



Prospective Randomized Placebo Controlled Trial To Evaluate The Efficacy Of Alpha Blockers for Distal Ureteric Stone

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Abstract

Aims and Objectives: This randomized, placebo controlled trial aims to evaluate the efficacy of tamsulosin and alfuzosin in the medical management of distal ureteric stones less than 10mm.

Methods: All patients attending the OPD of Vinayaka Mission's Kirupananda Variyar Medical College with diagnosis of distal ureteric stone less than 10mm and fit for medical expulsive therapy, were included in the study. After initial screening, a total of 150 patients were randomised into three groups; group A patients were given placebo, group B given tamsulosin 0.4mg and group C given alfuzosin 10mg. Primary objective was expulsion of stone and secondary objectives looked at time to expulsion, analgesic usage, need of endoscopic intervention and side effect profile.

Results: It was found that there was a significant rate of stone expulsion in the tamsulosin and alfuzosin groups as compared to placebo. There was a decreased need for analgesic in these two groups. The need for endoscopic intervention was significantly lower in the tamsulosin and alfuzosin groups. However, when tamsulosin was compared to alfuzosin, there was no difference in their efficacy. There was also no difference in the time to stone expulsion in the 3 groups. Only one patient had side effect due to tamsulosin, which needed stoppage of therapy.

Conclusion: Tamsulosin and alfuzosin are equally efficacious in the treatment of distal ureteric stones which are fit for medical expulsive therapy. However, the superiority of one drug over the other has not been established.

Keywords: alfuzosin, distal ureteric stone, medical expulsive therapy, tamsulosin

Introduction

The lifetime prevalence of renal calculi is estimated at 1% to 15%. Stone disease more prevalent in adult men than adult women^[1]. Recent advances in endo urology have allowed kidney stones to be treated using minimally invasive techniques, which has shown an upward curve in success rates and downward slop in treatment related morbidity. These recent advances are shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy to

name a few^[2]. Though they are expensive and have inherent risks, they have the advantage of being less invasive as compared to traditional open surgical approaches. However, for small ureteral stones with a high probability to pass that do not have absolute indications for surgical intervention, observation has been advocated. To improve spontaneous stone passage rates medical expulsion therapy (MET) has been investigated as a supplement to observation, but

it can be unpredictable^[3]. The advantage of α adreno-receptor antagonists has been demonstrated as it increased the frequency of stone expulsion, reduced the time to expulsion as well as a decreased need for analgesics when given to patients suffering from renal colic due to distal ureterolithiasis. Most of the studies evaluated the efficacy of tamsulosin, which is a selective α 1A and α 1D adrenoceptors antagonist [4].

Only very few studies describe the use of alfuzosin, which is an α adrenergic receptor blocker, not selective for any α 1 adrenergic receptor, for expulsion of distal ureteric stones^[5]. Alfuzosin is a drug with a proven efficacy and considered uroselective with high specificity and sensitivity, for the treatment of benign prostatic enlargement.

The present study was carried out to evaluate the efficacy of tamsulosin and alfuzosin versus placebo for expulsion of distal ureteral stones.

Material And Methods

This prospective study was carried out at Vinayaka Mission's Kirupananda Variyar Medical college and Hospitals, Salem, Tamil Nadu after obtaining ethical clearance from institutional ethical committee. All patients (>15 years) who presented to our outpatient department (OPD) with a history of acute renal colic, between March 2021 to August 2021 were screened for inclusion after taking written consent. Detailed history, physical examination and investigations such as urine routine and microscopy, urine culture sensitivity, kidney function tests, non-contrast computed tomography (NCCT) scan were done as part of evaluation. Patients diagnosed to have distal ureteric stone (defined as stone below the lower border of sacro-iliac joint till the vesico-ureteric junction) less than 10mm were included in the study. Patients who had evidence of urosepsis, multiple ureteric stones or concomitant renal stones, evidence of severe hydronephrosis, pregnancy, history of previous urological intervention, ureteric stricture, deranged renal function tests, were excluded from the study.

Included patients were randomised into three groups according to block randomisation with sealed envelope system. Group A patients received placebo, group B received tablet tamsulosin 0.4mg (taken once a day at night), group C received tablet

alfuzosin 10mg (once a day at night). Patients were asked to hydrate adequately with approximately 3lt/day. No other medications were added except for analgesics (diclofenac 100mg sustained release tablets) which was taken on demand. Treatment was continued for 4 weeks or till stone passage, whichever was earlier. They were followed up after 4 weeks with a repeat NCCT scan. Those who gave history of stone passage underwent the scan earlier. Patients who developed severe intractable pain, urosepsis, deterioration of renal function, drug related side effects, were managed appropriately and considered failure of medical management.

Primary outcome was to evaluate the rate of calculus passage. Secondary outcomes included time till expulsion, correlation of calculus size with expulsion rate, analgesic requirement, need for endoscopic intervention and side effects. The data were analysed using SPSS 22 (IBM SPSS Statistics for Windows, version 20.0.: IBM Corp.) and variables were evaluated using the chi-square test and $p < 0.05$ was considered statistically significant.

Results

During the study period 170 patients were screened, of which 150 patients met the inclusion/exclusion criteria and were analysed (figure1). The baseline demographic characteristics are summarized in table 1. The mean calculus size in all the groups varied from 6.34-6.98mm ($p=0.138$). Most patients presented to us after 2 days of acute colicky pain. No patient lost follow up.

Primary Outcomes

Calculus expulsion rate in Group A, Group B and in Group C were found to be 32%,72%,74% respectively (figure 2). Difference was statistically significant in the treatment arms as compared to placebo ($p=0.00001$). When assessing these results in terms of failure and need for ureteroscopic removal, it was found that 68% of patients in the placebo group needed surgery as compared to 28% and 26 % in the tamsulosin and alfuzosin groups respectively ($p=0.0001$).

Secondary Outcomes

It was seen that most of the patients who had failure of expulsion had calculus size > 6mm (60%) whereas only 7.1% of the failures had calculi <6mm. The

average time to expulsion of calculus ranged from 7.75 days to 8.63 days which was not significant amongst the three groups. When the time to expulsion with regards to calculus size was compared (<6mm and >6mm), no statistically significant findings were found. Most of the patients who needed surgery for failure of medical management had calculus size >6mm ($p < 0.05$). The analgesic requirement was more in the placebo group as compared to the tamsulosin and alfuzosin groups (6.60 doses vs 3.86 and 4.18). A multivariate analysis showed a statistically significant difference between the expulsion rate and need for ureteroscopic removal in the tamsulosin and alfuzosin groups as compared to placebo, but no difference when compared to each other (table 2). Only one patient had drug related side effect (dizziness) which was due to tamsulosin.

Discussion

Renal colic is one of the most common emergencies encountered in daily urologic practice. To improve spontaneous stone passage rates, medical expulsion therapy (MET) has been investigated as a supplement to observation. Alpha-1-adrenergic receptor antagonists have been studied in this regard and has taken precedence over calcium channel blockers as the main drug used for expulsion. Alpha-1 receptors are abundantly located in the ureter, especially in the distal ureter. Blocking these receptors leads to smooth muscle relaxation and passive dilatation of the ureter, making passage of stone easy. α Adreno-receptor antagonists has been demonstrated as it increased the frequency of stone expulsion, reduced the time to expulsion as well as a decreased need for analgesics during stone passage. In patients receiving shock wave lithotripsy, they promote stone passage, and may be able to relieve ureteral stent-related symptoms. The use of α -blockers is recommended in the conservative management of distal ureteral stones in the appropriate scenario.

The EAU guidelines 2021 has concluded that medical expulsion therapy is efficacious for treating patients with ureteral stones who are amenable to conservative management^[6]. The greatest benefit might be among those with >5 mm (distal) ureteral stones (level 1a evidence). However very few studies have compared the efficacies of different types of alpha blockers used for medical expulsion therapy. Tamsulosin is a receptor non selective alpha blocker

and has been known for its extra renal side effects such as postural hypotension, stuffiness of nose and retrograde ejaculation. Alfuzosin is considered more “uroselective” and theoretically has reduced side effects, while retaining all the properties of alpha blockage.

We conducted a randomized placebo controlled trial to evaluate the efficacy of tamsulosin and alfuzosin versus placebo in patients with distal ureteric calculus. 150 patients were included in the study. They were randomised into three groups; group A patients were given placebo, group B given tamsulosin and group C given alfuzosin. Analgesic tablets were given on demand. Majority of the patients were found to be in the age group of 21-30 years with similar age distribution amongst all 3 groups. Mean calculus size were similar amongst the three groups and ranged from 6.34mm to 6.98mm. Patients had colicky pain for about 1.8 days before presentation, duration ranged in between (1-5 days).

Expulsion rate of calculus in Placebo, Tamsulosin and in Alfuzosin groups were 32%, 72%,74% respectively. This is similar to the study done by Aykut Bug̃ra Sentürk et al[7] in Turkey where he found a 70.8% rate of expulsion in the tamsulosin group and 70.2% rate in the alfuzosin group. Another study done by Rikki Singal et al[8] found an expulsion rate of 72% and 68% in the tamsulosin and alfuzosin groups respectively. There was a statistically significant difference in calculus expulsion rate when group A and group B were compared with placebo but no significance when group B and C were compared themselves. This finding could be explained by the fact that receptor sub-selectivity is not a major factor in stone expulsion and that tamsulosin and alfuzosin are equally effective in medical expulsive therapy.

The duration of stone expulsion was similar in all our three groups. This is similar to the study done by Aykut Bug̃ra Sentürk et al, where they found no difference in the expulsion time between tamsulosin and alfuzosin. However, in their study they had also evaluated the role of silodosin and found that tamsulosin had a shorter expulsion time than silodosin.

Only 4/56 (7.1%) cases had failures in ≤ 6 mm groups, compared with 57/94 (60.6%) in > 6 mm groups. This is however in contrast to another

randomised controlled study which evaluated the efficacy of tamsulosin in distal ureteric stones. They had found that, in the sub analysis, tamsulosin was more efficacious in expulsion on distal ureteric stones >5mm. However, many studies have clearly shown that smaller the size of the stone, the more likely it is to pass. It is also to be noted that, in our study, the average size of the stones was more than 6mm and there were very less stones that were less than 5mm.

The analgesic requirement was more in the placebo group as compared to the tamsulosin and alfuzosin groups. However, there was no difference in the latter group. This is in contrast to the study done by Rikki Singal et al, where they found out that alfuzosin significantly lowered the pain attacks as compared to tamsulosin.

Forty percent of the patients required ureteroscopy & Lithotripsy in Placebo Group A 34 (68%), Tamsulosin Group B 14(28%), Alfuzosin Group C 13(26%). Reason for intervention were found to be intractable pain in 51 patients, non-expulsion of calculus in 9 patients and due to dizziness (adverse effect of Tamsulosin) in 1 patient.

Only one patient had an adverse effect due to tamsulosin (dizziness) and no patient with alfuzosin had adverse effects. This shows the relative safety of both the drugs. However, the events were too small to

make a comparison between the two drugs. Referring to literature, alfuzosin has been found to be associated with less retrograde ejaculation, less postural hypotension and rhinitis.

There were some limitations in our study. Firstly, there was a limited sample size to do adequate sub analysis of the patients. However, the study was adequately powered to find out the major differences. Secondly, the long term efficacy in stone expulsion was not studied as not giving any medication to patients with stones proved an ethical problem. It was also difficult to extend the study period beyond 4 weeks as the effects of stone on kidney function was unknown and there was a potential risk to the kidneys.

Conclusion

The alpha blockers Tamsulosin and Alfuzosin improve the spontaneous expulsion rate of distal ureteric calculus as compared to placebo. They reduced the need for analgesia and need for surgical intervention. There were minimal side effects of the drugs. However, they did not decrease the time to stone passage. There was no superiority of one drug over the other in expelling distal ureteric stones.

Disclosures: Nothing to disclose. No financial aid was taken for the study

Table 1

VARIABLES	GROUP A (PLACEBO)	GROUP B (TAMSULOSIN)	GROUP C (ALFUZOSIN)
Total patients	50	50	50
Age (years)	27±7.3	26.7± 7.4	25.4± 5.2
Sex ratio (M:F)	1.6:1	1.5:1	1.6:1
Stone size (mm)	6.98± 1.6	6.34± 1.7	6.7± 1.5
Mean duration of pain (days)	1.8	1.7	1.8

Figure 2

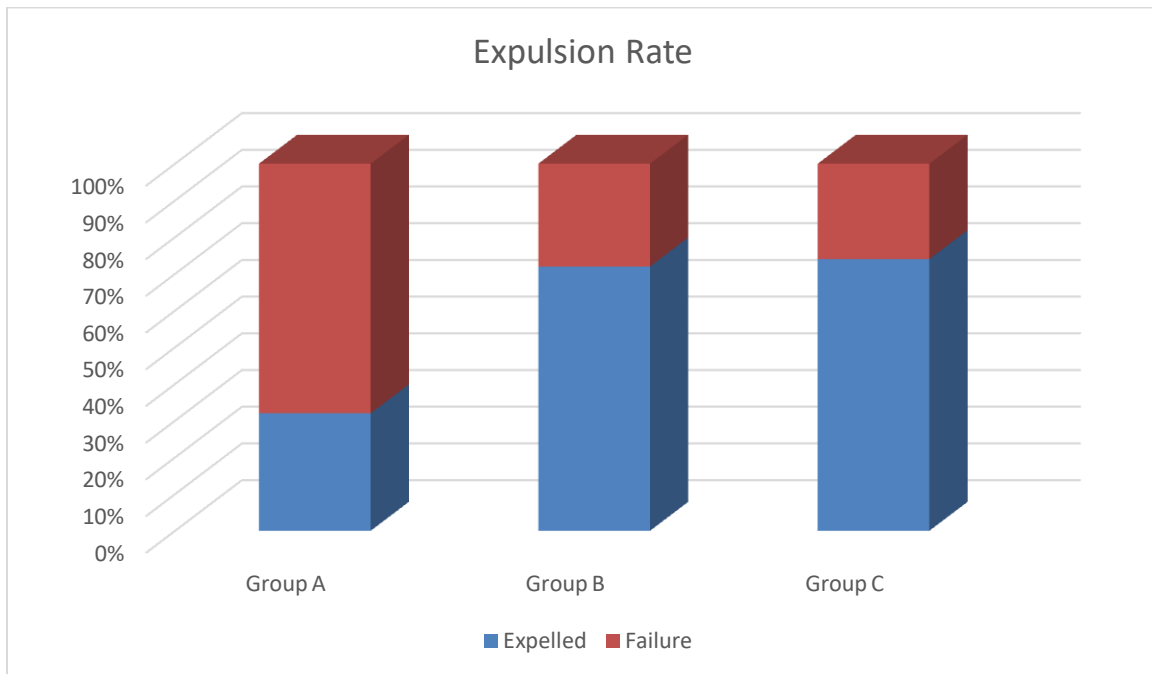
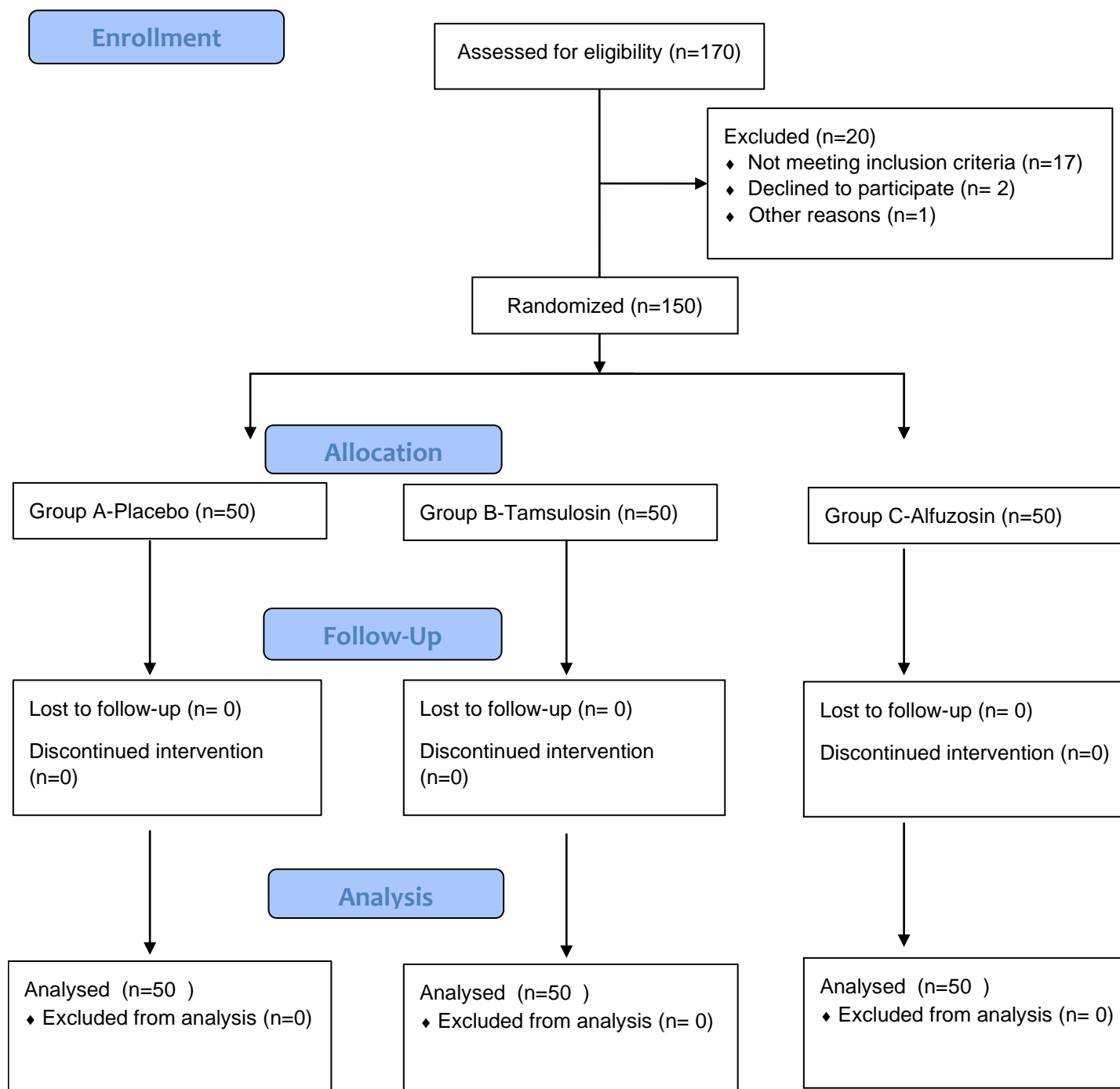


Table 2 Multivariate analysis

VARIABLE	GROUP A vs GROUP B	GROUP A vs GROUP C	GROUP B vs GROUP C
Age	NS*	NS	NS
Stone Size	NS	NS	NS
Expulsion Rate	0.00006	0.0003	NS
Expulsion time	NS	NS	NS
Need for ureteroscopy	0.0002	0.00005	NS

*NS: Non significant

FIGURE 1



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