Research Article

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The efficacy of alpha-blockers for expulsion of distal ureteral stones

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ABSTRACT

Background: Only very few studies describe the use of Alfuzosin, which is α adrenergic receptor blocker and not selective for any α 1 adrenergic receptor, for expulsion of distal ureteric stones. Alfuzosin is a drug with a proven efficacy and considered uroselective with high specificity and sensitivity, for the treatment of BPH. So, the present study was carried out to evaluate the efficacy of alpha blockers for expulsion of distal ureteral calculus. The objective of the study was to evaluate the efficacy of Alpha blockers for expulsion of distal ureteral calculus.

Methods: All the patients who presented to the Department of Urology in the period between January 2008 to January 2010 with history suggestive of ureteric colic were evaluated for inclusion in the study. Informed consent was obtained from all the patients. Patients were segregated into 3 groups. The investigator knew the patients in each of the groups before the start of the intervention, but the Patients didn't. All details regarding patient's demographics, Investigations, Outcome and complications were entered into the proforma.

Results: Calculus expulsion rate was highest in group C patients (receiving Alfusozin) and the difference was statistically significant. Patients with small calculus had low failure rate compared with patients having bigger calculus size. The analgesic requirement was more in the placebo groups with mean duration of more than 6 doses. The expulsion rate was more in alfusozin group than placebo. Also the intervention required was lower in alfusozin group.

Conclusions: Alpha blockers (Tamsulosin, Alfuzosin) improve the spontaneous expulsion rate of distal ureteric calculus. There is no difference in distal ureteric calculus expulsion rate between tamsulosin, and alfuzosin. Alpha blockers reduce the analgesic requirements but not the calculus expulsion time.

Keywords: Distal ureteric calculus, Tamsulosin, Alfuzosin

INTRODUCTION

The lifetime prevalence of kidney stone disease is estimated at 1% to 15%, with the probability of having a stone varying according to age, gender, race, and geographic location. Stone disease typically affects adult men more commonly than adult women. By a variety of indicators, including inpatient admissions, outpatient office visits, and emergency department visits, men are affected two to three times more frequently than women.¹

There is growing evidence that Medical Exclusive Therapy, the administration of drugs to facilitate stone passage, can be efficacious.²

Ureteral smooth muscle contraction is dependent on transcellular and intracellular calcium fluxes. Calculi may induce ureteral spasm that inhibits stone passage. An effective pharmacologic agent would inhibit spasm without significantly impacting ureteral peristalsis because the latter is thought to promote stone passage.

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Calcium channel blockers, which inhibit the influx of extracellular calcium, have been prescribed to facilitate stone passage. 3-6

Only very few studies describe the use of Alfuzosin, which is α adrenergic receptor blocker and not selective for any α 1 adrenergic receptor, for expulsion of distal ureteric stones. Alfuzosin is a drug with a proven efficacy and considered uroselective with high specificity and sensitivity, for the treatment of BPH. So, the present study was carried out to evaluate the efficacy of Alpha blockers for expulsion of distal ureteral calculus.

METHODS

2010 with history suggestive of ureteric colic were evaluated for inclusion in the study. Informed consent was obtained from all the patients. Patients were segregated into 3 groups. The investigator knew the patients in each of the groups before the start of the intervention, but the Patients didn't. All details regarding patients demographics, Investigations, Outcome and complications were entered into the proforma.

Type of the study

Prospective Cohort study with control.

Initial evaluation

All the patients who presented with history suggestive of ureteric colic were evaluated with history & physical Examination, Urinalysis & Urine culture Sensitivity, Complete Blood Count, Renal Function Test, USG KUB & X –ray KUB. Calculus size was measured based on X-ray KUB. X-ray KUB was taken initially, 28 days or after the calculus passed.

Inclusion criteria

Renal colic due to radiologically proven distal ureteric calculus

Exclusion criteria

Stone larger than 10 mm, Urosepsis, Additional calculus that might be the reason for the renal colic, Severe hydronephrosis, Known sensitivity to α blockers, Concomitant treatment with α blockers, β blockers, calcium Antagonist, nitrates, Pregnancy, Inability to provide informed consent, Previous history of surgery or endoscopic procedures in the urinary tract, History of spontaneous stone expulsion, and Known ureteral stricture

Patients were segregated into 3 groups

- 1. "A" group Patients were given Placebo
- 2. "B" group Patients were given Tamsulosin 0.4 mg/day

3. "C" group Patients were given Alfuzosin 10 mg/day

Analgesics 100 mg SR tablets were given on demand.

Duration of treatment: Until stone passage but not more than 4wks.

Primary endpoint of the study: Calculus passage.

Discontinuation of treatment

- 1. Intractable pain
- 2. Complications
 - i. Urosepsis
 - ii. Drug related complication

Statistical analysis

It was done using Chi-Square Test, Multiple range tests - Turkey -HSD Test, Levene's Test for equality of variance.

RESULTS

Total number of the patients studied was 150. Patients were segregated into 3 groups. 50 patients were allotted in each group.

Mean age of the patients in group A, B & C was 27.0, 26.8, and 25.4 years respectively. Majority of the patients were found to be in the age group of 21-30 years. Age distributions in all the 3 groups were found to be similar. In all the 3 groups Male and Female patients were distributed in equal proportions. There was no side predominance in any of the groups. Mean calculus size in group A, B & C was 6.98 mm, 6.34 mm, and 6.78 mm respectively. Patients had colicky pain for about 1.8 days before presentation duration ranged from 1-5 days.

Table 1: Comparison of calculus expulsion rate in three groups.

Groups	Expulsion	Failure	Total
A	16 (32%)	34 (68%)	50 (100%)
В	36 (72%)	14 (28%)	50 (100%)
C	37 (74%)	13 (26%)	50 (100%)

p=0.00001

Calculus expulsion rate in group a, group b and in group c were found to be 32%, 72%, 74% respectively. Calculus expulsion rate was highest in group c patients (receiving alfusozin) and the difference was statistically significant.

Only 4/56 (7.1%) cases had failures in ≤ 6 mm groups, compared with 57/94 (60.6%) in > 6 mm groups. This difference had high statistical significance in all the groups (Table 2).

Table 2: Expulsion of calculus in relation to stone size.

Cal	Group A	1	Group I	3	Group (7
c- ulu s size	Expulsi on	Failu re	Expulsi on	Failu re	Expulsi on	Fail ure
≤6 mm	11	2	24	1	17	1
>6 mm	5	32	12	13	20	12

 $p = 0.000001 \ p = 0.00016 \ p = 0.013$

Table 3: Expulsion time in relation to treatments.

Groups	No of days of treatment
A	$8.63 \pm 3.24 \text{ days}$
В	$7.75 \pm 3.14 \text{ days}$
С	$8.57 \pm 4.52 \text{ days}$

p = 0.5961

Average number of days required for expulsion of calculus was similar in all three groups and it was not statistically significant.

Table 4: Intervention requirement.

Groups	No of cases
A	34 (68%)
В	14 (28%)
С	13 (26%)

p = 0.00001

68% of patients in group A required intervention compared to only 26% in group and this difference was statistically significant.

Table 5: Analgesic requirements.

Groups	No. of doses of analgesic requirement
A	6.60 ± 1.82
В	3.86 ± 2.51
С	4.18 ± 3.02
0.02	

p = 0.03

The analgesic requirement was more in the placebo groups with mean duration of more than 6 doses.

In Placebo (Group A) Patients 16/50 (32%) of calculus found to be expelled and 34/50 (68%) patients required interventions, In Tamsulosin (group B) Patients 36/50 (62%) of calculus found to be expelled and 14/50 (28%) patients required interventions. In Alfuzosin (group C) Patients 37/50 (74%) of calculus found to be expelled and 13/50 (26%) patients required interventions. Calculus expulsion rate in Placebo, Tamsulosin and in Alfuzosin were 32%, 72%, 74% respectively (Table 6).

There was a statistically significant difference in calculus expulsion rate in between Placebo (group A) &

Tamsulosin (group B) patients and in between Placebo (group A) & Alfuzosin (group C) patients. But there was no significant difference between Tamsulosin (group B) & Alfuzosin (group C) patients, so receptor sub selectivity is not a major concern. Only 4/56 (7.1%) cases had failures in ≤ 6 mm groups, compared with 57/94 (60.6%) in ≥ 6 mm groups (Table 7).

Table 6: Comparison of various parameters.

Variable	Group A	Group B	Group C	Statistic al signific ance
No. of Patients	50	50	50	
Age (years)	27±7.3	26.7± 7.4	25.4± 5.2	NS
SEX M:F	1.6:1	1.5:1	1.6:1	NS
Side R:L	1.08: 1	1.08:1	1.6:1	NS
Stone size mm	6.98± 1.6	6.34± 1.7	6.7± 1.5	NS
Expulsio n rate	32%	72%	74%	0.00001
Expulsio n Time days	8.63 ± 3.24	7.75 ± 3.14	8.57 ± 4.52	NS
Uretero- scopy	68%	28%	26%	0.00001
Analgesi c requirem ents (doses)	6.60 ± 1.82	3.86 ± 2.51	4.18 ± 3.02	0.03

Table 7: Significance of variation among three groups.

Variables	Group A & group B	Group A & group C	Group B & group C
Age	NS	NS	NS
Stone size	NS	NS	NS
Expulsion rate	0.00006	0.00003	NS
Expulsion time	NS	NS	NS
Ureteroscopy	0.00002	0.00005	NS

DISCUSSION

150 Patients were included in the study. Patient was categorized into 3 groups. A group Patients were given Placebo, B group Patients were given Tamsulosin 0.4 mg/day and C group Patients were given Alfuzosin 10 mg/day. Each group comprised of 50 patients.

This difference had high statistical significance in all the groups [(Placebo) p value = 0.000001, (Tamsulosin) p =

0.00016, (Alfuzosin) p = 0.013] Calculus expulsion time were found to be in Placebo group A (8.63 \pm 3.24 days), in Tamsulosin group B (7.75 \pm 3.14 days) and in Group C $(8.57 \pm 4.52 \text{ days})$. There was no statistically significant difference found in between the groups. There was no statistical significance in expulsion time of calculus size of ≤ 6 mm and in > 6 mm in all the 3 groups. Analgesics requirements was more in the placebo groups, mean duration was more than 6 days. 61/150 of patients required ureteroscopy & Lithotripsy [Placebo (Group A) 34 (68%), Tamsulosin Group B 14 (28%), Alfuzosin Group C 13 (26%)]. Reason for intervention was found to be intractable pain in 51 patients, Non Expulsion of calculus in 9 patients and due to dizziness (Adverse effect of Tamsulosuin) in 1 patient. Interventions were found to be more in the Placebo Group A patients [34 (68%)]. Discontinuation of the treatment due to side effect of the drug is almost negligible. No patients complained of retrograde ejaculation, which may be due to short duration of treatment and or a possible decrease or absence of coitus due to ureteric colic.

Table 8: Distal ureteral stone expulsion rate (%).

Study	With alpha blocker	Without alpha blocker	p Value
Cervenakov et al ⁷	80.4	62.8	N/A
Dellabella et al ⁸	100	70	0.001
Porpiglia et al ⁹	85	43	< 0.001
Dellabella et al ¹⁰	97.1	64.3	< 0.0001
This study	72 (Tamsulosin) 74 (Alfuzosin)	32	0.00001

Treatments for distal ureteric calculus include watchful waiting, extracorporeal shock wave lithotripsy (SWL), Ureteroscopy and open ureterolithotomy. If possible, watchful waiting may be considered as the first choice of the treatment because it non invasive and low cost. Peschel and associates randomized 80 patients and found that those undergoing ureteroscopy achieved stone-free status more rapidly, regardless of initial stone size, than did those treated by SWL. ¹¹

There is no validated instrument available to assess the satisfaction of patients for either of these procedures, although this is an important concern. Peschel and associates measured patients' satisfaction after ureteroscopy or SWL. 11 They found that for patients with stones smaller than 5 mm, all patients undergoing ureteroscopy reported complete satisfaction, compared with 75% of those undergoing SWL. Pearle and associates also measured patients' satisfaction and found no significant difference between SWL (96%) and ureteroscopy (89%). 12

Borghi and associates, in a randomized double-blind controlled trial of 86 patients with ureteral stones less than 15 mm in width, demonstrated a statistically significant increased stone expulsion rate for patients given 40 mg nifedipine and 16 mg methylprednisolone daily for a maximum of 45 days than for patients receiving placebo and 16 mg methylprednisolone daily (86% vs 65%). 13 Furthermore, mean time to passage was also statistically significantly less with this regimen than with placebo (11.2 days vs 16.5 days). Most recently, Porpiglia and colleagues, in a randomized prospective trial, demonstrated the efficacy of nifedipine and deflazacort (an oral steroid) in treating distal ureteral stones ≤10 mm in length. The spontaneous passage rate for the control arm (75 mg diclofenac as needed) was statistically significantly lower, 35%, as compared to 79% for the treatment group (30 mg deflazacort daily for up to 10 days, 30 mg nifedipine daily for up to 4 weeks, 75 mg diclofenac as needed). Mean time to expulsion was also statistically significantly decreased with the treatment arm (7 days vs 20 days) as was average amount of diclofenac used (15 mg vs 105 mg). Serious side effects were minimal, but included transient hypotension and palpitations.

Stimulation of α-1 adrenergic receptors enhances contractile frequency and amplitude. A pharmacologic agent that antagonizes the α-1 receptor activity should therefore decrease contractile activity associated with ureteral spasm induced by calculi, thus facilitating passage. There have been reports indicating that the administration of selective α-1 blocking agents facilitates passage of ureteral calculi. Cervenakov and associates,⁷ in a nonrandomized study, administered 0.4 mg of tamsulosin, a selective α -1 antagonist, per day to 51 patients with ureteral calculi (mean W 4.0 mm and mean L 7.6 mm) and compared them to a similar number of patients with ureteral stones of similar size (mean W 3.8 mm and mean L 7.5 mm) receiving standard supportive care. Forty-one of the 51 (80.4%) receiving tamsulosin passed their stones spontaneously as compared to 32 (62.8%) in the other cohort. Time to passage was also more expeditious in the tamsulosin group. A recent randomized controlled trial by Dellabella and associates demonstrated that tamsulosin may be effective in facilitating the passage of distal ureteral calculi.8 The patients in this study had calculi ranging from 3.8 mm to 13 mm in width. Patients in the treatment group were given oral floroglucinetrimetossibenzene 3 times daily for up to 4 weeks, 30 mg deflazacort daily for 10 days, cotrimoxazole twice daily for 8 days, and 75 mg diclofenac intramuscularly as needed, while the treatment group received 0.4 mg tamsulosin daily for up to 4 weeks with the same dosages of deflazacort, co-trimoxazole, and diclofenac. Passage rates were 70% for the placebo group and 100% for the treatment group. Furthermore, mean hours to expulsion (111.1 vs 65.7), mean number of analgesic injections (2.83 vs 0.13), number of hospitalizations (10 vs 0), and number of stones requiring ureteroscopic intervention (9 vs 0) were all statistically significantly decreased in the treatment group. No drugrelated side effects were noted in any of the 60 patients included in the trial. More recently, Dellabella and associates showed, in another randomized controlled trial, that treatment of patients with distal ureteral calculi with tamsulosin was superior to both placebo and nifedipine.¹ All enrolled subjects received 30 mg deflazacort daily for 10 days, co-trimoxazole twice daily for 8 days, and 75 mg diclofenac intramuscularly as needed. The control group received floroglucinetrimetossibenzene tablets 3 times daily, and the treatment groups received either tamsulosin 0.4 mg daily or 30 mg slow-release nifedipine daily. The group treated with tamsulosin experienced a more statistically significant increase in passage rates than both the control and nifedipine groups (97.1% vs 65.7% and 75.6%, respectively). Furthermore, a statistically significant decrease in time to passage, lower analgesic requirement, decrease in work days lost, and decrease in hospitalization and need for endoscopic stone removal were also demonstrated for the group treated with tamsulosin. Terazosin, another selective α -1 adrenergic antagonist, has also recently been shown to facilitate stone passage.

Tekin and colleagues, in a prospective randomized trial of 75 patients with distal ureteral calculi ≤15 mm in width, found that patients treated with 5 mg terazosin daily for 4 weeks had a more statistically significant increase in stone passage rate than those patients receiving no treatment (77% vs 46%). Treatment with terazosin was particularly effective for stones <8 mm, as a statistically significant increase in passage rate was noticed for this subgroup (95% vs. 56%). Drug-related side effects were minimal and no patient dropped out of the study.

Our study also proved that alpha blockers are effective which is in agreement with all abovementioned studies.

CONCLUSION

Alpha blockers (Tamsulosin, Alfuzosin) improve the spontaneous expulsion rate of distal ureteric calculus. There is no difference in distal ureteric calculus expulsion rate between tamsulosin, and alfuzosin. Alpha blockers reduce the analgesic requirements but not the calculus expulsion time.

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Ethical approval: The study was approved by the

institutional ethics committee

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