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RESEARCH ARTICLE

A RANDOMIZED CONTROLLED STUDY OF NIFEDIPINE AND ALFUZOSIN IN THE MANAGEMENT OF DISTAL URETERIC STONES

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ABSTRACT

Introduction: Stone disease is a world wide health problem. We evaluated the efficacy of nifedipine and alfuzosin in the medical management of symptomatic, uncomplicated lower ureteral stones. **Materials & methods:** This was a randomized controlled prospective study to determine the efficacy of alfuzosin and nidedipine as medical expulsive therapy, to increase the stone-expulsion rates in distal ureteric calculus of size less than 10 mm. Patients were randomly divided into three equal groups of 70 patients each. Patients in group I received nifedipine 30 mg/day, group II received alfuzosin 10 mg/day and group III received a placebo in same dose frequency. Patients were followed up weekly until the patient was stone free or upto 28 days. Statistical analysis was performed and P<0.05 was considered to be significant. **Results:** Stone expulsion was observed in 60%, 85.7%, and 20% patients in group I,II,III respectively. A statistically significant difference was noted in between groups I vs III, groups II vs III and groups I and II (P<0001, P<0.0001 and P<0.0315 respectively). The mean pain attack episodes were 5.91+-1.01 for group I, 3.8+- 0.83 for group II, and 5.82+-1.12 for group III, which is statistically significant in group II versus III, and groups I versus II(P<0.001 and P<0.001). **Conclusions:** The use of alfuzosin and nifedipine as a medical expulsive therapy for distal ureteric stones is safe and effective in term of increased stone expulsion rate, reduced pain attacks and decreased hospital re-admissions.

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INTRODUCTION

A large number of patients presenting in surgical emergency have ureteric colic. Many of these patients suffer from distal ureteric stones (70%). Spontaneous expulsion of distal ureteral stones <-10 mm diameter occurs in 25-53% of cases. Medical expulsive therapy (MET) has been used in the management of distal ureteric stones as a supplement to conservative treatment. Tamsulosin is the most commonly studied α-1 blocker; however alfuzosin is a combined α -1 and α-1D selective adrenergic antagonist resulting in relaxation of distal ureteric smooth muscles to facilitate the passage of stone, and relieving pain. It is easily available and has less side effects. Nifedipine is a calcium channel blocker, which acts by relieving the smooth muscle spasm in the ureter without interfering with its peristaltic activity. It is effective in stone expulsion and relieving pain. We performed a comparative study to evaluate the efficacy of nifedipine and alfuzosin in the medical management of symptomatic, uncomplicated distal ureteral stones.

Aims & Objectives: To evaluate the efficacy of nifedipne and alfuzosin in the medical management of symptomatic, uncomplicated distal ureteral stones.

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MATERIALS AND METHODS

Type of study: randomized controlled study.

Duration of study: September 2016 to February 2019.

Sample size: 210.

Setting: Department of Urology, Government Stanley Medical College Hospital, Chennai

Procedure: The study was approved by the ethical committee of hospital. The sample size for each group was fixed at 70 and total for three groups was 210. After taking written informed consent, patients received tablet nifedipine 30 mg/day in Group I, tablet alfuzosin 10 mg/day in Group II and placebo in Group III as a control group. An intramuscular injection Tramadol hydrochloride 100 mg was given for persistent pain. Patients were followed-up weekly up to 28 days. USG KUB &CT KUB was performed for patients with radiolucent stones if the stone was not expelled by the end of the study. . Patients underwent ureteroscopic stone removal for persistent stones after 28 days. Patients having uncontrollable pain were readmitted for injectable analgesics, antibiotics and medication was continued. The blood pressure, stone position on imaging, number of pain attacks, time of stone-expulsion, hospital re-admission and any adverse events were recorded.

Table 1. Demographic data of all 3 groups

Variables	Group I Nifedipine (N=70)	Group II Alfuzosin (N=70)	Group III Control (N=70)	Test of significance
Sex (M:F)	38:32	52:18	46:24	
Mean Age (yrs)	32.74±9.58	30.82±7.85	33.06±8.76	0.52
Stone Size (mm)	6.5±1.78	6.26±1.85	6.37±1.85	0.86
Stone side (right/left)	42:28	46:24	44:26	
Stone Expulsion rate	42(60)	60(85.7)	14(40)	I versus III, p<0.0001 II versus III, p<0.0001 I versus II, p<0.0315
Duration of stone expulsion (days)	12.0±6.69	12.0±6.67	12.29±9.46	I versus III, p-0.927 II versus III, p-0.924 I versus II, p-0.876
Average episodes of pain	2.91±1.01	1.8±0.83	2.82±1.12	II versus III, p<0.001 I versus II, p<0.001
Hospital Readmission Rates	22(31.4)	10(14.3)	54(77.1)	I versus III, p<0.0001 II versus III, p<0.0001 I versus II, p-0.08748

Patients were assessed with history, physical examination and investigated with complete blood count, blood urea, serum creatinine, routine urine analysis, X-rays kidney, ureter, and bladder (KUB), ultrasonography, intravenous urography and helical computed tomography (CT) whenever was necessary. The distal ureter was defined as the segment from the lower border of the sacroiliac joint to the vesico-ureteric junction. Paediatric patients, Patients having previous surgery on the ipsilateral ureter, bilateral ureteric stones, multiple stones, solitary kidney, urinary tract infection, moderate or severe hydronephrosis, allergy for non-steroidal anti-inflammatory drugs, and pregnant or lactating women were excluded. Data analysis was performed using Statistical Package for the Social Sciences trial version 17.1 statistical software. Student's *t*-test, ANOVA, Chi-square, and Fisher's exact test were applied as required. The power of the study was 0.80, and the level of significance was 95%.

RESULTS

A total of 246 patients with symptoms of ureteric colic were assessed for inclusion, of which 36 patients were excluded as they did not have distal urolithiasis. The remaining 210 patients were eligible and included for the study. A statistical significant difference was observed for stone-expulsion rate between Group I versus Group II (60% vs. 85.7%, $P < 0.0315$), Group I versus Group III (60% vs. 20%, $P < 0.000$) and Group II versus Group III (85.7% vs. 20%, $P < 0.000$). Average time for stone-expulsion was 12.6 ± 6.69 days in Group Patients taking alfuzosin had fewer pain attacks compared with others. The average number of pain attacks was 2.91 ± 1.01 for Group I, 1.8 ± 0.83 for Group II, and 2.82 ± 1.12 for Group III patients. A significant statistical difference was observed between Groups II versus III, and Groups I versus II ($P < 0.001$ and $P < 0.001$, respectively). Hospital re-admissions due to uncontrollable pain occurred in 86 patients: 22 patient (31.4%) in Group I, five patients (14.3%) in Group II, and 27 patients (77.1%) in Group III. The difference was statistically significant ($P < 0.0001$) in Group I versus Group II and Group II versus Group III

DISCUSSION

Recent advances in ureteric stone management have allowed these to be treated using minimally invasive techniques, which have increased success rates and decreased treatment related morbidity. Observation can be supplemented by using MET.

The factors influencing expulsion of calculi include stone size, shape, and location. (Of these, the location of the calculus and its size are the most important factors). Characteristic distribution of α−1 receptor subtypes in distal, middle, and proximal segments is α 1D > α 1A > α 1B.[8] α−1D was the most common receptor present in all portions of the ureter. It has the strongest effect on the contractions of distal ureter and bladder detrusor, especially for the ureter-bladder wall section. α−1 receptor blockers relax ureteral smooth muscle, reduce peristalsis frequency and amplitude, decrease intraluminal pressure of the ureter, enhance transportation capability and pulses of urine. Moreover, they establish pressure gradient surrounding calculi by increasing the pressure above calculi, relax smooth muscles of the bladder neck and urethra, and finally form one thrust to expel calculi. α1-receptor blockers can also affect the C-type fast fiber of the spinal cord and the sympathetic post-ganglionic neuron; block the pain transmission pathway to central nervous system and reduce renal colic during the process of calculi expulsion.

Ideal MET drugs should inhibit incongruous contraction but without influencing the slow peristalsis. Previous studies indicated that calcium antagonist could inhibit the fast contraction phase of animal and human ureter, but without any effect on the tonic activities. Therefore, this kind of drug was thought to have potential use for calculi expulsion. Nifedipine is one potential calcium channel antagonist with less adverse effect. Our results confirmed the efficacy of nifedipine and alfuzosin for distal ureteric stones. Nearly60% of patient taking nifedipine and 85.7% of patients taking alfuzosin were able to expel their stones at the end of study compared to 20% in the control group. Alfuzosin was found to be significantly better in term of stone-expulsion compared to nifedipine and control group ($P < 0.05$). Moreover, both nifedipine and alfuzosin groups hade significantly less hospital re-admission rate as compared to the control group ($P < 0.0001$). Nifedipine and alfuzosin also decreased the frequency of pain attacks. Patients taking alfuzosin had significantly less pain as compared to nifedipine and placebo group ($P < 0.001$). The most frequently reported adverse event with α blockers was transient hypotension[19] Pedro *et al*. reported 12% adverse events in the alfuzosin group compared with 0% in the placebo group.[17] whereas Yilmaz *et al*. have reported no serious adverse events.[20] In the present study, MET related side effects were observed in eight patients (six patients taking alfuzosin developed retrograde ejaculation and two patients taking nifedipine developed an episode of hypotension), but they were able to complete the study.

Conclusions

Medical expulsion therapy is an effective add-on to observation in the conservative management of ureteral stones. The use of alfuzosin and nifedipine for uncomplicated distal ureteric stones is safe and effective in term of increased stone-expulsion rate, reduced pain attacks and decrease hospital re-admissions. Alfuzosin was found to be significantly better in terms of stone-expulsion rate and pain attacks as compared to nifedipine.

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