The role of corticosteroids along with alpha blocker in the expulsion of distal ureteric stones as compared to the alpha blocker alone

Yasir Murtaza[1], Nadia Shahid[2], Khurram Baqai[3], Faiza Quraishi[4], Jabbar Ahmed Qureshi[5], Ali Nawaz Bijarani[4]

1. Department of Urology, Ziauddin University, Karachi
2. Department of General Surgery, Ziauddin University, Karachi
3. Department of Gastroenterology, Ziauddin University, Karachi
4. Department of Pharmacology, Shaheed Mohtrmma Benazir Bhutto Medical College Lyari Karachi
5. Department of Pharmacology, Ziauddin Medical College, Ziauddin University, Karachi

Corresponding Author: Dr. Nadia Shahid (Department of General Surgery, Ziauddin University, Karachi

Abstract-
Alpha blockers have shown to increase the rates of expulsion for distal ureteric stones while corticosteroids in combination further help alpha blockers to decrease the stone expulsion time by decreasing the signs of inflammation at the site where the calculus is trapped. The main aim of this study is to compare the frequency of distal ureteral stone expulsion rate in patients given combination therapy (alpha-1 blocker and corticosteroid) as compared to monotherapy (alpha-1 blocker alone). About 108 consecutive cases of lower ureteric stones measuring between 5-10mm were selected with pre-defined inclusion and exclusion criteria. We divided the patients into two groups (A and B) with each group having 54 patients. Group A was given combination therapy with alpha blocker (tamsulosin) and corticosteroid (prednisolone) while group B was given alpha blocker (tamsulosin) alone for about 2 weeks to check the rate of expulsion of distal ureteric stones. Data was analyzed by statistical package of social sciences (SPSS) version-20. The average age of the patients was 45.31 +_9.33 years. The overall rate of stone expulsion at 14 days was 71.3(77/108) and was markedly higher in group A as compared to group B (81.5% vs 61.1%; p=0.019). age stratification analysis showed the rate of stone expulsion at 14 days was significantly higher in group A as compared to group B (85.7% vs. 46.2%; p=0.046) in 51 to 60 years of age. With respect to the size of the stone, the rate of stone expulsion at 14 days was markedly higher in group A as compared to group B (84.8% vs. 58.6%; p=0.021) for those cases who had 6-7 mm size of stone while there was no significant difference seen in the groups who had stone size >7mm. It is concluded that tamsulosin along with prednisolone has a significant impact on distal ureteric stone expulsion rate as compared to tamsulosin alone.

Index Terms- Ureteral stones, Alpha blockers, Corticosteroids

Introduction

Urolithiasis is a significant global health problem. Around 8% to 15% of the population gets affected from it in Europe and North America (1). Urolithiasis is the third most common problem of the urinary tract after urinary tract infection and pathological conditions related to prostate (2). Its prevalence is next to Malaria and Schistosomiasis. The morbidity rate secondary to urinary stones is 2% to 4%, which is similar to that of diabetes (3, 4). Geographically, Pakistan is considered to be located on the stone belt where urolithiasis is the commonest urological problem. The mean age group of people affected by this condition is 40 years (5-7).
Surgery has been the most important treatment modality for stone diseases and open surgery is still performed specially for large complicated staghorn stones (8, 9). However, association of surgery with anesthesia, long incisions, significant blood loss, post-operative pain, wound dehiscence, ugly scars and incisional hernias can't

be ignored. Surgical procedures also require prolonged hospitalization and patient experiences discomfort for several months (10, 11). However, for small ureteral stones which have high probability to pass and that no absolute surgical intervention is indicated, observation is advocated. Therefore, medical therapy for small size stones is an alternative tool to get rid of stones, as it is non-invasive. The main aim of treatment is to make the patients stone free as bacteria trapped in the stone fragments can lead to stone growth (12). The site (kidney and ureter) and size (dimensions) of the stone are the criteria for the choice of treatment (13).

The abundance of alpha 1 adrenergic receptor in the ureteral smooth muscle demonstrates the importance of sympathetic nervous system in the migration of stone process (14). Recently, in the process of observation, medical expulsive therapy (MET) has been investigated to supplement the spontaneous stone passage rates which can be unpredictable. The passage of stone gets affected by ureteral edema and spasm while these effects have been targeted by pharmacological therapy. Calcium channel blockers, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and alpha 1 adrenergic receptor antagonists have been evaluated as primary agents for MET (15). Among all above, alpha-blockers have shown to increase the expulsion rate of distal ureteral stones by decreasing the time and the need for analgesia (16). Corticosteroids in combination thus further helps alpha blockers to decrease the stone expulsion time by decreasing edema and inflammation at the site where the stone is trapped (17). It has been hypothesized that there is significant increase in the frequency of distal ureteral stone expulsion given combination therapy (using alpha -1 blocker and corticosteroids) as compared to monotherapy (alpha-1 blocker) alone. So the aim of this study is to compare the frequency of distal ureteric stone expulsion rate in patients given combination therapy (alpha-1 blocker and corticosteroid) versus monotherapy (alpha-1 blocker) alone.

Methodology:

A randomized controlled trial was conducted at the department of Urology, Liaquat National Hospital, Karachi from January to June 2021. Sample size was calculated by using the Open Epi calculator and was 108 in which 54 for each group was collected. In Group A, those patients who were enrolled who took combination of alpha blocker (tamsulosin) and corticosteroid (prednisolone) while patients in group B were taking alpha blocker (tamsulosin) alone for distal ureteric stones. Non-probability purposive sampling technique was used. Inclusion criteria for the study was (1) a total of 108 patients of either gender, (2) 18-70 years of age, (3) having history of lumbar pain (with or without radiation to groins), associated with nausea, vomiting and burning micturition and (4) radiological diagnosis of distal ureteral stones with a diameter >5 mm and < 10mm either on Xray KUB or CT KUB. Exclusion criteria included (1) Patients having moderate to severe hydronephrosis (on ultrasound), (2) elevated serum creatinine above normal (Cr $\geq$ 2), (3) Pregnancy and lactation, (4) Urinary congenital anomalies, (5) previous pyelo ureteral surgery, (6) known case of acid peptic disease, (7) diabetes mellitus, (8) Immuno-compromised patients. Approval from the ethical review committee was taken. The study was conducted after taking informed consent from the patients and also explaining them about the research protocol.

All those patients who presented to emergency room or Urology outpatient department of Ziauddin University Hospital, with symptomatic distal ureteric stones were evaluated on the basis of preformed proforma. Only those patients were enrolled who fulfilled the inclusion criteria and gave the consent. They were randomly allocated in two equal groups (Group A and B) by a computer generated list (Random allocation software version 1.0.0). Laboratory tests including blood Urea and Creatinine levels were checked to rule out renal disease; Urine detail report (DR) and culture and sensitivity (C/S) were performed to rule out Urinary tract infection (UTI); X-ray KUB/ CT scan KUB were done to diagnose ureteric stone. In the study Group A patients were given a combination of alpha-1 blocker (Tamsulosin 0.4 mg HS) and corticosteroid (Prednisolone 5mg 4 tab x O.D), while in the control group patients were given alpha-1 blocker (Tamsulosin 0.4 mg HS) alone. After the start of study patients were re-assessed with X-ray KUB or CT KUB (for radiolucent stones) at first and second week. Corticosteroid was stopped at the end of second week or earlier if the patient expelled stone spontaneously. Final outcome was measured by radiographic evidence (either X-ray KUB or CT KUB) of absence of stone on 14th day or earlier. All the data was recorded on predesigned Performa consisting of

information about patient's age, hospital registration number, stone size, location, clinical group and final outcome on the basis of radiologically proved stone expulsion.

Data was entered and analyzed by statistical package of social sciences (SPSS) version-20. Frequency and percentage were computed for categorical variables like gender, stone location and stone expulsion. Mean with standard deviation at 95% confidence interval were computed for quantitative measurement like age, stone size. Chi-square test was applied to compare proportion of gender, and stone expulsion rate between groups. Independent sample t test was applied to compare mean difference between groups for age and stone size. $P<0.05$ was considered level of significant. Stratification was done with regard to age, gender, stone size and site of stone to see the effect of these on outcome variables through chi-square test.

Results:

The total number of patients included in the study was 108, out of which fifty-eight patients in Group A were treated with a combination of alpha-1 blocker (Tamsulosin 0.4 mg HS) and corticosteroid (Prednisolone 5mg 4-tab x O.D), while fifty-four patients in the group B, were treated with alpha-1 blocker (Tamsulosin 0.4 mg HS) alone. Majority of the patients in both groups, were between 41 to 50 years of age as presented in figure 1. The average age of the patients was 45.31±9.33 years. Similarly, average stone size was 7.35±0.98 mm. Average age and stone size were not significant between groups as p-values were non-significant, presented in table 1. Looking over the gender, out of 108 patients, 84(77.8%) were male and 24(22.2%) were female as shown in figure 2. Significant difference was not observed between groups in gender (p=0.355).

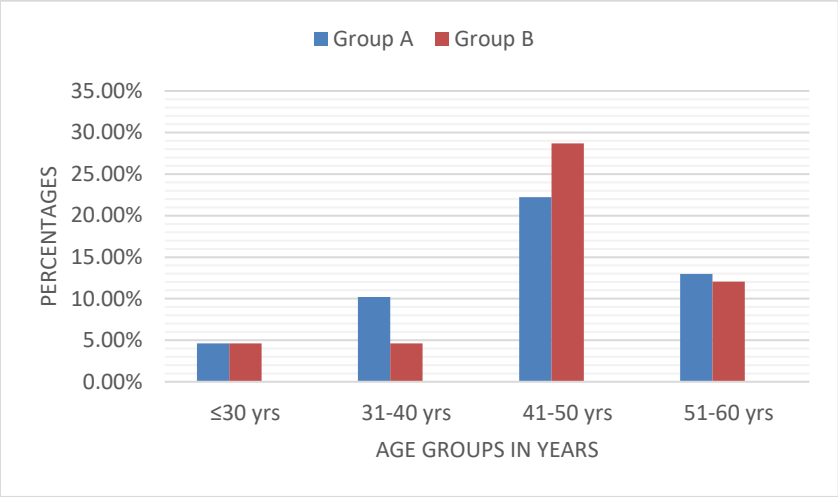

Figure 1 Age distribution with respect to groups (n=108)

Table 1 Comparison of mean age and stone size between groups

	Mean ± SD	Group A (n=54)	Group B (n=54)	95% CI	p-value
Age (years)	45.31±9.33	44.89±9.97	45.74±8.70	43.54 - 47.09	0.64
Stone size	7.35±0.98	7.24±0.89	7.46±1.07	7.16 - 7.54	0.24

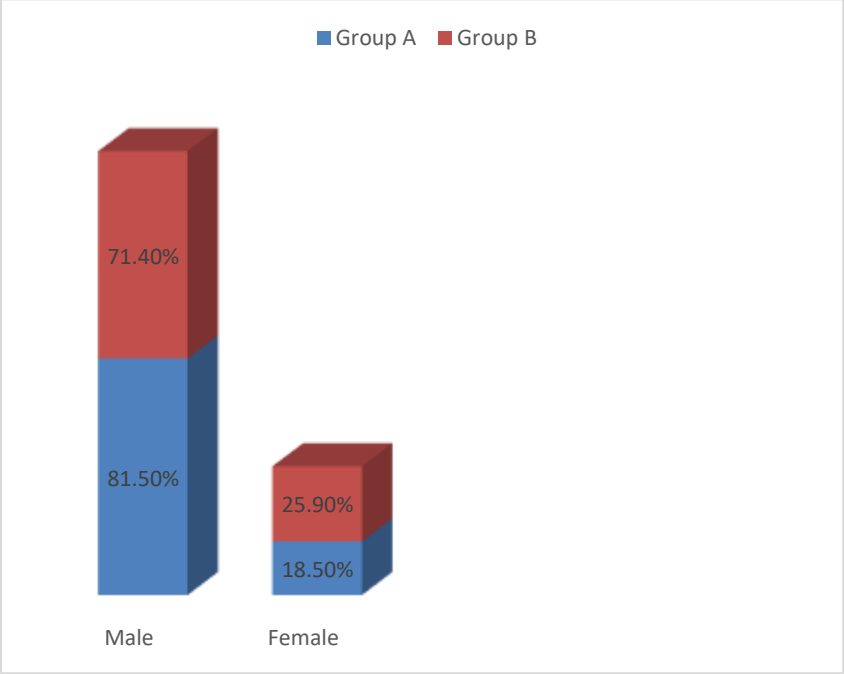

Figure 2 Gender distribution with respect to groups (n=108)

The overall rate of stone expulsion at 14 days was 71.3% (77/108) and was significantly higher in group A than group B (81.5% vs. 61.1%; p=0.019). Age stratification analysis showed the rate of stone expulsion at 14 days was significantly higher in group A than group B (85.7% vs. 46.2%; p=0.046) in 51 to 60 years of age while rate of stone expulsion at 14 days was not significant in other age group Gender stratification analysis showed that rate of stone expulsion at 14 days was significantly higher in group A than group B (84.8% vs. 58.62%; p=0.021) for male cases while significant difference was not observed between groups in female cases. With respect to size of stone, the rate of stone expulsion at 14 days was significantly higher in group A than group B (84.8% vs. 58.6%; p=0.021) for those cases who had 6 to 7 mm size of stone while significant difference was not observed between groups in those cases who had above 7 mm stone size. Location wise stratification analysis showed that the rate of stone expulsion at 14 days was significantly higher in group A than group B (85.7% vs. 58.4%; p=0.019) for distal ureter location. The comparison of the rate of stone expulsion at 14 days between groups are presented in Table 2.

Table 2 Comparison of frequency of distal ureteral stone expulsion between groups at 14 days

	Stone Clearance at 14 days				p-value
	Group A		Group B		
	Yes	No	Yes	No	
Age (years)					
≤30 yrs (n=10)	5(100%)	0(0%)	4(80%)	1(20%)	0.29
31-40 yrs (n=16)	8(72.7%)	3(27.3%)	4(80%)	1(20%)	0.75
41-50 yrs (n=55)	19(79.2%)	5(20.8%)	19(61.3%)	12(38.7%)	0.155
51-60 yrs (n=27)	12(85.7%)	2(14.3%)	6(46.2%)	7(53.8%)	0.046
Gender					
Male (n=84)	36(81.8%)	8(18.2%)	21(52.5%)	19(47.5%)	0.004
Female (n=24)	8(80%)	2(20%)	12(85.7%)	2(14.3%)	0.71
Stone size					
6 to 7 mm (n=62)	28(84.8%)	05(15.2%)	17(58.6%)	12(41.4%)	0.021
8 to 9 mm (n=46)	16(76.2%)	05(23.8%)	16(64%)	09(36%)	0.37
Location of stone					

Distal; ureter (n=59)	24(85.7%)	4(14.3%)	18(58.1%)	13(41.9%)	0.019
Uretero vesical junction (n=49)	20(76.9%)	6(23.1%)	15(65.2%)	08(34.8%)	0.53

Discussion:

In daily urologic practice ureteral stones play an important role. In the past 20 years, the treatment options for passage of ureteral stones have changed drastically (18). Because of their minimal invasiveness and low risk of complications, Extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy, are currently accepted as the first choice for ureteral stone management (19). Nevertheless, the definition of the best treatment option is still under debate among the urologists. The initial site of stone impaction and its size influences the probability of spontaneous stone passage (20). For stones of 5 and 10mm diameter, impacted in the distal ureter spontaneous expulsion occurs in 25–53% of the cases (21).

Nowadays, in order to enhance the expulsion rate and decrease the use of analgesics, there is a great deal of enthusiasm for medical expulsion therapy, especially for cases of distal ureteral stones (22). Researchers have reported that there is an increased efficacy of different pharmacologic therapies in ureteral stone expulsion by acting primarily on ureteral smooth muscles causing peristalsis. Porpiglia et al. have shown that the calcium channel blockers such as nifedipine when given with corticosteroids caused an overall increase in the rate of ureteral stone expulsion and reduced the time for stone passage (23). Furthermore, alpha1- adrenergic antagonist can cause a decrease in ureteral peristaltic frequency, reducing the episodes of colic pain. It has also been hypothesized that α-blockers inhibits peristaltic activity and relaxes the basal tone of the ureter thereby facilitating expulsion of the ureteric calculus (24). Corticosteroids inhibit the release of prostaglandins at the site of obstruction thus reducing the inflammation and edema.These anti-edema agents when used in association with other drugs, such as alpha-blockers seem to enhance their efficacy, as they cause a decrease in inflammation which ultimately facilitates stone expulsion.

A study done by Porpiglia et al, showed that patients receiving combination therapy of alpha blocker and corticosteroid had 84.8% expulsion rates for distal ureteric stones as compared to 60% for patients receiving alpha blocker alone. In his study the average stone size was between 5-6mm (23). In another study done by Dellabella M and colleagues showed that patients receiving combination therapy had 96.7% stone expulsion rate as compared to 90% for patients receiving alpha blockers alone (17).

More recently, in 2016, a study by Shabana in Egypt concluded that stone expulsion rate will be higher if combine corticosteroids with alpha-blockers. From 2012 to 2014, 240 patients with distal ureteral stones Currently, evidence indicates that corticosteroids when given in combination with α1-blockers (tamsulosin), there will be a higher expulsion rate over a shorter period of time when applied for distal ureteral stones (25, 27-29) and they are the most effective therapy. Current study focused on patients who had symptomatic distal ureteric stones with a diameter of between 5mm to 10mm. The therapy was administered only up to 14 days for two reasons: first, to prevent the side-effects of prolonged corticosteroid therapy, and second, in the literature, it is reported that therapy efficacy is maximum in the first few days (30). It was observed that 2 weeks of combination therapy with corticosteroid and alpha blocker had a significant impact on rate of the expulsion of stone.

Conclusion:

It is concluded that tamsulosin along with prednisolone has a significant impact on the rate of expulsion of distal ureteric stones as compared to tamsulosin alone.

Reference:

1. Sohgaura A, Bigoniya P. A review on epidemiology and etiology of renal stone. Am J Drug Discov Dev. 2017;7(2):54-62.
2. Stoller ML. Urinary stone disease. Smith's Urology. 2000.
3. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investigative and clinical urology. 2017;58(5):299-306.
4. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Reviews in urology. 2010;12(2-3):e86.
5. Samad N, Liaqat S, Anwar M, Tehreem K, Sadiq HM. Chemical nature of various types of renal stones in the population of district Multan Pakistan. Pakistan Journal of Pathology. 2017;28(2):56-60.
6. Jehangir K, Zeshan A, Bakht T, Faiz U. Burden of marble factories and health risk assessment of kidney (renal) stones development in district Buner, Khyber Pakhtunkhwa, Pakistan. Expert Opin Environ Biol 4. 2015;2:2.
7. Bangash K, Shigri F, Jamal A, Anwar K. Spectrum of renal stones composition; chemical analysis of renal stones. Int J Pathol. 2011;9(2):63-6.
8. Ghous MH, Hassan A, Afzal S. Renal stone clearance rates of PCNL and ESWL. IJISRT. 2019;4(8):787-92.
9. Rajpar ZH, PARYANI JP, SHAFIQUE-UR-REHMAN M, Abdullah A, Shaikh U. EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY. The Professional Medical Journal. 2012;19(05):636-41.
10. Kreydin EI, Eisner BH. Risk factors for sepsis after percutaneous renal stone surgery. Nature Reviews Urology. 2013;10(10):598-605.
11. Khalaf I, Salih E, El-Mallah E, Farghal S, Abdel-Raouf A. The outcome of open renal stone surgery calls for limitation of its use: A single institution experience. African Journal of Urology. 2013;19(2).
12. Blair B, Fabrizio M. Pharmacology for renal calculi. Expert opinion on pharmacotherapy. 2000;1(3):435-41.
13. Morgan MS, Pearle MS. Medical management of renal stones. Bmj. 2016;352.
14. Karabacak OR, Yilmazer D, Ozturk U, Sener NC, Saltas H, Karabacak Y, et al. The presence and distribution of alpha adrenergic receptors in human renal pelvis and calyces. Urolithiasis. 2013;41(5):385-8.
15. Barnela SR, Soni SS, Saboo SS, Bhansali AS. Medical management of renal stone. Indian Journal of Endocrinology and metabolism. 2012;16(2):236.
16. Campschroer T, Zhu X, Vernooij RW, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database of Systematic Reviews. 2018(4).
17. Dellabella M, Milanese G, Muzzonigro G. Medical-expulsive therapy for distal ureterolithiasis: randomized prospective study on role of corticosteroids used in combination with tamsulosin—simplified treatment regimen and health-related quality of life. Urology. 2005;66(4):712-5.
18. Gravina GL, Costa AM, Ronchi P, Galatioto GP, Angelucci A, Castellani D, et al. Tamsulosin treatment increases clinical success rate of single extracorporeal shock wave lithotripsy of renal stones. Urology. 2005;66(1):24-8.
19. Aboumarzouk OM, Kata SG, Keeley FX, Nabi G. Extracorporeal shock wave lithotripsy (ESWL) versus ureteroscopic management for ureteric calculi. Cochrane Database of Systematic Reviews. 2011(12).
20. Jendeberg J, Geijer H, Alshamari M, Cierzniak B, Lidén M. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. European radiology. 2017;27(11):4775-85.
21. Aldaqadossi HA. Stone expulsion rate of small distal ureteric calculi could be predicted with plasma C-reactive protein. Urolithiasis. 2013;41(3):235-9.
22. Abou Chakra M, Dellis AE, Papatsoris AG, Moussa M. Established and recent developments in the pharmacological management of urolithiasis: an overview of the current treatment armamentarium. Expert opinion on pharmacotherapy. 2020;21(1):85-96.
23. Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. The Journal of urology. 2004;172(2):568-71.
24. Sentürk AB, Aydin C, Ekici M, Yaytokgil M, Akkoc A, Baykam MM. Comparison of three most frequently used alpha blocker agents in medical expulsive therapy for distal ureteral calculi, result of a retrospective observational study. Archivio Italiano di Urologia e Andrologia. 2018;90(1):25-8.

25. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? European urology. 2006;50(2):339-44.
26. Bos D, Kapoor A. Update on medical expulsive therapy for distal ureteral stones: Beyond alpha-blockers. Canadian Urological Association Journal. 2014;8(11-12):442.
27. Ramesh A, Karthick P, Kumar RS. Medical expulsion therapy for ureteric calculus–possible! International Surgery Journal. 2016;3(1):113-8.
28. Smith RD, Shah M, Patel A. Recent advances in management of ureteral calculi. F1000 medicine reports. 2009;1.
29. Tanagho EA, McAninch JW. Smith's general urology: McGrawHill Professional.; 2008.
30. Sridharan K, Sivaramakrishnan G. Efficacy and safety of alpha blockers in medical expulsive therapy for ureteral stones: a mixed treatment network meta-analysis and trial sequential analysis of randomized controlled clinical trials. Expert review of clinical pharmacology. 2018;11(3):291-307.