

The Effective Medical Expulsion Therapy for Distal Ureteric Stones

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Abstract

The lifetime risk of developing genitourinary stone is 5-12%. Males are more prone to calculus formation as compared to females. The data for the Indian population suggests that 12% of the people develop urinary calculi and half of them end up with the loss of kidney functions. Symptomatic urolithiasis represents a common condition observed by surgeons and urologists in an emergency setting. The lower third/distal ureter is the most common site for the ureteric calculus. We did this study to evaluate the efficacy of tamsulosin in the management of distal ureteral stones when administered alone or in conjugation with low-dose corticosteroid (Deflazacort) over the watchful waiting therapy using only non-steroidal anti-inflammatory drugs. In this study the male-female ratio was 3:1. The mean age group of females was 36.04 and in males was 38.14. The mean size of stone in various groups was around 6mm. the left side of ureter was more symptomatic than the right side. Mean day use of NSAID was least in group B. Group B was the most benefitted by the medical expulsion therapy. We conclude that medical expulsive therapy is safe and effective for symptomatic and non-complicated distal ureteral stone. In addition, Tamsulosin used on its own as a medical expulsive therapy can be considered an alternative treatment in those patients who are unsuitable for steroid therapy. Deflazacort given even in low dose has the same effect as that of larger doses.

Keywords: MET, Medical expulsion therapy, Tamsulosin, Alpha 1 blockers, Low dose deflazacort for MET

INTRODUCTION

Urolithiasis is among the top three urological diseases. Around 2-3% of the population in the world is suffering from urolithiasis. Urolithiasis recurs in about 20% of the patients [1-3]. In India 12% of people develop urinary calculi and 50% end up with the loss of kidney function. Symptomatic urolithiasis represents the common condition observed by surgeons and urologists in an emergency room. The lower third/distal ureter is the most common site for the ureteric calculus. The passage of stones from the kidney into the bladder through the ureter is accompanied by three factors: 1) spasm of smooth muscles 2) submucosal oedema and 3) pain. The determining factors for the spontaneous passage of calculi are their size, configuration, and smooth muscle activity of the ureters. During the passage of calculi, the biggest obstacle is the terminal part of the ureter, mainly the intramural 'detrusor tunnel'. Many calculi of 4 mm or smaller pass spontaneously, although not without discomfort and expense to the patient. Ureteral calculi of any size are mostly associated with urinary obstruction, and we should take utmost care to prevent irreversible damage to the kidney while choosing an expectant or an active management.

There is still debate on the best treatment option for distal ureteric calculi. The size of the calculus and its initial location affects the probability of spontaneous stone passage. For distal ureteral calculi of 5 to 8 mm diameter, spontaneous expulsion occurs in many cases [4]. To increase the expulsion

rate, reduce analgesic consumption and avoid surgical intervention, there is a lot of enthusiasm for adjuvant pharmacologic therapy for cases of distal ureteral calculi.

The drugs used in medical expulsion therapies decrease the smooth muscle tone including the sphincter while maintaining a tonic contraction of the ureter. Anti-inflammatory drugs, such as corticosteroids can be used in combination with analgesic drugs (NSAIDs). Corticosteroids increase the efficacy of analgesics due to their action by decreasing inflammation thereby, reducing the obstacle to the passage of calculi.

The main aim of this prospective study is to evaluate the efficacy of α 1-blocker (tamsulosin) therapy in the

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management of distal ureteral stones when administered as the only drug or in conjugation with low-dose corticosteroid (deflazacort), when the watchful waiting therapy using only non-steroidal anti-inflammatory drugs (NSAIDs) is considered.

MATERIALS AND METHODS

Enrolment of Patients

This is a prospective study performed on first 200 patients with distal ureteral stones from 1st April 2019 to 31st March 2022 after calculating the sample size for each group by the standard formula.

$$[Z(1 - \alpha/2) + Z(1 - \beta)] \times [P1Q1 + P2Q2]/e^2 \quad (1)$$

This gave us a value of a minimum of 46 participants in each group. All the patients were treated at SMBT Institute of Medical Sciences and Research Centre, situated at Nandi Hills in the village Dhamangaon, PO-Ghoti, Taluka – Igatpuri, district - Nashik, Maharashtra, India. We took prior approval from the Institutional Ethical Committee of the SMBT Institute of Medical Sciences and Research Centre, with reference number SMBT/IEC/19/090, dated 10/04/2019.

Patient Randomization

The patients enrolled in the study were assigned into 3 groups by simple random sampling technique:

Group A: Tamsulosin and NSAIDs.

Group B: Tamsulosin and Deflazacort and NSAIDs.

Group C (control): only NSAIDs.

The group specified treatment was given for 7 days and stopped if the stone passed earlier. Ultrasonography (USG) of the abdomen was used to find whether stone had passed or not. If doubtful cases computed tomography (CT) of the KUB (kidney, ureter and bladder) region was done to confirm the stone.

• Selection of Subject Inclusion Criteria

- Patient age - 18 to 65 years.
- Size of the stone - 5 to 8mm.
- Single distal ureteric stone.

Exclusion Criteria

- Severe Hydronephrosis/fornicial rupture.
- Diabetes/peptic ulcer.
- History of spontaneous passage of stone
- previous surgical intervention for stones.
- Known hypersensitivity/ contraindication to Tamsulosin, steroid or NSAIDs.

- Not willing to be included in the study.

• Study Protocol

Patients of distal ureteral stones having size between 5 to 8 mm and fulfilling inclusion criteria were included in this study. All patients were clinically examined. complete blood counts, urine analysis, abdominal ultrasonography and plain abdominal x-ray kidney-ureter-bladder (KUB) and plain computed tomography of the KUB region were done, wherever indicated. All patients received initial treatment with oral analgesics (Diclofenac sodium). If the stone was located in the lower ureter, of size between 5mm to 8mm and if pain resolved, the patients were enrolled into the study, if they agree and willing to give a written consent. No smooth muscle relaxants/opioids were given as they might interfere with the process of stone expulsion. Three groups were formed based on the proposed therapy: Group A were given oral Tamsulosin (0.4mg) + NSAIDs, Group B were given Tamsulosin (0.4mg) + Deflazacort (12mg) + NSAIDs, and Group C (control group) were given only NSAIDs for a period of 7 days. All patients were instructed to drink 3-4 litres of water per day and were advised to use intramuscular/intravenous injection of Diclofenac if pain did not subside with the oral treatment. In case of uncontrollable pain during the present therapy or fever, the patients were given the authority to suspend the present treatment and then undergo other modalities of treatment. This was considered failure of therapy. Corticosteroids were stopped in five days by tapering the dose. Double blinding was done to prevent bias.

Treatment was given for 7 days and stopped if the stone passed earlier. All patients were advised to follow up after 7 days. If he/she passes the stone earlier, they were advised to report early. USG was used to confirm the presence or absence of the stone. CT KUB plain was done to confirm the stone if USG fails to localize the stone. Patients who did not pass stone, were given the choice to continue the medical management or to go with the other modalities of treatment like URS and ESWL.

RESULTS AND DISCUSSION

A total of two hundred patients were included in the present study. The mean age of the female patients was 36.04 and in males was 38.14 with a male-to-female ratio of 3:1. Most of the patients presented with complaints of pain in abdomen, followed by burning micturition, haematuria and fever. The mean size of stone in various groups was around 6mm. (**Table 1**) with the left side of the ureter more symptomatic than the right side. Group B patients had the minimum requirement of NSAID. (**Table 2**) and was most benefitted by the medical expulsion therapy (**Tables 3 and 4**). In the study 22 patients lost to follow-up as follows - 4 in group A, 6 in group B and 12 in group C.

Table 1. Distribution of sample by the mean size of the stone

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.	P-value
					Lower Bound	Upper Bound			
A	65	6.12	.992	.123	5.88	6.37	5	8	< 0.001
B	69	6.55	.883	.106	6.34	6.76	5	8	
C	66	5.88	.773	.095	5.69	6.07	5	7	
Total	200	6.19	.926	.065	6.06	6.32	5	8	

Table 2. Shows the Distribution of samples by use of NSAID for number of days

	N	Mean (Days)	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.	P-value
					Lower Bound	Upper Bound			
A	61	3.18	1.162	.149	2.88	3.48	2	10	< 0.001
B	63	2.80	.800	.100	2.60	3.00	1	5	
C	54	6.62	1.881	.254	6.11	7.13	3	10	
Total	178	4.09	2.142	.160	3.78	4.41	1	10	

Table 3. Mean days of passage of stone

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.	P-value
					Lower Bound	Upper Bound			
A	42	8.67	0.57	.088	8.49	8.84	7	9	< 0.001
B	56	8.07	1.35	.179	7.71	8.43	0	10	
C	25	9.65	0.49	.095	9.46	9.85	9	10	
Total	123	8.60	1.16	.103	8.40	8.80	0	10	

Table 4. Mean size of stone in patient who passed the stone

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.	P-value
					Lower Bound	Upper Bound			
A	42	5.53	0.55	.088	5.35	5.70	5	7	< 0.001
B	56	6.35	0.73	.099	6.15	6.55	5	8	
C	25	5.08	0.28	.055	4.97	5.20	5	6	
Total	123	5.81	0.79	.073	5.66	5.95	5	8	

MET (Medical expulsion therapy) has emerged as a good option for the conservative management of ureteral stones in properly selected patients. We did this study to demonstrate various medical management strategies to avoid surgical intervention in as many patients as possible.

Stone disease are three times more common in patients with a family history of stone disease and male gender. An imbalance between the stone inhibitors like citrate and the stone promoters like oxalate has been suggested to be the cause for stone formation. This could be the reason for the male preponderance of urinary calculi.

The rate of spontaneous stone passage varies from 25% to 53% for a stone size from 5mm to 10 mm [4]. Most of the studies included 5-10 mm stone size for MET [5]. But we included cases with a stone size of 5 mm to 8 mm only and excluded cases with a stone size <5 mm or > 8 mm in our study. Ye *et al.* included stone size of 4-7 mm for MET in their study [6].

The rate of stone expulsion in our study was 64% in patient on Tamsulosin, 88% in patients on Tamsulosin and Deflazacort, and on NSAIDs was 37%. This is comparable with other studies. A similar expulsion rate was shown by Sinha *et al.* [7].

In our study, the mean day use of NSAIDs was less when another drug was added for stone expulsion (Group II < Group I < Group III) which suggests decreased mean expulsion time of the stone as shown by Sinha *et al.* & Ali *et al.* in their studies [4, 7].

Ureteroscopy is considered the standard treatment for lower ureteral stones. The recent technological advances, reduction of the instrument calibre and powerful energy sources (holmium & thulium lasers), ureteroscopic intervention allows a success rate of upto 94% [8]. Though ureteroscopy is safe and effective as well, it requires anaesthesia and double J-stenting. Other implications include high cost, lowered quality of life, suspension of regular activities, and chances of various complications like ureteric stricture formation and ureteric perforation [9]. These aspects are of major importance when we think of treating a symptomatic distal ureteral stone which is suitable for expulsion therapy. For these reasons, an adjuvant pharmacologic intervention has been proposed by different groups during conservative treatment, in addition to analgesics. The aim is to increase the expulsion rate of ureteral calculi located in the lower ureter.

Pharmacologic drugs are used to decrease the tonic contraction of smooth muscles during the peristaltic phase, they maintain the tonic activity of the ureter and help preventing the formation of ureteral mucosal oedema surrounding the stones [4]. The rationale for using steroids is that the presence of a stone in the ureter creates an inflammatory reaction of the mucosa, which causes various oedematous reaction and augments the passage of the stone. The other pharmacological agents to reduce spasmodic contraction of ureter are calcium antagonist (nifedipine), alpha1-blockers and beta-adrenergic agonists. Among the anti-oedema agents, the steroidal pharmacological agents (methylprednisolone, deflazacort, prednisolone) are commonly used. Current evidence suggests that alpha1-blockers alongwith corticosteroids are the best therapy for distal ureteral stones due to the higher expulsion rate over a shorter period [10, 11].

In all the studies where deflazacort was used and its effects observed, it was used in a very high dosage or the combination of tamsulosin and deflazacort that is available in the market was used. But in our study, we used deflazacort in very low doses of 12mg per day as compared to other studies where it was used in a dosage of 30 mg per day. We observed that even in lower doses, the expulsion rate did not change when compared with other studies done in the past. So, we can say from the observations of our study that corticosteroids even in low doses are as effective as in high doses. This may reduce the side effect profile of the steroids when compared with the high doses. Phukan Mandeep *et al.* (2013) in their study also used low dose deflazacort and the expulsion rate of the stone was not affected [12].

Our study focuses on patients with symptoms of lower ureteral calculus with of size 5-8 mm. Because the distal ureter has the highest concentration of $\alpha 1$ -receptors, we included tamsulosin in our study. Deflazacort is a good anti-oedema with lesser side effects and good tolerance. The treatment was advocated for only 7 days for to prevent the complications of steroidal pharmacological agents. Moreover, the efficacy of the above-mentioned treatment regime is greatest in the first few days.

Analysis of the data shows that patients on α -blocker along with steroidal agents and patient on α -blockers alone has good rate of stone expulsion in comparison to patient who take NSAIDs alone (88%, 64% v/s. 37%). More ever, this group II demonstrated a greater reduction in the intake of analgesic (2.80, 3.18 v/s. 6.62 days), when the mean day of passage of stone was compared it was less (8.07, 8.67 v/s. 9.65). α -blockers given alone as single drug in patients of diabetes, peptic ulcer, or steroidal contraindications also have good effect over stone expulsion and should be used in such cases.

We did not record any side effects of the pharmacological drugs used in our study. During the one-week therapy period, it was observed that although the mean size of stones in patients on Tamsulosin with Deflazacort and on Tamsulosin alone is comparatively greater (but statistically not significant) from the patient on NSAIDs even than the expulsion rate, days of expulsion and days of use of NSAIDs is less in patient on Tamsulosin and Tamsulosin with Deflazacort when compared to the patient on NSAIDs (Control Group).

CONCLUSION

Medical expulsion therapy is safe and effective for symptomatic and non-complicated distal ureteral calculi. Tamsulosin can be used alone safely as a good treatment option in patients who have contraindications for steroidal therapy. Deflazacort can be used effectively even in low doses with concerning stone expulsion. A prospective randomized multicentre study should be designed to confirm this data.

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