I feel bad about because of my sexual concerns.	0.830	
M30	I feel uncomfortable with my sexual problems and ı am angry about them.	0.796	

Rotation Method: Varimax **Total described variance:** 64.707%
KMO = 0.928 $\chi 2(435) = 4337.492$; **Bartlett Sphericity Test (p)** <0.001; α=0.954

explained respectively: the first-factor "Concern" was a subdimension of 44.386% of the variance, the second-factor "Compatibility" was a subdimension of 9.160%, the third-factor "Communication" was subdimension of 6.646%, and the fourth factor "Contentment" was subdimension of 4.515% (Table 2).

SSS-M which is consist of 30 substances was evaluated in terms of satisfaction, communication, Compatibility and concern. In this framework, to disclose the tool's factor pattern explanatory factor analysis (EFA) was performed. After EFA it was found that factorization consisted of 4 sub-dimension and a structural equation model (SEM) of the experimental data was created. According to structural equation model tests, it was determined that ($p<0.001$) acceptivity of Compatibility was of ($p<0.05$, X2/SD =2.42). According to the results of the secondary level multi-factor model verification factor analysis, it was determined that other scale acceptivity of Compatibility indices were RMSEA 0.086, and GFI 0.866 (Figure I).

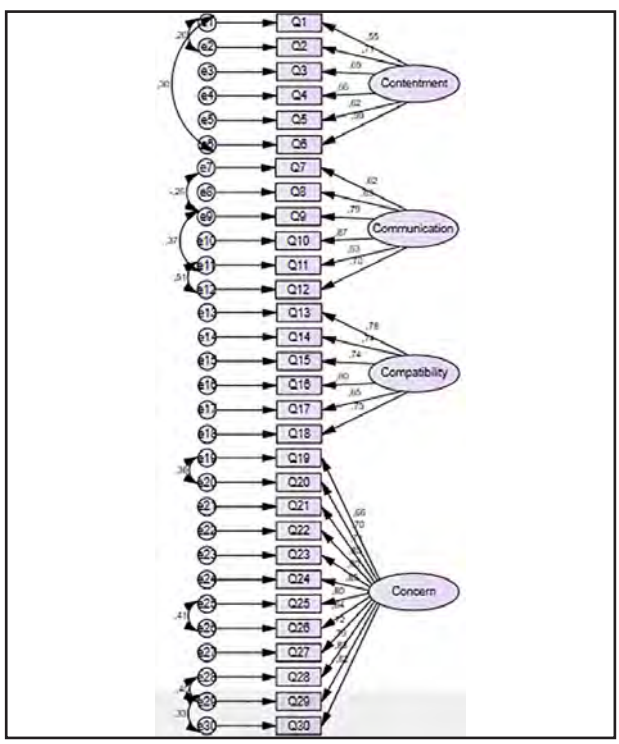

Figure 1. Scale's Structural Equalization Model for Secondary Level Multifactor Validation Factor Analysis

Internal consistency; Cronbach Alpha

Reliability was evaluated by using the Cronbach Alpha coefficient, which measures the internal consistency of measurements obtained with a tool. It was determined that the reliability coefficients of the SSS-M and its sub-dimensions of the participants in the questionnaire were: Satisfaction (0.817), Communication (0.866), Compatibility (0.881), Concern (0.951) and Total (0.954), which had very good reliability.

Test-Retest

In order to evaluate the scale of SSS-M and its sub-dimensions invariance over time scores averages taken from the reliability analysis test and test-retest were compared with t-test (Paired-Samples) in dependent groups and it was found that there was no statistically significant difference between the average scores of the two measurements performed with a two-week interval ($p>0.05$). The weighted kappa values of test-retest correlation values of the items were 0.79-0.90.

When the relationship between the points obtained from the first and second application was examined, it was determined that ($p<0.001$) the Pearson Moments Multiplication Correlation Coefficient was between r=0.91 and 0.96; there was a very strong, positive and statistically very significant correlation between the total score and the scores of two repeated measurements of all factors.

DISCUSSION

The most important result of this study is that the Turkish version of SSS-M shows acceptable reliability and validity for four sub-dimensions.

Content/scope validity and construct validity are the most preferred ones in assessing the validity of a scale (10). In the preparation of the Turkish version of the SSS-M, the language validity of the scale was tried to be ensured with translation and back translation method with experts in the subject and language field. Opinions of 8 experts were taken to evaluate the language and cultural compatibility of the items of the SSS-M, translated into Turkish. According to the experts' evaluations, a KGI score of ≥0.92 was

calculated as good content validity because a KGI score of >0.80 is recommended (18). In accordance with these results, it can be said that the expressions of SSS-M are suitable for Turkish culture and represent the area wanted to be measured. The scale, which was rearranged with expert opinions, was tested with a pre-test on 30 people, and the scale was given its final form (11,19,20).

In order to determine the contribution of the substances in the scale to the scale, the Item Scale Total Correlation values are the most explanatory criterion. For the total correlation of matter and factor load values, Çokluk et al.(2012) stated that the total correlation of substances 0.30 and higher distinguished well the individuals (21). No substance of the individual's ECM Scale is below 0.30 and the lowest value is M1 to 0.350. Therefore, it can be said that the contribution of substances to the scale is sufficient.

The suitability of the sample to be investigated in factor analysis to factor analysis can be realized with many different methodologies. The Kaiser-Meyer-Olkin sample adequacy measure is one of these methodologies. While KMO is changing between 0 and 1, taking a value around 1 shows that it is sufficient for the sample. The KMO value was determined as 0.928, and it was reasoned that this value for the size of the sample was '' excellent''(21). It is also necessary to measure the meaning of the correlation matrix of the substances involved in the factor analysis (21). Bartlett's globalization test, which measures whether the correlation matrix is a unit matrix or not, the p-value was calculated as <0.001, which measures whether the correlation matrix is a unit matrix.

In our study, the 4-factor consisting of 30 substances explains 64.707% of the total variance. In multi-factor patterns, it is considered that explained variance of more than 50% is sufficient (10,21). In this framework, it is seen that contribution which is done by a defined factor is enough.

The structural equation model tests provide evaluation measures (Compatibility indices) about which how suitable the model is for collected data for that model (20). The various compliance indexes formed as a result of the test of a model's compatibility or incompatibility with the data can be evaluated. The most common and sort of initial harmonization index is the statistic Chi-squared. The Chi-square test result is tested for consistency between data and model. With the developed model, the hypothesis is tested whether the model that emerges in the variance-covariance structure of the observation variables is different or not. As long as the calculated Chi-square statistical value is small, it is decided that the match is fine. In literature, the generally accepted level of the chi-square test degree of freedom is less than 5, however, when this level is less than 3, it indicates good Compatibility. According to the work, the obtained chi-squared value was calculated as 2.420, however, the proper value is p-value <0.001. Good compliance testing is tested by nonmeaningful Chi-squared analysis. However, the only valid statistical measurement for compliance measurement is not Chi-square testing. When the literature was examined (16,17,23,24), the validity of the model was tested by giving the Compatibility indices, RMSEA, k-squared/sd, CFI, GFI, IFI, and TLI, which are the most reported indices.

Based on the results of the secondary level multi-factor model verification factor analysis, it can be said that the consistency index of the scale; RMSEA 0.086, GFI 0.753, and CFI 0.866 are acceptable level and coherent. In addition, the regression coefficients in the model are each p-value < 0.05 small. Moreover, the correlation/covariance coefficients established between the variables, p-value<0.05 are small and significant.

One of the recommended methods for assessing internal consistency in Likert-type scales is the Cronbach Alpha reliability coefficient. If the Cronbach Alpha coefficient is less than 0.40, the measuring tool is not reliable. If it is between 0.80 and 1.00, it is considered highly reliable (10). Besides, the Cronbach Alpha coefficient is considered to be highly reliable, if it ranges from 80 to 1.00 (10,11). While In the analysis for internal consistency in the reliability study of the SSS-M, which was adapted into Turkish, the Cronbach

Alpha reliability coefficient was found as =0.95, the research carried out by Çetin and Aslan (2018) it was found as 96 and it was determined that internal consistency was highly reliable (25). The Cronbach Alpha reliability coefficients of the sub-dimensions of SSS-M were found between =0.81 and 0.95. It was determined that the Cronbach Alpha coefficients of the English and Turkish versions of the scale were similar. These results show that the Turkish version of the scale has a high level of internal consistency like the English version.

When the average scores obtained from the test and retest as a reliability analysis were compared with the t-test in the dependent groups, it was determined that there was no statistically significant difference between the average scores of the two measurements carried out with an interval of 2 weeks ($p>0.05$). That No difference indicate that the scale measures similar results in measurements made at certain intervals, and that there is consistency/validity between measurements (10). When the relationship between the points obtained from the first and second performances was examined, it was found that the Pearson Moment Multiplication Correlation coefficient was between r=0.91 and 0.96, and there was not much difference between the two performances and the stability of measurements obtained from the test (10).

CONCLUSION

In this study, in which the validity and reliability of the Male Sexual Satisfaction Scale (SSS-M) were tested for Turkish men, the adaptation studies were carried out in accordance with international scientific methods and it was determined that the Turkish version of the scale met the validity and reliability criteria. It was determined that the factor structure of the original was compatible with the factor structure of the Turkish form and the reliability values of the Turkish form were similar to the original scale and ultimately, it was concluded that the scale could be used for determining Turkish men's sexual satisfaction.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by İzmir Bakırçay University Non-Interventional Clinical Research and Publication Ethics Committee Board (approval date and number: 2021/236). Men were informed as to the study. And their verbal and written consent was taken. Plus, Permission was taken from Cind Mston and Bridget Freeihart, who are the first developers of scale, via e-mail.

Author Contributions

Conception and design; SÇ,GK Data acquisition; SÇ,GK, Data analysis and interpretation; SÇ,GK, Drafting the manuscript; SÇ, Critical revision of the manuscript for scientific and factual content; SÇ,GK, Statistical analysis; SÇ, Supervision; SÇ.

REFERENCES

1. Yoobin P, MacDonald G. Single and Partnered Individuals' Sexual Satisfaction as a Function of Sexual Desire and Activities: Results Using a Sexual Satisfaction Scale Demonstrating Measurement Invariance Across Partnership Status. Archives of sexual behavior. 2022; 51(1): 547-564. https://doi.org/10.1007/s10508-021-02153-y
2. Scott V.C, Sandberg J.G, Harper J.M, Miller R. B. The impact of depressive symptoms and health on sexual satisfaction for older couples: implications for clinicians. Contemporary Family Therapy. 2012;34,376-390. https://doi.org/10.1007/s10591-012-9198-2
3. Çetin S, Aslan E. The analysis of female sexual functions, sexual satisfaction and depressive symptoms according to menstrual cycle phases, Sexual and Relationship Therapy. 2022;37:2, 253-271. DOI: 10.1080/14681994.2020.1792875
4. Štulhofer A, Jurin T, Graham C, Enzlin P, Træen B. Sexual well-being in older men and

women: Construction and validation of a multidimensional measure in four European countries." Journal of Happiness Studies. (2019): 20(7) 2329-2350. https://doi.org/10.1007/s10902-018-0049-1

5. Lawrance K.A, Byers E S. Sexual satisfaction in long-term heterosexual relationships: The interpersonal exchange model of sexual satisfaction. Personal Relationships. 1995;2(4),267–285. https://doi.org/10.1111/j.1475-6811.1995.tb00092.x
6. Offman A, Matheson K. Sexual compatibility and sexual functioning in intimate relationships. Canadian Journal of Human Sexuality. 2015;1(2):31-39.
7. Nimbi, F. M., Tripodi, F., Rossi, R., & Simonelli, C. Expanding the analysis of psychosocial factors of sexual desire in men. The Journal of Sexual Medicine. 2018;15(2): 230-244. https://doi.org/10.1016/j.jsxm.2017.11.227
8. Meston C, Trapnell P. Development and validation of a five-factor sexual satisfaction and distress scale for women: the Sexual Satisfaction Scale for Women (SSS-W). Journal of Sexual Medicine. 2005;2,66-81. https://doi.org/10.1111/j.1743-6109.2005.20107.x
9. Freihart BK, Stephenson K, Crosby CL, Meston CM. The Sexual Satisfaction Scale for Men (SSS-M). https://labs.la.utexas.edu/mestonlab/the-sexual-satisfaction-scale-for-men-sss-m/ (Erişim Tarihi: 13.09.2022).
10. Çapık C, Gözüm S, Aksayan S. Kültürlerarası ölçek uyarlama aşamaları, dil ve kültür uyarlaması: Güncellenmiş rehber. Florence Nightingale Journal of Nursing. 2018;26(3):199-210. https://doi.org/10.26650/FNJN397481
11. Tavşancıl E. Tutumların ölçülmesi ve spss ile veri analizi. 2002, Ankara: Nobel Yayıncılık.
12. Beaton D.E, Bombardier C, Guillemin F, Ferraz M. B. Guidelines for the process of crosscultural adaptation of self-report measures. SPINE. 2000; 25, 3186–3191.
13. Erkut S, Alarcon O, Garcia Coll C, Troop L.R, Vazguez Garcia H. A. The dual-focus approach to creating bilingual measures. Journal of Cross Cultural Psychology. 1999; 30, 206–218.
14. Ghobadzadeh S, Hasani J, Mohammadkhani S, Akbari M. A Multidimensional Model of Sexual Health Scale for Men; Design and Psychometrically Evaluation of Iranian Version. Iranian Journal of Psychiatric Nursing. 2019; 7(2): 13-21. https://doi.org/10.21859/ijpn-07203
15. Sanders S.A, Herbenick D, Reece M, et al. The development and validation of a brief quality of sexual experience (QSE) scale: Results from a nationally representative sample of men and women in the United States. J Sex Med. 2013;10:2409–2417. https://doi.org/10.1111/jsm.12198
16. Viren S, Barron D. Translation and validation of body image instruments: Challenges, good practice guidelines, and reporting recommendations for test adaptation. Body image . 2019;3(1): 204-220. https://doi.org/10.1016/j.bodyim.2018.08.014
17. Şimşek Ö.F. Yapısal eşitlik modellemesine giriş: Temel ilkeler ve LISREL uygulamaları. 2007; Cem Web Ofset, Ankara.
18. Orçan F. Exploratory and confirmatory factor analysis: Which one to use first?. Journal of Measurement and Evaluation in Education and Psychology. 2018;9(4): 414-421. https://doi.org/10.21031/epod.394323
19. Ron D, Norton B. Investment and motivation in language learning: What's the difference?. Language Teaching. 2021:1-12. https://doi.org/10.1017/S0261444821000057
20. Goyal A.K, Bakshi J, Panda N.K., et al. A hybrid method for the cross-cultural adaptation of self-report measures. International Journal of Applied Positive Psychology. 2021;6(1): 45-54. https://doi.org/10.1007/s41042-020-00039-3
21. Çokluk Ö, Şekercioğlu G, Büyüköztürk Ş. Sosyal Bilimler İçin Çok Değişkenli İstatistik: SPSS ve Lisrel Uygulamaları. Pegem Akademi Yayıncılık. 2012; Ankara.
22. Şahin M, Eren A. Jamovi: an easy to use statistical software for the social scientists. International Journal of Assessment Tools in Education.

2019;6(4):670-692. https://doi.org/10.21449/ijate.661803

23. Mueller R. O, Hancock G.R. Structural equation modeling. The reviewer's guide to quantitative methods in the social sciences. Routledge. 2018; 445-456.(e-book)
24. Tabachnick BG, Fidell LS. Çok değişkenli istatistiklerin kullanımı. (Çev. Ed. Mustafa Baloğlu). Nobel Akademik Yayıncılık. 2015;Ankara.
25. Çetin SA, Aslan E. Validity and Reliability of the Turkish Version of the Sexual Satisfaction Scale for Women. Sexuality & Culture. 2018;22(3), 881-893. https://doi.org/10.1007/s12119-018-9499-1

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):156-165. doi: 10.33719/yud.2023;18-2-1220541**

Original Research / Özgün Araştırma

Changes in blood pressure, blood sugar and creatinine in patients undergoing pheochromocytoma surgery

Feokromositoma ameliyatı geçiren hastalarda kan basıncı, kan şekeri ve kreatinin değişiklikleri

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Geliş tarihi (Submitted): *2023-01-01*
Kabul tarihi (Accepted): *2023-06-09*

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Özet

Amaç: Kan basıncı ve kan şekeri seviyelerindeki değişiklikleri tahmin edebilecek değişkenleri keşfetmek ve feokromositomalı hastalarda bu tür değişikliklerin meydana geldiği zaman dilimini kesin olarak belirlemek.

Gereç ve Yöntemler: 20 aylık bir süre boyunca feokromositoma nedeniyle ameliyat edilen ardışık hastalar bu etik inceleme kurulu onaylı, prospektif kohort çalışmasına dahil edildi. Kan basıncı ve şeker seviyeleri, perioperatif dönemde ve ardından ameliyattan 3 ay sonra sabit bir protokol kullanılarak seri olarak izlendi. Değişiklikler karşılaştırıldı ve öngörücü faktörler için değerlendirildi.

Bulgular: Çalışmaya cerrahi girişim uygulanan 50 hasta dahil edildi ve bunların %32'sinde ameliyattan sonra hipotansiyon ve %10'unda hipoglisemi gelişti. Tüm hipotansiyon atakları ameliyattan sonraki 6 saat içinde meydana geldi. Ancak hipoglisemi gelişen 8 hastadan 7'si ameliyattan sonraki ilk 4 saat içinde ortaya çıkarken, biri 12 saat sonra ortaya çıktı. Hipotansiyon oluşumu, ameliyat öncesi 24 saatlik idrar vanililmandelik asit seviyeleri ile koreledir (p=0,024). 21 hipertansif hastadan 15'inde 3. ayda kalıcı hipertansiyon vardı ve bu yaş (p=0,04) ve başvuru anındaki diabetes mellitus (DM) ile ilişkiliydi.

Sonuç: Feokromositoma cerrahisi alan hastaların %32'si inotropik desteğe ihtiyaç duyan postoperatif hipotansiyon yaşadı. Daha yüksek dozlarda alfa-blokörlere ihtiyaç duyan veya 24 saatlik idrar VMA seviyeleri daha yüksek olan hastalar bunu yaşamaya daha

Abstract

Objective: To discover the variables that may predict changes in blood pressure and blood sugar levels and to pinpoint the time frame during which such changes occur in patient with pheochromocytoma.

Material and Methods: Consecutive patients undergoing surgery for pheochromocytoma over a 20-month period were included in this ethics review board-approved, prospective cohort study. Blood pressure and sugar levels were serially monitored using a fixed protocol in the perioperative period and subsequently at 3 months after surgery. Changes were compared and assessed for the predictive factors.

Results: Fifty patients undergoing surgical procedures were included in the study of whom 32% developed hypotension and 10% developed hypoglycaemias after surgery. All hypotension episodes occurred within 6 hours of surgery. However, while 7 of 8 patients who developed hypoglycaemia manifest in the first 4 h after surgery, one occurred after 12 h. Occurrence of hypotension correlated with preoperative 24-h urinary vanillylmandelic acid levels (p=0.024). Out of 21 hypertensive patients, 15 had persistent hypertension at 3 months and this was associated with age (p=0.04) and diabetes mellitus (DM) at presentation.

Conclusion: 32% of patients receiving pheochromocytoma surgery experienced postoperative hypotension needing inotropic support. Patients who require greater dosages of alpha-blockers or those with higher 24-h urine VMA levels are more prone to experience

The study was approved by Ethics Committee of SMS Medical College (Approval Date: 2022-03-19 and Approval Number: 911-MC-EC-2021). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

yatkındır. Bu, ameliyattan sonraki ilk altı saat içinde gerçekleşir. Daha yaşlı veya uzun süredir DM'si olan hastaların ameliyattan sonra kronik HTN'den muzdarip olma olasılığı daha yüksektir.

Anahtar Kelimeler: Feokromositoma, hipertansiyon, hipoglisemi, kreatinin

this. This happens within the first six hours following surgery. Patients who are older or who have had DM for a long time are more likely to suffer chronic HTN following surgery.

Keywords: Pheochromocytoma, hypertension, hypoglycaemia, creatinine.

INTRODUCTION

Pheochromocytoma (PC) are tumours that develop from chromaffin cells of the adrenal medulla. They can make, process and release catecholamines. Because of their influence on hemodynamic and metabolism, catecholamines produced by tumours are too responsible for a wide range of manifestations and symptoms (1, 2). Secondary hypertension (HTN) is commonly brought on by neuroendocrine tumours, which emit too much catecholamine (3). The main form of treatment is surgical extirpation, with minimally invasive surgery being the accepted method (4,5). These individuals are vulnerable to developing postoperative hypotension after the source of excessive catecholamines is eliminated, hence careful preoperative and intraoperative control is necessary to prevent hemodynamic instability (1). Moreover, PCs are suspected to trigger diabetic mellitus (DM) because to increased gluconeogenesis and glycogenolysis resulting from an excess of catecholamines, and following tumour removal, these patients may have serious hypoglycaemia, which can be lethal if not treated. (6, 7). Thus, it is crucial to keep an eye out for hypotension and hypoglycaemia in these individuals throughout the early postoperative period. The length and frequency of this monitoring have not been determined, though. In addition, following surgery, up to 90% of diabetes individuals risk becoming euglycemic and up to 50% of patients with hypertension may fully cure the condition over time, coupled with changes in body mass index (BMI) that may influence their quality of life (QoL) (8–10). Since muscle is the main source of creatinine, catabolic states are caused by an excess of catecholamines, and their reversal following surgery is shown by a rise in blood creatinine levels.

The purpose of this prospective cohort study is to identify the factors which may predict alterations in blood pressure and blood glucose level, as well as the timelines in which such changes occur. This might aid in identifying which individuals require more comprehensive and sustained monitoring. Furthermore, we examined the prevalence of chronic DM and HTN along with changes in BMI and serum creatinine.

MATERIAL AND METHODS

The SMS Medical College and Hospital's Institutional Ethics Committee accepted this prospective study, which was conducted from June 2021 to June 2022. The criteria of the International Conference on Harmonization's Good Clinical Practice (ICH-GCP) were observed for carrying out the present research. Written consent in vernacular language has been obtained from each participant before enrolling in to the study.

Inclusion Criteria

Adult patients (age 18 years or older) diagnosed with pheochromocytoma, patients scheduled to undergo surgical resection of pheochromocytoma, patients who are willing to participate in the study and provide informed consent, patients who are able to attend follow-up visits as per study protocol, patients with no history of previous pheochromocytoma surgery, patients with no known history of other medical conditions that may impact blood pressure or blood sugar levels, such as renal failure. Exclusion criteria were : Age less than 18 years were excluded, nonsurgical candidates of pheochromocytoma were excluded, patients with other metastatic disease were excluded, patients with a history of previous pheochromocytoma surgery, patients with known

history of other medical conditions that may impact blood pressure or blood sugar levels, such as renal failure, patients who are unable to provide informed consent or attend follow-up visits as per study protocol, patients who are pregnant or breastfeeding.

Pheochromocytoma was diagnosed using standard criteria for biochemical and radiological examination. Patients with metastatic disease and non-surgical candidates were excluded. Alpha-antagonists were used as the initial medicine in conjunction with antihypertensive drugs to reduce increased blood pressures prior to surgery. Prazosin was the primary alpha-blocker employed, with calcium channel blockers supplemented when the pressure control was insufficient. In order to manage the tachycardia brought on by alpha blockage, beta-antagonists were added. The preparation's ultimate objectives were a haematocrit below 40%, a healthy blood pressure, and minimum or even absence of orthostatic hypotension. To facilitate volume expansion, patients were advised to consume up to 5 g of salt per day and roughly 4-5 litters of water daily.

In an excel sheet, data were prospectively recorded. Demographic information, clinical and tumor features, BMI, serum creatinine and 24-hour urine catecholamine levels were all preoperative factors. Antihypertensive and hypoglycaemic medications with the appropriate dosages, baseline blood pressure and glucose levels, and other data were also collected.

The kind of surgery (laparoscopic or open), the length of the procedure, problems during the hospital stay, blood loss, and blood transfusions were all considered operational criteria. Intraoperative volume monitoring was performed using central venous pressure as well as a catheter placed across the right jugular vein. For the treatment of HTN and hypotension, there were established regimens. Sodium nitroprusside (SNP) was infused intravenously at a dosage of 0.5 to 5 g/kg/min to manage intraoperative hypertension. Boluses of esmolol (10–20 mg) were administered as necessary to manage tachycardia. Following tumour separation, crystalloids were first used to resuscitate the patient's volume. Colloids (hydroxyethyl starch) were administered if the hypotension, which is characterised by a systolic blood pressure less than 90 mmHg, did not improve after receiving a crystalloid stream. Noradrenaline (given as an infusion at a rate of 2–20 mcg/min) was initially selected as a vasopressor for the treatment of hypotension following volume resuscitation. Hypotension that did not respond to conventional vasopressors was treated with vasopressin, dopamine, and adrenaline.

Immediately following surgery, blood sugar levels were checked in interval of 2 hours for minimum 12 hours, and then every 4 hours after that. Until patients could begin oral intake, 2 ml/kg/h of postoperative intravenous fluids were administered. Ringer's lactate or acetate were the options for intravenous fluids; however, 5% dextrose normal saline was substituted if blood glucose levels ever fell below 120 mg/dL. Blood glucose levels of less than 80 mg/dL were considered hypoglycaemia and a 25% glucose bolus was used to treat it.

During the patient's stay in the intensive care unit (ICU) and after being shifted to the wards, postoperative blood pressure and blood sugar levels were checked until the patient was discharged. The database contained information on the dosage, duration, and need for dextrose bolus. Following surgery, the patients underwent reviews two weeks, six weeks and three months later with blood pressure and blood sugar readings taken at each session. At three months, BMI and serum creatinine were measured. Patients were classified as having persistent HTN or DM, respectively, if they still needed antihypertensive or hypoglycaemic therapy after three months.

Statistical Analysis

At the conclusion of the trial, the data were input into an excel spreadsheet and examined using the programme to look for preoperative and intraoperative factors that could have affected outcome metrics. GraphPad 3.0 was used to analyse the data, and the results were displayed as mean standard deviation or median (range). Frequency was used to depict categorical values (percentage).

Univariate and multivariate Cox proportional hazard regression models were used to investigate the associations between dependent and independent variables. Continuous variables were analysed using the Wilcoxon rank sum test, and categorical variables were compared using the Chi-square test. The paired t-test was used to evaluate within-group variations in scores. To determine the connection between two continuous variables, Spearman correlation coefficient was utilized. Statistics were deemed significant at $p<0.05$.

RESULTS

Total 50 patients, comprising 25 men and 25 women, met the inclusion criteria during the research period. Their average age was 40.6 ± 14.3 years, and the average number of months they had symptoms was 28.2 ± 6.5 months. Of these 50 individuals, 7 had inherited disorders, including 2 cases of von Hippel-Lindau disease and 5 cases of the multiple endocrine neoplasia-2 (MEN-2) syndrome, whereas the remaining 43 cases of PC were sporadic. Six patients got open surgery, whereas forty-four patients underwent laparoscopic surgery. In open surgery, larger masses were operated and the operation time was longer as compared to laparoscopic surgery. In Tables 1 and 2, respectively, the demographic and surgical parameters are shown.

Table 1. Baseline characteristics of patients

Age years	40.6 ± 14.3
BMI kg/m2	26.8 ± 5.2
Gender: Male/Female	25/25
Sporadic PC n (%)	43 (86%)
Hereditary syndromes n (%)	7 (14%)
MEN – 2 syndromes n (%)	5 (10%)
von Hippel–Lindau Disease n (%)	2 (4%)
Mean duration of symptoms Months	28.2 ± 6.5

Data were expressed as Mean ± SD. **BMI;** Body Mass Index, **PC;** Pheochromocytoma, **MEN – 2 syndromes;** Multiple Endocrine Neoplasia – 2 syndromes.

Inotropic assistance was needed in 16 patients (or 32%) in the postoperative term. None of these patients experienced delayed onset hypotension; all of them experienced it immediately after surgery. The first inotrope was a noradrenaline infusion. One patient needed an infusion of noradrenaline and adrenaline, and another needed an infusion of dopamine. The average time for infusion of noradrenaline was 16.6 hours, and the average dosage needed was 7.4 g/min. Preoperative 24-hour urine vanillylmandelic acid (VMA) levels and the incidence of hypotension were both linked (p=0.04). Urinary VMA and daily prazosin dosage were correlated with a 0.5 Spearman correlation value that was statistically significant (p=0.04). These relationships are shown in Table 3.

Table 2. Surgical Outcomes of patients

Parameter	Total	Open Surgery	Laparoscopic Surgery
Patients, n	50	6	44
Procedures, n	60	6	54
PC/PG, n	42/8	2/4	40/4
Tumor Size (cm)	5.06 ± 1.89	6.10 ± 2.10	4.02 ± 1.68
Operative time (min)	168.71 ± 64.51	198.14 ± 81.38	139.28 ± 47.64

Data were expressed as Mean ± SD. **PC;** Pheochromocytoma, **PG;** paragangliomas

Table 3. Variables predicting hypotension

Parameters	Inotropic required No (n=34) (%)	Inotropic required Yes (n=16) (%)	p value
Age (years)	38.49 ± 9.18	42.71 ± 9.42	0.81

Gender n (%)			0.99
Male	13 (52%)	12 (48%)	
Female	13 (52%)	12 (48%)	
Hypertension on presentation			0.99
Yes	31	16	
No	3	0	
Diabetes on presentation			0.37
Yes	8	5	
No	26	11	
Hereditary syndrome (MEN2/VHL), n (%)			<0.05
Yes	7 (100%)	0	
No	27 (62.79%)	16 (37.21%)	
S. Creatinine	0.5 ± 0.08	0.59 ± 0.09	0.02
Duration of symptoms months	12	12	0.99
Tumor size cm	5.22 ± 1.99	4.9 ± 1.79	0.68
24-hour urinary VMA (mg/24 hour)	18.60 ± 6.3	33.68 ± 9.2	0.024
Number of antihypertensive	2	2.5	0.14
Daily dose of prazosin (mg)	3	12.5	0.04

Data were expressed as Mean ± SD. **BMI;** Body mass index, **VHL;** Von Hippel-Lindau, **MEN2;** Multiple endocrine neoplasia 2, **VMA;** Vanillylmandelic acid, **HTN;** Hypertension

Table 4. Variables predicting persistent hypertension

Parameters	Hypertension at 3 months No (n=35)	Hypertension at 3 months Yes (n=15)	p value
Age (years)	34.59 ± 9.25	46.61 ± 9.35	0.03
Gender n (%)			0.98
Male	17 (48.57%)	8 (53.33%)	
Female	18 (51.43%)	7 (46.67%)	
Hypertension on presentation			0.96
Yes	32	15	
No	3	0	
Diabetes on presentation			0.04
Yes	4	9	
No	31	6	
Hereditary syndrome (MEN2/VHL), n (%)			0.63
Yes	6	1	
No	29	14	
S. Creatinine	0.69 ± 0.07	0.76 ± 0.13	0.03
Duration of symptoms months	18	24	0.41
Tumor size cm	5.3 ± 1.99	4.8 ± 1.79	0.21
24-hour urinary VMA (mg/24 hour)	20.30 ± 6.8	29.56 ± 8.4	0.70
Number of antihypertensive	2	3	0.26
Daily dose of prazosin (mg)	4	4	0.99

Data were expressed as Mean ± SD. BMI; Body mass index, VHL; Von Hippel-Lindau, MEN2; Multiple endocrine neoplasia 2, VMA; Vanillylmandelic acid, HTN; Hypertension

Following excision of the tumour, hypoglycaemias occurred in five individuals, necessitating dextrose infusion. At the presentation, just one of them had diabetes. One of these patients had hypoglycaemias after 12 hours, whereas the other four patients experienced it within the first four hours following surgery. These patients required dextrose infusion for a mean of 24 hours, and once dextrose infusion was terminated, none of these patients experienced any subsequent hypoglycaemias. Univariate analysis revealed no association between the requirement for a dextrose infusion and any preoperative catecholamine levels, clinical history, or tumour features.

At the time of presentation, 47 patients had hypertension, and 15 (31.91%) of these still had it after three months, necessitating the use of antihypertensive medications. None of the previously normotensive individuals experienced new-onset HTN, and all of these patients had hypertension upon discharge. One patient continued to require the same dosages of antihypertensives, while thirteen of the fifteen patients needed less antihypertensives overall. Age and diabetes mellitus at presentation showed a significant correlation in univariate analysis ($p=0.03$ and 0.04, respectively), and older patients or those with diabetes mellitus had a higher risk of continuing HTN (Table 4). Only one of the thirteen patients who had diabetes at the time of presentation still had it three months following surgery. For almost 4 years, this patient's diabetes had been well-known. No correlation analysis could be done since there was just one patient with chronic DM. Following surgery, there was a substantial rise in the mean BMI and serum creatinine, with increases in the mean BMI of 1.93kg/m^2 ($P<0.001$) and 0.12 mg/dl ($P<0.05$), respectively.

DISCUSSION

Patients who have surgical excision of a pheochromocytoma run the risk of developing severe hypotension as a result of the sudden removal of catecholamines from the bloodstream while still receiving ongoing alpha-blockade. This needs cautious monitoring since it might cause ischemic end-organ damage. Patients frequently require inotropic assistance to keep their blood pressure stable (1). In our research, 32% of the patients required inotropic assistance. We discovered a correlation between the total daily dose of alpha-blockers and the requirement for inotropic assistance. This might be the result of ongoing alpha-blockade following excision of the tumour, which results in unopposed vasodilation. Our results support a previous study that found postoperative hypotension occurs more frequently in patients with fewer intraoperative pressure increases (11). This effect is more pronounced following use of the long-acting alpha-blockers doxazosin and phenoxybenzamine. This effect may be caused by stronger and longer acting alpha-blockers. This is in line with recent studies examining the impact of alpha-blockers on postoperative hypotension, which show that patients on alpha-blockers experience postoperative hypotension more frequently than those taking calcium channel blockers (12,13). Namekawa et al. similarly reported that patients receiving higher doses of prazosin exhibited significant postoperative hypotension (14), which is consistent with our findings.

According to Shao et al., alpha-blockers had little effect for preserving intraoperative hemodynamic stability in patients with normotensive PC (15). Instead, they increase the necessity for colloid infusion and the use of vasoactive drugs. Although it raises the possibility of intraoperative severe HTN, this may help reduce such hypotension episodes.

Inotrope requirements were related to preoperative 24-hour urinary VMA levels. For blood pressure management, the individuals with higher VMA levels needed larger daily dosages of prazosin. This shows that more hormonal activity raises the risk of surgical hypotension and necessitates more preoperative alpha-blockade. According to some writers, there is a strong correlation between preoperative catecholamine levels and postoperative hemodynamic instability (14).

Additionally, the patients who had normotension at the time of presentation maintained it throughout the recovery period. This information is crucial for creating a plan for their postoperative care. For these

patients, a typical 24-hour stay in the ICU may be reduced to 6-8 hours. Bénay et al. have also made recommendations along the same lines (12).

Although five individuals required dextrose infusion due to hypoglycaemia, there were no risk factors and non-diabetic patients were equally vulnerable. Even in patients who initially stay normoglycemic in the postoperative phase, blood glucose level screening should be kept for up to 24-48 h since one patient developed hypoglycaemia after 12 h. According to Plouin et al., no correlation was found between surgical hypoglycaemia (15.15% of patients) and preoperative hyperglycaemia or plasma catecholamine concentrations (16). On the other hand, Chen et al. showed a relationship between bigger tumours and serum 24-hour urine metanephrine as well as longer operating times. (7) This consequence occurred between 0.4- and 142-hours following surgery, emphasising the need for continued blood sugar monitoring even after the patient was moved out of the intensive care unit (7).

Surgery for pheochromocytoma causes major metabolic alterations, including the remission of HTN, diabetes, and a more favourable body fat distribution, which raises BMI and serum creatinine (8,9,10). Pogorzelski et al. claim that the period between discharge and three months following surgery is when HTN and diabetes are improved the most, and that this period is followed by a year of benefits (10). After pheochromocytoma surgery, the frequency of chronic HTN ranges from 7% to 58% (8,17,18). We discovered that the patient's age (p=0.04) and diabetes (p=0.04) upon presentation were the only variables significantly linked with persistent HTN. In a long-term follow-up research after pheochromocytoma surgery, Poulin et al. discovered that age and family history of HTN were the only characteristics linked with persistent hypertension in 30.6% of patients at 1 year(16). They suggested that after removing the PC, there may still be an important HTN component that increases with age. In a different research, Sapienza et al. discovered that age was the only predictor that was substantially linked with chronic HTN, which affected 29% of patients (2).

The correlation between persistent HTN and DM at presentation may be caused by microvascular alterations brought on by chronic DM. In patients with chronic HTN, the median duration of diabetes at presentation was 48 months (ranging from 12 to 60), in contrast to 6 months in individuals who did not have ongoing high blood pressure. We were unable to locate another trial in which DM was linked to long-lasting HTN.

According to Pogorzelski et al., during the one-year follow-up, up to 90% of patients had euglycemia whereas 70% of patients promptly stopped taking hypoglycaemic medications after surgery (9). Spyroglou et al. recently showed that compared to 21% preoperatively, after a year, 9.3% of PC patients had diabetes. (comparable to the general population) (12). Only one patient had diabetes following surgery, indicating a sizable potential benefit.

Another significant symptom of pheochromocytoma is hypermetabolic state induced by the catecholamine, which causes weight loss even though normal appetite and food intake (6,2). Petrák et al. found that a small sample of 17 patients who had adrenalectomy for pheochromocytoma saw a considerable improvement in BMI and a good distribution of body fat (20). In their retrospective analysis including 43 PC patients, Spyroglue et al. similarly noted a substantial rise in BMI at 1 year (10). In prospective research, Bosanka et al. found that 18 PC patients' BMI significantly increased six months following surgery (21). After 3 months following surgery, we discovered a mean rise in BMI and serum creatinine of 1.93kg/m^2 ($P < 0.0001$) and 0.12mg/dl ($P<0.05$) respectively. The postoperative increase in creatinine in the entire group of patients demonstrates the catabolic condition generated by catecholamine excess and its reversibility after surgery. This might be due to muscle wasting, as muscular tissue is the major source of the circulating pool of creatinine, for example, and muscle loss has recently been documented in individuals with Pheochromocytoma. (22)

Limitation of the Study

Small sample size: Depending on the number of eligible patients, it may be difficult to recruit a large enough sample size to detect real statistically significant differences in outcomes.

Non-randomized design: Because this is a prospective cohort study, patients are not randomly assigned to treatment groups, which could introduce bias and affect the internal validity of the study.

Lack of blinding: Because this study involves surgical intervention, it may not be possible to blind participants or researchers to treatment group, which could also affect the internal validity of the study.

Follow-up period: The study may have a limited follow-up period, which could make it difficult to assess long-term outcomes or potential complications that may arise over time.

Single-centre study: The study may be limited to a single centre, which could limit the generalizability of the findings to other settings or populations.

Strength

Prospective Design: This study is prospective, which means that it will follow patients over time and collect data as events occur, which can provide more robust data than retrospective studies.

Cohort Design: The cohort design allows for comparison between patients who receive the surgical intervention, which can provide valuable information about the effectiveness of the intervention.

Multidimensional Outcomes: The study is evaluating multiple outcomes of interest, including blood pressure, blood sugar, predictors for their changes, which can provide a more comprehensive understanding of the impact of the surgical intervention on patients.

Consistent Protocol: The study will follow a consistent protocol for surgical intervention and data collection, which can reduce the potential for bias or error in the study results.

Clinical Relevance: Pheochromocytoma is a rare and potentially life-threatening condition, and the study has the potential to provide valuable information about predictors for the blood pressure, blood sugar changes, the effectiveness of surgical intervention on outcomes of interest to patients and clinicians.

CONCLUSION

In conclusion, this study highlights several potential complications that may occur following pheochromocytoma surgery. This complication was observed within the first six hours after surgery and mostly occurs in patients having higher 24-h urine VMA levels or who required higher doses of alpha-blockers. Additionally, postoperative hypoglycaemias were seen in a minority of patients, with a higher risk in those who were older or had a longer history of diabetes mellitus. These findings suggest that careful monitoring and management of blood pressure, blood sugar, and other relevant parameters in first six hours may be crucial and necessary for patients undergoing pheochromocytoma surgery, particularly in those with higher risk factors for complications. By considering these we may avoid the life-threatening complications.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethics Committee of SMS Medical College (Approval Date: 2022-03-19 and Approval Number: 911-MC-EC-2021). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

REFERENCES

1. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. The Lancet 2005;366:665–675. https://doi.org/10.1016/s0140-6736(05)67139-5
2. Zelinka T, Eisenhofer G, Pacak K. Pheochromocytoma as a catecholamine

producing tumor: Implications for clinical practice. Stress 2007;10:195–203. https://doi.org/10.1080/10253890701395896

3. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev. 2003;24(4):539-53. https://doi.org/10.1210/er.2002-0013
4. Williams DT, Dann S, Wheeler MH. Phaeochromocytoma--views on current management. Eur J Surg Oncol. 2003;29(6):483-490. https://doi.org/10.1016/s0748-7983(03)00071-4
5. Kercher KW, Novitsky YW, Park A, Matthews BD, Litwin DE, Heniford BT. Laparoscopic curative resection of pheochromocytomas. Ann Surg. 2005;241(6):919-26; discussion 926-928. https://doi.org/10.1097/01.sla.0000164175.26785.06
6. La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensivepatients. J Hypertens. 2003;21(9):1703-7. https://doi.org/10.1097/00004872-200309000-00020
7. Chen Y, Hodin RA, Pandolfi C, Ruan DT, McKenzie TJ. Hypoglycemia after resection of pheochromocytoma. Surgery 2014;156:1404–1409. https://doi.org/10.1016/j.surg.2014.08.020
8. Khorram-Manesh A, Ahlman H, Nilsson O, Friberg P, Oden A, Stenstrom G, et al. Long-term outcome of a large series of patients surgically treated for pheochromocytoma. Journal of Internal Medicine. 2005;258:55–66. https://doi.org/10.1111/j.1365-2796.2005.01504.x
9. Pogorzelski R, Toutounchi S, Krajewska E, Fiszer P, Łykowski M, Zapała Ł, Szostek M, Jakuczun W, Pachucki J, Skórski M. The effect of surgical treatment of phaeochromocytoma on concomitant arterial hypertension and diabetes mellitus in a single-centre retrospective study. Cent European J Urol. 2014;67(4):361-365. https://doi.org/10.5173/ceju.2014.04.art9
10. Spyroglou A, Adolf C, Hahner S, Quinkler M, Ladurner R, Reincke M, Beuschlein F. Changes in Body Mass Index in Pheochromocytoma Patients Following Adrenalectomy. Horm Metab Res. 2017;49(3):208-213. https://doi.org/10.1055/s-0042-124189
11. Rao N, Ramachandran R, Tandon N, Singh P, Kumar R. Surgical and Hemodynamic Outcomes in Pheochromocytoma Surgery: A Prospective Cohort Study. Urology. 2016;98:103-106. https://doi.org/10.1016/j.urology.2016.09.004
12. Bénay CE, Tahiri M, Lee L, Theodosopoulos E, Madani A, Feldman LS, Mitmaker EJ. Selective strategy for intensive monitoring after pheochromocytoma resection. Surgery. 2016;159(1):275-282. https://doi.org/10.1016/j.surg.2015.06.045
13. Brunaud L, Boutami M, Nguyen-Thi PL, Finnerty B, Germain A, Weryha G, et al. Both preoperative alpha and calcium channel blockade impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. Surgery. 2014;156:1410-1417. https://doi.org/10.1016/j.surg.2014.08.022
14. Namekawa T, Utsumi T, Kawamura K, Kamiya N, Imamoto T, Takiguchi T, Hashimoto N, Tanaka T, Naya Y, Suzuki H, Ichikawa T. Clinical predictors of prolonged postresection hypotension after laparoscopic adrenalectomy for pheochromocytoma. Surgery. 2016;159(3):763-770. https://doi.org/10.1016/j.surg.2015.09.016
15. Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui WB, Xie X, Zhou WL. Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? J Hypertens. 2011;29(12):2429-32. https://doi.org/10.1097/HJH.0b013e32834d24d9
16. Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. J Clin Endocrinol Metab. 2001;86(4):1480-1486. https://doi.org/10.1210/jcem.86.4.7392.

17. Yau JS, Li JK, Tam VH, Fung LM, Yeung CK, Chan KW, Lee KM, Lee KF, Cheung WS, Yeung VT, Yuen YP, Kwan WK. Phaeochromocytoma in the Hong Kong Chinese population. Hong Kong Med J. 2010;16(4):252-256. PMID: 20683066
18. Kazic MR, Zivaljevic VR, Milan ZB, Paunovic IR. Perioperative risk factors, morbidity, and outcome of 145 patients during phaeochromocytoma resection. Acta Chir Belg. 2011;111(4):223-227. PMID: 21954738
19. Sapienza P, Cavallaro A. Persistent hypertension after removal of adrenal tumours. Eur J Surg. 1999 Mar;165(3):187-192. https://doi.org/10.1080/110241599750007027
20. Petrák O, Haluzíková D, Kaválková P, Štrauch B, Rosa J, Holaj R, Brabcová Vránková A, Michalsky D, Haluzík M, Zelinka T, Widimsky J Jr. Changes in energy metabolism in pheochromocytoma. J Clin Endocrinol Metab. 2013;98(4):1651-1658. https://doi.org/10.1210/jc.2012-3625
21. Bosanska L, Petrak O, Zelinka T, Mraz M, Widimsky J Jr, Haluzik M. The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue. Physiol Res. 2009;58(3):319-325. https://doi.org/10.33549/physiolres.931483

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):166-172. doi: 10.33719/yud.2023;18-2-1247568**

Original Research / Özgün Araştırma

Comparison of the effects of sperm selection methods on assisted reproduction outcomes in male infertility

Erkek infertilitesinde sperm seçim yöntemlerinin yardımcı üreme sonuçları üzerine etkilerinin karşılaştırılması

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Geliş tarihi (Submitted): *2023-02-04*
Kabul tarihi (Accepted): *2023-05-08*

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Özet

Amaç: Şiddetli veya orta derecede oligoastenospermi olgularında fizyolojik intrasitoplazmik sperm enjeksiyonu (PICSI) ve hipoosmotik şişme testi (HOST) sperm seçim tekniklerini, embriyo gelişimi, implantasyon oranı ve canlı doğum oranları açısından karşılaştırmak.

Gereç ve yöntemler: Medipol Üniversitesi Tüp Bebek Merkezi'ne 2013-2022 yılları arasında başvuran olguların elektronik materyalleri ve dosyaları retrospektif olarak analiz edildi. Ağır veya orta derecede oligoastenospermi tanısı konulan toplam 143 olgu çalışmaya dahil edildi, 80 olguda sperm seçim tekniği olarak PICSI, 63 olguda ise HOST kullanıldı. Dünya Sağlık Örgütü (WHO) tarafından tanımlanan şiddetli veya orta derecede oligoastenospermi vakaları bu çalışmaya dahil edildi. Kadın yaşı, erkek yaşı, infertilite süresi, AMH (anti-Mullerian hormon), vücut kitle indeksi (VKİ), endometrial kalınlık ve önceki deneme sayısı dahil olmak üzere her iki grubun demografik parametreleri ve implantasyon oranı , gebelik kaybı ve canlı doğum oranları gibi transfer sonuçları iki grup arasında karşılaştırıldı.

Bulgular: Kadın yaşı, erkek yaşı, VKİ, AMH, endometrial kalınlık ve önceki deneme sayısı her iki grup arasında benzerdi. Gruplar arasında fertilizasyon (10,2±6,9 vs 9,1±6,4, p=0,345 çok iyi ve iyi kalitede (TQ-GQ) blastokist gelişimi (2,4±2,4 vs 2,6±1,4, p=0,097) ve transfer edilen embriyo sayısı (1,6±0,5 vs 1,8±0,4, p= 0,141) açısından anlamlı fark yoktu.

Abstract

Objective: To compare physiological intracytoplasmic sperm injection (PICSI) and the hypoosmotic swelling test (HOST) sperm selection techniques in terms of embryo development, implantation rate and live birth rates in cases of severe or moderate oligoastheneospermia.

Material and Methods: The electronic material and files of cases admitted to the Medipol University IVF Centre between 2013 and 2022 were analyzed retrospectively. This research included a total of 143 cases with moderate or severe oligoasthenospermia, as a sperm selection technique, PICSI has been used in 80 cases and HOST has been used in 63 cases. Cases of severe or moderate oligoasthenospermia as defined by the World Health Organisation (WHO) are included in this study. The demographic parameters of both groups, including female age, paternal age, duration of infertility, anti-Mullerian hormone (AMH), body mass index (BMI), endometrial thickness, and the number of prior fertility attempts, were analyzed. Implantation rate, pregnancy loss, and rates of live births were compared between two groups.

Results: Female age, paternal age, AMH, endometrial thickness, BMI, and the number of prior fertility attemps were similar between the groups. There were not any significant differences between the groups in terms of fertilization rate (10.2±6.9 vs 9.1±6.4, p=0.345), TQ-GQ blastocyst development (2.4±2.4 vs 2.6±1.4 , p=0.097), and the number of embryos transferred (1.6±0.5 vs 1.8±0.4, p= 0.141). Although the implantation

The study was approved by Ethics Committee of Istanbul Medipol University (Approval Date 2022-12-08 and Protocole Number: 1049). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

PICSI ve HOST grupları arasında canlı doğum oranı (p= 0,790) arasında fark olmamasına rağmen HOST grubunda implantasyon oranı PICSI grubuna göre anlamlı olarak daha yüksekti (p=0,043).

Sonuç: İki grup arasında embriyo gelişimi, gebelik kaybı ve canlı doğum oranları açısından fark bulunmadı, ancak HOST yöntemi kullanılan grupta implantasyon oranı daha yüksek idi.

Anahtar Kelimeler: PICSI, HOST, Erkek infertilitesi

rate is significantly higher in the HOST group than PICSI group (p=0.043), the live birth rates were similar.

Conclusion: There were no any differences in embryo development, pregnancy loss, and live birth rates comparing the two methods, however, the HOST group had a higher implantation rate.

Keywords: PICSI, HOST, Male infertility

INTRODUCTION

The aim of in vitro fertilization (IVF) is to achieve a live birth. Approximately 15% of couples who fail to conceive after one year of trying are infertile. 30% to 50% of infertile couples are not able to conceive because of male factor (1). In addition, around 7% of the global male population has been considered infertile (2).

In assisted reproductive technologies (ART), embryo development depends on both egg and sperm quality. There is a correlation between higher chromosomal abnormalities, apoptosis, and DNA damage in males with low sperm count (3, 4). In cases of male infertility, sperm selection methods are essential in order to choose competent sperm. In the female reproductive system, millions of sperm cells compete for fertilization and undergo natural selection, however, in the intracytoplasmic sperm injection (ICSI) process, the embryologist select the spermatozoa solely based on sperm motility and morphology. In terms of competent sperm selection, the separation processes based on motility and morphology, such as swim up (SU) and density gradient centrifugation (DGC), which are the most utilized procedures in ART laboratories today, have not produced satisfying results (5). There are several sperm selection methods that are used to improve IVF outcomes. Physiological ICSI (PICSI) is one of these methods and also based on the ability of the sperm to adhere to Hyaluronic acid (HA) which is present in the cumulus-oocyte complex (COC). The presence of HA in the COC is important for fertilization of the oocyte. Because HA-specific receptors are found in mature sperm. In PICSI technique, sperm that have been washed and centrifuged are put on a PICSI dish with HA-coated spots. After a period of incubation, the spermatozoa surrounded by HA are chosen for ICSI. Some studies have demonstrated that analysis of spermatozoa attached to HA gels revealed normal morphology, low DNA damage, and low chromosomal aneuploidy and PICSI has been shown to improve fertilization rates, embryonic development, and pregnancy outcomes in IVF cycles (6, 7).

The other sperm selection technique is the hypoosmotic swelling test (HOST) that evaluates the integrity of the sperm plasma membrane (8). This test is based on the theory of fluid movement across the cell membrane until equilibrium is established between the inside and outside of the sperm cell under hypo-osmotic conditions. The tails of live spermatozoa swell and bend under these hypoosmotic conditions. The test mainly evaluates the integrity of the tail membrane, however it also reveals that the plasma membrane in the sperm head is intact. Sperm membrane integrity is important for capacitation, sperm metabolism, acrosome reaction, and sperm binding to the oocyte surface. Therefore, HOST is an essential sperm selection technique in male infertility because it assures that sperm cells with better nuclear material will be selected for ICSI (9).

Although many studies have been performed to determine the ideal sperm selection technique, there is still no clear consensus on this issue. Accordingly, this study compared PICSI and HOST sperm selection techniques in patients with oligoasthenoospermia and evaluated the efficiency of these techniques on blastocyst development and clinical pregnancy rates.

MATERIAL AND METHODS

The electronic material and files of cases admitted to the Medipol University IVF Centre between 2013 and 2022 were analyzed retrospectively. The study was compiled according to the principles of the Declaration of Helsinki and was approved by the Medipol University Faculty of Medicine Ethics Committee with protocol number E-10840098-772.02-7443.

This research included a total of 143 cases with moderate or severe oligoasthenospermia, as a sperm selection technique, PICSI has beeen used in 80 cases and HOST has been used in 63 cases. Severe or moderate oligoasthenospermia as defined by the World Health Organisation (WHO) 2021 6th Edition (10) (Table 1). In the study, only ejaculated spermatozoa were used. The cases that not binded to HA on PICSI or a negative HOST test were not included to study. In order to minimize confounding factors, the study included only women with aged 20 to 35. The women with major endocrinological disease (such as congenital adrenal hyperplasia or Cushing's syndrome), endometrial factor, untreated hydrosalpinx, and uterine anomalies verified by hysterosalpingography or hysteroscopy were excluded from the study. The demographic parameters of both groups, including female age, paternal age, duration of infertility, anti-Mullerian hormone (AMH), body mass index (BMI) endometrial thickness, and the number of prior attempts, were analyzed. Implantation rate, pregnancy loss, and rates of live birth were compared between the two groups. On the second day of menstruation, all patients underwent ultrasonographic assessment to rule out ovarian cysts and other pelvic diseases. All research participants underwent a short antagonist protocol. The initial dose of recombinant follicle stimulating hormone (rFSH, Gonal-F®, Merck-Serono, Italy) was determined on BMI, AFC (antral follicle count), AMH, and previous ovarian stimulation responses, if any. Cetrorelix (Cetrotide®, Merck-Serono, Spain) was administered when at least one follicle throughout the cycle reached 12-13 mm in diameter. Every 2-3 days, transvaginal ultrasonography was performed to monitor the development of follicles. Recombinant human chorionic gonadotropin (r-hCG 250 mcg; Ovitrelle®; Serono; Spain) was administered, when three or more follicles reached 18 mm in diameter. Then, 36 hours after the injection of r-hCG, ultrasound-guided transvaginal oocyte retrieval was performed.

Table 1. World Health Organization (WHO) semen analysis 2021 (6th Edition)

Semen volume (mL)	1.4 (1.3-1.5)
Total sperm number (10^6per ejeculate)	16 (15-18)
Total motility (%)	42 (40-43)
Progressive motility (%)	30 (29-31)
Non progressive motility (%)	1(1-1)
Immotile sperm (%)	20 (19-20)
Vitality (%)	54 (50-56)
Normal forms (%)	4 (3.9-4)

On the oocyte pick up (OPU) day, after 3-5 days of ejaculatory abstinence, sperm samples were obtained. For 30 to 60 minutes, the sample of sperm was left at room temperature to liquefy. The analysis of sperm was conducted in accordance with WHO criteria. After performing a swim-up, gradient centrifugation was applied to separate the semen's cellular components. For the selection of mature sperm, sterile PICSI Petri dishes were used (PICSI® Sperm Selector, ORIGIO, Denmark). PICSI dishes are the standard plastic culture dishes pre-prepared with three drops of HA gel. To allow the sperm to bind to the glycosaminoglycan, approximately 2 µl of processed sperm sample was applied to the lateral surfaces of the HA hydrated droplets, and the temperature was retained at 36.8°C for a minimum of 5 minutes. Then, spermatozoa with normal morphology, which were bound to the surface of HA microdots from their heads, were collected using an ICSI injection pipette (ICSI Micropipettes; Humagen Fertility Diagnostics-Origio) and injected into the oocyte. Sperms of cases to be selected by the HOST test were incubated in a hypoosmotic 150 mOsm solution (75 mm) at 37°C for 5-10 minutes following Swim-up and gradient centrifugation (11) spermatozoa with B+ shape in the HOST classification

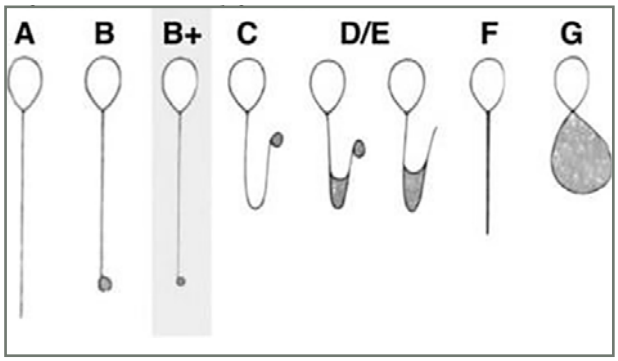

Figure 1. The different categories of HOST defined in the WHO laboratory guidelines for the process and examination of human semen, the addition of type B+

Following ICSI, oocytes were cultured (Life Global®, Belgium) and kept at 37°C and 6% CO2 in a conventional incubator. Additionally, pronucleus (PN) control was conducted on day 2, 18 to 20 hours following ICSI. On day 5, Gardner criteria were applied to grade blastocysts, and for embryo transfer (ET), the TQ and GQ (top quality and good quality) embryos were selected. The ET was conducted using ultrasound guidance. The transfer day and the number of embryos were selected by the doctor based on the patient's and cycle's parameters. Progesterone vaginal gel (Crinone® 8% vaginal gel 90 mg, Merck, UK) or a progesterone vaginal tablet (Lutinus® 100 mg, Ferring, Turkey) were used to support the luteal phase and were given intravaginally twice a day until 12 weeks of pregnancy. Following embryo transfer, serum beta-HCG was tested 9 or 11 days after embryo transfer, depending on the ET day and those with a positive result had pelvic ultrasound three weeks later to confirm intrauterine pregnancy. Detection of the gestational sac by transvaginal ultrasonography was defined as implantation. All cases that did not reach live births were defined as pregnancy loss.

In our study, the rate of live birth was the primary outcome. Fertilization rate, blastocyst development rate, and TQ-GQ blastocyst development rate were the secondary outcomes.

Statistical Analysis

SPSS "SPSS for Windows 22" was used for statistical analysis. $p<0.05$ was considered statistically significant. The distribution of continuous data was checked by the Kolmogrow-Smirnow test. Depending on their distribution, continuous data were compared using Student's t-test. For comparing categorical data, Chi-Square and Fisher Exact test were used. Using Spearman or Pearson correlation analysis, the relationships between continuous data were determined.

RESULTS

Female age, paternal age, AMH, BMI, endometrial thickness, and the number of previous trials were similar between the groups. In total, 143 cases were included in this study. This includes 80 cycles of sperm selection by PICSI and 63 cycles of sperm selection by HOST. The mean female age 30.4 ± 5.2 and 29.9 ± 5.3, p=0.143), male age (34.4 ± 5.4 and 32.9 ± 6.7 p= 0.602), and sperm concentration (7.0 ± 0.9 vs 6.5 ± 1.3, p=0.783) were similar between the groups. Total sperm motility (39.1 ± 14.5 vs 27.9 ± 18.9, p= 0.000) was lower in the HOST group In terms of fertilization rate (10.2 ± 6.9 vs 9.1 ± 6.4, p=0.345), TQ-GQ blastocyst development (2.4 ± 2.4 vs 2.6 ± 1.4, p=0.097), and the number of embryos transferred (1.6 ± 0.5 vs 1.8 ± 0.4, p= 0.141 respectively), no significant differences were determined between the PICSI and HOST groups (Table 2). Although there were not any statistical differences between the PICSI and HOST groups in terms of live birth rate [18/42(%42.8), 12/26(%46), p= 0.790 respectively], the HOST group had a significantly higher implantation rate (p=0.043) (Table 3).

DISCUSSION

In patients with male infertility, sperm selection is essential for embryo development. Sperm selected by ICSI that have normal morphology and motility may have DNA damage, which can have a negative effect on fertilization and IVF outcomes. Consequently, sperm selection techniques that contain sperm functions are

Table 2. Comparison of patient and cycle characteristic

	PICSI n(80)	HOST n(63)	p-value
Male age. (years)	34.4 ± 5.4	32.9±6.7	0.602
Female age. (years)	30.4 ± 5.2	29.9 ± 5.3	0.143
BMI (kg/m2)	26.1 ± 4.3	25.7 ± 4.7	0.583
AMH level. ng/ml	2.9 ± 2.6	3.2 ± 2.8	0.629
Infertility duration. years	5.0 ± 3.8	3.5 ± 2.6	0.009
Previous IVF cycles	0.6 ± 1.1	0.8 ± 1.6	0.370
Total gonadotropin dose (IU/L)	2221.6 ± 702.3	2073.2 ± 443.5	0.144
Endometrial thickness (mm)	10.5 ± 1.9	10.6 ± 1.7	0.673
Estradiol on triggering day. pg/ml	3434.0 ± 1962.0	2852.3 ± 1276.2	0.329
No. of oocyte retrieved	16.2 ± 9.7	14.33 ± 8.4	0.225
No. of mature oocyte	11.5 ± 7.4	10.4 ± 6.8	0.369
No. ICSI fertilizied	10.2 ± 6.9	9.1 ± 6.4	0.345
No.of TQ-GQ embriyos	2.4 ± 2.4	2.6 ± 1.4	0.097
No.of embryo transferred	1.6 ± 0.5	1.8 ± 0.4	0.141
Semen volume (ml)	3.4 ± 1.8	2.5 ± 1.3	0.001
Sperm concentration.10^6/ml	7.0 ± 0.9	6.5 ± 1.3	0.783
Sperm motility	39.1 ± 14.5	27.9 ± 18.9	0.000

Table 3. Comparison of cycle results

	PICSI n=80 n (%)	HOST n=63 n (%)	p-value
No of cancelled embryo transfer	38/80 (%47)	37/63 (%58.7)	
Preimplantation genetic test(PGT)	13/80 (%16)	12/63 (%19)	0.903[2]
Ovarian hyperstimülatıon syndrome(OHSS)	20/80 (%25)	19/63 (%30)	0.741[2]
Cleavage arrest	5/80 (%5)	6/63 (%9)	0.736[1]
No. of embryo transfer cycles	42/80 (%52)	26/63 (%41)	
Implantation rate	22/42 (%52)	20/26 (%76)	0.043[2]
Pregnancy loss rate	4/22 (%18)	8/20 (%40)	0.175[1]
Live birth rate	18/42 (%42.8)	12/26 (%46)	0.790[2]

[1]Fisher-Exact Test. [2]Chi-Square Test. [3]Student t test

crucial, especially in cases of male infertility. Currently, there is no consensus on which method should be used for sperm selection in these cases. Although several studies examine the efficacy of the sperm selection strategies PICSI and HOST, no study has analyzed and compared the outcomes in patients with severe or moderate oligoasthenospermia. All previously reported research compared PICSI to conventional ICSI. Our research is the first to compare PICSI and HOST methods. The primary outcomes of our study, including the rates of live birth, fertilization, and TQ-GQ blastocyst development, did not show differences significantly between the two groups. Although HOST was defined as a simple test to distinguish viable spermatozoa from non-viable spermatozoa at first, later studies have demonstrated that this test has the potential to select the best spermatozoa according to chromatin and membrane integrity, as well as

spermatozoa with a low DNA fragmentation rate (9, 12). In a randomised study comparing the outcomes of ICSI after morphology-based sperm selection with the HOST sperm selection technique, the researchers showed that fertilisation and the rates of pregnancy were significantly higher in the HOST sperm selection group (13). Comparing the sperm of patients whose partners had recurrent early pregnancy loss to the sperm of fertile males, Bhattacharya et al. found that the HOST test scores were lower in the early pregnancy loss group. Therefore, they suggested that the HOST technique for sperm selection may be used to evaluate the association between male factors and recurrent unexplained early pregnancy loss (14). Moskoviz et al. found that the implantation rate in male infertility cases with a normal HOST test was higher, likes the our study results (15).

In our study, the rate of pregnancy loss in cases with severe or moderate oligoastenospermia who underwent sperm selection by PICSI, the miscarriage rate was lower than in the HOST group. Nevertheless, this difference was not statistically significant. A randomised prospective multi-center study comparing ICSI and PICSI did not find any differences in the rates of live birth between the two groups, while PICSI had decreased miscarriage rates (16). Worrilow KC et al. found, in a prospective, multi-center, double-blind, randomized clinical study, that implantation and clinical pregnancy rates were higher in the group using PICSI sperm selection compared to conventional ICSI (17). Although studies comparing PICSI with ICSI in male infertile cases have shown that sperm selection technique with PICSI increases the chance of pregnancy (9, 11) it has been shown that PCSI does not contribute to pregnancy outcomes in cases of unexplained infertility (18).

Our research is the first to compare sperm selection methods, PICSI and HOST. The study is limited by the fact that we were unable to do DNA fragmentation and chromosomal analysis on spermatozoa and that it is a retrospective, single-center study and it has a small sample size. However, we believe that our research might lead to prospective randomized studies.

In conclusion, there is no consensus about the effects of sperm selection methods on the success of in vitro fertilization in male infertility. There were no differences in terms of live birth rate between the two methods. The HOST test that is a simple, cost-effective, rapid, and, non-invasive test, may be preferred in IVF practice.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethics Committee of Istanbul Medipol University (Approval Date 2022-12-08 and Protocole Number: 1049). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

REFERENCES

1. Brugh VM, Lipshultz LI. Male factor infertility: evaluation and management. Medical Clinics. 2004;88(2):367-85. https://doi.org/10.1016/S0025-7125(03)00150-0
2. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertility and Sterility. 2013;99(5):1324-31. https://doi.org/10.1016/j.fertnstert.2012.11.037
3. Simpson JL, Lamb DJ, editors. Genetic effects of intracytoplasmic sperm injection. Seminars in reproductive medicine; 2001: Copyright© 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New.
4. Yagci A, Murk W, Stronk J, Huszar G. Spermatozoa bound to solid state hyaluronic acid

show chromatin structure with high DNA chain integrity: an acridine orange fluorescence study. Journal of andrology. 2010;31(6):566-72. https://doi.org/10.2164/jandrol.109.008912

5. Vaughan DA, Sakkas D. Sperm selection methods in the 21st century. Biology of reproduction. 2019;101(6):1076-82. https://doi.org/10.1093/biolre/ioz032
6. Jakab A, Sakkas D, Delpiano E, Cayli S, Kovanci E, Ward D, et al. Intracytoplasmic sperm injection: a novel selection method for sperm with normal frequency of chromosomal aneuploidies. Fertility and sterility. 2005;84(6):1665-73. https://doi.org/10.1016/j.fertnstert.2005.05.068
7. Huszar G, Jakab A, Sakkas D, Ozenci C-C, Cayli S, Delpiano E, et al. Fertility testing and ICSI sperm selection by hyaluronic acid binding: clinical and genetic aspects. Reproductive biomedicine online. 2007;14(5):650-63. https://doi.org/10.1016/S1472-6483(10)61060-7
8. Jeyendran R, Van der Ven H, Perez-Pelaez M, Crabo B, Zaneveld L. Development of an assay to assess the functional integrity of the human sperm membrane and its relationship to other semen characteristics. Reproduction. 1984;70(1):219-28. https://doi.org/10.1530/jrf.0.0700219
9. Bassiri F, Tavalaee M, Shiravi A, Mansouri S, Nasr-Esfahani M. Is there an association between HOST grades and sperm quality? Human Reproduction. 2012;27(8):2277-84. https://doi.org/10.1093/humrep/des155
10. Organization WH. WHO laboratory manual for the examination and processing of human semen: World Health Organization; 2021.
11. Rouen A, Carlier L, Heide S, Egloff M, Marzin P, Ader F, et al. Potential selection of genetically balanced spermatozoa based on the hypo-osmotic swelling test in chromosomal rearrangement carriers. Reproductive BioMedicine Online. 2017;35(4):372-8. https://doi.org/10.1016/j.rbmo.2017.06.017
12. Stanger J, Vo L, Yovich J, Almahbobi G, editors. HypoOsmotic Swelling Test [HOST] Identifies Human Spermatozoa with minimal DNA Damage. Human Reproduction; 2010: Oxford Univ Press Great Clarendon St, Oxford Ox2 6dp, England.
13. Sallam H, Farrag A, Agameya A, Ezzeldin F, Eid A, Sallam A. The use of a modified hypo-osmotic swelling test for the selection of viable ejaculated and testicular immotile spermatozoa in ICSI. Human Reproduction. 2001;16(2):272-6.https://doi.org/10.1093/humrep/16.2.272
14. Bhattacharya SM. Hypo-osmotic swelling test and unexplained repeat early pregnancy loss. Journal of Obstetrics and Gynaecology Research. 2010;36(1):119-22. https://doi.org/10.1111/j.1447-0756.2009.01106.x
15. Moskovtsev S, Willis J, Azad A, Mullen J. Sperm DNA integrity: correlation with sperm plasma membrane integrity in semen evaluated for male infertility. Archives of andrology. 2005;51(1):33-40. https://doi.org/10.1080/014850190512770
16. Miller D, Pavitt S, Sharma V, Forbes G, Hooper R, Bhattacharya S, et al. Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect): a parallel, two-group, randomised trial. The Lancet. 2019;393(10170):416-22. https://doi.org/10.1016/S0140-6736(18)32989-1
17. Worrilow K, Eid S, Woodhouse D, Witmyer J, Khoury C, Liebermann J. Increased clinical pregnancy rates (CPR) and statistically significant decrease in loss rates using hyaluronan in sperm selection: prospective, multi-center, double-blind, randomized clinical trial. Fertility and Sterility. 2011;96(3):S179.n https://doi.org/10.1016/j.fertnstert.2011.07.696
18. Majumdar G, Majumdar A. A prospective randomized study to evaluate the effect of hyaluronic acid sperm selection on the intracytoplasmic sperm injection outcome of patients with unexplained infertility having normal semen parameters. Journal of assisted reproduction and genetics. 2013;30(11):1471-5. https://doi.org/10.1007/s10815-013-0108-9

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):173-182. doi: 10.33719/yud.2023;18-2-1270777**

Original Research / Özgün Araştırma

Relationship between the prostate cancer screening attitudes, beliefs, and knowledge levels of men working in a healthcare institution

Bir sağlık kurumunda çalışan erkeklerin prostat kanseri taramalarına yönelik tutum ve inançları ile bilgi düzeyleri arasındaki ilişki

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Geliş tarihi (Submitted): 2023-03-25
Kabul tarihi (Accepted): 2023-06-13

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Özet

Amaç: Bireylerin prostat kanseri taramalarına yönelik tutum ve bilgi düzeyi taramalara katılımı etkileyen önemli bir faktördür. Bu çalışmada, üçüncü basamak sağlık kurumunda çalışan erkeklerin prostat kanserine yönelik tutum ve inançları ile bilgi düzeyleri arasındaki ilişkinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya bir eğitim ve araştırma hastanesinde çalışan 236 sağlık personeli dahil edildi. Verilerinin toplanmasında; Bilgi Formu, Prostat Kanseri Taramaları Sağlık İnanç Modeli Ölçeği ve Prostat Kanseri Taramaları Bilgi Testi kullanılmıştır.

Bulgular: Araştırmaya katılan erkeklerin yaş ortalaması 46.7±5.9 yıl idi. Katılımcıların Prostat Kanseri Taramaları Bilgi testi puan ortalaması 5.80±3.15 ve %67.4'ü düşük düzeyde bilgi sahibidir. Katılımcılar Sağlık İnanç Modeline göre "Duyarlılık Algısı" alt boyutundan 12.6±3.8, "Ciddiyet Algısı" 11.9±3.6, "Sağlık Motivasyonu Algısı" 32.9±7.6, "Engel Algısı" 38.5±10.3, "Yarar Algısı" alt boyutundan 24.8±5.7 puan almıştır. Prostat kanseri taramaları sağlık inanç modeli ölçeği ile prostat kanseri taramaları bilgi testinden aldıkları puanlar arasında anlamlı ilişki bulunmamıştır.

Sonuç: Çalışmaya katılan erkeklerin bilgi düzeyleri düşük, prostat kanseri taramalarına yönelik duyarlılık, ciddiyet, engel algısı orta düzeyde, sağlık motivasyonu ve yarar algısının yüksek düzeyde olduğu belirlenmiştir. Sağlık çalışanları tarafından erken teşhisin yararları ve taramalara yönelik eğitimler ile farkındalık yaratmak önemlidir.

Anahtar kelimeler: prostat kanseri, tarama, tutum, İnanç

Abstract

Objective: The attitudes and knowledge level of individuals toward prostate cancer screening are important factors affecting participation in screening. This study aimed to determine the relationship between prostate cancer screening attitudes, beliefs, and knowledge levels of men working in a tertiary healthcare institution.

Material and Methods: A total of 236 healthcare personnel working in education and research hospital were included in the study. In the collection of data, an information form, the Health Beliefs Model Scale for Prostate Cancer Screenings (HBM-PCS), and the Knowledge About Prostate Cancer Screening Questionnaire (KPCSQ) were used.

Results: The mean age of the participating was 46.7±5.9 years. The mean score of the participants in the Prostate Cancer Screening Knowledge Test was 5.80±3.15 and 67.4% had a low level of knowledge. When the subscales of HBM-PCS were examined, the participants had a mean score of 12.6±3.8 on susceptibility perception, 11.9±3.6 on seriousness perception, 32.9±7.6 on health motivation perception, 38.5±10.3 on barrier perception, and 24.8±5.7 on benefit perception. There was no significant relationship in the participants' HBM-PCS scores according to their KPCSQ scores.

Conclusion: It was determined that the men participating in this study had a low level of knowledge, moderate levels of susceptibility, seriousness, and barrier perceptions, and high levels of health motivation and benefit perceptions concerning prostate cancer screening. It is important to raise the awareness of healthcare workers about the benefits of screening and early diagnosis of prostate cancer through training programs.

Keywords: prostate cancer, screening, attitude, belief

The study was approved by Ethics Committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital (Approval Date 2022-09-19 and Protocole Number: 2022-18). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

According to the GLOBOCAN 2020 data published by the International Agency for Research on Cancer, prostate cancer (PCa) is the second most common type of cancer in men both in Turkey and across the world (1). PCa rarely shows symptoms until it is incurable and may not present with any signs or findings until the tumor is locally advanced or metastatic (2). The European Association of Urology Guidelines recommend risk-based screening in patients with long life expectancies, although an individualized, risk-adapted strategy for early detection may still be associated with significant risks of unnecessary diagnosis and treatment (3). Despite the global applicability of a digital rectal examination and the wide accessibility of the prostate-specific antigen (PSA) test for the diagnosis of PCa, many studies have reported low rates of participation in PCa screening (4, 5).

It is very important to increase PCa screening participation rates and improve knowledge of and attitudes toward screening practices. The health belief model, which was developed by adapting the behavioral sciences theory to the field of health, is one of the oldest instruments frequently used in health behavior practices. This model is used to explain the relationship between a person's behaviors and beliefs and the effect of individual motivation on health behaviors. The health belief model defines what motivates individuals to take health-related actions, as well as the situations that are effective in the demonstration of healthy behaviors (6, 7).

When the literature on PCa screening among men is examined, it is seen that most have been conducted with patients and healthcare students (8-12), and none has targeted healthcare workers, such as physicians, nurses, and technicians. Determining the knowledge and attitudes of healthcare workers on this subject will increase the awareness of the society on the early diagnosis of prostate cancer by planning health training for both the promotion of screening and the protection and improvement of public health. Therefore, in this study, we aimed to determine the relationship between PCa screening attitudes, beliefs, and knowledge of men working in a healthcare institution.

MATERIAL AND METHODS

Research Design, Population, and Sample

The population of this descriptively designed research consisted of 424 men working in an education and research hospital affiliated with the University of Health Sciences. The sample size of the study was determined as 202 (95% confidence interval, 0.05 margin of error) using the sample number calculation formula for the known population. The study was carried out with 236 male participants aged 40-65 years who worked in a healthcare institution and were not diagnosed with any prostate-related disease.

Data Collection Tools: Data were collected using an information form, the Health Beliefs Model Scale for Prostate Cancer Screenings (HBM-PCS), and the Knowledge About Prostate Cancer Screening Questionnaire (KPCSQ).

Information Form: This form was prepared by the researchers in line with the literature and consisted of nine questions to obtain the descriptive data of the participants (age, occupation, marital status, education level, prostate examination history, PSA test history, PCa diagnosis in family/close contacts, thoughts about participating in PCa screenings in the future, and thoughts about whether prostate examination is embarrassing) (10-14).

HBM-PCS: This scale was developed by Çapık and Gözüm (2011) based on the health belief theory and found to be valid and reliable. In this five-point Likert-type scale, the response options are: 1- strongly disagree, 2-disagree, 3- undecided, 4- agree, and 5-completely agree. HBM-PCS comprises a total of 41 items presented under five subscales: susceptibility perception (five items), seriousness perception (four items), health motivation perception (12 items), barrier perception (16 items), and benefit perception (seven items). The score of each subscale is calculated separately, and there is no total score. Higher scores on the subscales of susceptibility, seriousness, health motivation, and benefit perceptions represent a positive situation, while a high score on the subscale of barrier perception indicates a negative situation. The Cronbach alpha coefficients of the HBM-PCS subscales were previously reported to be 0.90 for susceptibility

perception, 0.89 for seriousness perception, 0.96 for health motivation perception, 0.94 for barrier perception, and 0.91 for benefit perception (6). In the current study, the Cronbach's alpha coefficient values of the susceptibility, seriousness, health motivation, barrier, and benefit perception subscales were determined to be 0.76, 0.73, 0.84, 0.86, and 0.83, respectively, Accordingly, it can be stated that HBM-PCS was a very reliable instrument for this study.

KPCSQ: This scale was developed by Weinrich et al. in 2004, and the validity and reliability analyses of the Turkish version were undertaken by Çapık and Gözüm (15). KPCSQ consists of a total of 12 questions related to limitations (items 9-12), symptoms (items 2 and 4), risk factors (items 1 and 3), side effects (items 6-8), and screening age (item 5). There are three response options: "yes" (correct), "no" (incorrect), and "don't know". While each correct answer is scored 1, no points are given for the incorrect responses or the items marked "don't know". The correct answer of a total of eight questions (items 1, 2, 4, 5, 6, 7, 11, and 12) is "yes", while three questions (items 3, 8, 9, and 10) should be answered as "no". The score that can be obtained from the KPCSQ varies between 0 and 12, with a higher score indicating a higher level of knowledge (15). The KR-20 coefficient of the Turkish version of the prostate cancer screening knowledge test was determined to be 0.69.

Data Collection

Prior to data collection, the purpose of the study was explained to the participants. Data were collected from October 1, 2022, through December 1, 2022, from individuals who volunteered to participate in the study. The participants were informed that it was important for them to mark the most appropriate statement in each item included in the data collection forms and to fill in the forms completely. Whether all the forms were completed was checked by the researchers during the data collection phase to ensure that there would be no missing data and no sample loss.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 statistical software (Kaysville, Utah, USA) was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, first quartile, third quartile, frequency, percentage, minimum, and maximum) were used for the analyses of the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. The Student t-test was used for the comparison of normally distributed quantitative variables between two groups. One-way analysis of variance and Bonferroni-corrected pairwise assessments were used for the paired comparison of more than normally distributed quantitative variables. Pearson's correlation analysis was used to evaluate the relationships between quantitative variables. The level of statistical significance was accepted as $p < 0.05$ (16).

RESULTS

The study was conducted with a total of 236 participants, of whom 45.8% were healthcare professionals and 54.2% were non-healthcare professionals. The ages of the male individuals participating in the study ranged from 40 to 65 years, with a mean of 46.7 ± 5.9 years. The descriptive characteristics of the participants are presented in Table 1.

The participants' scores on KPCSQ ranged from 0 to 11, with the mean score being calculated to be 5.8 ± 3.1. The KPCSQ scores of the participants are presented in Table 2.

Table 3 presents the distribution of the participants' KPCSQ scores according to their descriptive characteristics. The healthcare professionals had statistically significantly higher KPCSQ scores than the non-healthcare professionals ($p = 0.001$; $p < 0.01$). According to the evaluation of education level, the participants with postgraduate degrees had statistically significantly higher KPCSQ scores than the remaining education level groups ($p = 0.001$ for all comparisons; $p < 0.01$). The KPCSQ scores of the participants who had previously undergone a prostate examination were statistically significantly higher than those without a prostate examination history ($p = 0.003$; $p < 0.01$). The participants with a history of PSA test had statistically significantly higher KPCSQ scores than those who had

not previously undergone this test or did not know if they had ($p = 0.001$ for both; $p < 0.01$). The KPCSQ scores of the participants who had a PCa diagnosis in family/close contacts were found to be statistically significantly higher than the remaining participants ($p = 0.003$; $p < 0.01$). Lastly, the KPCSQ scores significant differed according to whether the participants thought about participating in PCa screening in future and whether they considered the prostate examination to be embarrassing.

The HBM-PCS scores of the participants are given in Table 4. The participants' mean scores on the susceptibility, seriousness, health motivation, barrier, and benefit perception subscales were 12.6 ± 3.8, 11.9 ± 3.6, 32.9 ± 7.6, 38.5 ± 10.3, and 24.8 ± 5.7, respectively.

Table 5 shows the comparison of the participants' HBM-PCS scores by descriptive characteristics. The results revealed no statistically significant differences in the participants' scores in the susceptibility, seriousness, health motivation, and barrier perception subscales according to occupation ($p > 0.05$). However, the non-healthcare professionals had a statistically significantly higher mean score in the benefit perception subscale compared to the healthcare professionals ($p = 0.001$; $p < 0.01$). No statistically significant differences were found in any of the HBM-PCS subscale scores of the participants according to education level, marital status, PSA test history, or PCa diagnosis in family/close contacts ($p > 0.05$). The participants with a prostate examination history had a statistically significantly higher mean score in the barrier perception subscale and a statistically significantly lower mean score in the benefit perception subscale compared to those without this history ($p = 0.003$ for both; $p < 0.01$).

The participants who planned to participate in PCa screenings in the future had statistically significantly higher mean scores on the health motivation and benefit perception subscales of HBM-PCS than those who did not plan to participate in such screenings. In addition, the mean barrier perception subscale score of the participants who did not consider the prostate examination to be embarrassing was statistically significantly higher when compared to those who thought that this examination was embarrassing or were undecided about this statement ($p = 0.001$ and $p = 0.016$, respectively; $p < 0.05$) (Table 5).

No statistically significant relationship was found between the participants' KPCSQ scores and the scores they obtained from any of the HBM-PCS subscales ($p > 0.05$) (Table 6).

Table 1. Descriptive Characteristics of the Participants

		n (%)
Occupation	**Healthcare professional**	108 (45.8)
	Non-healthcare professional	128 (54.2)
Education level	**High school**	92 (39)
	Associate degree	42 (17.8)
	Undergraduate	41 (17.4)
	Postgraduate	61 (25.8)
Marital status	**Married**	175 (74.2)
	Single	61 (25.8)
Prostate examination history	**Present**	33 (14.0)
	Absent	203 (86.0)
PSA test history	**Present**	38 (16.1)
	Absent	175 (74.2)
	Don't know	23 (9.7)
Prostate cancer diagnosis in family/close contacts	**Present**	58 (24.6)
	Absent	178 (75.4)

Thoughts about participating in prostate cancer screening in future	**Positive**	139 (58.9)
	Negative	51 (21.6)
	Undecided	46 (19.5)
Thoughts about whether prostate examination is embarrassing	**Agree**	48 (20.3)
	Disagree	172 (72.9)
	Undecided	16 (6.8)

PSA: prostate-specific antigen

Table 2. Distribution of Participants' KPCSQ Scores

Total score	*Mean*±*SD*	5,80±3,15
	Median (Min-Max)	6 (0-11)
	Low level of knowledge	159 (67,4)
	Moderate level of knowledge	64 (27,1)
	High level of knowledge	13 (5,5)

Table 3. Distribution of Participants' KPCSQ Scores by Descriptive Characteristics

		KPCSQ Score	P
		Mean ± SD	
Occupation	Healthcare professional	7.7 ± 2.7	[a]***0.001*****
	Non-healthcare professional	4.1 ± 2.4	
Education level	High school	4.4 ± 2.4	[b]***0.001*****
	Associate degree	4.2 ± 2.4	
	Undergraduate degree	4.9 ± 2.6	
	Postgraduate degree	9.5 ± 1.2	
Marital status	Married	6.0 ± 3.2	[a]***0.108***
	Single	5.2 ± 2.7	
Prostate examination history	Present	7.3 ± 2.9	[a]***0.003*****
	Absent	5.5 ± 3.1	
PSA test history	Present	7.9 ± 2.5	[b]***0.001*****
	Absent	5.4 ± 3.1	
	Don't know	4.7 ± 3.1	
Prostate cancer diagnosis in family/close contacts	Present	6.8 ± 3.1	[a]***0.003*****
	Absent	5.4 ± 3.1	
Thoughts about participating in prostate cancer screening in future	Positive	6.1 ± 3.3	[b]***0.018****
	Negative	4.7 ± 2.6	
	Undecided	6.0 ± 2.9	
Thoughts about whether prostate examination is embarrassing	Agree	7.0 ± 2.6	[b]***0.008*****
	Disagree	5.4 ± 3.2	
	Undecided	5.6 ± 3.2	

[a]Student t-test [b]One-way analysis of variance & Dunn-Bonferroni test *p < 0.05, **p < 0.01
KPCSQ: Knowledge About Prostate Cancer Screening Questionnaire; ***min:*** minimum; ***max:*** maximum; ***SD:*** standard deviation; ***PSA:*** prostate-specific antigen

Table 4. HBM-PCS Scores and Internal Consistency Values

	Number of items	Mean ± SD	Cronbach's alpha
Susceptibility perception	5	12.6 ± 3.8	**0.76**
Seriousness perception	4	11.9 ±3.6	**0.73**
Health motivation perception	10	32.9 ± 7.6	**0.84**
Barrier perception	15	38.5 ±10.3	**0.86**
Benefit perception	7	24.8 ± 5.7	**0.83**

HBM-PCS: Health Beliefs Model Scale for Prostate Cancer Screenings; ***SD:*** standard deviation

Table 5. Comparison of HBM-PCS Scores by Descriptive Characteristics

		Susceptibility perception	Seriousness perception	Health motivation	Barrier perception	Benefit perception
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Occupation	**Healthcare professional**	12.3 ± 2.9	12.2 ± 2.7	31.9 ± 5.8	38.4 ± 8.4	23.5 ± 4.6
	Non-healthcare professional	12.9 ± 4.3	11.7 ± 4.2	33.8 ± 8.8	38.5 ± 11.6	25.9 ± 6.3
	p	***0.189***	***0.275***	***0.065***	***0.950***	***0.001****
Education level	**High school**	13.0 ± 4.6	11.6 ± 4.3	33.4 ± 9.3	39.8 ± 12.5	25.4 ± 7.1
	Associate degree	12.1 ± 3.5	12.1 ± 3.9	34.2 ± 7.1	37.3 ± 7.4	25.3 ± 4.5
	Undergraduate degree	12.2 ± 3.0	12.2 ± 3.6	31.7 ± 6.7	37.9 ± 9.2	24.1 ± 5.7
	Postgraduate degree	12.6 ± 2.9	12.2 ± 2.3	32.2 ± 5.6	37.6 ± 8.7	24.0 ± 3.9
	p	***0.497***	***0.761***	***0.377***	***0.469***	***0.377***
Marital status	**Married**	12.9 ± 3.5	11.9 ± 3.4	33.3 ± 7.3	38.0 ± 9.8	24.9 ± 5.5
	Single	11.8 ± 4.3	11.9 ± 4.2	32.0 ± 8.6	39.7 ± 11.5	24.4 ± 6.3
	p	***0.077***	***0.969***	***0.257***	***0.277***	***0.592***
Prostate examination history	**Present**	13.3 ± 3.4	10.9 ± 2.4	30.8 ± 5.2	43.4 ± 8.8	21.8 ± 4.0
	Absent	12.5 ± 3.8	12.1 ± 3.8	33.3 ± 7.9	37.6 ± 10.3	25.3 ± 5.8
	p	***0.235***	***0.071***	***0.082***	***0.003****	***0.001****
PSA test history	**Present**	13.6 ± 2.9	11.5 ± 2.8	31.5 ± 6.1	41.4 ± 9.9	23.7 ± 4.4
	Absent	12.3 ± 3.7	12.0 ± 3.7	33.1 ± 7.7	37.6 ± 9.9	25.0 ± 6.0
	Don't know	13.5 ± 4.9	12.2 ± 4.6	34.0 ± 9.3	40.1 ± 12.8	25.1 ± 6.0
	p	***0.072***	***0.745***	***0.406***	***0.089***	***0.424***
Prostate cancer diagnosis in family/ close contacts	**Present**	13.5 ± 3.5	12.2 ± 3.0	32.4 ± 7.5	40.4 ± 9.0	24.6 ± 4.7
	Absent	12.3 ± 3.8	11.8 ± 3.8	33.1 ± 7.7	37.8 ± 10.6	24.8 ± 6.0
	p	***0.059***	***0.462***	***0.559***	***0.094***	***0.786***
Thoughts about participating in prostate cancer screening in future	**Positive**	12.9 ± 3.6	12.1 ± 3.5	34.6 ± 7.6	37.0 ± 10.3	26.0 ± 5.1
	Negative	11.5 ± 4.2	11.4 ± 4.2	29.5 ± 8.1	40.6 ± 11.9	21.7 ± 7.3
	Undecided	12.9 ± 3.5	12.1 ± 3.2	31.8 ± 5.7	40.5 ± 7.1	24.6 ± 4.3
	p	***0.056***	***0.484***	***0.001****	***0.036****	***0.001****
Thoughts about whether prostate examination is embarrassing	**Agree**	13.0 ± 3.4	12.2 ± 3.3	31.2 ± 5.9	42.8 ± 7.1	24.2 ± 5.1
	Disagree	12.4 ± 3.8	11.8 ± 3.8	33.6 ± 8.0	36.7 ± 10.5	25.2 ± 6.0
	Undecided	13.5 ± 4.4	12.3 ± 3.3	30.6 ± 7.7	44.0 ± 10.6	22.6 ± 4.8
	p	***0.440***	***0.725***	***0.069***	***0.001****	***0.180***

[a]Student t-test; [b]One-way analysis of variance & Dunn-Bonferroni test; *p < 0.01

Table 6. The Relationship between Health Beliefs Model Scale for Prostate Cancer Screenings and the Knowledge About Prostate Cancer Screening Questionnaire

	Knowledge About Prostate Cancer Screening Questionnaire	
Health Beliefs Model Scale for Prostate Cancer Screenings	**r**	***p***
Susceptibility perception	-0,079	0,229
Seriousness perception	0,036	0,587
Health motivation perception	-0,020	0,760
Barrier perception	-0,097	0,139
Benefit perception	-0,002	0,970

r:Pearson Correlation Test

DISCUSSION

This study was conducted to examine the relationship between the PCa screening attitudes, beliefs, and knowledge levels of men working in a healthcare institution, considering the high prevalence of this cancer in this gender. According to the results, the majority of the participants had not previously undergone a prostate examination or a PSA test and had a low level of knowledge about PCa screening. Similar studies have shown that the majority of participants do not have a history of prostate examination, do not tend to participate in PCa screening, and have insufficient information about this subject (8,10, 11,12,17). The majority of men not having undergone a prostate examination or screening test can be attributed to their low knowledge and awareness levels in this area. This demonstrates the need for training programs to increase the related level of knowledge.

In the current study, the participants who had a prostate examination history, those who had a PCa diagnosis in family/close contacts, and those who had previously undergone a PSA test were found to have higher knowledge levels than the remaining participants. Similarly, higher levels of knowledge about screening were previously reported among those with a PSA test history (12) and those with a prostate examination history and a PCa diagnosis in the close circle (10). The PSA test aims to detect cancer in a treatable period, which ensures that curative treatment can be performed to reduce deaths due to PCa (18). In addition, one of the known risk factors for the development of PCa is a family history (19). Therefore, it can be considered that individuals who have a family member diagnosed with PCa may be more aware that they are also in the risk group and tend to seek information about PCa and receive counseling and education from physicians and nurses to participate in cancer screening, which can explain their higher levels of knowledge in this area.

We determined that the participants who were positive about participating in PCa screening in the future had a higher level of knowledge about PCa screening than those who objected to this idea or were undecided. Similarly, in a study by Ceyhan et al. (10), men who considered participating in screening in the future were found to have higher knowledge levels. Insufficient knowledge is a factor in the low rates of participation in PCa screening (20). It can be stated that individuals who have knowledge in this area tend to undergo PCa screening, while those without sufficient knowledge are not as willing. With this awareness, nurses should direct individuals to early diagnosis and evaluate people in the risk group. In addition, nurses have a critical role in educating men about PCa cancer screening and contributing to compliance with the latest screening recommendations.

The men participating in this study had moderate levels of susceptibility, seriousness, and barrier perceptions and high levels of health motivation and benefit perceptions related to PCa screening. In a study by Demirbaş and Onmaz (11), it was reported that the susceptibility, seriousness, and barrier perceptions of

men toward PCa screening were at moderate levels, while they had high health motivation and benefit perception levels. This finding suggests that men generally consider PCa screening to be beneficial, and that they have a high level of motivation for PCa screening. In addition, the moderate level of barrier perception related to PCa screening among men is an important factor affecting applications for early diagnosis and participation in screening.

We determined that the non-healthcare professionals had a significantly higher level of benefit perception concerning PCa screening compared to the healthcare professionals. According to previous studies in the literature, a high level of knowledge is associated with a high level of benefit perception (9,21). In contrast, the higher benefit perception level of the group with a low level of knowledge in the current study may be related to non-health professionals paying more attention to practices that would be beneficial in the prevention of the disease.

The participants who had a prostate examination history had a higher barrier perception level and lower benefit perception level concerning PCa screening than those without this history. Similar studies on this subject have shown that individuals who have a prostate examination history have high levels of susceptibility, seriousness, health motivation, and benefit perceptions, while those without this history have a higher level of barrier perception (9,22). The discrepancy concerning the higher barrier perception levels of the participants with a prostate examination history in our study may be due to their insufficient knowledge or misconceptions and misguided beliefs concerning screening tests.

We found that the participants who considered participating in prostate cancer screening in the future had higher levels of health motivation and benefit perceptions related to PCa screening than those who did not have positive attitudes toward future PCa screening. On the other hand, the undecided participants had a higher level of barrier perception than those who planned to participate in future PCa screening. In a study by Demirbaş and Onmaz (11), the susceptibility, health motivation, and benefit perception levels were found to be high in individuals who were positive about participating in PCa screening in the future. The low level of barrier perception and high level of benefit perception of individuals who are willing to participate in future screening can help provide an understanding of personal beliefs, attitudes, and perceptions in this area and guide the development of training programs for healthcare professionals. Especially for nurses who provide holistic care, understanding personal values from the perspective of not only disease management but also patient advocacy will be valuable in promoting participation in PCa screening.

In this study, no relationship was found between the participants' knowledge levels and their susceptibility, seriousness, health motivation, barrier, and benefit perceptions related to PCa screening. In contrast, in the literature, a significant relationship has been demonstrated between knowledge levels and positive attitudes toward participation in cancer screening (23,24). Unlike the literature, the absence of such a relationship in the current study can be attributed to all the participants working in a healthcare institution.

There are some limitations concerning the interpretation of the data obtained from this study. In particular, the study was conducted with men working in an education and research hospital, which limits the generalizability of the findings.

CONCLUSION

It was determined that 67.4% of the men participating in this study had a low level of knowledge about PCa screening. The participants with a prostate examination history, those with a PSA test history, and those who had family members/close contacts diagnosed with PCa had higher levels of knowledge in this area. The barrier perception level was significantly higher among the individuals with a prostate examination history, and the health motivation and benefit perception levels were significantly higher among those who considered participating in future PCa screening. PCa screening in individuals aged 40 years and over is crucial for early diagnosis and treatment. Among healthcare professionals, nurses help individuals make informed decisions by identifying factors affecting their health

behaviors and screening intentions, and increasing their level of knowledge. In addition, the integration of PCa screening into in-service training programs organized for healthcare workers will have a positive effect on knowledge, attitudes, and behaviors related to PCa. This will not only improve the health-protective behaviors of healthcare professionals themselves but will also be effective in raising the awareness of society in general within the scope of the roles of an educator and consultant for healthy/ill individuals served.

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial Disclosure

The authors declare that this study received no financial support. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Informed Consent

Participation in the study was on a voluntary basis, and verbal and written informed consent was provided by all participants.

Ethical Approval

Approval for the study was granted by the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2022-18, date: 2022-09-19). Permission was also received from the institution where the study was conducted. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki.

REFERENCES

1. Türkiye Kanser İstatistikleri, 2017. Ankara, 2021. available from: https://hsgm.saglik.gov.tr/depo/birimler/kanserdb/istatistik/Turkiye_Kanser_Istatistikleri_2017_OZETLI.pdf
2. Catalona WJ. Prostate cancer screening. Medical Clinics. 2018;102:199-214. https://doi.org/10.1016/j.mcna.2017.11.001
3. Mottet N, Bellmunt J, Bolla M, Briers E, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-629. https://doi.org/10.1016/j.eururo.2016.08.003
4. Arafa MA, Rabah DM, Wahdan IH. Awareness of general public towards cancer prostate and screening practice in Arabic communities: A comparative multicenter study. Asian Pac J Cancer Prev 2012;13(9):4321-6. https://doi.org/10.7314/APJCP.2012.13.9.4321
5. Sahu DP, Subba SH, Giri PP. Cancer awareness and attitude towards cancer screening in India: A narrative review. J Family Med Prim Care 2020;9:22148. https://doi.org/10.4103/jfmpc.jfmpc_145_20
6. Çapık C, Gözüm S. Development and validation of health beliefs model scale for prostate cancer screenings (HBM-PCS): Evidence from exploratory and confirmatory. European Journal of Oncology. 2011;15:478-485. https://doi.org/10.1016/j.ejon.2010.12.003
7. Baysal HY, Gözüm S. Effects of health beliefs about mammography and breast cancer and telephone reminders on re-screening in Turkey. Asian Pacific Journal of Cancer Prevention. 2011;12:1445-1450.
8. Awosan KJ, Yunusa EU, Agwu NP, Taofiq S. Knowledge of prostate cancer and screening practices among men in Sokoto, Nigeria. Asian Journal of Medical Sciences. 2018;6(6):51-56. http://dx.doi.org/10.3126/ajms.v9i6.20751
9. Bilgili N, Kitiş Y. Prostate cancer screening and health beliefs: A Turkish study of male adults. Erciyes Med J. 2019;41(2):164-169. https://doi.org/10.14744/etd.2019.45762
10. Ceyhan Ö, Göriş S, Demirtaş A, Kılıç, Z. Knowledge levels of male patients about prostate cancer screening. Kırıkkale Uni Med J 2018;20(2):184-191. https://doi.org/10.24938/kutfd.383092
11. Demirbaş N, Onmaz M. An evaluation of men's beliefs and perceptions and affecting factors on prostate cancer screenings with the health belief model. The Turkish Journal of Family Practice. 2021;25(4):137-144. https://doi.org/10.54308/tahd.2021.52714

12. Köse Tosunöz İ, Deniz Doğan S. Male's attitudes and levels of knowledge about prostate cancer screening. Izmir Democracy University Health Sciences Journal. 2022;5(3):651-663.
13. Arli SK, Bakan AB. Effects of the training about prostate cancer and screening methods on knowledge level. Nursing Science Quarterly. 2019;32(4):333-339. https://doi.org/10.1177/0894318419864345
14. Jeong JH, Park NH. A structural equation modeling of prostate cancer screening intention. J Korean Acad Community Health Nurs. 2019;30(4):471-483. https://doi.org/10.12799/jkachn.2019.30.4.471
15. Çapık C, Gözüm S. Turkish adaptation of the knowledge about prostate cancer screening questionnaire. Turkish Journal of Geriatrics. 2011;14(3):253-258.
16. Karagöz Y. SPSS 21.1 Uygulama, Biyoistatistik. 1. Basım. Ankara: Nobel Akademik Yayıncılık, 2014.
17. Tayhan A, Özmen D. Relationship between knowledge levels of men about prostate cancer screenings and their health literacy. Cukuova Med J. 2019;44(4):233-240. https://doi.org/10.17826/cumj.560673
18. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. The BMJ. 2018;362:1-12. https://doi.org/10.1136/bmj.k3519
19. Gandaglia G, Leni R, Bray F, et al. Epidemiology and prevention of prostate cancer. European Urology Oncology. 2021;4(6):877-892. https://doi.org/10.1016/j.euo.2021.09.006.
20. Odedina FT, Campbell ES, LaRose-Pierre M, Scrivens J, Hill A. Personal factors affecting African-American men's prostate cancer screening behavior. Journal of the National Medical Association. 2008;100(6):724-733. https://doi.org/10.1016/S0027-9684(15)31350-X
21. Ghodsbin F, Zare M, Jahanbin I, Ariafar A, Keshavarzi S. A survey of the knowledge and beliefs of retired men about prostate cancer screening based on health belief model. Int J Community Based Nurs Midwifery 2014;2:27985.
22. Alshammari S, Alojayri R, AlJehani M, et al. The association between the knowledge on prostate cancer screening with the beliefs and behaviors of Saudi men attending King Khalid University Hospital. J Family Med Prim Care. 2021;10(12):4423-4430. https://doi.org/10.4103/jfmpc.jfmpc_828_21
23. Çapık C, Gözüm S. The effect of web-assisted education and reminders on healthbelief, level of knowledge and early diagnosis behaviors regarding prostate cancer screening. Eur J Oncol Nurs 2012;16(1):71-7. https://doi.org/10.1016/j.ejon.2011.03.007
24. Weinrich SP, Seger R, Miller BL, et al. Knowledge of the limitations associated with prostate cancerscreening among low-income men. Cancer Nurs 2004;27(6):442-53. https://doi.org/10.1097/00002820-200411000-00003

Yeni Üroloji Dergisi - *The New Journal of Urology* **2023;18(2):183-185. doi: 10.33719/yud.2023;18-2-1210144**

Case Report / Olgu Sunumu

Gross hematuria associated with oral isotretinoin treatment in a young patient with acne vulgaris

Akne vulgarisli genç bir hastada oral izotretinoin tedavisiyle ilişkili gros hematüri

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Geliş tarihi (Submitted): *2022-11-25*
Kabul tarihi (Accepted): *2023-04-13*

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Özet

Amaç: İdrarda kırmızı kan hücrelerinin varlığı olarak tanımlanan hematüri, glomerulus, intersitisiyum veya böbrek damarlarından kaynaklanabilir, mikroskobik veya makroskopik olarak görülebilir. Bu olguda, akne vulgaris nedeniyle oral izotretinoin tedavisinden iki ay sonra gros hematüri gelişen 17 yaşında bir erkek hastayı sunuyoruz. Üriner sistemin radyolojik ve sistoskopik değerlendirmesi normaldi. Dermatoloji konsültasyonu sonrası izotretinoin tedavisi kesildi. İlacın kesilmesinden sonra iki hafta içerisinde gros hematüri ile birlikte dizüri ortadan kayboldu ve tam idrar analizi sonuçları normaldi.

Anahtar Kelimeler: akne vulgaris, yan etki, brüt hematüri, isotretinoin

Abstract

Hematuria is defined as the presence of red blood cells in urine, which may be observed microscopically or grossly. Hematuria may originate from any site throughout the urinary tract, glomerulus, interstitium, or the renal vasculature. Here, we present the case of a 17-year-old boy who developed terminal hematuria after two months of treatment with isotretinoin for acne vulgaris. Radiological and cystoscopic assessment of the urinary system were normal. Isotretinoin treatment was discontinued after dermatology consultation. After two weeks, terminal hematuria disappeared along with dysuria, and the urine sample showed normal findings.

Keywords: Acne vulgaris, adverse effect, gross hematuria, isotretinoin

All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Hematuria is defined as the presence of red blood cells in urine, which may be observed microscopically or grossly. Hematuria may originate from any site throughout the urinary tract, glomerulus, interstitium, or renal vasculature (1). There are few case reports of acute kidney injury and nephrotic syndrome (2) or terminal hematuria following isotretinoin treatment in healthy individuals (3).

CASE REPORT

Here, we present a 17 year-old boy who developed terminal hematuria after two months of treatment with isotretinoin for acne vulgaris. A boy with acne vulgaris was admitted to our dermatology outpatient clinic. The patient was started on isotretinoin treatment at a dose of 20 mg/day (0.25 mg /kg /day) of isotretinoin treatment. After two months, he visited our urology clinic complaining of dysuria and gross hematuria. He reported visible blood in the distal urethra at the end of urination, and the color of the blood was bright red. The patient claimed not to consume any food (e.g., rhubarb, paprika, blueberries) or drugs (e.g., rifampin, nitrofurantoin, phenazopyridine, metronidazole) that may cause red pigmenturia. On physical examination, body length was 1.80 m, weight 70.0 kg, heart rate 90/min, respiratory rate 15/min, blood pressure 110/70 mmHg, respectively. Other physical examination results were unremarkable. Renal function parameters were measured as follows: blood urea nitrogen level, 33 mg/dL; serum creatinine 0.73 mg/dL. Complete blood count (CBC), full chemistry panel, anti-glomerular basement membrane (anti-GBM), anti-double-stranded DNA (anti-dsDNA), anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), and complement (C3c and C4) were all normal.

In the urine sample, the urine specific gravity was 1020, protein was not present, and 5 red blood cells were seen on microscpy. The urine culture was sterile. Ultrasonography and computed tomography findings of the urinary system were normal. In the cystoscopic assessment of the patient, the urethra, prostate, bladder, and bilateral ureteric orifices were normal. Clear urine was noted to flow periodically through both ureteral openings. The urine cytology results were normal. Isotretinoin treatment was stopped after dermatology consultation. After two weeks, terminal hematuria disappeared along with dysuria, and the urine sample showed normal findings.

DISCUSSION

Urine blood may originate from any location along the urinary tract. As a result, gross or microscopic hematuria may be caused by a diversity of underlying conditions. When a patient is admitted for gross hematuria, the clinician should ask for specific details that offer hints to the reason for the hematuria. The description of the urine should be specific, and urine color can provide an idea of the severity and source of bleeding. Patients with vascular bleeding or lower urinary tract bleeding often define urine as bright red or cherry colored (1).

Isotretinoin (13-cis RA) is one of the most prominent and commonly used drugs for the treatment of acne vulgaris. Isotretinoin has a wide range of therapeutic effects (2). However, adverse reactions have also been reported with this agent. Common side effects include teratogenicity, mucocutaneous side effects such as cheilitis, dry skin and mucous membranes, epistaxis, desquamation, photosensitivity, pruritus, hypertriglyceridemia, and an increased frequency of depression or suicide (4).

Yesikaya et. al. examined the frequency of hematuria in acne vulgaris patients during isotretinoin treatment (5). Eighty-eight subjects were included in the study group and 52 subjects were included in the control group. In the treatment group, 17% of the patients had hematuria at least once during the study period, and in the control group, the hematuria ratio was 7.7%. No significant differences between the two groups was found. Hematuria was most frequently observed at the end of the second month of treatment. The authors attributed this finding to hematuria, especially at the beginning of the treatment (5).

Our literature search reported the effects of oral isotretinoin on terminal gross hematuria and dysuria

in only one case (3). The authors concluded that gross hematuria is probably due to the xerotic mucosal side effects of isotretinoin; similarly, drugs are known to affect the nasal mucosa, causing nasal bleeding (3).

This is the second case report documenting the impact of isotretinoin on terminal gross hematuria and dysuria. Although patients are already informed about the well-known side effects of isotretinoin, such as cheilitis, dry skin, epistaxis, desquamation, photosensitivity, pruritus, hypertriglyceridemia, and an increased frequency of depression, hematuria can be ignored. We should keep in mind that while prescribing isotretinoin, hematuria may be present, and patients should be informed about it.

Conflict of Interest

The authors declare to have no conflicts of interest.

Statement of all funding sources of support for this work: None

Author Contribution: AE and HIC was responsible for the literature search and preparation of the manuscript. YTA and DG analysed the data, revised the draft manuscript. HIC, final confirmation. AE and MP examined the patient. The cystoscopic assessment was performed by AE. All authors read and approved the final manuscript.

REFERENCES

1. C. G. Pan. "Evaluation of Gross Hematuria," Pediatr. Clin. North Am., vol. 53, no. 3, pp. 401-412, Jun. 2006. https://doi.org/10.1016/j.pcl.2006.03.002
2. B. Forouzani-Haghighi and I. Karimzadeh. "Isotretinoin and the Kidney: Opportunities and Threats.," Clin. Cosmet. Investig. Dermatol., vol. 13, pp. 485-494, 2020. https://doi.org/10.2147/CCID.S259048
3. E. Sarifakioglu, A. E. Yilmaz, S. Erpolat. "Terminal hematuria associated with oral isotretinoin treatment in a patient with acne vulgaris.," Pediatr. Dermatol., vol. 29, no. 5, pp. 668-669, 2012. https://doi.org/10.1111/j.1525-1470.2011.01552.x
4. J. Tan, S. Boyal, K. Desai, S. Knezevic. "Oral Isotretinoin: New Developments Relevant to Clinical Practice.," Dermatol. Clin., vol. 34, no. 2, pp. 175-184, Apr. 2016. https://doi.org/10.1016/j.det.2015.11.002
5. B. Yesilkaya, N. Alli, R. F. Artuz, E. Ulu, D. Kartal, S. L. Cinar. "The frequency of hematuria in acne vulgaris patients during isotretinoin treatment.," Cutan. Ocul. Toxicol., vol. 36, no. 1, pp. 74-76, Mar. 2017. https://doi.org/10.3109/15569527.2016.1155595

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