Research Article

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Medical expulsion therapy for ureteric calculus – possible!

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ABSTRACT

Background: Objective of the study was to compare the efficacy of combination of Tamsulosin and Deflazacort with that of analgesics alone, in medical expulsive therapy (MET) of solitary ureteric calculus ≤ 1 cm.

Methods: A prospective randomized study was conducted in 100 patients of Chennai medical college hospital & Research centre from General Surgery and Urology Out-Patient Department (OPD). Patients with symptomatic, solitary ureteric calculus ≤10mm were included. Patients with solitary functioning kidney, history of prior urinary surgery or endoscopic treatment, any associated complication or any contraindications of steroid usage were excluded. Patients were divided into two groups: Group I received Diclofenac 50mg on demand and Group II received Tamsulosin with Deflazacort (0.4mg+30mg respectively) along with analgesic for a maximum of 2weeks.

Results: Calculus expulsion was significantly higher in Group II (84%) compared to that in Group I (60%) (p=0.008). Higher expulsion rate in Group II was primarily seen in the patients with a calculus size of ≥ 5 mm. There was no difference in stone expulsion rates in patients with stones less than 5mm. 19 patients in group II were free of pain compared to 7 patients in group I (p= 0.006). Group II patients had significant reduction in expulsion time and analgesic requirement.

Conclusions: MET with alpha blocker and steroid combination is effective, safe and economical treatment for symptomatic urolithiasis and scores over treatment with analgesics, alone. This combination can be used as initial therapy for stone expulsion and symptomatic relief, thereby avoiding or delaying surgical intervention in selected patients.

Keywords: Adrenergic alpha-antagonists, Tamsulosin, Corticosteroid, Deflazacort, Ureteric calculi

INTRODUCTION

Urolithiasis has emerged as a global health issue. Almost 20% of urinary tract stones are found in the ureters. the life time risk of developing urinary calculi is between 5 and 12%, affecting more men compared to women.

Many minimally invasive interventional (ESWL and Ureteroscopy) as well as expectant (watchful waiting) treatments exist for the management of ureteric calculus. But the choice of the ideal treatment is largely decided based on the type and size of the stone, position of the

stone and the needs of the patient.³ The stone burden remains the primary factor in deciding the appropriate treatment for a patient with ureteric calculus.⁴ While a failed expectant treatment may well be complicated with deranged renal function or urosepsis, interventional techniques are not always free of complications and failure.

Recent studies have reported excellent results relating to medical expulsive therapy (MET) for ureteric calculi, in terms of stone expulsion rates and control of ureteric colic, using drugs (alpha blockers, nifedipine & prednisolone) that can modulate the function of the ureter obstructed by the stone. Recently, smooth muscle with steroid combination has been found to be effective for MET. In this study we will be evaluating the efficacy of alpha blocker with steroid for MET.

There is a paucity of trials of MET using the above combination in Indian patients. Therefore, a prospective randomised controlled trial was undertaken to compare the efficacy of Tamsulosin with Deflazacort combination against analgesics alone, for MET.

METHODS

A prospective randomized comparative study was carried out on all patients with ureteric calculus ≤ 1cm attending General Surgery and Urology OPD, CMCH&RC from January 2013 to June 2015. All patients with age of > 18yrs with a diagnosis of a symptomatic, solitary ureteric calculus, proved either on a plain Skiagram (X-ray) or Ultrasonography (USG) of the Kidney-Ureter-Bladder (KUB) or Non-Contrast Computed Tomography(NCCT) KUB with size less than or equal to 10 mm (in major axis) were included in this study. Cases having active urinary tract infection, fever, acute renal failure, chronic renal failure, history of prior urinary surgery or endoscopic treatment, history of previous ureteric calculus, Diabetes Mellitus, pregnancy, peptic ulcer disease and solitary functioning kidney were excluded from the study.

A total of 100 symptomatic cases of solitary ureteric calculus were divided randomly into a control group (Group I) and a study group (Group II).

Group I – The 50 patients included in this group were advised high fluid intake along with analgesics (Diclofenac 50 mg) as on demand during the study period.

Group II – The 50 patients in this group were given a combination of capsule Tamsulosin 0.4mg with Deflazacort 30mg (Tamfil-S) in morning, half an hour after breakfast for a maximum period of 14 days or till spontaneous passage of stone (which ever was earlier). Analgesics (Diclofenac 50 mg) on demand and high fluid intake were advised during the study period.

Prior to study, complete haemogram, blood urea, serum creatinine, urine complete examination, X-ray KUB or USG-KUB or NCCT-KUB were carried out on all patients enrolled for the study. Stone size was calculated on the plain X-ray or NCCT using a digital ruler. Patients who did not have adequate pain relief were taken up for stone removal even before completion of their follow-up period. The patients were instructed to record the date and time of stone passage. Final evaluation was done with symptom assessment and imaging with X-ray KUB and USG-KUB after completion of two weeks. A successful result was defined as complete stone

clearance. The intervention was deemed a failure if a) Patient failed to pass the stone at the end of 14 days, b) Uncontrolled pain and/or UTI and fever during study period.

The stone expulsion rate was the primary end-point of the study. The expulsion time, which was defined as the number of days from random allocation to stone expulsion, and the total diclofenac dosage were also evaluated as secondary endpoints. Statistical analysis was performed using the student 't' test and chi square test with p < 0.05 considered statistically significant.

RESULTS

The study comprised of 100 patients (Table 1). The mean age was 34.94 years (range: 19-62 years).

Table 1: Age distribution.

Age in years	Number of patients	
18-30	12	
31-40	60	
41-50	8	
51-60	16	
61-70	4	

Stone size ranged from 3 mm to 10 mm in size. Majority of patients (60%) were having stones in the range of 4-7 mm (Table 2).

Table 2: Calculus size.

Calculus size	Number of patients
1-4 mm	29
5-7mm	60
8-10mm	11

The mean stone size was 5.46 mm for Group I and 5.17 mm for Group II. There were 65 patients with right ureteric calculus and 35 with left ureteric calculus. There was no statistically significant difference between the groups, with respect to age, sex, stone size and stone localization (right/left) in the present study (Table 3).

Table 3: Stone location.

Stone location	Number of patients	
Right side	65	
Left side	35	
Stone location	Number of patients	

A stone expulsion rate of 60% (30 out of 50 patients) was observed for Group I and 84% (42 out of 50 patients) in Group II. Group II showed a statistically significant advantage in terms of the stone expulsion rate (p = 0.008). Stone expulsion as per calculus size is outlined in Table 4.

Table 4: Stone expulsion as per calculus size.

Calculus size	Stone expulsion	Group I (Analgesics)	Group II (Tamfil -S)	p- value
1-4 mm	Yes	11	16	0.79
	No	1	1	
5-7 mm	Yes	17	21	0.03
	No	16	6	
8-10 mm	Yes	2	5	0.13
	No	3	1	

The mean time taken for stone expulsion (in those who expelled) in Group I was 9.84 days, whereas it was 3.94 days in Group II. The p value was <0.005 which was highly significant.

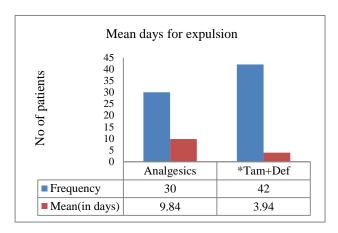


Figure 1: Mean days for expulsion. *Tam + Def = Tamsulosin + Deflazacort.

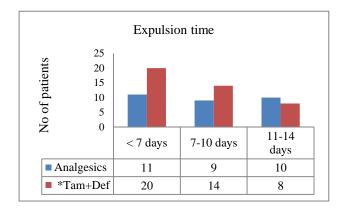


Figure 2: Expulsion time. *Tam + Def = Tamsulosin + Deflazacort.

As evident from chi square test, Group II showed a statistically significant advantage in terms of expulsion time (in days) with a p value of 0.03.19 patients in Group II, in contrast to only 7 patients in Group I were totally pain-free (p value = 0.006).

The mean number of episodes of pain, mean days of stone expulsion and mean amount of analgesic dosage used were significantly lower in group II as compared in group I (Figure 3A, 3B).

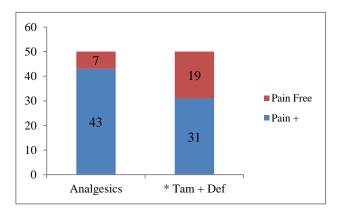


Figure 3A: Pain free patients. *Tam + Def = Tamsulosin + Deflazacort.

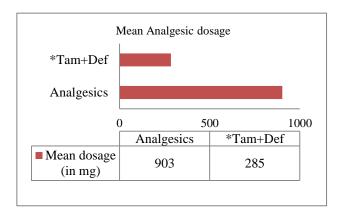


Figure 3B: Mean analgesic dosage. p value = <0.005 (highly significant). *Tam + Def = Tamsulosin + Deflazacort.

None of the patients underwent hospitalization or had emergency room visits. All the patients who were not stone free at the end of 14 days were successfully treated with ureteroscopy.

DISCUSSION

The management of patients having ureteric calculi has changed dramatically in this current era. Minimal invasiveness being the prime importance as far as selection of any treatment modality is concerned. Advances in endourological techniques and instrumentation have largely changed the management of ureteral stones from open surgeries to minimally invasive methods like ESWL and ureteroendoscopic removal of stones. However, these methods are not without complications.

Studies have reported an overall complication rate after ureteroscopy of 10-20%, with major complications such as ureteric perforation, avulsion and stricture occurring in 3-5% of procedures.⁵ Accumulation of perirenal fluid and subcapsular bleeds has been reported in 15-32% of patients treated with shock wave lithotripsy.⁶ Watchful waiting is appropriate for small stones that are not causing acute symptoms and that are likely to pass spontaneously.⁷ Spontaneous passage depends upon stone size, shape, location and associated ureteral edema.

Factors influencing stone passage can be divided into stone factors and patient factors.

Stone factors: Size, Location, Stone burden, Composition and Impaction

Patient factors: Anatomy, Symptoms, Infection, Level of obstruction, renal function and Patient need.

Majority of stones that pass do so within a period of 6 weeks after onset of symptoms. Smaller, more distal and right sided stones are more likely to pass spontaneously. However, the expectant approach may result in complications, such as infection of the urinary tract, hydronephrosis and renal function defects. There was a need to hasten the expulsion of stones in the ureter and that is where the medical expulsive therapy came in.

The presence of alpha (α) and beta (β) adrenergic receptors in the human ureter was first described in 1970. 11 It was shown later that alpha adrenergic receptors were classified into three different subtypes of $\alpha 1A$, $\alpha 1B$ and a1D, of which distribution in the human ureter was $\alpha 1D > \alpha 1A > \alpha 1B$. Alpha (α) adrenergic receptor agonists have a stimulatory effect on the ureteral smooth muscle, whereas beta adrenergic receptor agonists have an inhibitory effect. 13 a1D receptors are found in abundance in the detrusor and the intramural part of the ureter. α1A and 1D adrenergic receptors are present more densely in the distal 1/3 of ureter than other adrenergic receptors. When stimulated, they inhibit the basal tone, peristaltic wave frequency and the ureteral contractions even in the intramural part of lower ureter. $\alpha 1$ antagonists have a crucial impact in spontaneous painless elimination of the stones smaller than 8 mm located in the ureterovesical junction.¹⁴ They may work on the obstructed ureter by increasing in the intraureteral pressure gradient around the stone, there is an increase in the urine bolus above the stone (and consequently an increase in intraureteral pressure above the stone) with a decrease in peristaltic activity below the ureter (and consequently a decrease in intraureteral pressure below the stone). In addition there is a decrease in basal and micturition pressure at the bladder neck, thereby increasing the chance of expulsion.¹⁵

Successful medical expulsive therapy (MET) for patients with distal ureteric stones using the non-selective alpha blocker doxazocine was first reported in the late 1990s. 16 Since then, numerous clinical trials have been performed to investigate the efficacy of MET using the α -1A

selective alpha blocker tamsulosin alone and in combination with other drugs like corticosteroids and antibiotics. 17,18 Tamsulosin has been used in most of these studies, probably because of its tolerability and lack of need for dose titration.¹⁴ Although most studies used tamsulosin, which is a selective α -1D adrenergic receptor antagonist, efficacy with other alpha blockers such as doxazosin, terazosin, alfuzosin and naftopidil was also demonstrated. 19 The treatment by alpha-1 blockers considerably decreased not only lower urinary tract symptoms (LUTS) but also helped to accelerate the passing of minor calculi from the terminal parts of the ureters. It is also suggested that α -1 blockers potentiate the spasmoanalgesic action of drugs used in standard methods of treatment.²⁰ Tamsulosin, as a spasmolytic drug during episodes of ureteral colic due to juxtavesical calculi, observed an increased stone expulsion rate and a decrease in stone expulsion time, the need for hospitalization and endoscopic procedures. It also provided particularly good control of colic pain. 14

Steroids have also been used to aid stone passage. The rationale for this treatment is that it reduces stone induced edema and hence allows a calculus to pass. Recent studies have shown that corticosteroid drugs in association with tamsulosin seemed to induce more rapid expulsion.²¹ Deflazacort is an anti-edema agent, which is a corticosteroid drug showing good efficacy and few side effects.²² Steroids combined with alpha blockers proved more efficacious than either a steroid or alpha blocker alone. Porpiglia et al compared Tamsulosin, Deflazacort, a combination of Tamsulosin & Deflazacort and analgesics. Surprisingly, Deflazacort on its own was not very efficacious compared to tamsulosin or combination therapy. Patients benefit greatly from combination therapy but if steroids are contraindicated then adjuvant alpha blocker therapy alone will be beneficial.²³ In our study the expulsion rate in control arm (Group I-Analgesics) was 60% and in study arm (Group II -Tamsulosin with Deflazacort) was 84% with p value of 0.008 which was highly significant comparing to studies mentioned above. Our study was conducted over a period of 2 weeks, with a mean expulsion time of 4 days and the mean expulsion rate being 84%. Hence it is noted that α blockers, especially Tamsulosin, was superior to Calcium channel blockers. When combined with steroids. each was far more efficacious than when used alone. But steroid used alone was not as efficacious.

Dellabella et al showed the effectiveness of tamsulosin in improving overall stone expulsion rates whilst reducing the patient's analgesics requirements and risk of readmission to hospital, particularly when combined with a corticosteroid (which also reduced the time of expulsion). In our study, significance was seen only in the group with a calculus size of 5-7 mm. There was no difference in stone expulsion rate in patients with stones less than 5mm between MET and analgesics. This could possibly be due to the very small stone sizes, which would traverse the course of a normal ureter in due

course of time and which perhaps do not benefit by addition of MET. However, although we saw a numerical advantage for MET over analgesics in stone >7mm, the number were not statistically significant. This could be due to the small number of patients in our study with stones >7mm. A larger study with greater number of patients with the above stone denominates would perhaps yield significance in favour of MET in this group also.

MET with Tamsulosin and Deflazacort has significant benefits for both clinicians and patients. MET can induce stone expulsion in stones < 1 cm, within a few days without the need for hospitalisation or endoscopic treatments. Endoscopic treatments although widespread and largely available, result in significant costs to the healthcare system. Furthermore, it allows the patients with ureterolithiasis to continue their everyday activities using this home treatment, without the need for a great number of analgesics particularly in ureteric stones of size less than 10mm. MET can be recommended as an alternative to ureteroscopic removal. MET has been shown to be cost effective by reducing the number of ureteroscopic procedures that would require following observation alone.²⁴

CONCLUSION

This study has demonstrated the effectiveness of MET with Tamsulosin and Deflazocort, which can be easily provided in an outpatient setting and can obviate the need for an invasive procedure. This combination proved to be safe and effective, demonstrated by the low incidence of side effects and the increased stone expulsion rate with a reduced expulsion time. Moreover, MET with this drug combination considerably decreased the analgesic use and served as an effective bridge between watch & wait management and surgical intervention.

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institutional ethics committee

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