Research Article

Comparative Study of Efficacy and Safety of Tamsulosin plus Tadalafil Combination Therapy versus Tamsulosin Monotherapy as Medical Expulsive Therapy of Ureteric Stone

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ABSTRACT

Introduction: If surgical intervention is not indicated, current international guidelines and evidences recommend medical expulsive therapy (MET) involving the administration of drugs to improve spontaneous stone passage. Medical expulsive therapy has now become an established modality of treatment, and employs the use of various drugs that act on the ureter with different mechanisms. It is hypothesised that elevation of cyclic guanosine monophosphate in ureteral smooth muscle by phosphodiesterase type 5 (PDE5) inhibitors may result in ureteral relaxation and increased stone clearance.

Aims/ objective: To investigate whether we can achieve better ureteric relaxation and reduction in intramural pressure in order to facilitate stone passage by tamsulosin plus tadalafil combination therapy.

Materials and Method: Stone expulsion rate of tamsulosin + tadalafil when compared to tamsulosin was our primary endpoint. (Assessed by subjective response and confirmed by repeat plain X ray abdomen and if needed CT scan abdomen). The efficacy of the individual drugs was analysed and compared with the help of Pearson chi square test. p value <0.05 were considered as statistically significant.

Results: 33 patients (66%) receiving tamsulosin and 43 patients (86%) receiving combination therapy showed positive outcome (expulsion of stones). So, tamsulosin plus tadalafil combination therapy had significantly better efficacy. In tamsulosin group 30 patients among 33 (90.9%) expelled the stone in less than 5 days. In tamsulosin plus tadalafil group, 37 patients among 43 (86%) expelled in less than 5 days. But the difference was not statistically significant. Both drugs were well tolerated by the study patients.

Conclusion: Tamsulosin plus tadalafil is more efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones compared to tamsulosin. Medical expulsive therapy also doesn't carry post-operative morbidities as compared to surgical methods.

Keywords: Ureteric Stone, Tamsulosin, Tadalafil, Stone expulsion rate, Stone expulsion time.

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INTRODUCTION

Urolithiasis is a major health concern worldwide and there is increase in its incidence and prevalence. [1] After the diagnosis of ureteral stones, the management usually comprises of observation, drainage, shockwave lithotripsy (SWL), or ureteroscopy, depending on the clinical situation. The probability of spontaneous passage of stone usually decreases with greater stone size and location above the distal ureter. [2,3] Most common initial presentation of ureteric stone is colicky pain, and almost 50% patients have recuureence of ureteric stone within 5 years.[4]

If surgical intervention is not indicated, current international guidelines and evidences recommend medical expulsive therapy (MET) involving the administration of drugs to improve spontaneous stone passage and potentially avoid the need for surgical interventions. [5–9] Ureteric stones at the impaction site produce noticeable pathological changes; that is, an intense inflammatory reaction with mucosal oedema that could further worsen the ureteric obstruction, increasing the risk of impaction and retention.

The factors influencing stone expulsion are stone location, size, number and structure, presence of ureteral spasm, mucosal oedema or inflammation, and ureteral anatomy. Therefore, the use of medical therapy was justifiable to reduce oedema, spasm and relaxation of smooth muscles, which facilitates stone expulsion. [10, 11]

According to previous studies, the rate of expulsion stones in distal ureter by only watchful waiting is 25–54 percent and mean expulsion time was found to be more than 10 days, and is also associated with greater requirement of analgesic use even for stones less than 4 mm. In order to

improve the expulsion rate and reduce the analgesic requirement, conservative therapy is considered for distal ureteral stones. [12]

Therefore, studies have been conducted to determine the effect of a combined alpha-1A and alpha-1D selective antagonist, tamsulosin, which showed a better rate of expulsion of medium-sized stones (3-10 mm). Although medical expulsive therapy has become a standard treatment option, it is still underused by physicians in emergency departments. [13, 14]

Medical expulsive therapy has now become an established modality of treatment, and employs the use of various drugs that act on the ureter with different mechanisms. The wall of the ureter contains smooth muscle cells with α-1adrenergic receptors, especially in the distal third. The blocking of these receptors subsequently decreases basal smooth muscle contraction and causes propulsive antegrade peristalsis facilitating stone expulsion. [15, 16] Thus, by increasing the intra-ureteral pressure gradient around the stone, α1-adrenergic receptor blockers expel distal ureteral stones. Tamsulosin has a proven role of greater stone expulsion rate and less stone expulsion time. [17, 18]

It is hypothesised that elevation of cyclic guanosine monophosphate in ureteral smooth muscle by phosphodiesterase type 5 (PDE5) inhibitors may result in ureteral relaxation and increased stone clearance. This has been studied further in meta-analyses [19, 20] that concluded that tadalafil facilitated distal ureteral stone expulsion and reduced the time to stone expulsion, but most of the cited studies had an unclear chance of selection or performance bias; thus, high-quality placebo-controlled studies are needed before we can come to any conclusion regarding the role of PDE5 inhibitors.

Due to its smooth muscle relaxant properties, tadalafil has been granted approval by the United States Food and Drug Administration for lower urinary tract symptoms with benign prostatic hyperplasia and erectile dysfunction. It has also received US Food and Drug Administration approval for pulmonary arterial hypertension in men and women.

Therefore, by combining drugs that act through different mechanisms, our aim was to investigate whether we can achieve better ureteric relaxation and reduction in intramural pressure in order to facilitate stone passage. This was our main goal behind using tadalafil with tamsulosin.

MATERIALS AND METHODS

This was an open label, randomised, parallel design, prospective study done in department of urology of tertiary care hospital of east India. This study was started after approval of institutional ethics committee and taking informed consent from study participants.

Inclusion Criteria

Diagnosed case of Ureteric stone, Age > 18 Years, Size of Ureteric Stone (As Detected by USG) – 5-10 mm, Site of Ureteric Stone – Distal one-third of ureter, Solitary stone, short duration of pain < 2 week,

Exclusion Criteria

Significant Hydronephrosis, Urinary Tract Infection, Solitary kidney, Acute or chronic renal insufficiency, History of Multiple ureteral stones, Open surgery or endoscopic interventions, Concomitant treatment with β-blockers, calcium antagonists, or nitrates, Prostate Cancer, Hepatic dysfunction, Pregnancy and Breastfeeding women, Poor glycaemic control and immuno-compromised patients, Bilateral ureteric calculus, Abnormal renal/ureteric anatomy, Severe pain refractory to analgesics.

Primary Endpoint

Stone expulsion rate of tamsulosin + tadalafil when compared to tamsulosin (assessed by subjective response and confirmed by repeat plain X ray abdomen and if needed CT scan abdomen)

Secondary Endpoint

Time taken for stone expulsion when using tamsulosin + tadalafil combination therapy as compared to tamsulosin monotherapy, Analgesic use, Tolerability and Safety of tamsulosin + tadalafil combination therapy when compared to tamsulosin monotherapy

Patients who fulfilled the eligibility criteria were enrolled after screening with complete blood count, blood sugar, serum urea and creatinine estimation. Urine culture and sensitivity, ultrasound-KUB and plain X-ray KUB were also done for all the patients. Spiral CT-KUB was done when stone was not detectable in plain X-ray KUB.

Assuming expected stone expulsion rate as 60% with tamsulosin monotherapy and 85% with tamsulosin + tadalafil combination therapy as predicted from earlier evidences with 0.05 alpha value and 80% power and 1:1 allocation, minimum sample size for each group was found to be 49. So, 100 patients were randomised using web generated random numbers into **group A** (receiving tamsulosin 0.4 mg once daily) and **group B** (receiving tamsulosin 0.4 mg + tadalafil 10 mg once daily) with 50 patients in each group.

The patients were asked to come for follow up on the 7th day to the Out-Patient Department of Urology. Patients who failed to pass the stone after 7 days underwent ureteroscopy for stone removal. The compliance in both the group of patients was assessed using pill count method. Patients were asked to return the empty strips when they come for follow up.

Statistical Analysis

Statistical analysis was performed with the help of statistical package SPSS (Statistical Package for the Social

Sciences) version 21. The efficacy of the individual drugs was analysed and compared with the help of Pearson chi square test. p value <0.05 were considered as statistically significant.

RESULTS

Table 1: Baseline demographic characteristics and comparison of possible confounders

Parameters	Group A (n= 50)	Group B (n=50)	P-Value
Age	38.43 ± 7.59	39.10 ± 6.87	0.64 (Unpaired t test)
Sex			0.52 (Chi-Square)
Male	32	35	
Female	18	15	
Stone Size			0.58 (Chi-Square)
5-7 mm	43	41	
8-10 mm	7	9	
Urine Culture Result			0.45 (Chi-Square)
Negative	43	40	
E. Coli	5	9	
Klebsiella	2	1	
Dysuria			0.41 (Chi-Square)
Yes	32	28	
No	18	22	
Serum Uric Acid			0.17 (Chi-Square)
Normal	34	40	
Elevated	16	10	

Table 2: Comparison of Two Study Groups based on Outcome (Stone Expulsion)

Outcome	Number of Patients in Group A	Number of Patients in Group B	P-Value (Chi-Square)
Positive	33	43	0.019208
Negative	17	7	
Total	50	50	

Stone expulsion was much successful in patients of group B. The overall difference between two groups in term of stone expulsion was significant (P<0.05).

Table 3: Comparison of Two Study Groups based on Stone Expulsion Time

Days	Number of Patients in Group A	Number of Patients in Group B	P-Value (Chi-Square)
< 5 Days	30	37	0 .515506
>5 Days	3	6	
Total	33	43	

Stone expulsion time was generally less in group B. But this difference was not significant (P>0.05).

Table 4: Comparison of Two Study Groups based on Use of Analgesic

Use of NSAIDs	Number of Patients in Group A	Number of Patients in Group B	P-Value (Chi-Square)
1 Dose per Day	20	30	0 .012982
2 Dose per Day	13	15	
3 Dose Per Day	17	5	
Total	50	50	

There was less use of analgesic among patients of group B. The overall difference between two groups in term of analgesic use was significant (P<0.05).

Table 5: Comparison of Two Study Groups based on Adverse Drug Reaction (ADR)

ADR	Number of ADRs in Group A	Number of ADRs in Group B
Headache	8	11
Backache	7	6
Weakness	6	9
Dizziness	5	2
Penile Tumescence	3	5
GI Upset	1	4
Nausea/Vomiting	1	2
Total	31	39

There was more incidence of headache, penile tumescence and gastro-intestinal adverse effects in group B. Dizziness was reported more frequently by patients of group A.

DISCUSSION

The present study evaluated the efficacy and safety of tamsulosin plus tadalafil combination therapy as compared to tamsulosin monotherapy in the management of distal ureteric calculi as a medical expulsive therapy. Variables such as age, gender, symptoms presented with, duration of symptoms, laboratory report finding like creatinine and urine culture, and stone parameters like stone size, shape location and laterality were comparable between the two groups. The mean age of the subjects in both groups fall under the age group of 31-40 years which is similar to studies conducted by Chirag Parikh et al. [21] In this study majority of subjects in both groups were males. This male preponderance (67% males versus 33% females) is similar with studies conducted by Chirag Parikh et al. [21] It can be due to males working out in fields in hot environment which leads to dehydration. The quality of water which has been consumed is also an important factor for the development for renal stones.

Occurrence of stones was almost equal on either side in both groups. In this study 49 subjects had stones on right side and 51 had stones on left side of ureter. Regarding stone size 84 subjects had stone size between 5-7 mm and

both the groups were similar in respect of stone size. This factor may contribute to the higher positive outcome of this study. This is similar with a study conducted by Hasanain et al in which medical therapy with tadalafil 10mg with the mean stone size of 7.91mm for treatment group and 7.55mm for placebo group (p> 0.05) was significantly more effective (93% of patients) in pushing out lower ureteric stones than in the control group (67% of patients) (p value is < 0.05). [22]

Regarding the primary endpoint, the rate of expulsion of stones were assessed in both the study groups. 33 patients (66%) in group A and 43 patients (86%) in group B showed positive outcome (expulsion of stones). This result was similar with the earlier studies. [21, 23, 24] In their study, complete expulsion was seen in 86.7% cases on tamsulosin plus tadalafil as compared to only 63.3% cases on tamsulosin (p<0.05), 84.1% vs. 61.0%, (p=0.017), and 84.0% in Group as compared with 68.0% in Group B (P = 0.0130) respectively. Time taken for stone expulsion time was also assessed and compared between two groups. In tamsulosin group 30 patients among 33 (90.9%) expelled the stone in less than 5 days. In tamsulosin plus tadalafil group, 37 patients among 43 (86%) expelled in less than 5 days. But the difference was not statistically significant.

Compared with group A, the average analgesic use was less in group B and this difference was statistically significant. This result corresponds with the study conducted by Hasan et al [22] and Hari Bahadur et al [23]. This lower analgesic requirement in tamsulosin plus tadalafil group may favour its use as medical expulsive therapy.

No serious side effect occurred in any patient of both study groups. Both drugs were well tolerated by the study patients. Painful erection was significantly higher in tamsulosin plus tadalafil group. But study conducted by Bahadur et al showed 75% patients had mild penile tumescence. [23] Although frequently asked about by patients, priapism is rarely associated with PDE5 inhibitors. Several case reports have found an extraordinarily uncommon link between sildenafil and priapism, and only a single case report exists in the literature implicating tadalafil with priapism. [25]

Our study had certain limitation also. Sample size of our study was low, and patients were not followed up for longer period for recurrence or chronic adverse effects. Cost of drugs and relation of prescribing to the socio-economic status of the patient was not included in our study.

CONCLUSION

Our study results showed that tamsulosin plus tadalafil combination therapy has a significantly better ureteric stone expulsion rate as compared to tamsulosin monotherapy. This regimen also provides early stone expulsion, and a significant decrease in analgesic requirement. Both drugs were safe, effective, and well tolerated with minor side effects. So, Tamsulosin plus tadalafil is more efficacious, and well tolerated as medical expulsive therapy for distal ureteric stones compared to tamsulosin. Medical expulsive therapy also doesn't carry post-operative morbidities as compared to surgical methods.

However, sample size of our study was small and study with comparatively large sample size is need of the time to highlight better outcomes and uncommon or rare adverse effects.

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