

## ALPHA 1 BLOCKERS IN COMBINATION WITH OTHER DRUGS FOR MEDICAL TREATMENT OF URETERIC CALCULI

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**ABSTRACT: OBJECTIVE:** To compare affectivity of adrenergic alpha1 receptor antagonists (Alpha 1 blockers) in different combinations, with simple observations in terms of distal ureteric stone expulsion. **STUDY DESIGN:** Randomized trial. **MATERIALS AND METHODS:** This study was conducted in Kanpur during period of 2 years from May Dec. 2010 to Nov 2012. Total 120 patients were divided into four groups containing 30 patients in each group. Group A patients were offered alpha 1 blocker (Tamsulosin) alone while group B patients treated with alpha1 blocker (tamsulosin) with synthetic steroid (Deflazacort), group C patients were treated with alpha 1 blocker (tamsulosin) with calcium channel blocker (Nifedipine) and group D were given NSAIDS analgesics only as control group. Data regarding stone size, stone expulsion rate and passage time, and Pain control were collected and analyzed. Frequency and percentages were calculated for categorical variables while mean  $\pm$  SD was used to express continuous variables. Chi square test and Student t test were used to compare categorical and numerical variables respectively. **RESULTS:** After randomization, data for 30 patients in each group were analyzed. The mean age of patients in groups A, B, C and D was  $37.37 \pm 7.51$  years,  $37.90 \pm 10.34$  years,  $38.78 \pm 8.82$  years and  $37.34 \pm 7.6$  years respectively (p 0.756). The mean stone size was  $6.39 \pm 1.78$  mm in group A compared to  $6.47 \pm 1.71$  mm in group B,  $7.42 \pm 1.2$  in group C and  $6.12 \pm 2.4$  in group D (p 0.81). In group A, for stone size of  $<5$ mm, 12 (90%) patients expelled the stone, while for the same stone size, in group B expulsion noted in 13 (96%), patients in group C expulsion noted in all 12 patients(100%) while in control group expulsion noted in just 9 (60%). The expulsion rate in group A, B, C and D for stone size of more than 5 mm, was in 16(87%), 16( 90%) , 17(92%)and 8(38%), respectively (p < 0.001). The mean time taken for stone expulsion was  $8.32 \pm 2.73$  days in group A,  $6.88 \pm 2.46$  days in group B,  $7.22 \pm 2.3$  days in group C and  $12.23 \pm 2.12$  days in group D (p < 0.001). Patients taking tamsulosin alone or in combination experienced significantly less pain attacks compared to patients on control therapy (p 0.017). **CONCLUSION:** Alpha1 blocker (tamsulosin) is a safe and effective treatment modality for distal ureteral stones of appropriate size. Alone & different combination of tamsulosin with deflazacort and with nifedipine has definite edge over tamsulosin alone, but needs larger schoolwork for Safety and efficacy.

**KEY WORDS:** Adrenergic alpha1 receptor Antagonists, Tamsulosin, Ureter, Nifedipine, Deflazacort.

**INTRODUCTION:** Renal lithiasis is very common in northern part of India. The life time risk of developing urinary calculi is between 5 and 12%, affecting more men compared to women.<sup>1</sup> Almost 20% of urinary tract stones are found in the ureters with majority (70%) being located in the lower third of the ureter.<sup>2</sup> Recent advances in endoscopic stone management have allowed kidney stones to be treated using minimally invasive techniques, which have increased success rates and decreased treatment-related morbidity. These advances include shock wave lithotripsy (SWL), ureteroscopy,

and percutaneous nephrostolithotomy. Observation has been advocated for small ureteral stones with a high probability to pass that do not have absolute indications for surgical intervention. The rate of spontaneous passage with no medical intervention for a stone of 5 mm or smaller in the proximal ureter is estimated to be 29% to 98%, and in the distal ureter 71% to 98%<sup>3</sup>. The most important factors in predicting the likelihood of spontaneous stone passage are stone location and stone size. The choice of most appropriate modality of treatment depends on many factors such as location and size of the stone, patient's preference, and the expertise available<sup>4</sup>. The inherent complications of minimally invasive therapies are balanced by complications of failed expected treatment such as hydronephrosis, urinary tract infection and renal function derangement.<sup>5</sup>

The disease spectrum and its outcome is different in our part of the world due to various reasons such as the lack of advanced minimally invasive therapies, delay in diagnosis and investigations and less awareness. This in addition to the sparse local studies further compounds the problem<sup>6</sup>. Keeping these issues in mind and also the socio-economic conditions of the majority of our patients, this study was carried out. This study on one hand would provide local perspective of the issue, and on the other hand offer an additional treatment modality for a suitable group of patients having distal ureteral stones.

**MATERIALS AND METHODS:** This study was conducted in Kanpur extending over a period of 2 years from Dec.2010 to Nov 2012. This was a randomized controlled trial. The objective of the study was to compare the efficacy of tamsulosin alone and with combination of deflazacort and nifedipine and observation using only analgesics as control, in lower ureteral calculi in terms of stone size, stone expulsion rate, passage time, and Pain control. Approval for the study was obtained from the Ethics Committee of the hospital.

In this study, one hundred and twenty patients, presenting to outpatient department with clinical diagnosis (history and clinical examination) of ureteric colic due to ureteral calculi were included. Patients with age 18 years or older with a single unilateral stone in the lower segment of the ureter measuring less than 10 mm in the greatest dimension were included in the study. Patients with pregnancy or lactation, history of previous surgery on the ipsilateral ureter, solitary kidney, urinary tract infection, moderate or severe hydronephrosis, currently on alpha-blocker therapy, known allergy to tamsulosin, contraindications for non-steroidal anti-inflammatory agents (e.g., gastritis) or renal insufficiency, were excluded.

The diagnosis was confirmed with x-ray kidney-ureter-bladder (KUB), abdominal ultrasonography, intravenous urography (IVU), and computerized tomography scan (CT scan) where necessary. In addition investigations such as CBC, urine R/E, serum urea and Serum Creatinine were also carried out. Patients were selected through consecutive non-probability sampling and were divided into four groups A, B, C and D using lottery method. Patients in group A given alpha 1 blocker (tamsulosin) alone, Group B alpha 1 blocker (tamsulosin) with synthetic steroid (Deflazacort), group C with alpha1 blocker (tamsulosin) with calcium channel blocker (Nifedipine) and D were given NSAIDS analgesics diclofenac sodium as control group.

All patients in 4 groups received a first treatment of tramadol hydrochloride 100 mg by intravenous injection if in acute pain. After the pain resolved, the patient was enrolled in the study. Patients were explained the risks and benefits of the modality of treatment and an informed written consent was obtained.

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All 30 patients in the A group received Tab. Tramadol 50 mg. every 12 hours if required. No NSAIDS used except in study group D. Patients in group A (n=30) received a daily oral dose of tamsulosin (0.4 mg), while patients in group B (n=30) received oral tamsulosin (0.4 mg) with deflazacort 30 mg once daily. Patients in group C (n=30) were given oral tamsulosin 0.4mg with 20 mg .of Nifedipine slow release daily while Group D(n=30) was given 75 mg of diclofenac sodium only daily.

The study medications were discontinued after spontaneous stone expulsion, intervention, or at the end of the study period. Absences of stone expulsion at the end of the study or intervention before the end of the study due to uncontrollable pain or adverse events were considered failed therapy.

Follow-up visits were performed on a bi-weekly basis. At the follow-up visit, every patient underwent urine analysis, serum creatinine measurement, a plain x-ray KUB, and abdominal ultrasonography. Also patients were asked if they had seen any stone passage during urination. Abdominal CT was performed for patients with radiolucent stones if the stone was not expelled by the end of study. For patients with a stone-free ureter on the last imaging study but unnoticed stone expulsion, the date of last positive stone status was recorded. Patients who failed to spontaneously expel the stone during the study period or developed complication were offered alternative therapies in the form of ESWL, or ureteroscopy.

The efficacy of treatment was evaluated in terms of rate and time of stone passage, and frequency of pain attacks. Distal ureteral segment was defined as the part of ureter below the lower border of sacroiliac joint up to the uretero-vesical junction.

The data were analyzed using SPSS version 15 for windows. Continuous variables such as age were presented with mean  $\pm$  SD while categorical variables such as gender were expressed with frequency and percentages using 95% confidence interval. Student t test was used to compare the means of continuous variables while categorical variables were compared using Chi square or Fisher exact test, as appropriate. Probability equal to or less than 0.05 was considered statistically significant.

**RESULTS:** A total of 120 patients were enrolled in the study. Each group consist 30 Patients. All patients followed protocol and none removed from study. The mean age of patients in Group A B C D was  $37.37 \pm 7.51$  years  $37.90 \pm 10.34$  years,  $38.78 \pm 8.82$  years and  $37.34 \pm 7.6$  years respectively (p 0.756). The mean stone size was  $6.39 \pm 1.78$  mm in group A compared to  $6.47 \pm 1.71$  mm in group B,  $7.42 \pm 1.2$  in group C and  $6.12 \pm 2.4$  in group D (p 0.81).Table 1.

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<b>TABLE NO. 1 BASE LINE PATIENTS CHARACTERSTICS</b>				
<b>Patients</b>	<b>Group A</b>	<b>Group B</b>	<b>Group C</b>	<b>Group D</b>
	<b>(n=30)</b>	<b>(n=30)</b>	<b>(n=30)</b>	<b>(n=30)</b>
<b>Age</b>				
<b>Mean</b>	37.37	37.90	38.78	37.34
<b>S.D.</b>	7.51	10.34	8.82	7.6
<b>Gender</b>				
<b>Male</b>	21	24	22	20
<b>Female</b>	9	6	8	10
<b>Stone Size</b>				
<b>Mean</b>	6.39	6.47	7.42	6.12
<b>S.D.</b>	1.78	1.71	1.21	1.34
<b>Stone Side</b>				
<b>Left</b>	15	18	11	12
<b>Right</b>	18	12	19	18

In group A, for stone size of <5mm, (90%) patients expelled the stone, while for the same stone size, in group B expulsion noted in (96%), patients in group C expulsion noted in (100%) patients while in control group expulsion noted in just (60%). The expulsion rate in group A, B, C and D for stone size of more than 5 mm was 87%, 90%, 92% and 38%, respectively (p < 0.001). The mean time taken for stone expulsion was 8.32 ± 2.73 days in group A, 6.88 ± 2.46 days in group B, 7.22±2.3 days in group C and 12.23 ± 2.12 days in group D (p < 0.001). table2.

<b>TABLE NO. 2 PRIMARY OUTCOME CHARACTERSTICS</b>				
<b>Patients</b>	<b>Group A</b>	<b>Group B</b>	<b>Group C</b>	<b>Group D</b>
	<b>(n=30)</b>	<b>(n=30)</b>	<b>(n=30)</b>	<b>(n=30)</b>
<b>Stone Expulsion Rate ≤5 mm size</b>				
<b>N=%</b>	90%	96%	100%	68%
<b>Stone Expulsion Rate ≥5 mm size</b>				
<b>N=%</b>	87%	90%	92%	38%
<b>Stone Expulsion Time (Days)</b>				
<b>Mean</b>	8.3	6.8	7.2	12.2
<b>S.D.</b>	2.73	2.33	2.12	2.16
<b>No. Of pain Attacks</b>				
<b>Mean</b>	1.32	1.14	1.42	1.70
<b>S.D.</b>	0.69	0.58	0.70	0.97

Patients taking tamsulosin and deflazacort experienced significantly less pain attacks compared to patients on other therapy (p 0.017).

**DISCUSSION:** Alpha-1-adrenergic receptors are located throughout the human ureter<sup>3, 13</sup>. The physiologic response to antagonism of these receptors is decreased force of contraction, decreased peristaltic frequency, and increased fluid bolus volume transported down the ureter<sup>6, 12</sup>. These responses are likely how alpha-blockers assist in ureteral stone passage. Alpha-blockers, specifically Alpha 1 antagonists, are highly effective in increasing the expulsion rate of distal ureteral stones, reducing the time to stone passage, and decreasing the amount of pain medication needed during passage stones<sup>5</sup>. Alpha blockers may also be a useful adjunct in the treatment of both ureteral and renal stones with SWL. Although increased success has been shown with calcium channel blockers with or without steroids and/or NSAIDs, Alpha1 blockers, with their high success rates, excellent safety profile, low side effect profile, and ease of use, have become the leading candidate in MET and should be used as first-line therapy in any appropriate candidate on an observation protocol during the passage of a distal ureteral stone<sup>7-10</sup>. Additionally, Alpha1 adrenergic receptor antagonists may be considered during the conservative treatment of proximal and mid-ureteral stones, and after surgical intervention of renal stones.

In this study statistically significant proportion of patients expelled ureteral stones in the tamsulosin alone group. This was the finding in patients with stone size less or more than 5 mm. This observation is corroborated by others.<sup>6, 13-15</sup> In our study however, alpha1 blockers with deflazacort or nifedipine were found to be more effective in stone expulsion as compared to tamsulosin alone, but results of tamsulosin along with deflazacort and nifedipine are almost equal so superiority of one combination over other cannot be established<sup>10</sup>. The present study confirms that patients taking tamsulosin in combination expelled the stones in significantly less time compared to patients taking analgesics only<sup>19</sup>. These results are in concordance with others who affirm our results.<sup>1, 17, 19</sup> Alpha1 blockers cause a change in the pressure gradient above, around and below the obstructing stone, thereby facilitating and expediting its passage.<sup>5</sup> while deflazacort reduces mucosal edema and nifedipine decreases the ureteric spasm<sup>8</sup> and thereby facilitating the expulsion of stone and thus adds in reduction of stone passage time.

It would be befitting to consider the shortcoming of the present study. The patients were not blinded which could have caused bias in the study results. The follow up period was short. The pain assessment and dose of analgesics was subjective, totally dependent on the patients' compliance.

**CONCLUSIONS:** Alpha 1 receptor antagonist tamsulosin is an effective and safe treatment modality for distal ureteral stones of less than 10 mm and may prove to be a useful adjunct to watchful waiting approach in these patients. When taken in combination of deflazacort or nifedipine it facilitates expulsion of stone of less than 10 mm size within short duration. Patients with distal ureteral stones given tamsulosin alone or in combination reported decreased pain using a visual analogue scale (VAS). It is therefore, recommended as a first line therapy in patients with suitable stone size and uncomplicated stone disease. This fact is even more applicable in our setting where cost and available facilities ultimately alter the treatment modality.

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