Original article

Tamsulosin And Corticosteroid In The Medical Expulsive Therapy For Distal Ureteral Stones: A Prospective Comparative Study

Hari Bahadur KC, Suman Sharma

Abstract

Introduction: Medical Expulsive Therapy (MET) has become an established treatment option for small ureteral stones. While alpha blockers are commonly used agents, the addition of anti-inflammatory medications such as corticosteroids seems to increase efficacy. This study aims to know the efficacy of the addition of a corticosteroid prednisolone, to tamsulosin in the medical management of symptomatic distal ureteral calculi.

Methods: In this prospective study, patients with symptomatic distal ureteral stones of size 5 to 10mm were randomly assigned to two groups: group A received tamsulosin 0.4 mg and group B received tamsulosin 0.4 mg plus prednisolone 30 mg for 2 weeks. The number of colicky pain episodes, stone expulsion rate, time to stone expulsion, analgesic use, and side effects of drugs were noted in both groups. Statistical analysis was carried out using Student's t-test and chi-square test.

Results: Total of 120 patients (59 in group A and 61 in group B) were enrolled in the study and their average age was 32.13±10.5 years and male: female ratio was 1.55:1. There was a significantly higher rate of stone expulsion in tamsulosin plus prednisolone group than in tamsulosin alone group (82.0% vs. 64.4%, p=0.03). The demographic profiles, baseline investigations, stone size, pain score, analgesic used, and occurrence of side effects were comparable between the two groups.

Conclusions: The combination of tamsulosin with prednisolone has significantly higher stone expulsion rate than tamsulosin as a medical expulsive therapy. Hence, this combination seems to be effective and safe for the treatment of distal ureteral stones.

Keywords: Prednisolone; Tamsulosin; Ureteral calculi.

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Introduction

Urinary tract stone is one of the most common diseases of the urinary tract with lifetime prevalence of ranging from 1% to 15%.[1] Ureteral stones comprise 20% of urolithiasis, of which two thirds are present in the lower third of the ureter at the time of presentation.[2]

Stone size and the location are the key factors for spontaneous passage. Stones located at lower ureter and smaller than 5mm are more likely to pass spontaneously with success rate of 90%. For stones 5-10mm size, spontaneous expulsion rate decreases to 25–53% while those larger than 10mm are unlikely to pass even with medications.[3,4] Thus, for stones of size 5 to 10mm, different medications like alpha-blocker, calcium channel blocker (CCB), phosphodiesterase-5 (PDE5) inhibitors have been used as medical expulsive therapy (MET) with good results. Although various minimally invasive surgical procedures can be used to treat these stones, they are costly as well as carry some surgical risks.

When renal stones descend to ureter, they induce ureteral spasm, stimulate synthesis of prostaglandins and subsequent mucosal edema due to inflammation, which interfere with stone expulsion.[5-7] Nonsteroidal anti-inflammatory drugs are used as one of the first line drugs to treat renal colic for their analgesic and anti-inflammatory effects.[8] Similarly, spasmolytic drugs reduce the spasm while maintaining normal peristaltic activity and thus facilitate stone expulsion. Tamsulosin, which is a selective alpha blocker, reduces the spam and relaxes the smooth muscle of ureter. Hence, it has been extensively used as MET and has proved to increase the stone expulsion rate and decrease the expulsion time.[1,3] On the other hand, anti-inflammatory agents such as corticosteroids, may decrease the inflammation and mucosal edema more effectively at the site of stone presence, which will eventually facilitate the stone expulsion.[9]

Thus, combination of anti-spasmodic agent tamsulosin with anti-inflammatory agent corticosteroid may have synergistic action on stone expulsion and many studies have supported the fact. Tamsulosin has been widely used for ureteral stones in our practice and has been found to be efficacious. There are limited studies in our country which use corticosteroids for treatment of ureteral stones.

Methods

This prospective comparative study was performed in Gandaki Medical College Teaching Hospital, Pokhara, Nepal over a period of 6 months. This study was reviewed and approved by the Institutional Review Committee of the institute (approval number: 99/081/082). Written informed consent was obtained from each patient before they were enrolled in the study. Patients who presented to the Urology Outpatient Department (OPD) with symptomatic distal ureteral stones of size 5–10 mm were included in the study. Non-contrast computed tomography (NCCT) was used for diagnosis. Patients younger than 18 years of age, patients with severe refractory pain, moderate to severe hydronephrosis, acute or chronic renal failure, urinary tract infection, a single functioning kidney, multiple ureteral stones, bilateral ureteral calculus, and any history of ureteral surgery were excluded. Also, patients with peptic ulcer, history of UGI bleeding, complicated hypertension, diabetes, patients receiving concomitant treatment with alpha-blockers or steroids, and pregnant or lactating mothers were also excluded from the study.

A total of 135 patients who fulfilled the criteria were included in the study. Informed written consent was taken from these patients and randomly recruited into two groups (group A and B) by use of a computer-generated random number table , however, blinding was not done. The patients in group A received Tamsulosin 0.4 mg once daily and those in group B were prescribed Tamsulosin 0.4mg plus Prednisolone 30mg once a day. These medications were continued for a period of two weeks or until stone expulsion. Patients were encouraged to drink plenty of fluids. Patients were asked to take Nimesulide 100mg tablets as needed for painful episodes. The patients were assessed weekly and were asked if they passed stone. However, expulsion of the stone was confirmed by X-ray of the kidneys, ureters, and bladder (KUB) and ultrasonography. In cases where X-ray KUB and ultrasound were inconclusive, NCCT was performed for confirmation. The stone expulsion time was noted as the day in which the stone was passed during urination. In remaining cases where patients didn't know the stone passage, the day in which the imagings reported the absence of stone was taken as the stone expulsion time. The stone expulsion time, analgesic use, number of colicky pain, pain score and occurrences of any drug side effects like headache, postural hypotension, epigastric pain, nausea, and vomiting were recorded. The amount of analgesic use was calculated by recording the number of Nimesulide 100mg tablets consumed during the MET therapy. The pain intensity was calculated by using the World Health Organization numerical pain score of 0 to10 (where 0 refers to no pain and 10 denotes the maximum pain a person has ever experienced). The pain score was recorded at each weekly visit. Patients failing to pass the stone after two weeks of treatment were treated by ureteroscopic lithotripsy. The primary outcome was the stone expulsion rate. The secondary endpoints were stone expulsion time, number of colicky attacks, analgesics requirement, and incidence of drug side effects.

Data were recorded in preformed semi-structured proforma sheets, and were analyzed using the SPSS, ver. 23.0 (SPSS Inc., Chicago, IL, USA). Discrete variables were evaluated by chi-square test and the continuous variables by unpaired Student t-test. All statistical tests were based on two-tailed probability, and a p-value <0.05 was considered statistically significant.

Results

Total of 162 patients were assessed for eligibility in the study, but 27 were excluded based on exclusion criteria. Out of remaining 135 patients included in the study, 15 patients were excluded as 12 lost follow up and three experienced allergies to the drug. Finally, 120 patients completed the study and hence analyzed (**Figure 1**). The mean age of the patients was 32.13 ± 10.5 years. There was male preponderance with male: female ratio of 1.55:1. Most of the patients were young and more than 60% were under 30 years (**Figure 2**). The demographic parameters were comparable between the two groups.

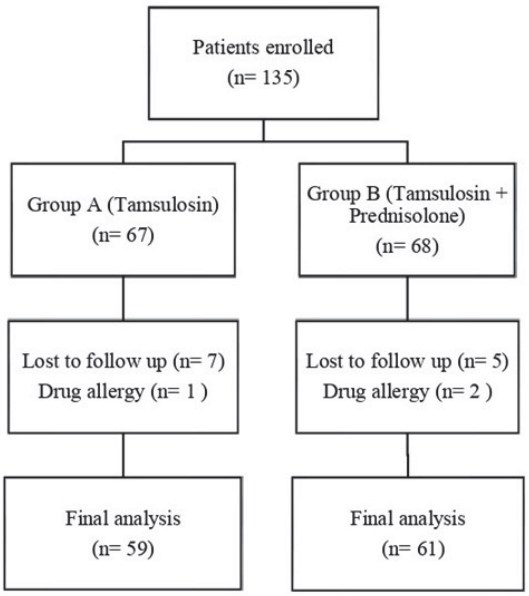

Figure 1. The flow diagram of the study

The average stone size was 7.30 ± 1.4 and, the stone size and stone laterality were not significantly different in both groups. The number of colicky pain episodes and the pain score were higher in group A, while, and the dose of analgesics needed were higher in group B. But these differences were not significant statistically (**Table 1**). The overall stone expulsion rate was 73.3%, and it was significantly higher in group B (82.0%) as compared to group A (64.4%), p= 0.030. The stone expulsion time was 12.34 ± 3.0 days in group A and 12.04 ± 3.1 days in group B, and thus statistically not significant.

The incidence of side effects in general was lower in group A (11.9% vs 18%, p=0.344). The patients in group B experienced more incidence of gastritis related side effects like nausea, vomiting and epigastric pain. However, all the side effects were mild and well tolerated, comparable between two groups and statistically insignificant (**Table 2**).

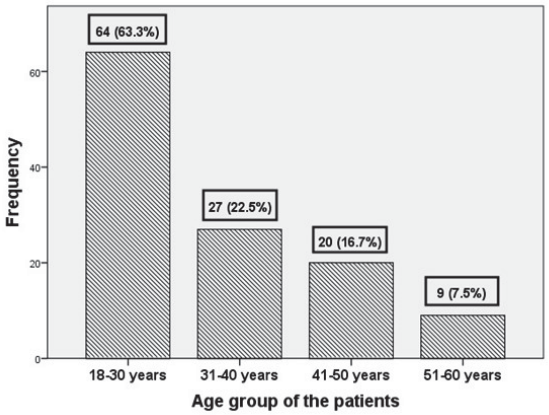

Figure 2. Age distribution of the patients

Table 1. Patients' demographic characteristics and the results of the study

Parameters	Total (n=120)	Group A (n=59)	Group B (n=61)	P value
Age in years	32.13 ± 10.5	31.41 ± 9.4	32.82 ± 11.4	0.462
Male / Female (n)	73 / 47	34 / 25	39 / 22	0.479
Stone laterality, (n) Right / Left	64 / 56	29 / 30	35 / 26	0.367
Stone size (mm)	7.30 ± 1.4	7.23 ± 1.4	7.37 ± 1.4	0.591
Stone expulsion rate, n (%)	88 (73.3%)	38 (64.4%)	50 (82.0%)	**0.030**
Stone expulsion time (days)	12.17 ± 3.1	12.34 ± 3.0	12.04 ± 3.1	0.653
No of colicky episodes	0.88 ± 0.81	0.97 ± 0.89	0.79 ± 0.73	0.230
Pain score (0-10)	2.69 ± 1.9	2.85 ± 1.8	2.54 ± 1.9	0.377
Analgesic used (Nimesulide, mg)	116.6 ± 144.9	101.7 ± 132.6	131.1 ± 155.7	0.268

Table 2. Side effects experienced by the patients in each group

Parameters	Group A (n=59)	Group B (n=61)	P value
Overall incidence of side effects, n (%)	7 (11.9%)	11 (18.0%)	0.344
Headache	6 (10.2%)	7 (11.5%)	0.818
Dizziness	4 (6.8%)	4 (6.6%)	0.623
Postural hypotension	3 (5.1%)	4 (6.6%)	0.519
Gastritis (epigastric pain, nausea, vomiting)	3 (5.1%)	8 (13.1%)	0.113
Upper GI bleeding	None	None	-

Discussion

Urolithiasis is a chronic disease with huge economic consequences because it affects young people. It has a high recurrence rate of approximately 50% within 5 years and 75% at 10 years, and thus, has great public health importance.[10] Ureteral stones account about one fifth of all urinary tract stones, however, they are the most symptomatic ones and can lead to significant renal damage if not treated promptly. Spontaneous passage of ureteric stone depends not only on the stone size and location, but also on the ureteral spasm, mucosal edema or inflammation, and ureteral anatomy.[11]

In present study, the age, sex, stone laterality and size of the stones were comparable between two groups, and similar results were shown by other studies.[14-16] Tamsulosin has an established role in distal ureteral stones. Al-Ansari et al, [17] in their study of 100 patients of lower ureteral stones reported 82% stone expulsion rate in tamsulosin group as compared to 61% in the control group (P = 0.02). In another study, KC et al[18] reported the stone clearance rate of 61.0% when tamsulosin was used in MET for distal ureteral stones of size 5-10 mm.

The stone clearance rate in our study was significantly higher in tamsulosin and steroid group as compared to tamsulosin alone group (82% vs 64.4%, p=0.03). The role of concomitant usage of steroids and alpha-blockers has been found in literature with favorable outcomes. **Table 3** demonstrates the stone expulsion rates of different studies using tamsulosin and steroid as MET. In a study by Shabana W et al,[14] they compared tamsulosin with tamsulosin plus methylprednisolone, and alfuzosin with alfuzosin plus methyl prednisolone (n=53 in each group) as MET therapy for lower ureter stones. The stone expulsion rate was significantly higher in combination group (71.9% vs 54.7% and 73.6% vs 52.8% respectively, p<0.05), thus supporting the role of steroid as adjunct to alpha blockers. Other studies used deflazacort as concomitant therapy to tamsulosin. Porpiglia F et al[19] and Sinha AR et al[20] compared the stone clearance rate of tamsulosin with tamsulosin plus deflazacort combination. The stone expulsion rate was 60.0% versus 84.8% (p<0.001) and 52.0% versus 76.0% (p=0.038) respectively, suggesting the significant role of steroids in stone clearance. In similar studies by Sitharamaiah K et al[16] and Dellabella M et al,[15] the stone clearance rate of tamsulosin group and tamsulosin plus deflazacort were 80.0% vs 89.0% and 90.0% vs 96.7% respectively. Although the success rate was higher in steroid combination group, there was no statistical significance (p=0.66 and p=0.612).

MET not only facilitates stone passage, but also decreases the stone expulsion time, colicky pain episodes, and analgesic requirement. . In the study by Dellabella M et al[15], the median time to stone expulsion was 120 hours (mean 139.2 ± 113.8) in the tamsulosin group and 72 hours (mean 103.3 ±136.2) in tamsulosin plus deflazacort group (P = 0.036), which was statistically significant. However, Shabana W et al[14] found that there were no significant differences in stone expulsion time between tamsulosin group and tamsulosin plus methylprednisolone group (13 days vs 10 days p=0.082). In the present study, there is no difference in stone expulsion time between two groups (12.34 ± 3.0 days vs 12.04 ± 3.1 days, p= 0.653).

In our study, the number of colicky pain episodes experienced, the pain score and the requirement of analgesics during the treatment period was comparable between the two groups and statistically insignificant (p= 0.230, p= 0.377 and p= 0.268 respectively) (**Table 1**). Porpiglia F et al[19] demonstrated in their study that the consumption of analgesics has significantly reduced in tamsulosin plus deflazacort group as compared to tamsulosin only group (27.3 ± 0.5mg vs 42.5 ± 0.4 mg, p <0.001). Jain S et al[21] studied the efficacy of tamsulosin and steroids to facilitate the stone clearance after extracorporeal shock wave lithotripsy (ESWL) and found that the number of analgesics tablet required was lower in Group A (tamsulosin and deflazacort) as compared to Group B (tamsulosin), but the difference was not significant (2.00 ± 1.40 vs 2.35 ± 1.60, P = 0.340).

The incidence of overall side effects was higher in steroid group, but the difference was statistically insignificant: 7(11.9%) vs 11(18.0%), p=0.344. The patients in prednisolone group experienced more gastritis related side effects, but there was no incidence of upper gastrointestinal bleeding. All the reported side effects in our study were mild and well tolerated. No serious adverse effects were

Table 3. Stone expulsion rate in other studies using alpha blockers and steroids for distal ureteral stones

Studies	Tamsulosin	Tamsulosin + Prednisolone	Tamsulosin + Deflazacort	Tamsulosin + Methyl prednisolone	Placebo
Present study*	64.4%	82.0%	-	-	-
Porpiglia F et al, 2006 [19] *	60.0%	-	84.8%	-	33.3%
Sinha AR et al, 2019 [20] *	52.0%	-	76.0%	-	-
Sitharamaiah K et al, 2015 [16]	80.0%	-	89.0%	-	45.0%
Shabana W et al, 2016 [14] *	54.7%	-	-	71.9%	-
Dellabella M et al, 2005 [15]	90.0%	-	96.7%	-	-

** Statistically significant.*

Table 4. Comparison of parameters between MET success vs MET failure group

Parameters	MET success (n=88)	MET failure (n=32)	P value
Age in years	31.77 ± 10.8	33.09 ± 9.3	0.543
Male / Female (n)	54 / 34	19 / 13	0.844
Stone size (mm)	6.91 ± 1.3	8.37 ± 1.2	0.000
Stone laterality, (n) Right / Left	48 / 40	16 / 16	0.659
Duration of pain (days)	2.63 ± 2.6	3.78 ± 3.5	0.056
No of ureteric colics	0.77 ± 0.7	1.16 ± 0.8	0.022
Pain score (0-10)	2.31 ± 1.8	3.75 ± 1.4	0.000
Analgesic used (Nimesulide, mg)	102.8 ± 142.7	154.7 ± 146.6	0.083
Overall incidence of side effects	14 (15.90%)	4 (12.5%)	0.444

encountered in either group, or no patients needed to suspend therapy. Comparable results were reported by Porpiglia F et al,[19] Sinha AR et al,[20] and Dellabella M et al,[15] where the side effects were milder, well tolerated, and comparable between tamsulosin and tamsulosin plus steroid group.

Subgroup analysis was performed between the patients who successfully cleared the stone during treatment (MET success group) and those who failed to pass the stone (MET failure group) irrespective of the treatment group (**Table 4**).

The demographic parameters including age (p=0.543) and the male-to-female ratio (p=0.844); analgesics requirement (p=0.083), and incidence of drug side effects (p=0.444) were comparable between two groups. However, the mean stone size was larger in the MET failure group (8.37 ± 1.2 mm) as compared to MET success group (6.91 ± 1.3 mm), which was statistically significant (p<0.001). The MET failure group also experienced a significantly higher number of ureteric colics (p<=0.022). and greater pain score (p<0.001).

Limitations

Our study was not devoid of limitations. The sample size was small, the treatment duration was short, there was no placebo group, and this study was performed in a single hospital. The time taken for stone expulsion was reported subjectively by the patients, which may carry some risk of inaccuracy. Further larger, multi-institutional prospective studies will help to establish the role of steroids as an adjunct to alpha-blockers in MET for the treatment of distal ureteral stones.

Conclusion

The use of a steroid in association with tamsulosin has a significantly higher stone expulsion rate than tamsulosin alone in MET therapy for distal ureteral stones of 5-10 mm size. However, there will be no advantages in terms of stone expulsion time, experiences of pain and requirement of analgesia. These drugs are well tolerated with minor side effects. Thus, the combination of tamsulosin with prednisolone seems to be effective and safe for the treatment of distal ureteral stones.

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