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Medical expulsion therapy in the management of ureteric calculi: a comparative real-life experience

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ABSTRACT

Background: One of the conservative management of ureteric caculi is by medical expulsive therapy by targeting common causes of obstruction such as edema, ureteral spasm and infection which will favour expulsion of calculi. The objective of this study was to assess comparative efficacy and safety of medical expulsive therapy of ureteric calculi

Methods: This was a randomized, prospective, open label, comparative study. Subjects satisfying inclusion and exclusion criteria were randomized into 4 groups tamsulosin, nifedipine, progesterone and control. Medical expulsion of calculi of 6mm to 15 mm size was carried out in 120 patients. Patients were followed up on OPD basis every third day. Calculi expulsion until day 28 as confirmed by abdominal ultrasonography was taken as the end point.

Results: Expulsion rate in tamsulosin group was 90%, whereas nifedipine, progesterone group were 83.33% and 70% respectively which was significant compared to control group which was 36.6% (p < 0.005). Expulsion time was also reported to be significantly less in these groups as compared to control group. Therapy related adverse effects were minor and were seen in only 6 patients.

Conclusions: Medical expulsive therapy of ureteric calculi of size 6 to 15mm with Tamsulosin, nifedipine and progesterone were safe and efficacious and could be implemented for initial management in selected patients.

Keywords: Nifedipine, Progesterone, Tamsulosin, Ureteric calculi

INTRODUCTION

According to national health and nutrition examination survey of 2012 the incidence of renal calculi in men was 10.6% and in women 7.1% and it is increasing. Symptomatic urolithiasis represents the most common condition. Incidence of urolithiasis is more common in the age group of 20 - 40 years. 2

Spontaneous passage of calculi is determined by their size and configuration, and also the smooth muscle activity of the ureter. In the passage of calculi, the greatest obstacle is usually the terminal part of the ureter, mainly in the intramural 'detrusor tunnel'. Most calculi of 5 mm or smaller, pass spontaneously with minor or no discomfort. Ureteric calculi of any size are often associated with renal obstruction, and care must be taken

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to prevent irreversible damage to the kidney by choosing definitive management plan.³

The American urological association guidelines reported that about 98% of the calculi <5mm pass spontaneously, Whereas in only 68% of the cases of 5-10mm of calculi size pass spontaneously without any treatment. Broadly the treatment options can be divided as, observation and medical therapy, shock wave lithotripsy and ureteroscopy and open surgery, laparoscopic calculi removal, or percutaneous antegrade ureteroscopy. In patients with newly diagnosed ureteric calculi of <10mm and whose symptoms are controlled, periodic evaluation and observation is an option. An appropriate medical therapy can be offered to facilitate calculi passage during observation period with regular follow up and imaging to assess the calculi position and any kidney injury. Calculi removal is indicated when there is persistent obstruction, failure of calculi passage or in presence of increasing/ unremitting colic. Last option of surgical/endourological calculi removal should be considered when all the above options fail or seems to be unlikely to be successful.4

The possible causes of calculi retention such as edema, ureteral spasm and infection can be treated with the use of drugs which can assist in expulsion of the calculi. Medical expulsive therapy is an excellent treatment option in selected patients having advantages being conservative, no hospital stays, no operative pain or protracted convalescence, safe and efficacy have been proved in a number of clinical trials.

Drugs like corticosteroids alone or in combination with alpha receptor blocker have proven to reduce inflammation that might be due to calculi and thus promote calculi passage. Alpha blockers like tamsulosin, terazosin, doxazosin have proven to benefit in expulsion of calculi in 81% according to pooled data met analysis from 6 studies and 75% with calcium channel blocker nifedipine according to pooled data of met analysis of 4 studies. Alpha blockers and nifedipine promote calculi passage mainly by their smooth muscle relaxation properties.⁴

Objective of this study was to assess comparative efficacy and safety of medical expulsive therapy of ureteric calculi.

METHODS

It was a randomized, prospective, open label, comparative study in a real-life scenario at tertiary care centre in rural parts of India.

Patients in the age group of 18 - 45 years of either sex presenting with signs and symptoms of ureteric calculus including fever, abdominal pain radiating from loin to groin, burning micturition, hematuria, nausea and vomiting, confirmed on X-ray KUB or ultrasound for ureteric caculi of size between 6 - 15mm were included in

the study. Patients with active urinary tract infection, moderate to gross hydronephrosis, hydroureter, bilateral calculi on USG, H/O hypersensitivity to study drugs and patients who were pregnant and lactating were excluded.

Patients were randomly divided into four groups. Tamsulosin group received 0.4 mg of tab tamsulosin once a day for 28 days or until the expulsion of calculus. Nifedipine group patients were admitted for atleast one week for blood pressure monitoring, received 30 mg nifedipine (slow-release) daily for a maximum of 28 days or until the expulsion of calculus. Progesterone group received 150 mg of Inj. depo (Medroxyprogesterone Acetate) on day one as a single dose. The control group received conventional hydrotherapy. All patients were advised to drink 2-2.5 litres of water per day and to strain while passing urine.

After initial analgesics for acute pain management, no regular analgesics was presumed. Oral diclofenac was given as and when needed.

Follow up

Patients were followed up on OPD basis every third day. Weekly urine analysis, S. creatinine measurements, abdominal USG and X-ray KUB in the case of radiopaque calculi was done. Patients were advised to keep a diary to record the day on which the calculi were expulsed to calculate the time for expulsion. The absence of calculi expulsion after day 28 was considered failed therapy. In these cases, ureterorenoscopy (URS) or ESWL was considered.

End point

Calculi expulsion until day 28 as confirmed by abdominal ultrasonography.

This study was conducted in accordance with the principles of declaration of Helsinki, after ethics committee approval. Written and informed consent was taken from each patient.

Statistical analysis

The study data was analyzed by using descriptive statistical analysis. Continuous variables are presented as mean±standard deviation and categorical variables are described in frequency and percentage. The difference was analysed using Mann-Whitney U test and chi square test. Statistical tests were interpreted at 5% significance level.

RESULTS

Majority of patients i.e. 43% were in the age group of 25-35 years. Percentage in number of men were more i.e. 73% than women having 27% in our study. Most common presenting symptom of the study population was

loin pain in 98.33% (118 cases) followed by burning micturition in 33.33% (40 cases) and 8% of patients presented with fever. The mean calculus size was found to be 9.15 mm. Out of total 120 patients, 58 (48%) patients presented with calculi sized 9-11 mm whereas only 19 (16%) patients presented with calculi of size between 12-15 mm and this difference was found statistically significant. Around 47% of the patients presented with the calculi in lower third of ureter and 34% of the patients in vesicoureteric junction, whereas only 19% of the patients presented with calculi in the middle third of ureter (Table 1).

Table 1: Demographic details.

Characteristics		Number	Percentage (%)
Gender	Female	32	26.67
	Male	88	73.33
Age	18-25	30	25
	26-35	52	43.33
	36-45	38	31.66
Therapy	Control	30	25
	Nifedipine	30	25
	Tamsulosin	30	25
	Progesterone	30	25
Symptoms	Loin pain	118	98.33
	Burning micturition	40	33.33
	Vomiting	20	16.16
	Hematuria	16	13.33
	Fever	8	6.66
Size of calculus	6-8	43	35.83
	9-11	58	48.33
calculus	12-15	19	15.83
Side of calculus in KUB	Left	38	55.88
	Right	30	44.11
Location of calculi in the ureter	Middle 13rd	23	19.17
	Lower 1/3rd	56	46.66
	VUJ	41	34.17

VUJ - Vescico ureteric junction.

The rate of calculi expulsion in the treatment groups compared to control group was significantly greater (p <0.001). The rate of expulsion of mid and lower ureteric calculi was not significant. Whereas there were significant results obtained with the calculi at vesicoureteric junction.

There were no significant differences between intertreatment groups comparison revealed. Rate of calculi expulsion with lower ureteric calculi reported, 86% tamsulosin, 79% nifedipine, 64% progesterone and 28% in control group. Rate of calculi expulsion with the calculi at vesicoureteric junction in the groups are; 100% tamsulosin, 90% nifedipine, 81% progesterone and 50% control group. Tamsulosin had better expulsion rate

in comparison with nifedipine which is better than Progesterone (Table 2).

Table 2: Comparative pharmacotherapeutic expulsion of uretreric calculi.

Drugs	Calculi expulsion	Percentage %
Control	11	36.6
Nifedipine	25	83.33
Tamsulosin	27	90
Progesterone	21	70

The rate of calculi expulsion in the treatment groups compared to control group is highly significant with p <0.001.

When average calculi expulsion days were compared, Tamsulosin had the least time taken for calculi expulsion of 6.29 days which was significantly lower compared to other groups (P <0.0001) followed by nifedipine with 9.04 days, progesterone with 9.76 days and control with 13.54 days (Table 3 and 4).

Table 3: Average expulsion days of calculi according to different medical expulsion therapy.

Therapy given	Mean expulsion days
Control	13.54
Nifedipine	9.04
Tamsulosin	6.29
Progesterone	9.76

The average expulsion days of calculi of treatment groups compared to control group were highly significant with P < 0.0001 and tamsulosin group having the least number of days to calculi expulsion.

Table 4: Internal comparison of difference in methods in terms of average expulsion time.

Expulsion time (Days)	Expulsion time (Days)	P-value
Tamsulosin (6.29)	Progesterone (9.76)	< 0.0001
Tamsulosin (6.29)	Nifedipine (9.04)	< 0.0001
Nifedipine (9.04)	Progesterone (9.76)	< 0.0001
Nifedipine (9.04)	Control (13.54)	< 0.0001
Progesterone (9.76)	Control (13.54)	< 0.0001
Tamsulosin (6.29)	Control (13.54)	< 0.0001

By applying two tailed Mann Whitney test, difference in terms of average expulsion time between different modalities of treatment is statistically significant except between Nifedipine and progesterone.

Therapy related adverse effects were minor and they were seen in 6 patients. Two patients experienced weakness and nasal congestion in tamsulosin group while 4 patients experienced headache and gastrointestinal disturbances in nifedipine group.

DISCUSSION

During the past 3 decades, the incidence of colorectal This study is in accordance with Griwan et al and Smith et al who observed that men were affected two times more frequently than women with ureteric calculi (Table 1), but does not comply with the study done by Francesco Porpglia et al. ^{5,6,7}

Morse and Resnic showed in the series of 378 patients, 200 patients had calculi on left side, which doesn't agree with our study but supported the presenting symptoms results which include 87% had loin pain, 17% of patients had vomiting, hematuria was seen in 3% presented with fever. Rizvi et al reported 53% of pts with lower ureteric calculi, which was similar to our study results (Table 2).9

In control group, the percent of expulsion in the present study was 36.60% which was comparable with, Priminger GM et al and Hübner WA, Irby P, Stoller ML studies. 10,11 The percent of expulsion in nifedipine group was 83.33% which was comparable with Borghi et al; Porpiglia et al, Dellabella et al. 7,11-13 The expulsion rate in tamsulosin group was 90% which was in concordance with the studies conducted by Cervenacov et al and Yilmaz et al. 14,15

The mean expulsion rate in control, nifedipine and tamsulosin group were 13.5 days, 9.5 days, 6.3 days respectively which were similar to the previous studies of Yilmaz E et al and Sayed MA et al. 15,16 Whereas, the mean expulsion rate in progesterone group was 9.76 days which does not agree with the study conducted by Mikkelson AL, et al whose mean expulsion rate with progesterone was 5.2 days. 17

It can be suggested that the effect of tamsulosin, nifedipine and progesterone on the obstructed ureter is to induce an increase in the intra-ureteral pressure gradient around the calculi, that is an increase in the urine bolus above the calculi (and consequently an increase in intraureteral pressure above the calculi) as well as decreased peristalsis below the ureter (and consequently a decrease in intraureteral pressure below the calculi) in association with the decrease in basal and micturition pressures even at the bladder neck. ¹⁶ For these reasons, there would be a stronger urge to expel the calculi.

Furthermore, the decreased frequency of phasic peristaltic contractions in the obstructed ureteral tract induced by tamsulosin might determine a decrease in or the absence of the algogenic stimulus, as in our study.

The strengths of our study are being a randomized, prospective, multi arm, comparative study. The results of our study must be interpreted cautiously as it had few limitations like being done in a single centre, having a smaller sample size, open label and additionally patients who received NSAID's for the pain management were also included in the assessment.

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institutional ethics committee

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