Journal of Chemical Health Risks

sanad.iau.ir/journal/jchr

ORIGINAL ARTICLE

Effect of Tamsulosin on Ureteral Stones Expulsion before Performing Transureteral Lithotripsy: A Randomized Clinical Trial

Mostafa Heidari[1], Faramarz Beigi[*2], Soleiman Kheiri[3]

[1]*Assistant Professor of Ophthalmology Department of Ophthalmology, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[2]*Department of Urology, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[3]*Department of Epidemiology and Biostatistics, School of Health Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

(Received: 30 August 2024 Accepted: 17 November 2024)

KEYWORDS

Tamsulosin;
Flomax;
Lithotripsy;
Kidney calculi;
Kidney stones

ABSTRACT: Prevalence of ureteral stones has been increasing, and has direct effect on patients' quality of life and the number of phases of renal colic which patients destined to suffer from it. This study aims to investigate the effect of Tamsulosin administration before transureteral lithotripsy (TUL) on the expulsion rate of ureteral stones. In this single-blind clinical trial, 80 patients who were diagnosed with ureteric stones and referred to Ayatollah Kashani Shahrekord Hospital in Southwest Iran were randomly divided into two groups. The first group was given the drug Tamsulosin (0.4 mg day^{-1}) one week before undergoing TUL, along with an oral painkiller (Naproxen 250 mg every 12 hours). The second group only received the painkiller. We evaluated the two groups based on the rate of stone elimination, number of phases of renal colic, painkiller intake, ease of access to the stone at the start of TUL, the need for Stent ventilation during TUL, and additional TUL. The intervention group showed a significantly higher rate of stone expulsion compared to the control group ($p=0.046$). The number of renal colic phases before TUL ($p<0.001$) and the use of painkillers were significantly lower in the intervention group compared to the control group ($p<0.01$). Additionally, the stone expulsion in the first week was significant for the intervention group ($p=0.034$). Based on the study results, it is recommended that the drug Tamsulosin be administered before performing TUL for patients with stones larger than 6 mm in diameter. This is because it not only helps the stone pass in many patients before TUL but also reduces post-TUL pain, shortens the procedure duration, and speeds up the stone passage.

INTRODUCTION

Ureterolithiasis, also called kidney stones, is a common and troublesome urological issue that impacts millions globally [1]. Symptomatic urinary stones are one of the most important problems faced by urology specialists in emergency clinics. 20% of all urinary tract stones are ureteral stones, and 70% of these ureteral stones are placed in the distal ureter [2]. Change in lifestyle (sedentary lifestyle, obesity and inappropriate nutrition), could play a role in the growing incidence of kidney stones in recent years [3-5]. It is identified by the

*Corresponding author: farazbeigi@yahoo.com (F. Beigi)
DOI: 10.60829/jchr.2024.1130537

development of mineral deposits in the urinary system, leading to severe flank pain, nausea, hematuria, fever and vomiting, creating significant difficulties for patients and healthcare providers [6]. Ureteral stones can impair the patient's quality of life and administration of analgesia and antiemetics. Tamsulosin (0.4 mg day^{-1}) can improve their quality of life [7]. Tamsulosin is α1-adrenergic receptor antagonist and specifically inhibits α1-adrenergic receptors that are in the prostate tissue, thus leading to relaxation of the smooth muscles of the prostate capsule and bladder neck [8-9]. Therefore, the output of urine is accelerated and the symptoms of benign prostate enlargement are alleviated. Tamsulosin affects vascular smooth muscles less, and therefore, in comparison with other α-blocker drugs, orthostatic hypotension is seen with this drug [8, 10].

Various studies revealed that the administration of Tamsulosin reduces the need for surgery, facilitates the removal of stones and reduce the risk of urinary retention after surgery, reduced the time to clearance and need to use painkillers after surgery [11-13]. A study demonstrated that tamsulosin is effective in the management of distal ureteral stones. Tamsulosin reduces the frequency of ureteral colic episodes by functioning as a spasmolytic agent, thereby enhancing and accelerating stone expulsion rates, shortening the duration of stone passage, and lowering the required dosage of analgesics [14]. However, a meta-analysis was inconclusive regarding the effect of tamsulosin on more proximal ureteral stones. Additionally, the potential benefits of the drug for stones larger than 10 mm remain uncertain [15]. Therefore, this study is conducted to investigate the effect of tamsulosin administration before transureteral lithotripsy (TUL) on the expulsion rate of ureteral stones.

MATERIALS AND METHODS

Study design

This research was conducted as a randomized, single-blind clinical trial.

Study population

All patients who presented with symptoms of ureteric stones at Ayatollah Kashani Educational and Therapeutic Hospital in Shahrekord and were diagnosed with distal ureteric stones larger than 5 mm by ultrasound were included in the study.

Inclusion and exclusion criteria

The inclusion criteria for the study are the presence of distal ureteric stones larger than 5 mm, no contraindications for Tamsulosin use (e.g., absence of advanced liver disease), and patient cooperation with the study protocol. The exclusion criteria are patient withdrawal from the study at any time and the occurrence of any adverse drug reactions related to Tamsulosin.

Sample size

According to previous research [16], assuming a stone expulsion rate of 85% in the intervention group (Tamsulosin + Naproxen) and 55% in the placebo group (Naproxen only), with a 95% confidence level and 80% statistical power, the sample size was determined to be 40 patients per group, resulting in a total sample size of 80 patients (Figure 1). Patients were recruited through convenience sampling and randomly assigned to either the intervention or the control group.

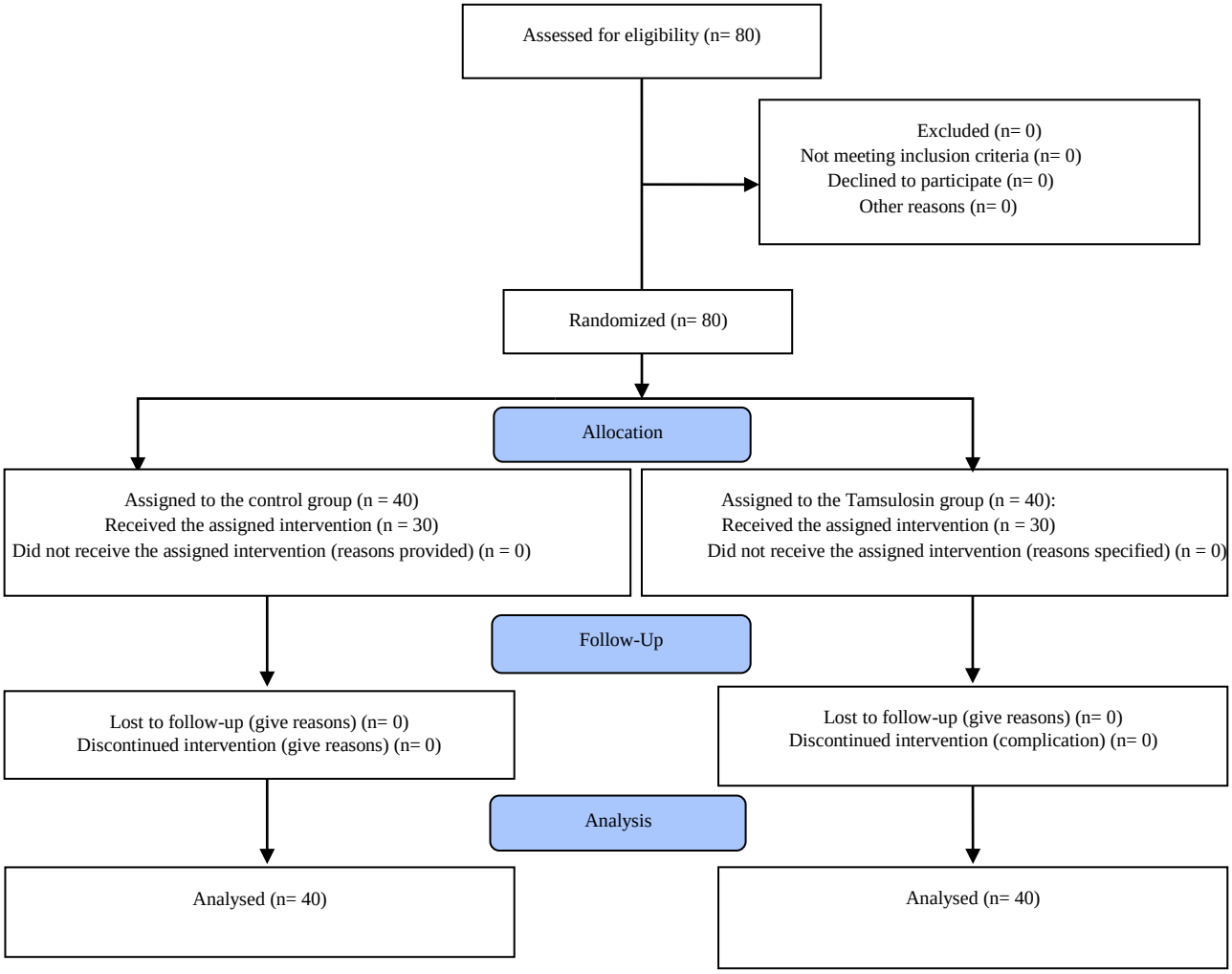

Figure 1. CONSORT flow diagram of the study population.

Study setting and duration

The study was conducted in 2018 at Ayatollah Kashani Educational and Therapeutic Hospital in Shahrekord.

Data collection method

Data were collected using a checklist that included demographic information such as age and gender, as well as details regarding the type and size of the stone and the effect of the drug on the frequency of TUL (Transurethral Lithotripsy). After obtaining approval from the Vice-Chancellor for Research and the University, the principal investigator visited the hospital, explained the study's objectives and methods to the patients, and coordinated with the hospital management. Trained interviewers completed the questionnaires after obtaining informed consent from the patients.

Intervention

Patients with distal ureteric stones larger than 5 mm who visited Ayatollah Kashani Educational and Therapeutic Hospital were randomly assigned to one of two treatment groups. One group was given a placebo along with a painkiller (Naproxen 250 mg every 12 hours), while the other group received Tamsulosin (0.4 mg day^{-1}) along with the same painkiller (Naproxen 250 mg every 12 hours). The medications were administered starting one week before TUL and continued until the stone was expelled. The study compared the two groups based on stone expulsion rate before TUL, the number of renal colic phases, painkiller consumption after TUL, time to stone expulsion after TUL, the extent of stone expulsion, and the need for additional TUL. Patients were monitored weekly through ultrasound, and they were

provided with the principal investigator's contact information to address any issues or adverse drug reactions. Following the study, questionnaires were completed, and the data was analyzed.

Randomization method

A total of eighty patients who had been diagnosed with distal ureteric stones larger than 5 mm were randomly divided into two treatment groups. To ensure impartial assignment, a computer-generated randomization list was used. The randomization was done using a simple randomization method, giving each patient an equal chance of being placed into either the intervention group (Tamsulosin + Naproxen) or the control group (Placebo + Naproxen).

In order to uphold allocation concealment and reduce selection bias, an impartial researcher not involved in patient recruitment, treatment administration, or outcome assessment prepared the randomization sequence.

Blinding

The research was conducted using a single-blind methodology, meaning the patients did not know the treatment they received. Those in the control group were given a placebo pill that looked identical to the Tamsulosin pill and was administered at the same dosage and frequency (0.4 mg day^{-1}) as the actual Tamsulosin.

Data analysis

The analysis was conducted using SPSS software version 20. Descriptive statistics, such as mean values, were computed, and group comparisons were performed using independent T-tests for continuous data and Chi-square tests for categorical data.

RESULTS

In this section, we examine the impact of administering Tamsulosin before ureteroscopic lithotripsy (TUL) on the rate of stone expulsion, based on the collected data.

A total of 80 patients were evaluated in this study. Forty patients received Tamsulosin for one week before TUL (intervention group), while the remaining 40 patients underwent TUL without Tamsulosin as the control group. As shown in Table 1, no significant difference between both groups in terms of age, sex, stone size and stone location ($P > 0.05$).

Table 1. Characteristics of the study participants

Variable	Intervention group	Control group	P-value
Age (years)	39.86 ± 14.42	41.22 ± 12.57	0.659
Gender (Male/Female)	80% / 20%	82.5% / 17.5%	0.778
Stone size (mm)	7.83 ± 1.12	8.12 ± 1.28	0.290
Stone location (Right/Left)	57.5% / 42.5%	55% / 45%	0.824

Based on the results in Table 2, the number of renal colic episodes before TUL significantly differed between the two groups ($P < 0.001$). The average number of episodes in the intervention group was 3.30 ± 3.4, compared to 7.5 ± 5.43 in the control group. However, there was no significant difference in the number of Renal Colic episodes after TUL between the two groups ($P = 0.146$), with an average of 1.87 ± 1.4 in the intervention group and 2.28 ± 1.3 in the control group.

Stone expulsion before TUL occurred in 15 patients (37.5%) in the intervention group and 7 patients (17.5%) in the control group, a statistically significant difference ($P = 0.046$). The ease of stone access at the start of TUL differed significantly between the groups ($P < 0.001$), with 81.8% of cases in the intervention group achieving easy access using a guidewire, compared to 35% in the control group. The stone expulsion rate during the first week after TUL was 45% (18 patients) in the intervention group and 22.5% (9 patients) in the control group ($P = 0.034$). In the second week after TUL, 17.5% (7 patients) in the intervention group and 55% (22 patients) in the control group expelled the stone, a significant difference ($P < 0.001$). The need for repeat TUL did not significantly differ between the two groups ($P = 0.160$).

The average number of days of pain experienced by patients in the intervention group was 2 ± 1.3 days, compared to 4.6 ± 2.3 days in the control group ($P <$

0.001). The amount of injectable pain medication used also significantly differed between the groups (P < 0.001), with 75% of patients in the intervention group requiring 25 mg, while 71.4% of the control group required 50 mg, and 14.3% required 75 mg. There was no significant difference between the groups in the need for stent placement during TUL (P = 0.873).

The trend of stone removal during the study in two groups is shown in Figure 2. It should be noted that in this study, no special side effects were seen in the patients under study.

Table 2. Stone expulsion and other outcomes in the intervention and control groups.

Variable	Intervention Group	Control Group	P-value
Number of renal colic episodes before TUL	3.30 ± 3.40	7.5 ± 5.43	< 0.001
Number of renal colic episodes after TUL	1.78 ± 1.30	2.34 ± 1.28	0.146
Stone expulsion before TUL	15 (37.5%)	7 (17.5%)	0.046
Ease of stone access at TUL start	81.8%	35%	< 0.001
Stone expulsion in week 1 after TUL	18 (45%)	9 (22.5%)	0.034
Stone expulsion in week 2 after TUL	7 (17.5%)	22 (55%)	< 0.001
Average number of days of pain after TUL (days)	2 ± 1.29	4.6 ± 2.27	< 0.001
Need for repeat TUL	0 (0%)	2 (5%)	0.160
Injected painkillers on day 1	**25 mg**: 21 (75%) **50 mg**: 7 (25%) **75 mg**: 0 (0%)	**25 mg**: 5 (14.3%) **50 mg**: 25 (71.4%) **75 mg**: 5 (14.3%)	< 0.001
Need for stent placement during TUL	12 (52.2%)	18 (50%)	0.873

Qualitative variables are reported as frequency (percentage), and quantitative variables are reported as mean ± standard deviation.

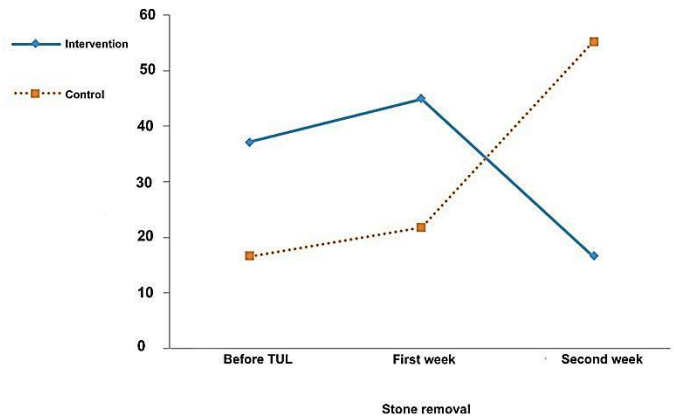

Figure 1. Percentage of stone removal during the study in two groups.

DISCUSSION

The aim of this clinical trial study is to investigate the effect of Tamsulosin administration prior to TUL on the rate of ureteral stone expulsion, the facilitation of ureteroscopy, and the reduction of its associated complications. In the current study the intervention group showed a significantly higher stone expulsion rate and reduction in the number of renal colic phases before TUL and the use of painkillers were seen compared to the control group. Additionally, the stone expulsion in the first week was significant for the intervention group.

In a study conducted by Sauermann et al., the effect of Tamsulosin on the expulsion of distal ureteral stones was evaluated in 100 patients divided into two groups. Although there was no significant difference in stone expulsion rates between the drug group and the placebo group, patients in the drug group experienced less pain compared to the placebo group. However, in our study, not only was the stone expulsion rate before TUL (Transurethral Lithotripsy) higher in the drug group (37.5%) compared to the placebo group (17.5%), but also

after TUL in the first week, the expulsion rate was higher in the drug group (45%) compared to the placebo group (22.5%). This discrepancy can be justified for several reasons: in the study by Sauermann et al., the average stone size was 4.1 mm (2-7 mm) [17]. Whereas in our study, the average stone size was significantly larger. This indicates that smaller stones (less than 5 mm) have a high rate of spontaneous expulsion and do not require medication, whereas for larger stones, drug administration increases stone expulsion. Additionally, the pain level was lower in both the study by Sauermann et al. and our study in the intervention group, indicating that patients who receive the drug have a lower degree of obstruction compared to the placebo group, resulting in less pain for these patients. In a study conducted by Ohki et al. two human ureter samples were examined to evaluate α1-adrenergic receptors. It was shown that sympathetic nerve bundles are distributed throughout the entire ureter, with the highest concentration in males near the bladder and in females at the point where the ureter crosses the iliac vessels [18]. Another study reported that the majority of cases observed passed the stones within the initial three weeks of Tamsulosin plus diclofenac sodium administration. It is suggested that this duration is suitable for patients with distal ureteral stones ranging from 5 to 10 mm in size [19].

Therefore, the use of α1-adrenergic receptor inhibitors may be beneficial for improving stone expulsion and reducing pain attacks, as also clearly demonstrated in our study, which shows that they are effective in stone expulsion and pain reduction. Furthermore, the presence of these receptors in the ureter, as we know, significantly aids in reducing ureteral tonicity, facilitating access to the stone and the entry of the ureteroscope during lithotripsy.

Our study demonstrates significantly easier access to the ureter in the Tamsulosin group (81.8%) compared to the placebo group (35%). In another study by John et al. on the effect of Tamsulosin for stone expulsion after ureteroscopic lithotripsy of large ureteral and renal stones, the average stone size was 11 mm (8 mm-2 cm). The stone expulsion rates were 94.6% in the Tamsulosin group and 83.1% in the control group. Additionally, the incidence of renal colic was 4.3% in the Tamsulosin group compared to 23.4% in the control group, which was statistically significant. They concluded that Tamsulosin is highly effective for the expulsion of large ureteral stones (greater than 1 cm), a finding that our study also confirms. Tamsulosin can reduce renal colic and increase stone expulsion rates [20].

Additionally, the use of analgesics in the Tamsulosin group was significantly lower on the first day, and the use of painkillers in the following days was also markedly reduced, indicating a decrease in the level of obstruction in the Tamsulosin group. Griwan et al. in their study on 60patients undergoing ureterorenoscopy and extracorporeal shock wave lithotripsy (ESWL), indicated that Tamsulosin enhance and speed up the expulsion rate, decrease sudden episodes by functioning as a spasmolytic, shorten the average duration for stone expulsion, and reduce the use of analgesics [21]. Another study on 104 patients with distal ureteral calculi also revealed that use of Tamsulosin reduced time of stones expulsion and average dose of analgesics in intervention group [14].

In this study, no specific side effect was observed in the patients. In this regards, a review study revealed that Tamsulosin without significant side effects can improved the renal stone clearance rate, and reduced the expulsion time [22].

By acting as an alpha-blocker with spasmolytic properties, tamsulosin promotes muscles relaxation in the urinary tract, which not only accelerates stone expulsion but also alleviates the frequency and intensity of ureteral colic episodes. These benefits are particularly evident in stones less than 10 mm in size, for which tamsulosin appears to be most effective [15, 23]. Moreover, the timing of tamsulosin administration relative to the decision to perform TUL is vital. The use of tamsulosin as a preemptive measure before TUL can potentially decrease the number of surgical procedures required, thereby minimizing patient morbidity and healthcare costs [11]. However, the decision to delay TUL in favor of medical expulsive therapy should be carefully considered, particularly in patients presenting with severe symptoms or complicated stone disease.

Furthermore, our study is the first to establish the role of Tamsulosin in facilitating access to ureteral stones, a comparison that has not been made in previous studies. Moreover, due to easier access to the stone in the

Tamsulosin group, the incidence of ureteral trauma is reduced, which explains the lower pain levels in patients receiving Tamsulosin compared to the control group.

CONCLUSIONS

Therefore, administration of Tamsulosin before performing TUL in patients with stones larger than 5 mm, as it not only facilitates stone expulsion in some patients before the lithotripsy procedure but also reduces the pain experienced by patient's post-procedure and allows for earlier stone expulsion. It is suggested to investigate the effect of this drug in removing different types of stones from the urinary tract.

ACKNOWLEDGEMENTS

Declared none.

ETHICAL CONSIDERATION

The study was conducted on patients with distal ureteric stones, which poses no ethical issues. Follow-up of the patients for stone expulsion was performed via ultrasound, a non-invasive and safe test. This study ethically approved by Vice-Chancellor of Research and Biomedical Ethics Committee of Shahrekord University of Medical Sciences (ID: 7-4-91).

Conflict of interest

The authors declared no conflict of interest, financial or otherwise.

Funding

This study was funded by Shahrekord University of Medical Sciences with grant no 1126.

REFERENCES

1. Glazer K., Brea I.J., Leslie S.W, Vaitla P., Ureterolithiasis. [Updated 2024 Apr 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www. ncbi.nlm. nih.gov/books/NBK560674/.

2. Küpeli B., Irkilata L., Gürocak S., Tunç L., Kiraç M., Karaoğlan U., Bozkirli I., 2004. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? Urology. 64(6), 1111-1115.

3. Stamatelou K., Goldfarb D. S., 2023. Epidemiology of Kidney Stones. Healthcare (Basel). 11(3), 424.

4. Peerapen P., Thongboonkerd V., 2023. Kidney Stone Prevention. Adv Nutr. 14(3), 555-569.

5. Emami E., Heidari-Soureshjani S., Oroojeni Mohammadjavad A., Sherwin C.M., 2023. Obesity and the Risk of Developing Kidney Stones: A Systematic Review and Meta-analysis. Iran J Kidney Dis. 1(2), 63-72.

6. Almaghlouth A.K., Alqutayfi H.M., Bohamad A.H., Almarzooq A.J., Alamer M.A., Alqattan D.J., 2023. Urolithiasis Symptoms and Risk Factors Among the General Population of Alahsa, Saudi Arabia. Cureus. 15(5), e39645.

7. Talamini S., Wong D., Phillips T., Palka J., Vetter J., Chow A., Paradis A., Desai A., Sands K., Nottingham C., Venkatesh R., 2024. Improved stone quality of life in patients with an obstructing ureteral stone on alpha-blocker medical expulsive therapy. Int Urol Nephrol. 56(4), 1289-1295.

8. Wade C.A., Goodwin J., Preston D., Kyprianou N., 2019. Impact of α-adrenoceptor antagonists on prostate cancer development, progression and prevention. Am J Clin Exp Urol. 7(1), 46-60.

9. Chavez-Tapia N.C., Kinney-Novelo I.M., Sifuentes-Rentería S.E., Torres-Zavala M., Castro-Gastelum G., Sánchez-Lara K., Paulin-Saucedo C., Uribe M., Méndez-Sánchez N., 2012. Association between cholecystectomy for gallstone disease and risk factors for cardiovascular disease. Ann Hepatol. 11(1), 85-89.

10. Yoosuf B.T., Panda A.K., Kt M.F., Bharti S. K., Devana S.K., Bansal D., 2024. Comparative efficacy and safety of alpha-blockers as monotherapy for benign prostatic hyperplasia: a systematic review and network meta-analysis. Sci Rep. 14(1), 11116.

11. Li H., Zhang W., Xu G., Wang D., Xu C., Zhang H., Zhang L., Li J., Tang P., 2022. Prophylactic tamsulosin can reduce the risk of urinary retention after surgery in male patients: A systematic review and meta-analysis. Front Surg. 9, 930707.

12. Choi C.I, Kim J.K., Choo M.S., Lee S.H., Chang J.D., Han J.H., 2021. Preventive effects of tamsulosin for postoperative urinary retention after lower limb arthroplasty: A randomized controlled study. Investig

Clin Urol. 62(5), 569-576.

13. Basri C., Sinanoglu O., Mahmure U., 2013. The effect of tamsulosin on pain and clearance according to ureteral stone location after shock wave lithotripsy. Curr Ther Res Clin Exp. 74, 33-35.

14. Nuraj P., Hyseni N., 2017. The Role of the Tamsulosin in the Medical Expulsion Therapy for Distal Ureteral Stones. Med Arch. 71(2), 137-140.

15. Hughes P., Lyon C., 2018. PURLs: Tamsulosin for patients with ureteral stones? J Fam Pract. 67(1), 37-38.

16. Yilmaz E., Batislam E., Basar M. M., Tuglu D., Ferhat M., Basar H., 2005. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. J Urol. 173(6), 2010-2012.

17. Sauermann P., Hermanns T., Frauenfelder T., Rufibach K., Sulser T., Strebel R., 2009. Expulsive effect of tamsulosin on distal ureteral stones? Results of a double-blind randomised, placebo-controled single-centre trial. Eur Urol Suppl. 4(8), 206.

18. Ohki K., Ohno Y., Suzuki K., 2010. The investigation of ureteral sympathetic innervation, using semi-serial sections: why does the alpha1-adrenergic receptor antagonist work well for ureteral stones? Int Urol Nephrol. 42(1), 113-117.

19. Erdoğan E., Şimşek G., Aşık A., Yaşar H., Şahin C., Sarıca K., 2024. Optimal duration of medical expulsive therapy for lower ureteral stones: a critical evaluation. Urolithiasis. 52(1), 48.

20. John T. T., Razdan S., 2010. Adjunctive tamsulosin improves stone free rate after ureteroscopic lithotripsy of large renal and ureteric calculi: a prospective randomized study. Urology. 75(5), 1040-1042.

21. Griwan M. S., Singh S. K., Paul H., Pawar D. S., Verma M., 2010. The efficacy of tamsulosin in lower ureteral calculi. Urol Ann. 2(2), 63-66.

22. Sun Y., Lei G. L., Yang L., Wei Q., Wei X., 2019. Is tamsulosin effective for the passage of symptomatic ureteral stones: A systematic review and meta-analysis. Medicine (Baltimore). 98(10), e14796.

23. Campschroer T., Zhu X., Vernooij R. W., Lock M. T., 2018. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 4(4), Cd008509.