



**ORIGINAL RESEARCH PAPER**

**Urology**

**A PROSPECTIVE STUDY OF EFFICACY OF  $\alpha$ -1 BLOCKERS FOR EXPULSION OF DISTAL URETERAL STONES**

**KEY WORDS:** Medical expulsive therapy, Alpha-1 blocker, Distal ureteral calculus

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**ABSTRACT**

**Background:** Urolithiasis affects all ages of the population and its incidence is constantly rising. The medical expulsive therapy for distal ureteral stone disease focuses on the passing of stones as well as provides symptomatic relief, reducing spasm, pain, nausea and vomiting. The efficacy of  $\alpha$ -1-blockers in MET for expulsion of distal ureteral stones (3-10 mm) is evaluated in this prospective study. **Materials & methods:** A total of 100 patients with distal ureteral calculus (3-10mm) were included in the study from May 2015 to April 2017. All patients were given medical expulsive therapy with alpha 1 blocker medication as a part of it for maximum 4 weeks. The stone expulsion rate, time to expulsion and analgesic dose and adverse effects of drug were noted. **Results:** The age, sex, side affected were statistically not significant for stone expulsion. The overall stone expulsion rate was 80%, and it was significantly higher in stone size <5mm (98.1%) than for stone size >5mm (59.6%). The time to expulsion (7.81 days) was significantly less compared to placebo arm of different other studies. The need for analgesic was average 3 doses (150mg). 13 patients could not continue drug therapy due to repeated colic attacks while 7 patients had persistent stone at the end of study requiring intervention. Adverse effects were minimal and did not require drug discontinuation. **Conclusion:** Medical expulsive therapy with alpha 1 blocker is an effective and safe modality in the management of uncomplicated distal ureteral calculi <10mm. It has been found that alpha1 blockers increase stone expulsion rate, decrease mean days to stone expulsion and decrease acute attacks leading to decrease in analgesic dose required.

**INTRODUCTION**

The formation of stones in the urinary tract is an ancient disease known to the mankind for ages. Urolithiasis includes stone diseases in the kidney, ureter, bladder & urethra.

Ureteric stones are a common problem in daily emergency & outpatient department practice. All urinary tract stones and ureteric stones in particular, have a significant impact on patients' quality of life. The pain leads to a requirement for analgesia, time off work and often repeated hospital admissions for therapeutic interventions.

Most ureteral stones will pass spontaneously. Those that do not can be removed by either shock wave lithotripsy or ureteroscopy. The spontaneous passage rate for stones 1 mm in diameter was 87% for stones 2-4 mm, 76% for stones 5-7 mm, 60% for stones 7-9 mm, 48% for stones larger than 9 mm. Spontaneous passage rate as a function of stone location was 48% for stones in the proximal ureter, 60% for mid ureteral stones, 75% for distal stones, and 79% for ureterovesical junction stones.<sup>2</sup> The addition of a calcium channel blocking agent, steroids, antibiotics, and more acetaminophen effected a higher stone passage rate and fewer lost to work days, emergency room visits, and surgical interventions.<sup>3</sup>

In the past 25 years, the treatment of these calculi has evolved from ureterolithotomy to ureterorenoscopy URS, extracorporeal shockwave lithotripsy (ESWL), and endoscopic lithotripsy.<sup>4,5,6,7</sup> Current therapeutic options for lower ureteral stones include active intervention as well as conservative approach i.e. Medical Expulsive Therapy (MET). Medical expulsive therapy consists of adequate hydration with or without diuretic, antispasmodic, analgesic and anti-inflammatory (steroidal/non-steroidal) with alpha blocker or calcium channel blocker. Those who fail Medical expulsive therapy or who subsequently develop complications, undergo active treatment, such as ureteric stenting, ureteroscopy with stone retrieval or *in-situ* lithotripsy. ureteroscopic manipulation, an overall stone-free rate of 87.8% was obtained regardless of the size of the stones. The success rates according to the location of stones were 75.0 (proximal), 94.6 (mid), and 86.4% (distal).<sup>8</sup>

Patients with favourable features and with medium sized stones (3-10mm) in the lower ureter can be offered medical

expulsive treatment as initial treatment option. In past years, a growing understanding of ureteric function and pathophysiology had led to the hypothesis that drugs that cause relaxation of ureteric smooth muscle can enhance the spontaneous passage of ureteric stones. The selective  $\alpha$ -1-blocker, tamsulosin has specificity for  $\alpha$ -1A receptor subtype, whilst many other  $\alpha$ -blockers block all  $\alpha$ -1 receptor subtypes in a non-specific manner. Human ureter was endowed with each alpha AR subtype, with the highest density of alpha 1 ARs in the distal ureter and a lower similar density in the mid and proximal ureters.<sup>9</sup>

Numerous clinical trials have been performed to investigate the efficacy of MET using the  $\alpha$ -1a selective  $\alpha$ -blocker alone and in combination with other drugs like NSAIDs, antispasmodic, diuretics, corticosteroids and antibiotics. Results of the various systematic reviews and meta-analyses have suggested that MET is effective, however, such analyses incorporate the biases and limitations of smaller cohort studies, resulting in their conclusions being based upon lower-quality evidence.

Alpha-blockers tend to decrease intra-ureteral pressure and increase fluid passage which might increase stone passage. Stone expulsion will decrease the need for invasive interventions and eventually decrease healthcare costs. A study on the effect of alpha-blockers as medical expulsive therapy in ureteral stones is therefore warranted. This study evaluates the efficacy of  $\alpha$ -1-blockers in MET (Medical Expulsive Therapy) for expulsion of distal ureteral stones (3-10 mm).

**MATERIALS AND METHODS:** A total of 100 patients with distal ureteral calculus were included in this prospective study from May 2015 to April 2017. Patients between 18 to 65 years of age presenting acutely with ureteric colic and unilateral distal ureteric stone  $\leq$ 10 mm confirmed by non-contrast computed tomography of the kidney, ureter and bladder (CT KUB) were included in the study. Patients with severe obstructive uropathy, infection, contraindication to  $\alpha$ -blockers, pregnancy, chronic kidney disease, bilateral ureteric stone, and stone in solitary kidney were excluded.

The selective alpha-1 blocker (tamsulosin) was used to evaluate the efficacy of medical expulsive therapy in distal ureteric medium sized calculi (3 to 10 mm). Patients were

prescribed 1 tablet of alpha-1 blocker daily at bedtime along with other medications like plenty of water with mild diuretic as oral hydration therapy (3-3.5 litres), antispasmodic, proton pump inhibitor and antiemetic till the stone expulsion or for maximum period of 28 days. Instructions were given to take analgesic drug (oral diclofenac 50 mg tablet) on colic attack and to keep chart of number of colic attacks & cumulative analgesic required during drug therapy. Patients were asked to report to hospital in the event of intractable pain not relieved on oral analgesic drug or in case of intractable vomiting, fever, and decreased urine output. Any adverse effects of drug therapy in the form of postural hypotension, dizziness, abnormal ejaculation, nausea, diarrhea were noted. Patients were advised to watch for stone-expulsion and medications were stopped after spontaneous stone-expulsion. Patients who did not pass the stone by the end of study period were investigated and those with persistent stone were referred for intervention.

All the data were entered on Excel sheet M.S. Office Excel-2010 and analyzed statistically using SPSS Statistical software (ver.22.0.0) and primer. All the Outcome variables i.e. quantitative data were summarized in the form of Mean ± SD. Study results were statistically analysed by using appropriate statistical methods such as Pearson test, ANOVA test. The differences between proportions were analyzed using Chi square test, z test. The levels of significance and error were kept 95% and 5% respectively, for all statistical analyses. P values <0.05 were considered as statistically Significant (S).

**OBSERVATIONS & RESULTS**

A total of 296 patients with symptoms of ureteric colic coming in urology department were assessed for inclusion, of which 152 patients were excluded as they did not have distal ureteric stone <10mm. The remaining 144 patients were informed of the available methods of managing distal ureteric stones and asked for their consent to enter the study; 40 refused consent for medical expulsive therapy with alpha blocker and chose surgical management in first instance. 4 patients were lost to follow up for unknown reasons hence not included in study. 100 patients of distal ureteric medium sized stones (3-10mm) were enrolled for the study.

**Table 1 Descriptive Statistics**

Parameters	Mean	Standard Deviation
Stone Size (mm)	5.71	1.58
No. of hospital visits	1.05	0.66
Analgesic Use (Diclofenac 50mg tab)	3.12	1.60
Expulsion time ( days)	7.81	2.47

**Table 2 Comparative stone expulsion rate results**

	With alpha blocker	Without alpha blocker
Cervenakov et. al. <sup>79</sup>	80.4 (41 out of 51)	62.8 (32 out of 51)
Reddy and Reddy <sup>91</sup>	72 (50)	32 (50)
Pickard et. al. <sup>96</sup>	81 (307 of 378)	80 (303 of 379)
This study	80 (100)	--

**Table 3 z-test result for difference between stone expulsion rate in study group (tamsulosin) and placebo group of other studies**

	Expulsion Rate	Failure	z-test	p-value	Interpretation
Tamsulosin 0.4 mg/day Study (100)	80	20			

Placebo	Reddy and Reddy <sup>91</sup> (50)	16	34	5.74	0.000	Significant
	Cervenakov et. al. <sup>79</sup> (51)	32	19	2.284	0.02449	Significant
	Pickard et. al. <sup>96</sup> (379)	303	76	0.000	1.000	NS

**Interpretation:** Since p-value for the z-test is less than that of 0.05 indicates that the observed expulsion rate of our study arm when compared against the placebo group expulsion rate with different studies is significant in 2 while non significant with 1 study group.

**Table 4 z test results for Expulsion Time difference in tamsulosin study group and placebo from other studies.**

	Mean Expulsion Time	SD	z-test	p-value	Interpretation
Tamsulosin 0.4 mg/day Study	7.81	0.47			
	Pickard et. al. <sup>96</sup>	12.6	331.52	0.000	Significant
Placebo	Reddy and Reddy <sup>91</sup>	3.24	-2.960	0.004	Significant

**Interpretation:** Since p-value for the t-test is less than that of 0.05 indicates that the expulsion time is significantly lesser than that of placebo expulsion time.

**Table 5 Association between stone size and stone Expulsion**

Association between Stone Size & Stone Expelled/Not	Stone Expulsion	Stone Size
	Chi-square	23.123
	Df	1
	Sig.	0.000*

**Interpretation:** Since p-value for the chi-square test is less than that of 0.05 indicates that there is significant of association between Stone size and expulsion rate. It is observed that the stone expulsion rate is significantly more for the Stone Size 5 or less.

**DISCUSSION**

Recent advances in technology and endourology have allowed ureteric stone to be treated effectively using minimally invasive techniques, which have increased success rates and decreased treatment related morbidity. MET is treatment option for patients with newly diagnosed, uncomplicated ureteric stones <10 mm in size, whose symptoms are controlled. Even ardent proponents of medical expulsive therapy concede that many supporting data come from small, single centre, low quality studies, and a large confirmatory trial has been recommended. This prompted a recent multicentre randomized controlled trial by Pickard et al<sup>10</sup> in the United Kingdom that involved over 1100 patients with ureteric stones. The trial showed this treatment to be no more efficacious than placebo at decreasing four week rates of intervention for stone clearance. This study brought into question the effectiveness of alpha blockers in patients with ureteric colic, leading to calls from the urologic community to reformulate treatment guidelines and even abandon medical expulsive therapy altogether.

To help reconcile the issue Hollingsworth et al<sup>11</sup> did a systematic review and meta-analysis of 55 RCT's. They concluded that medical expulsive therapy is beneficial for multiple health outcomes such as passage of ureteric stone and need for surgical interventions and adverse effects associated with alpha blocker use were relatively infrequent

and not severe. They recommended use of alpha blockers in patients with distal ureteric stones.

Mean age of cases was 36.66 years. In a study of Reddy et al mean age was 27 years in tamsulosin group, while in study of Pickard et al<sup>10</sup> & Furyk JS et al<sup>12</sup> it was 43 & 45 years in tamsulosin group respectively. While mean age was 40.7 years in meta-analysis of Hollingsworth et al.<sup>11</sup> There was no statistical significant difference in the age distribution and stone expulsion in our study which is similar to other studies.<sup>13,14,15</sup> In this study there were 66 males and 34 females suggesting male preponderance which was similar to studies by Pickard et al<sup>10</sup>, Furyk JS et al<sup>12</sup> and Reddy et al<sup>13</sup>. Out of 66 males, stone was expelled in 53 males while among 34 females 27 expelled stone. There was no statistical difference with respect to stone expulsion in different genders. This was similar to most of the studies and meta-regression analysis by Hollingsworth et al<sup>11</sup> in which there was no association between sex and stone passage (P=0.85).

Average analgesic required by the patients were 3.12 doses making cumulative analgesic dose as 150 mg. This was comparable to Reddy et al<sup>13</sup> in which it was 3.86 doses while placebo group had 6.60. Many studies like Dellabella<sup>16</sup>, Porpiglia<sup>17</sup>, Autorino<sup>18</sup> have shown analgesic requirement is significantly less in tamsulosin group as compared to placebo arm. However, there is considerable variation in the absolute value of the analgesic dose which may be due to various factors like route of administration, use of different analgesic in different studies and patient's threshold for pain. 54 patients were having right sided ureteral stone, while 46 had left lower ureteric stone. Incidence of stone on either side is more or less similar with no significant association with respect to stone expulsion rate and time. This was similar to Gandhi et al<sup>19</sup> making side affected insignificant while deciding treatment choice.

Colic episode while on treatment was experienced for at least twice in 56% while single colic episode was experienced by 21%. Colic episodes 3 or more were experienced by 23% patients. Patients with intractable and repeated colic attacks were advised admission and intervention, 13 out of 100 patients required intervention due to this cause. Alpha blockers by inhibiting muscular contraction lead to relaxation of lower ureteral tone thereby causing decrease in colic episodes.

Since patients were well informed and ready to accept minor side effects, alpha blockers found to be quite safe and adverse effects were reported in only 2 patients. The adverse effects were also of mild degree and did not compel patients to stop treatment. One patient had an episode of first dose postural hypotension and dizziness. Since he was already primed for this possible complication he lied down with head low position and took plenty of fluids orally and was better. He didn't have any further episode of hypotension and could continue with medication. Better side effect profile is consistent to most of the other studies which have confirmed safety of using this drug in patients with distal ureteric stone.<sup>13,14,15,19</sup>

13 patients could not continue medical expulsive therapy and had to undergo intervention due to repeated episodes of intractable colic. 7 patients of study sample at the end of study interval showed persistence of stone. This marks the importance of follow up, thus only those who are willing for follow up should be offered this therapy. All patients who failed medical expulsive therapy underwent ureteroscopic intervention successfully. Thus alpha blockers can be offered as initial treatment choice in properly selected patients failing which patients can undergo intervention.

The mean stone size in this study was 5.7 mm with standard deviation of 1.5 making average stone size range as 4-7 mm.

Furyk JS et al<sup>12</sup> had mean stone size of 4mm in tamsulosin arm and Reddy et al<sup>13</sup> had mean stone size 6.7mm in tamsulosin arm. In meta-analysis by Hollingsworth et al<sup>11</sup> the mean stone size in treatment group derived from 41 studies was 5.7mm which is exactly similar to our study. On subgroup analysis there were 53 patients with stone 5mm or less in size while 47 patients were having stone size greater than 5mm.

Stone expulsion rate was 80% in this study. This was similar to trials by Abdel-Meguid et al<sup>14</sup> (n=150) and Al Ansari et al<sup>15</sup> (n=96) in which stone expulsion rates was 81% and 82%, respectively, in tamsulosin arm. Stone expulsion rate in stone size less than 5mm was 98.1% while it was 59.6% in patients having stone size more than 5mm. On statistical analysis stone expulsion was significantly greater in stone size less than 5 mm which is consistent with other studies like Al ansari et al<sup>15</sup>. They had also found significantly high rate of stone expulsion in stone < 5mm in patients receiving tamsulosin.

Since this study does not include placebo arm, so comparison and statistical analysis was done with placebo group of 3 studies namely pioneering work by Cervenokav et al<sup>20</sup>, recent multicentre large RCT by Pickard et al<sup>10</sup> and study by Reddy et al<sup>13</sup> from India. On statistical analysis it was noted that expulsion rate was statistically significantly higher when compared with placebo group of Cervenokav et al<sup>20</sup> and Reddy et al<sup>13</sup> confirming efficacy of alpha blocker medical expulsive therapy.

Mean stone expulsion time was 7.81 days. In male population it was 8 days while in females it was 7.2 days. There was no significant association between stone expulsion time and age group or gender. In a study by Reddy et al<sup>13</sup> mean stone expulsion time in tamsulosin group was 7.75 days which is very similar to this study. While in a study by Pickard et al<sup>10</sup> mean stone expulsion time was 16 days. This difference in expulsion time may be because study population by Pickard et al<sup>10</sup> comprised of patients having stones anywhere in the ureter upper, middle or lower. Moreover the highest concentration of alpha receptors is in distal ureter thus alpha blocker drugs will act maximally in distal ureter.

## CONCLUSION

Medical expulsive therapy (MET) which consists of adequate hydration with mild diuretic, antispasmodic, anti-inflammatory with prime constituent being alpha blocker is safe and effective treatment modality for treatment of uncomplicated distal ureteric stone less than 10mm. Age, sex, side affected were not significantly associated with stone expulsion. Alpha blockers being selective, cause relaxation of smooth muscles of distal ureter thereby increasing stone expulsion rate, decreasing mean days to stone expulsion and simultaneously decreasing acute colic and need for analgesia. Appropriately used it may have substantial cost effective benefits by reducing the number of interventional procedures and the acute attacks too. Thus well informed properly selected patients who are willing for conservative treatment option medical expulsive therapy with alpha blocker can be safely recommended.

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