# Alfuzosin Stone Expulsion Therapy for Distal Ureteral Calculi: A Double-Blind, Placebo Controlled Study

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**Purpose:** We evaluated the efficacy of alfuzosin as medical expulsive therapy for distal ureteral stone passage.

**Materials and Methods:** A total of 76 patients with a distal ureteral calculus provided consent for the study. Patients were randomized between placebo and study medication, and investigators and patients were blinded to the randomization scheme. Followup was done on a weekly basis and continued until the patient was rendered stone-free. The patient blood pressure, discomfort level, stone position on imaging, number of remaining pills and any adverse events were assessed. Statistical analysis was performed with the Student t test with $p < 0.05$ considered significant.

**Results:** The overall spontaneous stone passage rate was 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. ($p = 0.003$). There was no difference in the size or volume of stones that passed spontaneously between the placebo and alfuzosin arms, as measured on baseline computerized tomography (4.08 ± 1.17 and 3.83 ± 0.95 mm, $p = 0.46$) and by a digital caliper after stone expulsion (3.86 ± 1.76 and 3.91 ± 1.06 mm, respectively, $p = 0.57$). 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 ($p = 0.0005$).

**Conclusions:** Alfuzosin improves the patient discomfort associated with stone passage and decreases the time to distal ureteral stone passage but it does not increase the rate of spontaneous stone passage.

*Key Words: ureter, ureteral calculi, alfuzosin, pain*

The incidence of nephrolithiasis in industrialized countries is increasing. Indeed, the number of ER admissions for ureteral colic increased 55% from 1994 to 2000.[1] Most visits to the emergency room are secondary to distal ureteral stones smaller than 5 mm, which would be ideal candidates for conservative management or stone expulsive therapy.[2]

The clinical management of distal ureteral stone has benefited from an increased understanding of the molecular aspects of the ureteral muscle. Identification of $\alpha$1a-adrenergic receptor as the specific subtype responsible for the muscular tone and contraction of the ureter[3] directed the evaluation of a new line of pharmacological interventions aimed at promoting stone passage.

Blocking the action of $\alpha$1a receptors and, therefore, promoting muscle relaxation is the basis of expulsive medical therapy for ureteral stones. This relatively new treatment modality offers an attractive and less invasive option to patients. However, success rates depend not only on stone size and location, but also on the degree of obstruction and periureteral inflammation.[4] Recently several subtypes of $\alpha$-blockers were analyzed for their efficiency for facilitating stone passage.[5]

We evaluated the efficacy of the selective $\alpha$1a-blocker alfuzosin as medical expulsive therapy for distal ureteral stone passage. To our knowledge this is the first randomized, placebo controlled clinical trial of the efficacy of this drug for uncomplicated distal ureteral stone management.

## MATERIALS AND METHODS

After receiving approval from our institutional review board 76 consecutive patients who spontaneously sought medical attention for renal colic secondary to a distal ureteral calculus from January 2005 to June 2007 provided consent for the study. Patients were recruited directly from the emergency room at presentation with renal colic. Patients with stones larger than 8 mm on stone protocol CT, renal insufficiency (serum creatinine greater than 1.8 mg/dl), a solitary kidney and urinary infection were excluded from study. Other exclusion criteria were current $\alpha$-blocker use, pregnancy, or history of ureteral stricture or allergic reaction to the study medication.

Before patient recruitment the sample size needed in each study arm was estimated with the power calculation. The population required in each study arm was 35 according to the formula, $N = ([P1(100 - P1) + P2(100 - P2)]/(P2-P1)^2) \times 7.9f(\alpha\ 0.2, \beta\ 0.05) = 35$, where P1 equals 63% (the spontaneous stone passage rate in previous studies) and P2 equals 90% (study end point).

Patients were randomized between placebo and study medication using a random number assignment. A computerized random number generator was used at our research pharmacy

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for sequence generation. Randomization was done at a 1:1 ratio. Personnel at the research pharmacy generated the pill bottle labeling. Patient enrollment was performed by trained research fellows who were contacted by pager by ER physicians.

Investigators were blinded to the randomization scheme, and patients and investigators were blinded to medication until termination of the study. Patients were instructed to ingest 1 pill of the study medication per day after breakfast until the stone was passed. Subjects recorded daily pain using a visual analog pain score and they maintained a narcotic diary that recorded the number, dose and type of pain medication consumed per day. The date and time of stone passage were recorded. The criteria for treatment discontinuation as well as the need for hospitalization and/or endoscopic treatment were uncontrollable pain, fever and/or severe hydronephrosis, or lack of success of stone expulsion after 4 weeks. Patients were also instructed on the potential side effects of the study medication (fig. 1).

Stone size and volume were calculated on the first (ER) CT using ×4 zoom magnification and a digital ruler. Cross-sectional dimensions were obtained on axial images, while length was measured on coronal reconstructions. Followup was done on a weekly basis with plain x-ray if the stone was radiopaque, and with pelvic noncontrast CT if the stone was radiolucent. Followup continued until the patient was rendered stone-free by intervention or spontaneous stone expulsion. Stones were measured with a digital caliper after stone passage. If a discrepancy existed between predicted size on imaging and actual size, the patient was re-imaged with pelvic noncontrast CT. At each weekly followup the patient blood pressure, discomfort level, stone position on imaging, number of remaining pills (study compliance) and any adverse events were assessed.

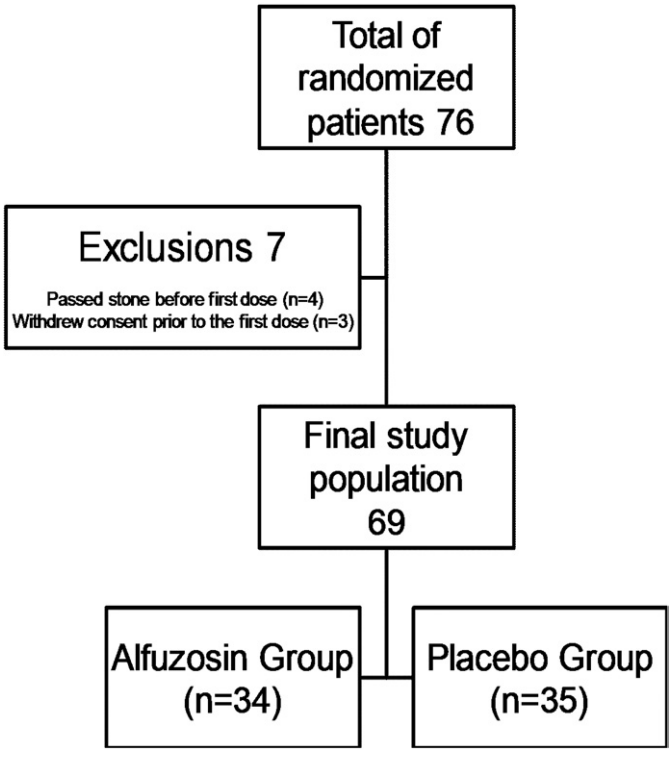


FIG. 1. Study diagram

Study data were compiled and examined with Microsoft® Excel®. Statistical analysis was performed using the Student t test with $p < 0.05$ considered significant.

## RESULTS

Seven of 76 patients were discontinued from the study due to inconsistent followup, primarily due to insurance issues that prevented followup at our clinic. No statistically significant differences were found between the groups in age, gender distribution, baseline diastolic and systolic blood pressure, degree of hydronephrosis and stone size at presentation. The alfuzosin arm unexpectedly showed a significantly higher mean ± SD baseline pain score at ER presentation than the placebo arm (8.94 ± 1.09 vs 7.59 ± 2.50, $p = 0.01$, table 1). Mean stone size on CT axial cuts in the entire study population was 3.96 ± 2.01 and 3.67 ± 0.22 mm, respectively.

The overall rate of spontaneous stone passage was 75% with no significant difference between the placebo and alfuzosin groups (77.1% and 73.5%, respectively, $p = 0.83$). Average time to stone passage was 6.78 ± 6.11 days. In the placebo arm mean time to stone passage was 8.54 ± 6.99 days, while in the alfuzosin arm it was significantly shorter at 5.19 ± 4.82 days ($p = 0.003$).

When stratifying for stone size using a range of cutoff points, alfuzosin did not impact the rate of spontaneous passage for stones 4 mm or less ($p = 0.70$), 5 mm or less ($p = 0.86$) or 6 mm or less ($p = 0.91$). There was no significant difference in the size or volume of stones passed spontaneously between the placebo and alfuzosin arms, as measured on baseline CT (4.08 ± 1.17 and 3.83 ± 0.95 mm, $p = 0.46$) and by digital caliper after stone expulsion (3.86 ± 1.76 and 3.91 ± 1.06 mm, respectively, $p = 0.57$, fig. 2).

A total of 13 patients who did not pass stones after the 4 weeks of followup were treated with semirigid ureteroscopy and 4 passed the stones in week 4. The risk of requiring surgical intervention was 17% in the alfuzosin arm and 20% in the placebo arm ($p = 0.45$).

Patients in the placebo group reported an average pain score of 3.96 ± 2.40 during followup, representing a 55% decrease from the baseline pain score of 7.59 ± 2.50 at presentation to the ER. In the alfuzosin group the average pain score during followup was 4.10 ± 2.68, representing a 61% decrease from the baseline pain score of 8.94 ± 1.09. When comparing the improvement from the baseline pain score, the alfuzosin arm experienced a greater decrease in the pain score in the days after the initial ER visit to the stone passage date ($p = 0.0005$, figs. 2 and 3).

There was no significant difference between placebo and alfuzosin with regard to the mean number of opioid derived medications consumed (9.41 ± 9.08 vs 8.63 ± 8.58 pills per patient, $p = 0.45$) or morphine equivalents consumed (8.36 ± 16.06 vs 7.59 ± 12.67 mg, respectively, $p = 0.83$, fig. 2).

Four patients (12%) in the alfuzosin arm reported minor side effects, including dizziness and transient orthostatic hypotension, and 12% in the treatment arm discontinued therapy because of side effects. No patients in the placebo arm reported side effects or discontinued therapy. Mean followup systolic and diastolic blood pressure with the patient supine or standing did not show a significant difference from baseline in the alfuzosin or placebo arm (table 2).