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Comparison of Tadalafil and Tamsulosin in Medical Expulsive Therapy for Ureteric Calculus: Prospective, randomized, placebo controlled study

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ABSTRACT

Introduction and objectives: Ureteric calculi usually present as acute episode of ureteral colic. Primary aim of our study was to compare the stone expulsion rate for tadalafil and tamsulosin. We also compared time to stone expulsion, need for an analgesic requirement and side effect associated with these drugs.

Methods: 150 patients presenting with single lower ureteral stone (juxtavesical ureteral lithiasis at lower 5 cm of the ureter), 4 to $\leq$ 10 mm in size were randomized in three groups. Patients in group one received placebo and served as control, group two received phosphodiesterase 5 inhibitors (tadalafil 10mg OD) and group 3 received alfa one blockers (tamsulosin 0.4 mg OD) for accelerating the passage of the stone.

Results: The stone expulsion rate was 58% (36 of 50 patients) for the placebo group, 80 % (40 of 50 patients) for tadalafil group and 74 % for the tamsulosin group (37 of 50 patients). Tadalafil was superior to placebo in terms of stone expulsion rate (p-value: 0.017) but comparable to tamsulosin (p: 0.139). Patients in the tadalafil group had significantly less pain scores at 1 and 2 weeks follow up in comparison to the other two groups. Mean analgesic requirement for placebo, tadalafil and tamsulosin was 331, 132.93 and 277.08 mg of diclofenac respectively.

Conclusion: Tadalafil has better stone expulsion rate and faster stone expulsion as compared to tamsulosin but the difference is not statistically significant. Tadalafil results in statistically significant improvement in pain scores and decreased requirement of analgesic as compared to other two groups.

Key words: Medical expulsive therapy–ureteric calculi–tadalafil–tamsulosin

1 INTRODUCTION

Ureteric calculi form an important place in daily urologic practice, usually presenting as acute episode of ureteral colic by obstructing the urinary tract. Ureteric calculi account for 20 % of all urinary tract stones and out of those 70 % of these stones are located in distal ureter. [1, 2]

With technical advancement safety and efficacy of shock wave lithotripsy and ureteroscopy has increased resulting in its wide spread acceptance with considerable increase in cost , at the same time use of medical expulsive therapy for distal ureteric stones has decreased considerably. [3, 4]

MET has attracted many investigators worldwide and many drugs have been proposed some are used clinically, some under clinical trial , list is long and includes the calcium channel blockers, corticosteroids, α blockers, cyclo-oxygenase inhibitors, phosphdiesterase (PDE) inhibitors,

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neurokinin receptor antagonists, potassium channel openers, and nitrous oxide donors. Most of clinical trials have focused on α blockers and calcium channel blockers either alone or in combination with corticosteroids, only recently PDE inhibitors have been used for medical expulsive therapy had have proved to be safe and effective for medical management of distal ureteric stones. [5] we in our present study wanted to compare PDE inhibitors and α blockers the present standard of care for medical expulsive therapy.

2 PATIENT AND METHODS

Patient who visit urology outpatient department for lower ureteric stone disease meeting our inclusion criteria (Single ureteral stone located at lower 5 cm of the ureter 4 to $\leq$ 10 mm in size) between July 2013 to Dec 2017 were included in our study.

Patient who have active urinary tract infection, bilateral ureteral stones, moderate or severe hydronephrosis, renal insufficiency, hypotension, age less then 18 years, solitary kidney, pregnant or lactating women, history of previous surgery on the ipsilateral ureter, have any ophthalmic disorder, history of cardiac diseases or patient currently taking nitrate /Steroids/CCBs drugs, having any liver disease, peptic ulcer disease, bleeding disorders were excluded from study. Patient not willing to sign informed form or not willing for regular follow up as per study protocol were also be excluded from study.

In our institute we routinely give the choice of available treatment modalities. All patients willing to participate in study underwent history and physical examination including demographic profile , routine investigation including serum creatinine, complete blood counts and urine routine microscopy , radiology imaging including plain X ray KUB, ultrasonography , plain CT KUB or CT IVP, to calculate the size of calculus (measured along its longest axis in millimeters),stone characteristics and location.

Out of 576 patients with lower ureteric calculi visiting our out clinic department, 150 patients meet the study criteria and were randomized in three groups. All patients received patient information sheet in their preferred language of communication. Patients in all three groups received Diclofenac 50 mg SOS for pain and ciprofloxacin t ablet 500 mg twice daily for 5 days. All patients were advised to take more than 3 liters of fluids p er day.

Group one received placebo (Multivitamin tablets in same container as for tadalafil and tamsulosin.), group two received phosphodiesterase 5 inhibitor (tadalafil 10 mg OD), and group three received alfa one blockers (tamsulosin 0.4 mg OD) for accelerating the passage of stone. Each group had 50 patients. As possibility of stone passage is maximum during first 2 weeks, duration of treatment lasted until stone expulsion or 14 days whichever came first. All three groups were followed on day 7 and 14 and underwent ultrasonography and measurement of serum creatinine. Any episode of pain with its intensity according to visual analog scale (VAS) was noted. All patients were advised to filter their urine and note passage of stone (day and time), analgesic use and any side effect of drug were also noted.

Minor Symptoms were defined as symptoms not requiring the discontinuation of medical therapy. Such as asthenia dizziness, increased or decreased libido etc. Failure to pass stone till 14^{th} day was considered as failure according to study protocol and patient were given options of ureteroscopy and removal of stone. Patient who reported passage of stone were reconfirmed by ultrasound examination and X ray KUB (for radio opaque calculi) in all the cases.

Medical expulsive therapy was discontinued in patients who needed hospitalization and/or intervention due to uncontrolled pain not relieved by medications, high grade fever, severe or increasing hydronephrosis, rise in serum creatinine (more than 2 mg/dl) , failure to pass stone by two weeks or patient who desired surgical treatment and removal of stone before 2 weeks.

Those patients who wanted to continue medical expulsive therapy were followed up outside study protocol after 2 weeks and all who failed medical management underwent ureteroscopy at 2 weeks or at 4 weeks.

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using ANOVA. Multiple comparison test was used to assess the differences between the individual groups using Bonferroni test. Categorical variables were analyzed using the chi square test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

3 RESULTS:

The demographic profile consisting of age, sex, co morbidity and laterality and blood chemistry were comparable in all three groups. The demographic profile is as in table 1.All three groups were comparable with respect to blood chemistries such as hemoglobin, serum creatinine, serum uric acid and serum calcium.

Mean stone size was 0.60 $\pm$ 0.123, 0.63$\pm$0.14, and 0.61$\pm$0.14 in placebo tadalafil and tamsulosin group respectively. There was no statistical difference w ith r espect to the average diameter of the stones between three groups. (p value 0.635). [Table 1]

The stone expulsion rate was 58% (36 of 50 patients) for placebo group, 80 % (40 of 50 patients) for tadalafil group and 74 % for the tamsulosin group (37 of 50 patients). Tadalafil was superior to placebo in terms of stone expulsion rate (p value: 0.017). The difference in stone expulsion rate between tadalafil and tamsulosin is not statically significant (p : 0.139).The mean expulsion time was 9.77$\pm$2.50 days for placebo group, 7.21$\pm$3.29 days for tadalafil group and 8.32 $\pm$ 3.14 days in tamsulosin group. [Table 2]

Table 1. Demographic profile

Demographic parameters	Placebo group	Tadalafil group	Tamsulosin group	p Value
Mean age {years} (S.D and range)	45.02±13.65 (21-72)	45.38 ± 13.16 (21-73)	43.18±15.52 (22-76)	0.688
Sex				
• Male	41 (82 %)	39 (78 %)	34 (68 %)	0.240
• Female	9 (18 %)	11 (22 %)	16 (32 %)	
Co- morbidity				
• None	46 (92 %)	45 (90 %)	48 (96 %)	0.541
• Diabetic	2 (04 %)	1 (02 %)	0 (0%)	
• Hypertensive	2 (04 %)	4 (08 %)	2 (04 %)	
Side				
• Left	27 (54 %)	23 (46 %)	31 (62 %)	0.276
• Right	23 (46 %)	27 (54%)	19 (38 %)	
Hemoglobin {gm/dl} (S.D and range)	11.69 ± 2.36 (7.90 - 17.20)	11.94 ±2.32 (7.60 -16.10)	12.79 ± 2.31 (7.60 - 16.80)	0.051
Serum creatinine {mg/dl} (S.D and range)	0.95 ± 0.28 (0.40 - 1.40)	1.00 ± 0.27 (0.50 - 1.40)	1.02 ± 0.30 (0.40 - 1.50)	0.388
Serum Uric acid {mg/dl} (S.D and range)	4.98 ± 1.52 (2.70 - 8.10)	5.05 ± 1.31 (2.70 - 8.00)	5.28 ± 1.51 (2.90 - 8.20)	0.550
Stone size { in cm} (S.D and range)	0.60 ± 0.13 (0.4-0.9)	0.63 ± 0.14 (0.4-0.9)	0.61 ± 0.14 (0.4-0.9)	0.622

Table 2. Results

Parameters	Placebo group	Tadalafil group	Tamsulosin group	p Value
Stone clearance rate	29 (58 %)	40 (80 %)	37 (74 %)	0.044
Yes	21 (42 %)	10 (20 %)	13 (24 %)	
No				
Time to clearance (in days) {S.D and range}	9.77 ± 2.50 {4 – 14}	7.21 ± 3.29 {1 – 13}	8.32 ± 3.14 {2 – 13}	0.002
Visual analog score(Minimum score 1 , maximum score 10)	6.36 ± 0.90 (4 - 8)	4.30 ± 2.49 (0 - 8)	5.78 ± 1.84 (0 – 8)	<0.001
1st Follow up (S.D and range)	4.35 ± 2.77 (0 – 8)	2.59 ± 2.80 (0 – 8)	4.75 ± 2.36 (0 – 8)	
2nd Follow up (S.D and range)				
No. of colicky episodes	2.80 ± 0.90	1.28 ± 0.95	2.28 ± 1.03	<0.001
1st Follow up	(1 - 4)	(0 - 4)	(0 - 4)	
(Range)	1.55 ± 1.19	0.59 ± 0.67	1.39 ± 0.90	<0.001
2nd Follow up	(0 – 5)	(0 – 2)	(0 – 3)	
(S.D and range)				
Requirement of analgesic(diclofenac in mg)	331.00 ± 102.47	132.93 ± 82.62	277.08 ± 103.12	<0.001
(S.D and range)	(50 - 500)	(50 – 300)	(50 - 450)	

When we did split analysis of the above clearance rate we found out that with increasing stone size the clearance falls dramatically in all the groups. [Table 3] Mean VAS score at 1 week follow up for Placebo group was 6.36 ± 0.9, for tadalafil group 4.30±2.49 and for tamsulosin group is 5.78 ± 1.84. Similarly at 2 week follow up mean VAS score for Placebo group was 4.35 ± 2.77, for tadalafil group 2.59± 2.8 and for tamsulosin group is 4.75 ± 2.36. Patients in tadalafil group had significant less VAS scores at 1 and 2 week follow up in comparison to other two groups.

Patients who received tadalafil had less number of colicky episodes and none of the patient in tadalafil group required admission for the control of pain. Placebo group had on average 2.8±0.9 colicky episodes during first week and 1.55±1.19 episodes during second week, for tadalafil group it was 1.28±0.95 during first week and 0.59 ± 0.67 during second week, similarly for tamsulosin group it was 2.28±1.03 during first week and 1.39 ± 0.9 during second week.

Requirement of analgesic was significantly less in tadalafil group. Mean analgesic use was 331 mg of diclofenac by placebo group, 132.93 mg of diclofenac by tadalafil group and 277.08 mg of diclofenac by tamsulosin group. None of patients in tadalafil group required admission for the control of pain although 10 (20 %) patients had minor symptoms such as increased libido in 8 patients and mild headache in 2 patients. None of the patient discontinued the treatment for such symptoms.

4 DISCUSSION:

Alternation of natural history of ureteric stone passage by medical expulsive therapy (MET) is a encouraging approach as addition of drugs prevents surgical intervention in number of patients.

Spontaneous passage of ureteric calculi is supported by ample of literature. Ureteric relaxation at the site of im-

Table 3. Clearance rate in each group by stone size.

Groups	Clearance Status	Size (in cm)					
		0.4	0.5	0.6	0.7	0.8	0.9
Placebo	Yes (n=29)	5 (17.2%)	8 (27.6%)	14 (48.3%)	2 (6.9%)	0 (0%)	0 (0%)
	No (n=21)	0 (0%)	4 (19%)	8 (38.1%)	1 (4.8%)	5 (23.8%)	3 (14.3%)
Tadalafil	Yes (n=40)	6 (15%)	7 (17.5%)	18 (45%)	6 (15%)	3 (7.5%)	0 (0%)
	No (n=10)	0 (0%)	0 (0%)	0 (0%)	2 (20%)	6 (60%)	2 (20%)
Tamulosin	Yes (n=37)	5 (13.5%)	10 (27%)	16 (43.2%)	4 (10.8%)	1 (2.7%)	1 (2.7%)
	No (n=13)	1 (7.7%)	0 (0%)	1 (7.7%)	3 (23.1%)	7 (53.8%)	1 (7.7%)

paction by drugs helps in passage of stone [6] .

There is ample of evidence in literature supporting the spontaneous ureteral stone passage. Intervention by means of drugs which help in ureteral relaxation in the region of a concretion could aid in stone passage. Various medications have been utilized to support the passage of ureteral stones.

In experimental study in rabbit, a phosphodiesterase 4 inhibitor has shown to cause more marked ureteral relaxation than the nonspecific phosphodiesterase inhibitors papaverine and theophylline without the circulatory side effects seen with the nonspecific phosphodiesterase inhibitors. Rolipram had similar effect in human and rabbit in vitro ureteral segments, thus phosphodiesterase inhibitors were proposed as useful drugs for treatment of renal and ureteric colic that could aid in facilitation of stone passage [7]

In addition to PDE phosphodiesterase 4 inhibitor rolipram, phosphodiesterase 5 inhibitors relax in vitro human ureteral segments. [8] Nonspecific phosphodiesterase inhibitor papaverine decreased the frequency of uretral peristalisis in pig, no such effect was observed with phosphodiesterase 4 inhibitor rolipram. [9]

The likelihood of ureteral stone spontaneous passage fundamentally depends on stone size, site, and the internal anatomical structure of the ureter, which are un modifiable factors. [10] The possible causes of stone retention are spasm, edema, and ureteral infections, which are modifiable factors. [11]. The goals of medical conservative therapy are to prevent modifiable factors and control painful symptoms until stone expulsion. [12]

Hasan et al in similar study found no difference by gender in terms of stones clearance and tolerance to pain in relation to the ureteric calculi. [5] Extensive literature search does not support the difference in stone expulsion rate by two sexes; hence we did not consider any stratification of patients on the basis of gender.

Hasan et al in their randomized prospective study of 60 patients evaluated the role of tadalafil 10 mg for the lower ureteric calculi and stated that it was significantly more effective then placebo (93 % vs 67 %, p value is < 0.05), mean time to stone expulsion was also low in tadalafil (5.5 days) vs control group (8.84 days) (P=0.001). They concluded that MET with tadalafil was safe effective and without serious side effects and increased stone expulsion rate. The tadalafil group also had very good control of pain in comparison to placebo group. [5]

In comparison to Hasan et al we compared both tadalafil and tamsulsoin with placebo as control. The stone clearance rate with tadalafil and placebo was 80 % (40 out of 50 patients) and 58 % (29 out of 50) in comparison to 93 % and 67 % respectively as reported by Hasan et al [5] . Hasan et al in their study mentioned stone expulsion by all patients in tadalafil group within 10 days. In our study we have seen stone expulsion upto 13 days, mean time for stone expulsion in our study with tadalafil was 7.21 ± 3.29 (range 1 to 13 days) in comparison Hasan et al in their study reported mean time for stone expulsion of 5.5 days. [5]

A ureteral stone usually causes severe colicky pain as a result of an increase in intraureteral pressure above the site of ureteral obstruction. The goals in the treatment of renal and ureteric colic are to alleviate the pain and release the obstruction. Although morphine and pethidine have been the traditional agents, today, non–steroidal anti–inflammatory drugs (NSAIDs) are generally used for relieving the pain caused by acute ureteral obstruction. [13]

Experimental and clinical studies have shown that anti–spasmodic drugs are effective for the relief of ureteral colic and possibly for the promotion of stone passage, but such drugs are generally considered unsatisfactory in term of efficacy and safety. [14, 15]

Hasan et al reported that patients who received tadalafil 10mg had significantly better outcome in that they had less VAS (Visual Analogue Scale) scores, less attacks of acute colic, and they used less NSAIDs during therapy (P<0.0001, P<0.0001, and P<0.0001 respectively). [5] Similar results were obtained in our study, patients in tadalafil group had mean VAS score of 4.30 ± 2.49 in comparison patients on tamsulosin and placebo had mean VAS scores during first week were 5.78 ± 1.84 and 6.36 ± 0.90 respectively (p value : <0.001). Similarly during second week patients on tadalafil, tamsulosin and placebo had mean VAS scores of 2.59 ± 2.80 , 4.75 ± 2.36 and 4.35 ± 2.77 respectively. (p value : 0.003).

Mean Analgesic requirement was least in tadalafil group. Patients on Tadalafil required on an average 132.93 ± 82.62 mg of diclofenac while waiting for stone expulsion while patients on tamsulosin and placebo required on an average 277.08 ± 103.12 and 331.00 ± 102.47 respectively.

The findings in both studies conform the effect of tadalafil in reducing the need for analgesic while waiting for stone clearance and thus avoid loss of work and anxiety associated with stone passage. Not only intensity of pain but also number of episodes of pain associated with stone passage are reduced.

No serious side effects were encountered in any patient during the study, many patients experience erotogenic effect of tadalafil. We recommended that patient education before

giving tadalafil improves compliance and reduces anxiety.

Good expulsion rate were achieved in all the patients with stone size of up to 7 mm, poor outcomes with stones larger than 8 mm were obtained, So we suggest that for Indian patients stone size of 8 mm should be recommended rather than western guidelines which recommend MET for stones up to 10 mm in size.

Excellent pain control and good expulsion rates associated with addition of tadalafil while awaiting stone clearance results in better compliance to MET. Although available and accessible, endoscopic treatment is associated with considerable cost to patients. Decrease in requirement of hospitalization, no loss of work days with reduced need for analgesics makes tadalafil first choice of treatment for small lower ureteric calculi.

5 CONCLUSION:

Medical expulsive therapy improves stone expulsion rate for lower ureteric calculi. Tamsulosin and tadalafil both are effective and safe during watchful waiting period with minimal side effects. Both result in better and faster stone removal as compared to placebo.

Tadalafil has better stone expulsion rate and faster stone expulsion as compared to tamsulosin but difference is not statistically significant. MET with tadalafil resulted in significantly better control of pain resulting in less likely need of emergency hospital admission as compared to other two groups. Tadalafil results in statistically significant improvement in pain scores and decreased requirement of analgesic as compared to other two groups.

Based on our results we recommend that tadalafil can be considered as first line treatment for distal urteric calculi up to 8 mm in size. Tamsulosin is equally effective alternative to tadalafil with regards to stone clearance rate but inferior in terms of pain control. Larger studies are required to find out adequate duration and dose of tadalafil for medical expulsive therapy.

Compliance with ethical standards: All procedures performed in study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its amendments.

Informed consent in vernacular language was obtained from all individual participants included in study

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