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Original Research Article.

A Study to Evaluate the Efficacy of Alfuzosin in Clearance of Distal Ureteric Calculi

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ABSTRACT

Introduction: Urinary stone disease is a major health problem not only because of high prevalence but also because it affects the young and productive population of the society. The current study was performed to assess and compare the expulsive effects of orally administered Afluzosin as medically expulsive therapy for distal ureteral calculi less than 8 mm in diameter when administered upto 21 days after the first painful manifestation.

Materials and Methods: A total of 60 patients with distal ureteric calculi were enrolled in the study and were divided in two groups. The control group comprised of 30 patients with distal ureteric calculi who were given Cap. Becosule (Vitamin B Complex) (Placebo) once a day for clearance of ureteric calculi with plenty of fluids and analgesics as and when required. The study group comprised of 30 patients with distal ureteric calculi who were given Tab. Alfuzosin hydrochloride 10 mg once a day for clearance of ureteric calculi with plenty of fluids and analgesics as and when required. The outcome was measured in terms of passage of calculi, no. of days taken for passage of calculi and no. of analgesic tablets consumed until passage. The statistical analysis was done using chi-square test for proportions and Independent samples "t" test for comparing means between the two groups and a p value less than 0.05 indicated statistically significant difference.

Results: In study group, stone was passed within 21 days of study period in 26 (86.7%) subjects whereas in control group, it could pass in only 14 (46.7%) patients thus showing a significant statistical difference between two groups (p=0.001). Mean analgesic intake was 6.63±1.38 tablets in study group and 8.63±3.26 tablets in control group, thus showing that the mean analgesic intake was significantly high in control group as compared to study group (p=0.009).

Conclusion: In our study Patients in Alfuzosin group demonstrated a higher incidence of spontaneous stone passage, more rapid stone passage and a decreased need for analgesic. This selective α1 blocker should therefore be included in different schedules used worldwide, when a conservative approach to this very common urological problem is considered.

Keywords: Medical Expulsive Therapy (MET); Renal Pain; Ureteric Calculi.

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INTRODUCTION

Urinary stone disease is a major health problem not only because of high prevalence but also because it affects the young and productive population of the society. Urolithiasis accounts for 16% of all urological admissions and 1-2% of total hospital admissions.[1] In the literature, several studies in animal models have tested the effects of different groups of drugs such as antihistamines, prostaglandins, parasympatholytic agents, etc. on ureteral function. However, the clinical use of many drugs that may be potentially beneficial in patients with ureteral stone diseases has been limited by serious side effects.[2] Alfuzosin is a quinozoline based alpha 1 receptor antagonist with similar affinity at all of the alpha 1 receptor subtypes. Alfuzosin is well absorbed after oral administration and bioavailability is about 64 % it has a half life of about 3-5 hours. The drug is 3-tightly bound to plasma proteins and only 5% of the drug is free in the circulation, alfuzosin is extensively metabolized in the liver, and little unchanged drug is excreted by the kidneys.[3]

The current study was performed to assess and compare the expulsive effects of orally administered Afluzosin as medically expulsive therapy for distal ureteral calculi less than 8 mm in diameter when administered upto 21 days after the first painful manifestation.

MATERIALS AND METHODS

The present prospective study was conducted on patients with distal ureteric calculi in the adult age group in the department of general Surgery in collaboration with Department Radiology, Era's Lucknow Medical College and Hospital, Lucknow. A total of 60 patients were enrolled in the study and were divided in two groups. The control group comprised of 30 patients with distal ureteric calculi who were given Cap. Becosule (Vitamin B Complex) (Placebo) once a day for clearance of ureteric calculi with plenty of fluids and analgesics as and when required. The study group comprised of 30 patients with distal ureteric calculi who were given Tab. Alfuzosin hydrochloride 10 mg once a day for clearance of ureteric calculi with plenty of fluids and analgesics as and when required.

Inclusion criteria comprised of all those cases who were above 18 years of age and all those patients having <8 mm ureteral calculus below the pelvic brim as identified by USG/ noncontrast CT scan and/or intravenous Pyelogram. Patients with known hypersensitivity to Alfuzosin Hydrochloride or any component of Alfuzosin hydrochloride tablet, renal or hepatic Insufficiency, urinary Infection and patients taking other alpha blockers were excluded from the study.

Alfuzosin Hydrochloride: The hydrochloride salt of alfuzosin, a quinazoline compound with smooth muscle-relaxing activity. Alfuzosin selectively binds to and antagonizes post-synaptic alpha1-adrenoreceptors in smooth muscle of the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra, initiating relaxation of smooth muscle and resulting in improvement of urine flow and the symptoms of benign prostatic hyperplasia (BPH). This agent also blocks alpha1 adrenoreceptors in peripheral vascular smooth muscle, resulting in vasodilatation and a decrease in peripheral vascular resistance.[4] Alfuzosin doesn't shrink the prostate. Instead, it relaxes the muscle around it, freeing the flow of urine and decreasing urinary symptoms. Owing to its muscle relaxant property, it is being tried as a medication for expulsion of urinary stones. It is a selective antagonist of post-synaptic alpha1-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, lower ureter, prostatic capsule and prostatic urethra. Blockade of these adrenoreceptors can cause relaxation of smooth muscle in the bladder neck.[5]

After enrolment, all the subjects were subjected to the investigations that comprises urine – routine and microscopy, culture and sensitivity, renal function tests, X ray KUB, ultrasonography KUB, excretory urograms and non-contrast CT Scan (optional).

All the patients in the study group were advised to take Tab. Afluzosin (10 mg) once a day after the last meals of the day. All the patients in the control group were advised to take Capsule Becosule (vitamin B complex) once a day after the last meals of the day. The patients were followed up at 7, 14 and 21 days. At each follow up Ultrasonography KUB was performed to assess the passage of ureteric calculi.

The outcome was measured in terms of passage of calculi, no. of days taken for passage of calculi and no. of analgesic tablets consumed until passage. The statistical analysis was done using chi-square test for proportions and Independent samples "t" test for comparing means between the two groups. The confidence level of the study was kept as 95%, hence a "p" value less than 0.05 indicated statistically significant difference.

Table I: Genderwise Distribution of patients in two groups

Gender	Study Group (n=30)		Control Group (n=30)	
	No.	%	No.	%
Male	25	83.3	26	86.7
Female	5	16.7	4	13.3

χ^2=2.095 (df=1); p=0.553

Table II: Past Treatment History

Past Treatment	Study Group (n=30)		Control Group (n=30)	
	No.	%	No.	%
No	27	90.0	28	93.3
Yes	3	10.0	2	6.7

χ^2=0.218 (df=1); p=0.640

Table III: Outcome

Finding	Study Group (n=30)		Control Group (n=30)		Statistical Significance	
	No.	%	No.	%	χ^2/t	P
Passage of stone	26	86.7	14	46.7	10.800	0.001
Day on which stone was passed						
Day 7	16	43.3	8	26.7	14.38	0.002
Day 14	10	46.7	4	13.3		
Day 21	0	0	2	6.7		
Not passed	4	13.3	16	60.0		
Mean analgesic intake	6.63±1.38		8.63±3.26		3.092	0.003

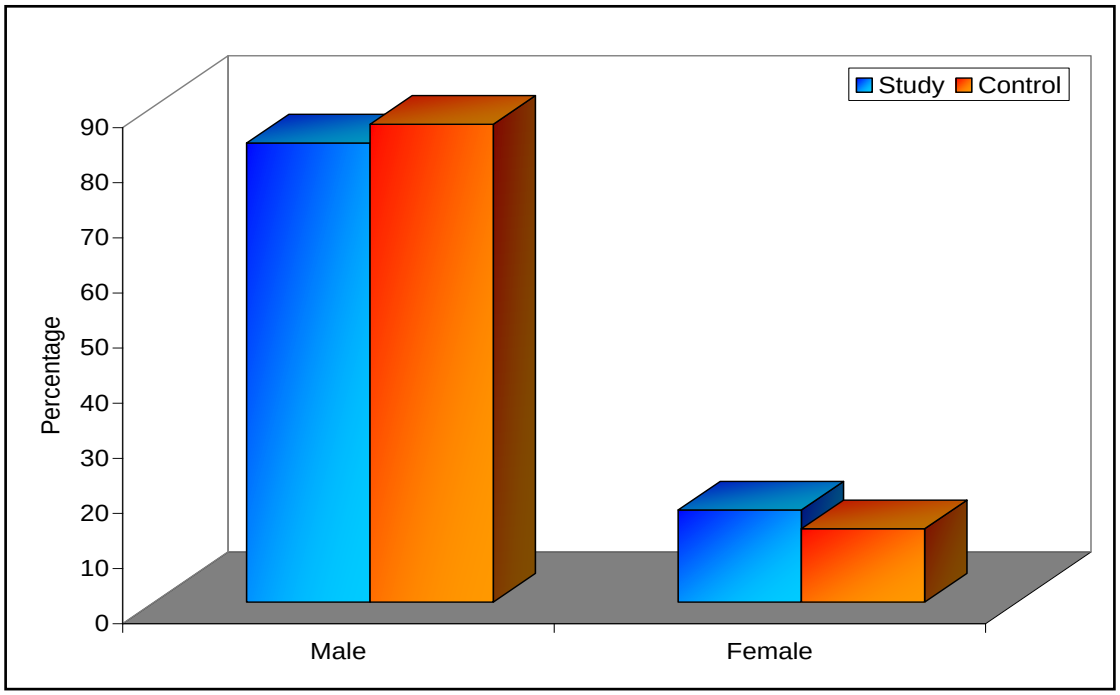

Fig 1:

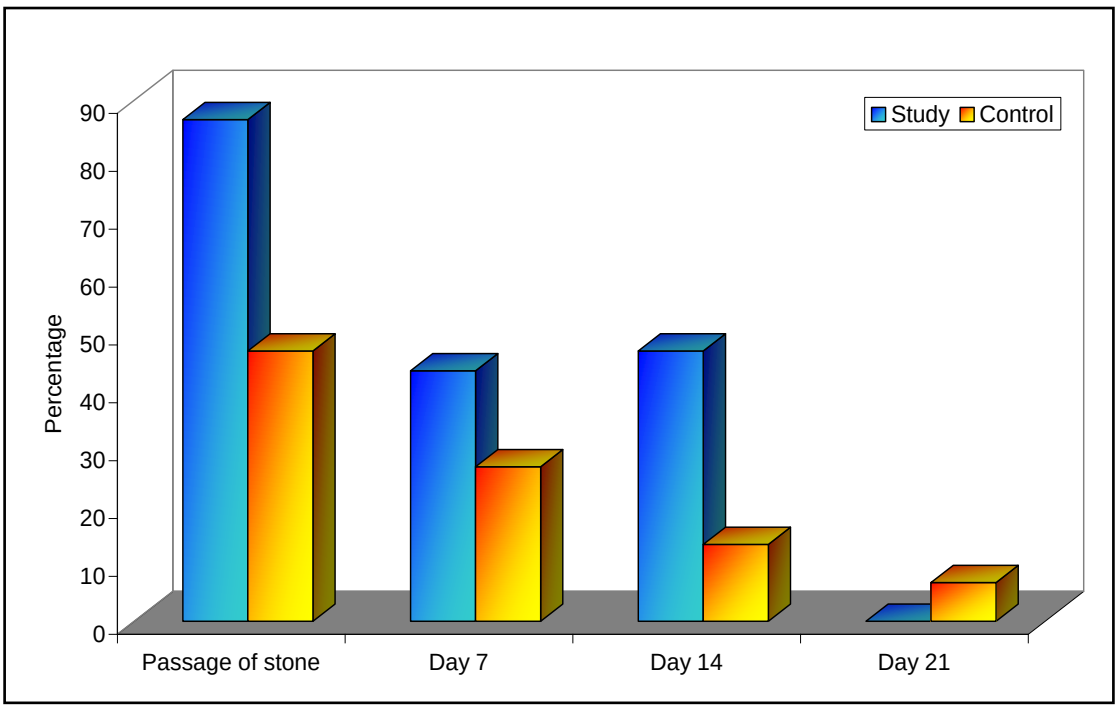

Fig 2:

RESULTS

Gender wise distribution of subjects showed that in both the groups majority of subjects were males (table 1). The male to female ratio of the study subjects was 5.67:1. Statistically, no significant difference was seen between two groups (p=0.553).

Three subjects in study group and 2 subjects in control group had a history of past treatment (Homoeopathy and Ayurveda) (table II). All the patients had a poor outcome in past treatment.

Table III shows outcome of patients. In study group, stone was passed within 21 days of study period in 26 (86.7%) subjects whereas in control group, it could pass in only 14 (46.7%) patients thus showing a significant statistical difference between two groups (p=0.001).

In study group in 16 (43.3%) patients the stone passed by the day 7 itself, in remaining 10 (46.7%) it passed by day 14 while in remaining 4 (13.3%) it could not pass even by day 21 whereas in control group on day 7 only 8 (26.7%) patients showed passage of stone, on day 14 and on day 21 the stone passed in 4 (13.3%) and 2 (6.7%) patients respectively. There were 4 (13.3%) of study group and 16 (53.3%) of control group subjects in whom stone could not pass even after 21 days. A statistically significant difference between two groups was observed (p=0.002).

Mean analgesic intake was 6.63±1.38 tablets in study group and 8.63±3.26 tablets in control group, thus showing that the mean analgesic intake was significantly high in control group as compared to study group (p=0.009). Those patients who did not pass their stone either with the active medication or on conservative line were operated. There were no side effects in either of two groups. None of the patients required hospital stay.

DISCUSSION

The treatment of ureteric calculi has significantly changed over last 20-30 years. Some conservative pharmacological approaches have been proposed in recent years. In our randomized trial, we compared the clinical efficacy of Alfuzosin α1 adrenergic antagonist) that act on ureteral smooth muscle with placebo (B-complex) group. Rest of the treatment regimen remained the same, plenty of fluids and analgesics as and when needed.

From the pioneering work of Borghi et al.[6] in which steroid and calcium channel blockers were found to increase the rate of spontaneous passage, various medications have been used. Some groups have implemented an observational approach based only on the control of pain, while others treat the mentioned cause of stone retention pharmacologically in order to facilitate expulsion.

Ukhal et al[7] were the first to report positive results in accelerating lower tract ureter stone passage using an α 1-blocker. More recently, it has been demonstrated that specific adrenoreceptor subtypes of α_{1A} and α_{1D} are prevalent in the distal part of ureter, a finding which supports the interesting results obtained by different groups with the use of tamsulosin in the treatment of selected distal ureteral calculi. Ueno et al[8] evaluated more than 500 patients and reported a spontaneous stone expulsion rate of 57% for 5 mm stones. Morse et al[9] reported that 0.6 cm stone in distal ureter was spontaneously expelled in 35% of cases at the expense of recurrent ureteric colic. Kinder et al[10] focused lower ureteric calculi and calculated a 94% frequency of passage of stones less than or equal to 5 mm and 45% for calculi greater than 5 mm. Therefore, it is difficult to choose between ESWL or ureteroscopy and observation, although the later approach can be improved by addition of pharmacological therapy which can help stone expulsion and reduce renal colic. Coll et al[11] too reported that rate of spontaneous passage of ureteral stones does vary with stone size and location.

Cervenakov et al[12] in a randomized study registered a significant statistical difference in stone expulsion rate between group treated with tamsulosin and the control group. They compared a group of 104 patients with distal ureteral calculi no larger than 10 mm in diameter receiving tamsulosin (0.4 mg daily for 8 days) plus tramadol HC, diazepam, yellon and veral with a group of similar patients receiving tramadol, diazepam, yellon and veral alone, in a non-randomized trial. A significant higher stone passage rate was observed, in the patients receiving tamsulosin than in those receiving supporting measures only (80% and 63% respectively). Furthermore, the time to spontaneous passage was shorter in the tamsulosin group.

Porpiglia et al[13] demonstrated efficacy of slow release nifedipine and corticosteroid (deflazacort 30 mg/day upto 10 days) in a prospective, randomized controlled trial. Among 96 patients with distal ureteral calculi no larger than 1 cm in diameter who were randomized to drug therapy (n=48) or conservative management (n=48), 38 (79%) of the patients in the treatment arm versus only 17 (35%) of control patients passed their stones. The mean time to passage was significantly shorter in the treatment group than in control group (7 and 20 days respectively). Furthermore, 86% less pain medication was required by the patients in the treatment group than in control group. Palpitations and transient hypotension were reported adverse effects in the treatment group.

Pedro et al[14] in their study comparing the efficacy of Alfuzosin against a placebo for spontaneous passage of stone found the overall spontaneous stone passage rate to be 75%, including 77.1% for placebo and 73.5% for alfuzosin (p = 0.83). Mean ± SD time needed to pass the stone was 8.54 ± 6.99 days for placebo vs 5.19 ± 4.82 days for alfuzosin. (p = 0.003). When comparing the improvement from the baseline pain score, the alfuzosin arm experienced a greater decrease in pain score in the days after the initial emergency department visit to the date of stone passage (p = 0.0005. In a double blind study, Ahmed et al[15] evaluated and compared the efficacy of tamsulosin and alfuzosin in the medical treatment of symptomatic, uncomplicated distal ureteral stones. In their study they assessed the efficacy of tamsulosin and alfuzosin against a placebo and found the stone expulsion rate to be 86.2%, 76.6%, and 50% in Tamsulosin, Alfuzosin and placebo group respectively. The mean expulsion time for Tamsulosin, Alfuzosin and placebo group was 7.52±7.06, 8.26±7.34, and 13.90±6.99 days, respectively. Patients taking tamsulosin and alfuzosin had fewer pain attacks than did patients taking placebo (1.24±0.57 vs. 1.43±0.67 vs. 1.75±1.17).

Agarwal et al[16] compared the efficacy of alfuzosin compared with tamsulosin in the management of lower ureteral stones. Stone expulsion was observed in 28 of 34 patients (82.3%) in tamsulosin group (Group I), 24 of 34 patients (70.5%) in alfuzosin group (Group II), and 12 of 34 patients (35.2%) in group placebo group (Group III). The average expulsion time for groups I, II, and III was 12.3, 14.5, and 24.5 days, respectively. The results of both study groups (groups 1 and 2) were superior to those in the placebo group (P = .003 and P = .001, respectively), but the study failed to show any statistically significant differences between tamsulosin and alfuzosin (P = 0.25). Despite different drug regimens, control groups and inclusion criteria, these studies all demonstrated a benefit with regard to spontaneous stone passage rates and in some cases with regard to time interval to spontaneous passage for nifedipine and corticosteroids. The role of steroid in conjunction with nifedipine could not be specifically assessed since both groups received steroid in some trials, and nifedipine and steroids were used together in all trials. However, the efficacy of calcium channel blockers is undisputable. In present study, the passage of stone within 21 days was observed in 86.7% of study group (Alfuzosin group) as compared to 14 (46.7%) of control group (Placebo) thereby indicating a statistically significant difference between the two (p=0.001). The findings are in conformity with the observations made by Pedro et al,[14] Ahmad et al[15] and Agarwal et al[16]as detailed above. In 43.3% of study group subjects the stone could pass within 7 days while in 46.7% the stone was seen to be passed by 14th day. The mean expulsion time was thus 9.69 days in study group whereas in control group it ranged from 7 days (26.7%) to 21 days (6.7%) thus showing a mean expulsion time to be 12.44 days. The relative difference between control and study group for mean expulsion time (MET) as observed in present study is comparable to the findings in literature.[17]

Although the MET reported by Pedro was much lower than that reported in present study whereas in the study of Agarwal et al[16] the values were higher than those obtained in the present study. One of the reasons for difference in these values could be the method of evaluation. In present study, we adopted a weekly follow-up schedule and the passage of stone could be confirmed ultrasonologically on the scheduled day only. Thus, in present study the confirmation of passage of stone could be made only at a 7 day interval. It might be possible that the passage of stone had taken place in any day in between yet owing to our limitations within the design of the study, these could be confirmed on the scheduled day only.

In our study we have focused on distal ureteral stones because ultrasound follow up was easy to perform, allowing a more homogenous case study with fewer possible variables. Based on literature data the distal ureteral stone expulsion rate produced by a watchful waiting approach in 25% to 54% with a mean expulsion time of greater than 10 days. With regard to the primary end point of our trial, Alfuozosin in our study proved to be superior to the watchful waiting approach, highlighting the validity and efficacy of MET rationale. In addition, the results of our trial confirm the excellent efficacy of Alfuzosin in favouring the rapid expulsion of distal ureteral stones <8 mm, clinically supporting the validity of the hypothesis of the role of α-adrenergic receptors in the physiology of ureteral motility and the pathophysiology of ureteric colic. Furthermore, in our trial, Alfuzosin therapy proved to be superior to placebo treatment for relieving the pain associated with ureteral colic. The excellent pain control observed in the group treated with Alfuzosin was also demonstrated by fact the mean analgesic intake in Study group was significantly lower as compared to that of Placebo group (p=0.003). This finding is in conformity with the findings of Pedro et al[14] and Ahmed et al.[15]

No side effect of the drug was noticed in any patient thus indicating that it is well-tolerated and can be given safely with good patient satisfaction without serious adverse effects. Therefore, medical expulsion therapy with alfuzosin hydrochloride can be suggested as first choice treatment for distal ureteric calculi less than 8 mm due to its excellent expulsive efficacy, good pain control and patient satisfaction.

CONCLUSION

In our study patients in Alfuzosin group demonstrated a higher incidence of spontaneous stone passage, more rapid stone passage and a decreased need for analgesic. This selective α1 blocker should therefore be included in different schedules used worldwide, when a conservative approach to this very common urological problem is considered. Thus the use of alfuzosin in the management of ureteric stone should be the first line approach for urologist, general surgeon and family physician. This can be done as an outpatient department, management in the patients of lower ureteric stones up to a size of 8mm. This regimen has high efficacy, decrease side effects and excellent patient satisfaction. This will also substantiate decrease in expenditure incurred.

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