Original Article

Outcome of Tamsulosin and Tamsulosin Plus Tadalafil as Medical Expulsive Therapy for Lower Ureteric Stones: A Quasi-experimental Study

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Abstract

Background:
Each year throughout the world, people seek more than a million visits to healthcare providers and emergency rooms for urinary stone problems. The goal of the treatment of ureteral calculi is to achieve complete stone clearance with minimal morbidity. This research was studied to evaluate the safety and efficacy of tamsulosin alone and its combination with tadalafil therapies for the treatment of lower ureteral stones.

Objectives:
To compare the efficacy of tamsulosin versus tamsulosin plus tadalafil as medical expulsive therapy for lower ureteric stones.

Methods:
Between May 2015 and April 2016, 152 patients presenting with lower ureteric stones (size 5-8 mm) in the Urology outpatient department of Sir Salimullah Medical College Hospital (SSMCH), Dhaka were randomized equally to group A (tamsulosin) or group B (tamsulosin plus tadalafil). Therapy was given for a maximum of 4 weeks. Stone expulsion rate, time to stone expulsion, analgesic use number of a hospital visit for pain episodes, endoscopic treatment, and adverse effects of drugs were recorded. Statistical analyses were carried out using Student's **t**-test and the Pearson's Chi-square test.

Results:
There was a statistically significant higher expulsion rate in group B compared to group A (82.9% vs 65.7% P-value = 0.01) and shorter expulsion time (11.2±6.2 days vs 8.5±4.2 days **p**-value = 0.03). Statistically significant differences were noted in the analgesic requirement, the number of hospital visits, and endoscopic treatment in favor of group B. There was no serious adverse event.

Conclusion:
Medical expulsive therapy for lower ureteric stones using tamsulosin plus tadalafil is safe, effective, and well-tolerated.

Keywords: Outcome, Tamsulosin, Tadalafil, Lower Ureteric Stone

Introduction:

Urolithiasis is one of the most common disorders of the urinary tract. Each year throughout the world, people seek more than a million visits to healthcare providers and emergency rooms for urinary stone problems.[1] A total of 22% of all urinary tracts stones are found in the ureter of which 68% are seen in the distal ureter.[2] Symptomatic ureterolithiasis is one of the important issues that urologists face in their clinical settings. The goal of the treatment of ureteral calculi is to achieve complete stone clearance with minimal morbidity. At present, multimodalities of treatment are available but none of them are risk-free. Ureteral calculi of any size may be associated with renal obstruction and care must be taken to prevent irreversible kidney damage, whether by expectant or active treatment.[3] Medical expulsive therapy has now become an established modality of treatment and it employs the use of various drugs acting on the ureter by different mechanisms.[4] The physiology of the ureter and the changes that occur with ureteral obstruction have been well studied.[5] The wall of the ureter contains

smooth muscle cells with α1-adrenergic receptors, especially in the distal third. Blocking these receptors reduces basal smooth muscle contraction and produces propulsive antegrade peristalsis, which aids in stone expulsion.[6] In general, the intramural detrusor tunnel is the principal barrier to the transport of lower ureteral stones, hence inhibiting these receptors might facilitate stone passage.[7,8] Tamsulosin, an alpha1-adrenergic antagonist it has an inhibitory effect on alpha1A receptors in relaxing prostatic and bladder neck smooth muscles[9], it has also effect on alpha adrenoceptors of ureteric smooth muscles in facilitating expulsion of stone from its juxtavesical part.[6] Tadalafil, a novel PDE5 inhibitor, has recently developed, acting on the nitric oxide-cyclic guanusin monophosphate-signaling pathway of smooth muscles, resulting in higher levels of cyclic guanusin monophosphate and ureteric relaxation.[4] As a result, combining tadalafil with tamsulosin promotes ureteric stone removal while also significantly reducing discomfort, using fewer analgesics, and requiring fewer hospital visits.[1] We can produce improved ureteric relaxation and lower intramural pressure by combining medications that work through distinct mechanisms, which will assist stone transit.

Methods:
Total 152 cases were selected purposively according to selection criteria from the patients attending urology Out-Patients Department (OPD) of Sir Salimullah Medical College Hospital (SSMCH), Dhaka with lower ureteral stone during the period from May 2015 and April 2016. Group-A was comprised of 76 cases and group-B of 76 cases. Patients of Group-A were given Tamsulosin 0.4mg daily and patients of Group-B were given Tamsulosin 0.4mg daily along with the Tadalafil 10mg daily. Each of the patients continues the therapy was follow-up weekly until stone expulsion or for 4weeks. All patients of both groups were asked during weekly follow-up about stone expulsion time, episodes of colic, analgesic use, and side effects of drugs. Results were reviewed and analyzed with the help of SPSS-17.

Results:
The mean age was found 33.74±11.52 years in Group A and 37.37±11.74 years in Group B which was not significant (p=0.07) between the two groups in an unpaired t-test. The majority of patients was male (Table-I).

Table-I: Age and gender distribution of the patients in study groups (n=140)

	Group A (n = 70)		Group B (n = 70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Age (Years)							
16-25	24	34.3	12	17.1	36	25.7	
26–35	22	31.4	22	31.4	44	31.4	
36–45	12	17.1	20	28.6	32	22.9	0.07^{ns}
46–55	10	14.3	12	17.1	22	15.7	
56–65	2	2.9	4	5.8	6	4.3	
Mean±SD Range (min – max)	33.74±11.52 (18 – 65)		37.37±11.74 (18 – 60)		35.56±11.73 (18 – 65)		
Sex							
Male	46	65.71	44	62.86	90	64.29	
Female	24	34.29	26	37.14	50	35.71	0.73^{ns}
Total	70	100.0	70	100.0	140	100.0	

ns = Not significant (p>0.05)

Clearance of stone occurred in 65.7% patients of group A and 82.9% of group B which was significantly (p<0.01) more in group B. Mean stone size in Group A and Group B was 6.8±1.2 mm and 7.1±1.4 mm respectively. The difference was not statistically significant (p=0.18). Mean expulsion time of stone in Group A and Group B was respectively 11.2±6.2 days and 8.5±4.2 days indicating that stone expulsion time was significantly less (p<0.05) in group B (Table-II).

Table-II: Stone expulsion rate, stone size and expulsion time in two study groups (n=140)

Stone expulsion	Group A (n=70)		Group B (n=70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Stone expulsion rate	46	65.7	58	82.9	104	74.3	0.01[s]
Stone size (mm) Mean±SD	6.8±1.2		7.1±1.4				0.18[ns]
Stone expulsion time (days) Mean±SD	11.2±6.2		8.5±4.2				0.03[s]

[s] = Significant (p<0.05), [ns] = Not significant

Mean episodes of pain in patients of Group A and Group B were respectively 1.34±1.1 and 0.46±0.60; the difference was statistically significant (P<0.05) (Table-III).

Table-III: Pain and urinary tract infection among the two study groups (n=140)

Stone expulsion	Group A (n=70)		Group B (n=70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Pain episodes (Number) Mean±SD	1.34±1.1		0.46±0.60				<0.001[s]
Urinary tract infection	31	44.3	20	28.6	51	36.4	0.04[s]

[s] = Significant (p<0.05)

Table-III depicted that urinary tract infection significantly more occurred in Group A (44.3%) patients than group B (28.6%) (P=0.04). The mean analgesic number was observed (2.25±0.60 vs 1.44±0.55) in group A and group B respectively. There was a significant difference between group A and group B in terms of the number of analgesic use (p=<0.001) (Table-IV).

Table-IV: Frequency of analgesic use between two study groups (n=140)

Frequency of analgesic use	Group A (n=70)		Group B (n=70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Used	58	82.9	35	50.0	93	66.4	
Not used	12	17.1	35	50.0	47	33.6	<0.001[s]
Total	70	100.0	70	100.0	140	100.0	
Mean number of analgesic use (Mean±SD)	2.25±0.60		1.44±0.55				

[s] = Significant (p<0.05)

Table-V demonstrated the drug-related adverse effects, such as headache, dizziness, and back-ache occurred more in group B but retrograde ejaculation occurred more in group A. They were not significant enough to exclude them from the study (p>0.05).

Table-V: Comparison of adverse effects between two study groups (n=140)

Adverse outcomes	Group A (n=70)		Group B (n=70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Headache	9	12.9	13	18.6	22	15.7	0.35[ns]
Dizziness	8	11.4	12	17.1	20	25.6	0.33[ns]
Backache	7	10.0	13	18.6	20	25.6	0.15[ns]
Retrograde ejaculation	9	7.1	4	5.7	14	6.4	0.73[ns]

[ns] = Not significant

Table-VI: Frequency of ureteroscopic intervention in two study groups (n=140)

Ureteroscopic intervention	Group A (n=70)		Group B (n=70)		Total (n=140)		p-value
	Number	%	Number	%	Number	%	
Yes	24	34.3	12	17.1	36	25.7	0.01[S]
No	46	65.7	58	82.9	104	74.3	

[S] = Significant (p<0.05)

Discussion:

This prospective study was performed to compare the outcome of Tamsulosin and Tamsulosin plus Tadalafil in the management of lower ureteric stone having a size up to 8 mm. A total of 152 patients were grouped into two on an alternate basis, 76 patients in group A treated with Tamsulosin only 76 patients in group B were given Tamsulosin 0.4mg daily plus Tadalafil 10mg daily. Therapies in both groups continued for 4 weeks or until stone expulsion which came first. In this study, the age distribution of the patients was above 18 years. In group A, the age range was 18 to 65 years with a mean age of 33.74 years. In group B, the age range was 18 to 60 years with a mean age of 37.37 years and mean age was 35.56 years. There was no significant difference (P>0.05) in age among the groups.In a study conducted by Kumar,[4] mean age was reported 32.45±9.36 years in a group treated with Tamsulosin and 35.23±13.54 years in Tamsulosin plus Tadalafil in combination with Prednisolone group for lower ureteric stones which were similar with this study. In group A, there were 65.71% male and 34.29% female patients and in group B male and female patients were 62.86% and 37.14% respectively. The sex distribution of the study population did not have a significant difference between the groups. In group A, the male and female ratio was 2:1, and that in group B was 1.70:1. In this study, the mean stone size was 6.8±1.2 mm (range 5-8) for group A and 7.1±1.4 mm (range 5-8) for group B. There was no statistically significant difference between the two groups with respect to stone size.The above distribution correlates with the study done by Cervenakov.[10] It is evident from the study that the stone expulsion rate is higher in group B compared with group A which is 65.7% and 82.9% respectively (p<0.05). This is consistent with the study conducted by Jayant1 where the stone expulsion rate was 65.5% in the Tamsulosin group and 83.6% in the group where Tamsulosin was supplemented by Tadalafil. Similarly,in another study conducted by Kumar[4], Tamsulosin plus Tadalafil in a combination group showed 83.9% stone expulsion in comparison to 74.2% stone expulsion in a group treated with only Tamsulosin. In this study, the average time for stone expulsion was 11.2±6.2 days in group A and 8.5±4.2 days in group B. A significant statistical difference was observed in expulsion time between group A and group B (p<0.05). The expulsion time of this study correlates with the study done by Jayant[1] where expulsion times were 9.9±4.4 days and 11.7±4.8 days respectively with or without Tadalafil. But expulsion time of lower ureteric was significantly less in the study conducted by Dellabella[6] where the average expulsion time was 111.1 hours in a group of patients who did not take tamsulosin and 65.7 hours in the group treated by Tamsulosin. In that study, less expulsion time may be due to the use of steroids in both groups in addition. The steroid-sparing approach is another important feature of this study.Episodes of pain in this study were statistically significantly lower in group B patients compared to group A (<0.05). Mean episodes of pain in group A was 1.34±1.1 and that in group B was 0.46±0.60. Patients in the studies of Jayant[1] and Kumar[4] suffered from the same pain episodes of 1.60±1.00 and 0.45±0.68 without and with Tadalafil respectively. In this study, although patients with urinary tract infections were excluded from the study some were encountered with these events during the study period. Urinary tract infections were encountered in 44.3% patients of group A and 28.6% patients of group B during 4 weeks of therapy and were treated with appropriate antibiotics. The difference was statistically significant (p<0.05). The above findings correlate with different studies conducted by Jayant[1] and Kumar[4].The reported side-effect was mild to moderate and was well tolerated in the present study, probably because of the younger study population and the lack of any associated co-morbidity. In this study, 34.3% group A patients and 17.1% group B patients needed hospitalization because of unsuc-

cessful stone expulsion after 4 weeks of treatment. A statistically significant difference was observed between the two treatment groups in relation to the need for hospitalization for ureteroscopy. In the study by Yilmaz[11] 46.43%of patients of the conventional therapy group and 20.79%of patients treated by additional Tamsulosin were not stone free at the end of 4 weeks of therapy and treated by ureteroscopy or ESWL which was similar with this study. But Dellabella[6] showed in their study 100% of the patients who were treated with Tamsulosin were stone-free at end of 4 weeks of therapy while 70% of patients were stone-free in that group who treated by conventional therapy which was probably due smaller stone size.The current study found that combining Tadalafil with Tamsulosin greatly boosts stone evacuation, as well as considerable pain management, significantly decreased analgesic use, and fewer hospital visits.

Conclusion:

This study showed a potentially important role of Tamsulosin and Tadalafil for conservative expulsive therapy of lower ureteral stones, broadening pharmacological indications rather than endoscopic treatments for the resolution of this disease. As medical expulsive therapy for lower ureteric stones Tamsulosin plus Tadalafil therapy is more effective than Tamsulosin alone. Source of funding: Self

Conflict of interest: None

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