Efficacy of tamsulosin versus silodosin as medical expulsive therapy on stone expulsion in patients with distal ureteral stone: A retrospective single center study

Distal üreter taşı olan hastalarda taş düşürmede medikal ekspulsif tedavi olarak tamsulosinin silodosine karşı etkinliği: Geriye dönük tek merkezli bir çalışma

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Özet

Amaç: Bu çalışma ile, semptomatik komplike olmayan distal üreter taşı olan hastalarda medikal ekspulsif tedavi olarak tamsulosin ve silodosinin etkinliği karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Haziran 2019 ile Ocak 2022 tarihleri arasında 4-10 mm boyutlarında distal üreter taşı olan ve medikal ekspulsif tedavi uygulanan erişkin hastaların verileri geriye dönük olarak belgelendi. Hastalar iki gruba ayrıldı. Grup 1'deki hastaları 4 mg silodosin tedavisi verilen ve Grup 2'deki hastaları 0,4 mg tamsulosin verilen hastalar oluşturdu. Tedaviye maksimum 3 hafta devam edildi. Taş düşürme oranı, taş düşürme süresi, taş yükü ve taş boyutu kaydedildi. Yardımcı tıbbi tedavi olarak tamsulosin ve silodosinin etkinliği belirlendi.

Bulgular: Çalışmaya toplam 152 hasta dahil edildi. Demografik veriler iki grup arasında benzerdi. 116 (%76,3) hasta takip sonunda taşsızdı. Grup 1' de 47 hastada (%73,4), Grup 2' de 69 hastada (%78,4) taşın düştüğü hesaplandı (P = 0,477). Çok değişkenli analizde taşın üreterovezikal bileşkeye olan mesafesi, başarılı taş düşürme ile anlamlı şekilde ilişkiliydi (P=0,032).

Sonuç: Distal üreter taşları için medikal ekspulsif tedavi olarak tamsulosin ve silodosin arasında anlamlı bir üstünlük yoktu. Taşın üreterovezikal bileşkeye olan mesafesi, çok değişkenli analizde taş düşürülmesinin tek bağımsız belirleyicisiydi.

Anahtar Kelimeler: Medikal ekspulsif tedavi, üreter taşı, silodosin, tamsulosin

Abstract

Objective: This study aimed to compare the efficacy of tamsulosin and silodosin as medical expulsive therapy in patients with symptomatic uncomplicated distal ureteric stones.

Material and Methods: The data of adult patients who had distal ureteric stones in size between 4 and 10 mm and were treated with medical expulsive therapy between June 2019 and January 2022 were retrospectively documented. Patients were divided into two groups. Patients in Group 1 received silodosin 4 mg, and Group 2 received tamsulosin 0.4 mg. Therapy was given for a maximum of 3 weeks. Stone expulsion rate, time to stone expulsion, stone burden, and stone size were recorded. The efficacy of tamsulosin and silodosin as adjunctive medical therapy was determined.

Results: A total of 152 patients were included in the study. Demographic profiles were comparable between the 2 groups. 116 (76.3%) patients were stone-free at the end of the follow-up. The stone expulsion rate was calculated in 47 patients (73.4%) in Group 1, and 69 patients (78.4%) in Group 2 (P = 0.477). The distance of the stone to the ureterovesical junction was significantly associated with successful stone expulsion in multivariate analysis (P=0.032).

Conclusion: There was no significant superiority between tamsulosin and silodosin as medical expulsive therapy for distal ureteral stones. The distance of the stone to the ureterovesical junction was the only independent predictor of stone expulsion in multivariate analysis.

Keywords: Medical expulsive therapy, ureteral stone, silodosin, tamsulosin

The study was approved by Antalya Training and Research Hospital Ethics Committee (Approval number: 2022-017). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Urolithiasis is one of the most prevalent urological conditions worldwide with increasing incidence (1). Twenty-two percent of all urinary tract stones are located at the ureter and 68% of ureteral stones are found in the distal part (2). Treatment modalities for patients with ureteral stones comprise extracorporeal shock wave lithotripsy (ESWL), endoscopic lithotripsy, and surgical stone removal (open, laparoscopic, and robotic approaches). Conservative management rather than an intervention may reduce the complications of the therapy. Medical expulsive therapy (MET) has proven to be a non-invasive treatment choice and has comparatively inexpensive features for distal ureteral stones in recent years (3). MET is a broad term and consists of plenty of fluid intake and medications such as alpha blockers, calcium channel blockers, corticosteroids, or phosphodiesterase type 5 inhibitors (PDE5i). The objective of MET is to increase the spontaneous stone passage possibility and improve the quality of life by reducing pain. Alpha-1-adrenergic receptors (AR) are highly concentrated in the smooth muscle of the ureter. Blockade alpha-1-AR in the distal part of the ureter decreases basal smooth muscle tonus and produces propulsive antegrade peristalsis that facilitates spontaneous passage and reduces associated renal colic (4). The European Association of Urology (EAU) and the American Urologic Association (AUA) recommend that patients with distal ureteral stones should be offered MET (5,6). However, the results of MET in the treatment of ureteral stones were conflicting with the high-quality trials and meta-analyses (7-9). Additionally, there is a paucity of studies comparing the efficacy of alpha-blockers. MET prescription has been under controversy for distal ureteric stones. Thus, this study aimed to evaluate tamsulosin and silodosin as MET in patients with symptomatic uncomplicated distal ureteral stones.

MATERIAL AND METHODS

Adult patients who presented with renal colic and were diagnosed as uncomplicated distal ureteral stones in size between 4 and 10 mm, and subsequently treated with MET from June 2019 to January 2022 were retrospectively assessed. Ethics Committee approval was obtained at Antalya Training and Research Hospital (Approval number: 2022-017). Exclusion criteria were as follows patients with urinary tract infection, fever, pregnancy, multiple or bilateral ureteral stones, impaired renal function, solitary kidney, history of intake of an alpha-adrenergic blocker due to benign prostatic hyperplasia, and requiring emergency intervention. Patients lost to follow-up and who wished immediate surgical removal of stone were also excluded from the study.

After physical examination, urinalysis, complete blood count, serum creatinine, urinary ultrasonography (USG), and X-ray kidney, ureter, and bladder (KUB) were generally used as the primary diagnostic tools. Non-contrast computed tomography (CT) was performed for all patients to confirm the diagnosis. We prescribed tamsulosin 0.4 mg or silodosin 4 mg once daily for 3 weeks as MET. Additionally, 50 mg/day of diclofenac sodium was prescribed to all patients for pain relief. Patients were instructed to strain their urine to detect stone expulsion and take plenty of fluids. Patients were warned to note the period of stone expulsion. The patients were followed up weekly for 3 weeks and reassessed by physical examination, serum creatinine levels, urinalysis, and USG or X-ray KUB. Medications were continued until the stone passed or up to 3 weeks. The expulsion of the stone was determined based on physically seeing the stone in the urine. Suspicious expulsions or unsuccessful stone passes were verified with a control CT at the end of the 3rd week. Persistent stone at 3 weeks was accepted as an unsuccess of MET. For those patients, endoscopic lithotripsy was performed.

The patients' characteristics (age, gender, and body mass index [BMI]) and the stone features (stone size, stone burden, and the distance of stone to the ureterovesical junction[UVJ]) were noted. The stone size was identified as the maximum diameter of the stone. The stone burden was calculated by multiplying the largest length of the stone by the shortest perpendic-

ular length and was recorded in square millimeters. A clinician (HA), blinded to medications and the clinical outcomes, evaluated all CTs separately.

Two main groups were created according to the medication. Group 1 included patients who were given silodosin 4 mg. Group 2 was prescribed tamsulosin 0,4 mg. Firstly, the stone factors, the stone expulsion rate, and the stone expulsion interval were evaluated for comparison between the two groups. Furthermore, the factors affecting the expulsion rate were evaluated by univariate and multivariate analyses.

Statistical Analysis

The data of the study are presented as mean ± standard deviation, or median and interquartile range (25th - 75th, IQR) according to the type of data. The assumption of normality distribution was evaluated with the Shapiro-wilk test. Student's t-test was used for normally distributed continuous variables. Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables are presented as frequency (n) and percentage (%). Chi-squared or Fisher exact test was used for categorical data. Univariable and multivariable binary logistic regression analyses were used to identify the predictive factors of spontaneous passage. A P value of < 0.05 was accepted as statistical significance. All statistical analyses were done using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY).

RESULTS

A total of 152 adult patients who completed the treatment and follow-up period, were included in the study. Group 1 (64 patients) consisted of 51 men and 13 women, and Group 2 (88 patients) consisted of 78 men and 10 women. Table 1 demonstrates the comparison of parameters between Group 1 and Group 2. There were no significant differences between the groups in terms of age, BMI, male to female ratio, stone size, stone burden, and distance to UVJ. (all, p>0.05). Overall 116 (76.3%) patients successfully passed the stone. The stone expulsion interval and spontaneous expulsion rate were also similar between groups. The distance of the stone to the UVJ was significantly associated with a successful stone pass in univariate and multivariate analyses (Table 2).

Table 1. Comparison of baseline characteristics according to groups

Variables	Group 1 (n:64)	Group 2 (n:88)	P value
Median (IQR) age, years	43.5 (36.2-52)	43 (31.7-59)	0.94†
Mean ±SD, BMI, kg/m^2	25.3±2.6	25.1±2.9	0.676ᵀ
Gender (male/female)	51/13	78/10	0.128¥
Median (IQR), maximum diameter of stone, mm	5 (4-7)	5 (4-6.5)	0.399†
Median (IQR), stone burden, mm^2	15 (10-30)	15 (11-26.5)	0.195†
Median (IQR), distance to UVJ, mm	10 (6-14)	8 (5-12)	0.611†
Median (IQR), expulsion time, day	9 (6-13)	9 (6-13)	0.638†
Expulsion rate, n, (%)	47 (73.4)	69 (78.4)	0.477¥

***Group 1**: silodosin, **Group 2:** tamsulosin. **BMI:** Body Mass Index, **SD:** standard deviation, ᵀ: Student's t test*

***IQR:** interquartile range, †: Mann Whitney-u test, **¥:** Chi-Sqaure test*

Table 2. Multivariate analysis of factors affecting the spontaneous passage

					95% C.I. for EXP (B)	
	B	**S.E.**	**P value**	**Exp (B)**	**Lower**	**Upper**
Treatment						
Silodosin	Reference					
Tamsulosin	-.010	.445	.982	.990	.414	2.366
Age, year	.006	.020	.777	1.006	.967	1.046
Gender						
Male	Reference					
Female	.066	.593	.912	1.068	.334	3.410
Stone size, mm	.235	.388	.544	1.265	.591	2.706
Stone burden, mm^2	-.073	.039	.059	.929	.861	1.003
Distance of stone to the UVJ, mm	-.105	.049	**.032**	.900	.817	.991
BMI, kg/m^2	-.127	.098	.196	.881	.727	1.067

DISCUSSION

ESWL, surgical stone removal, and endoscopic lithotripsy are the treatment options for distal ureteral stones. But, these approaches are associated with complications and high costs. Most ureteral stones can pass spontaneously and intervention is usually not required. The spontaneous stone passage rate was reported as 76% for stones 2-4 mm and %75 for distal ureteral stones (10). Therefore, conservative management is a more suitable and cost-effective strategy than active stone removal (11). MET has recently emerged as a conservative treatment for patients with uncomplicated distal ureteral stones. The main aims of MET are to increase the rate of stone expulsion, reduce renal colic pain, and avoid the need for invasive interventions. The EAU and AUA stone disease guidelines recommend the utilization of MET for distal ureteral stones (5,6).

Many medical agents have been used as MET which includes alpha-blockers, calcium channel blockers, corticosteroids, antispasmodics, and PDE5i. Additionally, combination therapies and herbal medicines have been also investigated to improve stone passage (8,12). Alpha-blockers are the most investigated and widely used treatment option. Park et al. demonstrated that alpha-1-ARs were present in all ureters and the distal ureter had a higher density of alpha-1-ARs than the proximal and mid ureter (13). In the distal ureter, the distribution of alpha-1-ARs was α1D > α1A > α1B (14). Blockade of alpha-1-ARs reduces the tone of ureteral smooth muscle, the frequency of peristalsis, intraluminal pressure, and amplitude of the ureter. These effects have been used for promoting stone expulsion (3,7,9).

High-quality randomized controlled prospective studies have reported conflicting results. Several studies reported no significant benefit to alpha-blockers (7,15,16). The others demonstrated that alpha-blockers had a significantly higher stone expulsion rate when compared to placebo (17,18). Despite contradictory results, a recent meta-analysis showed that there was a significantly better expulsion rate and lower mean expulsion time in tamsulosin, alfuzosin, and silodosin groups compared to placebo (19). The success rate for tamsulosin in distal ureteral stones smaller than 10 mm ranges between 50% and 87% (7,9,16,17). The rate of the stone pass in patients who were given silodosin was between 78.6% and 91.4% (18,20,21). In our cohort of patients with unilateral uncomplicated distal ureteral stones managed by silodosin and tamsulosin, we had a successful spontaneous expulsion rate of 73.4% and 78.4%, respectively, the difference being statistically insignificant. Success rates for silodosin and tamsulosin were comparable with the earlier studies.

Hsu et al. conducted a meta-analysis to evaluate the effectiveness of silodosin and tamsulosin as MET for ureteral stones and concluded that silodosin had a significantly better stone passage rate for patients with ureteral stones compared to tamsulosin (22). Furthermore, the findings of another meta-analysis demonstrated that silodosin was the most efficacious alpha-blocker as MET for distal ureteric stones (19). The results of two meta-analyses suggest that silodosin is more effective than tamsulosin for the spontaneous stone pass (19,22). However, in our study, we did not identify a better expulsion rate as MET with silodosin than with tamsulosin. The reason for a similar expulsion rate between silodosin and tamsulosin in our study may be due to the use low dose of silodosin. On the other hand, two recent meta-analyses found that the combination of different drugs was shown to be superior to the use of individual agents such as MET (8,23). The possible explanation for a higher success rate in combination therapy may be due to the different and more mechanisms of action. More studies are needed to confirm the advantage of combination therapy.

Previous studies also evaluated the secondary outcomes of MET. The patients treated with tamsulosin had a shorter expulsion time compared to the placebo (17). The results of Hsu et al. demonstrated that the expulsion time in the silodosin group was significantly shorter than in the tamsulosin group (22). However, Arda et al. reported that the stone expulsion interval was similar between the tamsulosin and silodosin groups, in line with our results (20). For pain management, the patients in the tamsulosin group experienced fewer pain episodes and consumed fewer analgesics compared with the placebo (17). We could not conduct a quantitative analysis of the pain episodes and the amount of analgesic require due to the retrospective nature of the study. Furthermore, previous studies also found METs were well tolerated by most patients, and no severe adverse effects required discontinuation of the study medication (17, 19,20,22). Thus, it seems safe and well-tolerated to receive MET for reducing the need for surgical intervention.

Accurately selecting those patients with an uncomplicated ureteral stone who might benefit from MET is crucial. Factors affecting the spontaneous expulsion of stones, such as stone location, stone size, stone structure, and stone volume have been investigated. Stone size and location have been proven as predictive factors in patients with ureteral stones (24). We evaluated the factors influencing the passage of ureteral stone, the distance of the stone to the UVJ was the only independent predictor of stone expulsion in multivariate analysis. Pain control and diuresis by drinking water are important for facilitating the passage of ureteral stones. Smoking habits, BMI, and the frequency of sexual intercourse could also affect the successful stone passage.

The present study had some limitations. First of all, it was a retrospective study with relatively few patients. Secondly, the frequency of pain attacks, side effects of medications, and additional analgesic usage could not be evaluated. Lastly, there was no control group to show the efficacy of silodosin and tamsulosin. Larger sample-sized prospective studies can help to negate these issues.

CONCLUSION

There was no significant superiority between tamsulosin and silodosin as medical expulsive therapy for distal ureteral stones. The distance of the stone to the ureterovesical junction was the only independent predictor of stone expulsion in multivariate analysis.

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 Antalya Training and Research Hospital Ethics Committee (Approval number: 2022-017). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design: Karamık K, Kısaarslan M, Ateş N, Data acquisition: Karamık K, Kısaarslan M, Ateş N, Data analysis and interpretation: Karamık K, Kısaarslan M, Anıl H, Drafting the manuscript: Karamık K, Anıl H, Critical revision of the manuscript for scientific and factual content: Karamık K, Anıl H, Statistical analysis: Anıl H, Supervision: Kısaarslan M, Ateş N.

REFERENCES

1. Trinchieri A, Coppi F, Montanari E, Del Nero A, Zanetti G, Pisani E. Increase in the prevalence of symptomatic upper urinary tract stones during the last ten years. Eur Urol. 2000;37:23–5. doi: 10.1159/000020094
2. Pak CY. Kidney stones. Lancet. 1998; 351: 1797-1801. doi: 10.1016/S0140-6736(98)01295-1
3. Somani BK, Aboumarzouk O, Traxer O, Baard J, Kamphuis G, de la Rosette J. Medical expulsive therapy for ureteral stones: where do we go from here? Nat Rev Urol. 2016;13(10):608–612. doi: 10.1038/nrurol.2016.146
4. Troxel SA, Jones AW, Magliola L, Benson JS. Physiologic effect of nifedipine and tamsulosin on contractility of distal ureter. J Endourol. 2006;20(8):565-568. doi: 10.1089/end.2006.20.565
5. Türk C, Petrík A, Sarica K, et al. EAU guidelines on diagnosis and conservative management of urolithiasis. Eur Urol. 2016;69:468–474. doi: 10.1016/j.eururo.2015.07.040
6. Assimos D, Krambeck A, Miller NL et al: Surgical management of Stones: American Urological Association/ Endourological Society Guideline, PART I. J Urol. 2016; 196: 1153. doi: 10.1016/j.juro.2016.05.090
7. Meltzer AC, Burrows PK, Wolfson AB, et al. Effect of Tamsulosin on Passage of Symptomatic Ureteral Stones: A Randomized Clinical Trial. JAMA Intern Med 2018;178:1051-1057. doi: 10.1001/jamainternmed.2018.2259
8. Liu H, Wang S, Zhu W, Lu J, Wang X, Yang W. Comparative efficacy of 22 drug interventions as medical expulsive therapy for ureteral stones: a systematic review and network meta-analysis. Urolithiasis. 2020;48(5):447-457. doi: 10.1007/s00240-019-01159-5
9. Shah TT, Gao C, Peters M, et al. Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: results from the Multi-centre cohort study evaluating the role of Inflammatory Markers In patients presenting with acute ureteric Colic (MIMIC) study. BJU Int. 2019;124(3):504-513. doi: 10.1111/bju.14777
10. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. AJR Am J Roentgenol. 2002;178:101–103. doi: 10.2214/ajr.178.1.1780101
11. Bensalah K, Pearle M, Lotan Y. Cost-effectiveness of medical expulsive therapy using alpha-blockers for the treatment of distal ureteral stones. Eur Urol. 2008; 53(2):411-418. doi: 10.1016/j.eururo.2007.09.012
12. Kızılay F, Ülker V, Çelik O, et al. The evaluation of the effectiveness of Gilaburu (Viburnum opulus L.) extract in the medical expulsive treatment of distal ureteral stones. Turk J Urol. 2019; 45(Supp. 1): S63-S69. doi: 10.5152/tud.2019.23463
13. Park HK, Choi EY, Jeong BC, Kim HH, Kim BK. Localizations and expressions of alpha-1A, alpha-1B and alpha-1D adrenoceptors in human ureter. Urol Res. 2007;35:325–329. doi: 10.1007/s00240-007-0118-0
14. Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. Int J Urol. 2007;14(8):749-753. doi: 10.1111/j.1442-2042.2007.01812.x
15. Pickard R, Starr K, MacLennan G, et al. Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre, placebo-controlled, randomised controlled trial and cost-effectiveness analysis of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin) (the SUSPEND trial). Health Technol Assess. 2015;19:1–171. doi: 10.3310/hta19630
16. Furyk JS, Chu K, Banks C, et al. Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. Ann Emerg Med. 2016;67:86-95.e2. doi: 10.1016/j.annemergmed.2015.06.001

17. 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;73:385-391. doi: 10.1016/j.eururo.2017.10.033
18. Yuksel M, Yilmaz S, Tokgoz H, Yalcinkaya S, Baş S, Ipekci T, Yildiz A, Ates N, Savas M. Efficacy of silodosin in the treatment of distal ureteral stones 4 to 10 mm in diameter. Int J Clin Exp Med. 2015 Oct 15;8(10):19086-92 doi: 26770537
19. Sharma G, Pareek T, Kaundal P, et al. Comparison of efficacy of three commonly used alpha-blockers as medical expulsive therapy for distal ureter stones: A systematic review and network meta-analysis. Int Braz J Urol. 2022;48(5):742-759. doi: 10.1590/S1677-5538.IBJU.2020.0548.
20. Arda E, Cakiroglu B, Yuksel I, et al. Medical Expulsive Therapy for Distal Ureteral Stones: Tamsulosin Versus Silodosin in the Turkish Population. Cureus 2017; 9(11): e1848. doi: 10.7759/cureus.1848
21. Celik S, Akdeniz F, Yildirim MA, et al. Tadalafil versus alpha blockers (alfuzosin, doxazosin, tamsulosin and silodosin) as medical expulsive therapy for < 10 mm distal and proximal ureteral stones. Arch Ital Urol Androl 2018;90(2):117-122. doi: 10.4081/aiua.2018.2.117
22. Hsu Y-P, Hsu C-W, Bai C-H, Cheng S-W, Chen K-C, Chen C. Silodosin versus tamsulosin for medical expulsive treatment of ureteral stones: A systematic review and meta-analysis. PLoS ONE 2018;13(8): e0203035. doi: 10.1371/journal.pone.0203035
23. Sharma G, Kaundal P, Pareek T, et al. Comparison of efficacy of various drugs used for medical expulsive therapy for distal ureter stones: A systematic review and network meta-analysis. Int J Clin Pract. 2021;75(9):e14214. doi: 10.1111/ijcp.14214
24. Jendeberg J, Geijer H, Alshamari M, Cierzniak B, Liden M. Size matters: the width and location of a ureteral stone accurately predict the chance of spontaneous passage. Eur Radiol.2017; 27(11):4775–4785. doi: 10.1007/s0033 0-017-4852-6