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Role of low-dose deflazacort with tamsulosin versus tamsulosin alone for medical expulsive therapy of ureteric stone

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ABSTRACT

Background: Urolithiasis is a common condition in daily urological practice. Medical Expulsive Therapy (MET) is non-invasive approach for removal of ureteric stone. In MET, alpha-blocker Tamsulosin is commonly used in treating urolithiasis but it does not address the pathology of inflammation presents in such condition. With addition of low dose Deflazacort as anti-inflammatory agent, there may have a potential to improve the pathology and outcome of the treatment. **Aims and Objectives:** This study aims to find the efficacy of low-dose deflazacort combined with tamsulosin in the MET for distal ureterolithiasis. **Materials and Methods:** This prospective randomized controlled trial was conducted from December 2022 to December 2023 in Rampurhat Government Medical College and Hospital. A total of 130 patients with ureteric stone ≤10 mm were randomized into two groups. Tamsulosin group received tamsulosin (0.4 mg once daily for 28 days). Deflazacort group received tamsulosin (0.4 mg once daily for 28 days) with deflazacort (12 mg once daily for 10 days). All subjects were reviewed on 14 days and 28 days. Stone expulsion rate, time to stone expulsion, analgesic use, number of colic episodes, and hospitalization were recorded. Adverse effects of drugs were noted. **Results:** Among 130 patients randomized, 4 patients were lost to follow-up and 8 patients required early intervention. Deflazacort group had similar rate of stone expulsion (88% vs. 80%, P = 0.548). There were significantly shorter expulsion time (10.15 days vs. 14.28 days, P < 0.001) and less number of colic episodes (33 episodes vs. 21 episodes, P = 0.026) and less analgesic requirements (65% vs. 82.5%, P = 0.022) in deflazacort group. No significant side effects were noted during the study. **Conclusion:** Low-dose deflazacort added to tamsulosin provides a significant advantage in ureteric stone expulsion without any extra side effects. With a comparable rate of stone passage, there are more rapid stone expulsion, low analgesic requirement, and less colic episodes when low-dose deflazacort is added to tamsulosin for ureteric stone ≤10 mm.

Key words: Low-dose deflazacort; Medical expulsive therapy; Tamsulosin; Ureteric stone

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INTRODUCTION

Urolithiasis is a common condition of urinary tract and accounts for 15–20% of cases appearing in our outpatient department (OPD).[1] Available treatment options are watchful waiting with medical expulsive therapy (MET), extracorporeal shock wave lithotripsy (ESWL), and ureteroscopic lithotripsy (URSL). Although URSL is the gold-standard treatment for the management of lower ureteric calculi, it is invasive and requires anesthesia and required facilities are not readily available in developing countries like India.[2] On the other hand, MET is a reasonable non-invasive approach for lower ureteric stone measuring <10 mm in size.

Varied combinations of medical treatments, including corticosteroid, non-steroidal anti-inflammatory drug,

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calcium channel blockers, PDE-5 inhibitors, and α-adrenergic blockers have been studied.[3,4] At present, different MET guidelines have found that there is a significant benefit from tamsulosin in improving stone passage rates.[5-7] Various other studies have also shown that steroid deflazacort at dose 30 mg/day alone or added to tamsulosin can also be effective modality for medical expulsion therapy in urolithiasis although at a cost of increased adverse effects related to corticosteroids.[8-11] Considering potential hazards of high-dose corticosteroid, we intended to conduct a study with low-dose deflazacort at 12 mg/day in combination with tamsulosin for the expulsion of distal ureteric calculi ≤10 mm.

Aims and objectives

The study aims to find the efficacy of low dose Deflazacort combined with Tamsulosin in the medical expulsive therapy for distal ureterolithiasis measuring less than 10 mm. The secondary objective of this study is to assay the symptomatic improvement and tolerability of the treatment.

MATERIALS AND METHODS

Study design and ethical permission

It was planned as a single center, prospective, open-label, randomized, controlled comparative trial with two parallel treatment groups. Permission for this trial was obtained from IEC of Rampurhat Government Medical College and Hospital (Memo no: IEC/2022/05/003) and the trial was registered at Clinical Trial Registration of India (Reg No: CTRI/2022/12/048094). The trial was conducted at Surgery department of Rampurhat Government Medical College and Hospital from December 2022 to December 2023.

Sample size

Considering results of previous studies with similar protocol,[11] the target sample size to ensure statistical significance was calculated to be 65 evaluable subjects in each group. This has been estimated to detect a difference, between groups, of 10% in expulsion rate, with 80% power and 5% probability of type I error.

Study participants

Subjects presenting at surgery OPD between age group 18 and 60 years with ureteric calculus size 10 mm or below were included in the study. Patients with diabetes, impaired kidney function, peptic ulcer, liver failure, active UTI, pregnancy, prior history of urinary surgery, or endoscopic treatment were excluded from the study. Concomitant treatment with alpha-blocker drugs, beta-blockers, calcium channel blockers, or nitrates was also excluded.

Study procedure

All eligible subjects were informed about the opportunity to be recruited into the trial. After having written informed consent, a detailed history was taken and evaluation of presenting symptoms was done. Investigations included Hb, BT, CT, blood sugar, urea, serum creatinine, urine analysis and culture, plain X-ray kidney, ureter, and bladder (KUB) region, and ultrasonography (USG) of kidney, ureter, and urinary bladder region were done. Non-contrast CT abdomen was done in cases where high suspicion is there but stone is not detected with USG and X-ray KUB. Patients were randomized into two groups using computer-generated random numbers. Patients in tamsulosin group were prescribed tamsulosin (0.4 mg once daily orally for 28 days) and acted as active control arm. Deflazacort group used as study arm was given tamsulosin (0.4 mg once daily orally for 28 days) with deflazacort (12 mg once daily orally for 10 days). All subjects were reviewed on 14 days and 28 days with clinical examination and radiological investigation and asked for spontaneous stone passage and adverse effects experienced. Diclofenac 75 mg IM on demand was advised for pain. In case of uncontrolled colic, fever, raised serum creatinine, or severe hydronephrosis, subjects were withdrawn from trial and subjected to endoscopic/surgical treatment. We determined efficacy in terms of stone clearance rate, expulsion time, and analgesia requirements.

Statistical analysis

Data were collected and analysis was done using GraphPad InStat statistical software. Data were presented as number (%) and mean ± standard deviation (SD) wherever appropriate. Unpaired Student's t-test and the Chi-square test were used for the analysis of the variables and categorical data. Differences were considered significant when $P<0.05$.

RESULTS

Out of 138 patients, 130 met inclusion criteria and after taking informed consent, they were randomized into two groups (tamsulosin group and deflazacort group) with 65 patients each (Figure 1). 58 patients in tamsulosin group and 60 patients in deflazacort group have completed the study. Both groups were comparable in age, sex distribution, and stone size measurement (Table 1). Although complete stone clearance was better in deflazacort group (expulsion rate 88%) compared to tamsulosin group (expulsion rate 80%), the difference is not statistically significant (P=0.548). The mean stone clearance time deflazacort group (10.15±4.15 days, range 3–19 days) was less compared to tamsulosin group (14.28±5.52 days, range 4–28 days) and the difference was strongly significant statistically

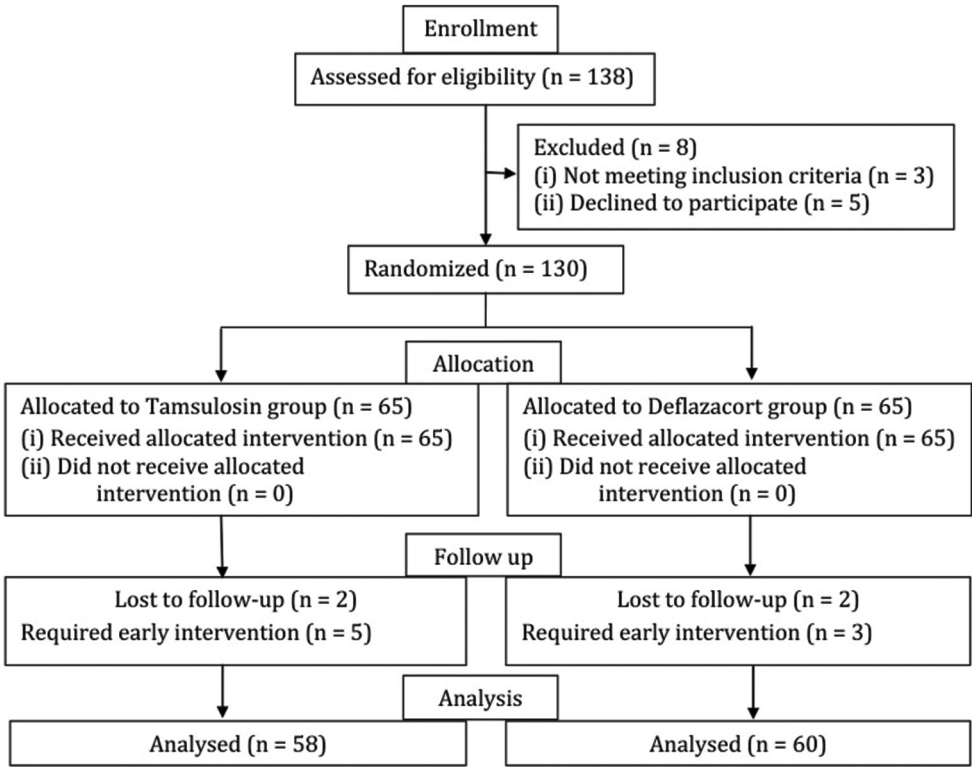

Figure 1: Patient flow diagram

Table 1: Demographics and results

Parameter	Tamsulosin group	Deflazacort group	P-value
Age (mean±SD years)	43.29±9.9	42.43±9.1	0.611
Gender (male/female)	42/16	45/15	0.912
Stone size in mm (mean±SD)	7.62±1.25	7.27±1.28	0.135
Expulsion rate (%)	48/58 (80%)	53/60 (88%)	0.548
Expulsion time (mean±SD days)	14.28±5.52	10.15±4.15	0.001
No. of colic episodes (mean±SD)	33	21	0.026
No. of hospitalization	5	3	0.481

*Statistical significance was analyzed by unpaired t-test and Chi-square test

Table 2: Analgesic used by participants

Amount of diclofenac used	Tamsulosin group (%)	Deflazacort group (%)	P-value
No analgesic used	10 (17.5)	21 (35)	0.046
Analgesic used	48 (82.5)	39 (65)	0.022
Up to 150 mg	36 (62)	33 (55)	
More than 150 mg	12 (20.5)	6 (10)	

*Statistical significance was analyzed by Chi-square test

Table 3: Adverse effects

Parameter	Tamsulosin group	Deflazacort group	P-value
Abnormal ejaculation	7	6	0.77
Orthostatic hypotension	2	1	0.61
Dizziness	8	5	0.39
Headache	5	6	0.98
Gastritis	7	11	0.17

*Statistical significance was analyzed by Chi-square test

(P<0.001). Number of subjects who experienced colic episodes in tamsulosin group was significantly higher compared to deflazacort group (33 episodes vs. 21 episodes, P=0.026). Similarly number of hospitalizations was also higher in tamsulosin group compared to deflazacort group (5 vs. 3 admissions) but this difference was statistically insignificant (P=0.481). Overall requirement of analgesic (Diclofenac) was significantly higher in tamsulosin group (Table 2) where 82.5% in tamsulosin Group experienced the need for analgesic medication compared to 65% in deflazacort group (P=0.022).

Adverse effects such as gastritis were more common in deflazacort group but were not significant enough when compared to tamsulosin group (P>0.05). Incidence of other adverse effects such as headache, abnormal ejaculation, dizziness, and orthostatic hypotension was almost similar in both tamsulosin and deflazacort groups (Table 3).

DISCUSSION

Nearly 20% of all urinary tract stones are ureteral stones.[12] Management of ureteral stones has dramatically changed

in recent times with the introduction of minimally invasive procedures such as ESWL and URSL. However, requirement of anesthesia, instruments, and high-cost factor associated with invasive procedures make conservative management with the pharmacological agent as treatment of choice, especially in uncomplicated ureteral stones measuring <10 mm in size.[13] Both the European (EAU) and American (AUA) guidelines recommend alpha blockers like tamsulosin as first choice for these cases.[14] Tamsulosin acts by inhibiting the smooth muscle contraction in ureter and facilitating passage of ureteric stone into bladder.[15] However, tamsulosin does not address the pathology of inflammation-induced local edema formation and partial occlusion of ureter resulting from ureteric stone. Hence, addition of an anti-inflammatory agent like steroid may be helpful to reduce the edema and facilitate stone expulsion.[9,10] Deflazacort is a synthetic corticosteroid, oxazoline derivative of prednisolone with strong anti-inflammatory activity, and good tolerability. It was found to be effective in other studies.[10,11] Considering the adverse effects of corticosteroid agents, this study used lower dose of deflazacort (12 mg) for a shorter duration (10 days). This duration of corticosteroid therapy was thought to be useful as Malin Jr., et al., have found that efficacy of corticosteroid therapy in ureteric stones was more in initial few days.[16]

In this study, we found good ureteric stone expulsion with tamsulosin use (80%), comparable to earlier randomized controlled studies done.[11,17,18] Stone expulsion rate got better when deflazacort was added to tamsulosin (88%) but difference was not statistically significant in our study. A similar non-significant result was seen in a randomized trial done by Dellabella et al.[19] Sinha and Siwach[11] had shown significant positive results with deflazacort but dose used (30 mg) was much higher compared to our study (12 mg).

While comparing mean stone expulsion duration, deflazacort plus tamsulosin combination facilitates stone passage by decreasing stone expulsion time significantly compared to tamsulosin used alone (10.15 days vs. 14.28 days, P<0.001). Dellabella et al.,[19] also concluded that the use of a corticosteroid drug in association with tamsulosin causes significantly rapid stone expulsion. Colic episodes in deflazacort group were significantly less with respect to tamsulosin group (21 episodes vs. 33 episodes, P=0.026). This better pain control was also translated as significantly less analgesic requirements (65% vs. 82.5%, P<0.001) and hospital admission deflazacort group. These improvements may be due to additional strong anti-inflammatory effect of deflazacort on inflammation and edema that accompany ureteric obstruction.

No serious side effects were observed in any patients related to the use of study drugs. Observed adverse effects were mild and well tolerated by study population. There was no significant difference in other side effects between two groups and side effects were less compared to other studies using higher dose of deflazacort.[10,11,17,19]

Limitations of the study

Due to financial and logistic constraints, blinding of the study was not done. Double blinded multicentric study would give a more promising results.

CONCLUSION

Low-dose deflazacort added to tamsulosin in MET provides significant advantage in ureteric stone expulsion without any extra side effects. In spite of a comparable rate of stone passage, there is more rapid stone expulsion, low analgesic requirement, and less colic episodes when low-dose deflazacort added for short period. In our best knowledge, no study till date had compared low-dose deflazacort-tamsulosin combination with tamsulosin alone. Therefore, further multicentric studies with larger number of cases are needed to validate these promising and statistically significant results and explore the complete potential of short-term low-dose deflazacort use in MET.

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AB- Principal Investigator, data collection, data analysis; **PKG-** Co-investigator, data collection, clinical protocol; **HM-** Pharmacologist, design of study, statistical analysis and interpretation, manuscript preparation, editing, and manuscript revision.

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