



Comparative study between Silodosin alone and Silodosin plus Tadalafil for the medical management of lower Ureteric Stone in South-Western part of the Bangladesh

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Abstract

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Conflicts of interest: None

Objective: To compare the treatment outcome of Silodosin alone and Silodosin plus Tadalafil as a medical expulsive therapy (MET) of lower ureteric stone in south-western part of Bangladesh.

Methodology: The study was conducted in a tertiary hospital in Khulna, over a period of 12 months (January 2019 to December 2019). Out of 108 patients, 100 meet the inclusion criteria who were purposively assigned into 2 groups. 48 patients included in Silodosin alone group and 52 in Silodosin plus Tadalafil group.

Result: There was a significant higher stone expulsion rate in Silodosin plus Tadalafil than Silodosin alone which was 88.46% vs 75% respectively (P value 0.02). The mean stone expulsion time of Silodosin alone was 14.33 (± 3.1) days and Silodosin plus Tadalafil was 11.48 (± 2.3) days (P value 0.001). The episodes of pain in Silodosin alone were 0.7 (± 0.06) and 0.6 (± 0.2) in Silodosin plus Tadalafil group that was statistically significant.

Keywords: Silodosin, Tadalafil, Ureteric calculi. Medical Expulsion Therapy.

Conclusion: The present study concludes that Silodosin plus tadalafil combination therapy significantly increases ureteric stone expulsion rate and decreases the expulsion time and pain episodes than treatment with silodosin alone.

Introduction

Urolithiasis is one of the common diseases and affects 5-10% of people globally. Renal stones are most prevalent between the ages of 20 and 40 years and are three times more common in men than women. 20% of all urinary stones are located in the ureter. Out of them, 2/3rd stones present in lower ureter. Medical expulsive therapy (MET) is one of the routine treatment options for small lower ureteric stones, and the therapy uses various drugs acting on the ureteric smooth muscle by different mechanism. There has been a steep

rise of minimally invasive procedures for ureteric stones as well as renal stones management.^{1,2,3} However, medical expulsive therapy is still regarded as an established treatment option for the management of distal ureteric stones (DUS). Stone location, size, number, ureteric spasm, mucosal edema or inflammation and ureteric anatomy are the key factors that influence the passage of ureteric stones.⁴ Ureterscopy and shock wave lithotripsy (SWL) remain the most effective treatments for DUS; however, they are expensive and not risk free. Spontaneous stone

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expulsion can occur in up to 50% of cases of stone less than 6 mm. Nevertheless, many complications such as ureteric colic, UTI, and hydronephrosis may occur. Recently, the use of various drugs as MET for DUS has escalated the rate of stone clearance and reduced complications. Silodosin is a more selective α 1A-adrenergic receptor antagonist and has a better stone expulsion rate than tamsulosin.⁵Tadalafil, a PDE-5 inhibitor either alone or combined with tamsulosin is safe, efficacious and well tolerated for the treatment of lower ureteric stones.⁶Tadalafil has replaced sildenafil due to less visual problems and its absorption does not appear to be affected by meals.⁷The combination of silodosin and tadalafil has greater potency than either drug alone for the treatment of LUTS associated with BPH, but no study has been reported using these two drugs in combination for the treatment of lower ureteric stones in this region.

Methodology:

This prospective study (Quasi experimental) was conducted at Khulna Medical College Hospital, a tertiary Hospital in this region and few private hospitals in Khulna over a period of 12 months (January 2019 to December 2019). All patients with lower ureteric stone from 5mm to 10mm in size, diagnosed by non-contrast CT Scan, Ultrasound (USG) of KUB or IVU/ X-ray KUB and given informed written consent were only included in the study. CT scan was not done in all patients due to financial reason. Patients with the presence of multiple ureteric stones, radiolucent stones, urinary tract infection, pregnancy, pediatric population and history of ureteral surgery or previous endoscopic procedures and who did not give written consent were excluded in this study. The exclusion criteria also extended with patients having ischemic heart disease, congestive cardiac failure, or complicated hypertension, raised serum creatinine and those requiring emergency intervention. Patients were purposively divided into two groups in Group A patient who taken only Silodosin alone and in Group B patient who taken Silodosin plus Tadalafil. Out of 108 patients, 100 meet the inclusion criteria. Five patients from Group A (Silodosin alone) and three patients from Group B (Silodosin plus Tadalafil) dropped out during follow up for various reasons. Finally, we included 48 patients in Group A (Silodosin alone) and 52 in Group B (Silodosin plus Tadalafil). Group A was given silodosin 8 mg once daily and Group B was given silodosin 8 mg plus Tadalafil 5mg once daily. In both groups, drugs were continued till

stone expulsion, but not more than 3 weeks. There was no strong evidence that the long duration use of these drugs will increase the expulsion rate or minimize the deleterious effect of obstructive uropathy. Patients were instructed to drink plenty of fluids and take one tablet of diclofenac 50 mg orally during episode of pain with a maximum dose of 150 mg per day². Patients who either could not present the stone or present the stone that did not match the original size and shape were evaluated by physical examination, serum creatinine and the same imaging by which lower ureteric stones were confirmed previously. In case of doubt, NCCT KUB was done despite previous imaging modality to confirm stone expulsion. Expulsion of the ureteric calculi, total dose of analgesic used, number of colic episodes and emergency room visits, and side effect of drugs were recorded. Semi-rigid ureteroscopy was done to those who did not pass stones after 3 weeks of follow-up for stone removal. Unpaired Student's *t*-test and the χ^2 -test were used for the analysis of the variables and categorical data. Differences were considered significant at a *P* value less than 0.05.

Results:

Table-I shows that baseline characteristics of mean age was 36.25(\pm 11.17) years in Silodosin alone group and 37.38(\pm 12.10) years in Silodosin plus Tadalafil group, mean BMI (kg/m²)23.65(\pm 4.16) was in Silodosin alone group and 24.12 (\pm 5.12) was in Silodosin plus Tadalafil group, mean stone size 7.6(\pm 1.25) mm in Silodosin alone group and 7.7 (\pm 1.30) mm in Silodosin plus Tadalafil group. Sex, age, BMI, stone size and side of stone were not statistically significant ($p > 0.05$) between two groups. Table-II shows higher stone expulsion rate in Silodosin plus Tadalafil than Silodosin alone which was 88.46% vs75% respectively (*P* value 0.02) that was statistically significant. The mean expulsion time Silodosin alone was 14.33(\pm 3.1) and 11.48 (\pm 2.3) was in Silodosin plus Tadalafil group (< 0.001). The pain episodes 0.7(\pm 0.06) were in Silodosin alone and 0.6(\pm 0.2) were in Silodosin plus Tadalafil group (< 0.001) that were statistically significant (Table-II). Regarding adverse effects, such as headache, dizziness, backache, orthostatic hypotension and retrograde ejaculation were similar in Silodosin alone groups and Silodosin plus Tadalafil Group (Table-III). That was not statistically significant ($P > 0.05$)

Table I : Baseline characteristics of the study patients (n=100)

Baseline characteristics	Silodosin alone (n=48)	Silodosin plus Tadalafil (n=52)	P value
Male	27 (56.25%)	33 (63.46%)	0.414 ^{ns}
Female	21 (43.75%)	19 (36.54%)	
Age (years)	36.25 (±11.17)	37.38 (±12.10)	0.629 ^{ns}
BMI (kg/m ²)	23.65 (±4.16)	24.12 (±5.12)	0.616 ^{ns}
Stone size (mm)	7.6 (±1.25)	7.7 (±1.30)	0.695 ^{ns}
Stone side			
Right	30 (62.5%)	31(59.62%)	.409 ^{ns}
Left	18 (37.5%)	21 (40.38%)	

Ns=not significant, P value reached from Chi square and unpaired t-test

Table II : Treatment outcome (n=100)

Treatment outcome	Silodosin alone(n=48)	Silodosin plus Tadalafil(n=52)	P value
Expulsion rate (%)	75.0 %	88.46 %	0.029 ^s
Expulsion time (days)	14.33(±3.1)	11.48 (±3.1)	0.001 ^s
Pain episodes	0.7 (±0.06)	0.6 (±0.2)	0.001 ^s

s=significant, P value reached from Chi square and unpaired t-test

Table III : Distribution of the study patients by side effects (n=100)

Side effects	Silodosin alone (n=48)	Silodosin plus Tadalafil (n=52)	p value
Headache	5 (10.42%)	7 (13.46%)	0.538 ^{ns}
Dizziness	4 (8.33%)	5 (9.62%)	0.822 ^{ns}
Backache	4 (8.33%)	5 (9.62%)	0.822 ^{ns}
Orthostatic hypotension	3 (6.25%)	2 (3.85%)	0.581 ^{ns}
Retrograde ejaculation	8 (16.67%)	8 (15.38%)	0.790 ^{ns}

Ns=not significant, P value reached from Chi square test and Fisher's exact test

Discussion

This study observed the mean age was 36.25(±11.17) years in Silodosin alone group and 37.38(±12.10) years in Silodosin plus Tadalafil group, mean BMI (kg/m²) 23.65(±4.16) was in Silodosin alone group and 24.12 (±5.12) was in Silodosin plus Tadalafil group, mean stone size 7.6(±1.25) mm in Silodosin alone group and 7.7 (±1.30) mm in Silodosin plus Tadalafil group. Rahman et al.⁹ reported there was no statistically significant difference between the groups for patient's age, gender, body mass index, or stone size. They observed that the mean age was found 34(±12) in

Silodosin alone and 35 (±10) in Silodosin plus tadalafil group, stone size 7.4 (±1.30) mm in Silodosin alone and 7.6 (±1.35) mm in Silodosin plus tadalafil group.

Elgalaly et al.⁵ reported that mean age was found 33.6 (±9.9) in group A and 35.5 (±11.3) in group B. Similar observation found in Hari Bahadur KC et al.¹⁰ They reported that the patients' mean age was 31.72±12.63 years (range, 18–68 years) and the male to female ratio was 1.5. The mean stone size was 7.09±1.2 and 7.13±1.5mm in groups A and B, respectively.

Many factors influencing the spontaneous expulsion of stones, such as stone location, stone size, stone

number, stone structure, ureteral spasm, mucosal edema or inflammation and ureteral anatomy. Therefore, the use of MET is justifiable to reduce edema and spasm and relax the smooth muscles for stone expulsion. The American Urological Association (AUA) as well as the European Urological Association (EUA) ureteric stones clinical guidelines support the use of MET for patients with distal ureteral calculi of <10 mm. In comparison with surgical intervention for ureteric stones, MET has a high safety profile and very low cost⁹.

Jayant et al reported that a combination of tadalafil with tamsulosin had better outcomes in ureteric stone expulsion. In their study, the stone expulsion rate was 83.6% ($P = 0.031$). In our present study, Group B (Silodosin plus Tadalafil) had a significant higher stone expulsion rate (88.46%) compared to Silodosin alone ($P = 0.029$)¹¹.

Highly selective $\alpha 1A$ -adrenoceptor blockers have been developed to minimize the cardiovascular adverse effects while maintaining their efficacy on the urinary tract. Tamsulosin is a selective $\alpha 1$ -blocker with a 10-fold greater affinity for the $\alpha 1A$ -adrenoceptor than for $\alpha 1B$ -adrenoceptor subtype, while the affinity of silodosin for the $\alpha 1A$ -adrenoceptor is 50-fold greater which explains the weak cardiovascular adverse effects of silodosin¹⁵. For this reason, Silodosin is better than Tamsulosin.

In current study observed that Silodosin plus Tadalafil showed a higher stone expulsion rate than Silodosin alone which was 88.46% vs 75% respectively (P value 0.02) that was statistically significant. The mean expulsion time Silodosin alone was 14.33(± 3.1) and 11.48(± 2.3) was in Silodosin plus Tadalafil group.

This study showed, the episode of pain was 0.7(± 0.06) in Silodosin alone and 0.6(± 0.2) in Silodosin plus Tadalafil group (< 0.001) that was statistically significant. In Rahman et al.⁹ study, Silodosin+tadalafil Group had a significantly higher stone expulsion rate (90%) compared to Silodosin alone groups. They observed that the mean stone expulsion time in Silodosin plus tadalafil Group was also significantly less (12 \pm 2.2) days compared to Silodosin alone Group (15 \pm 3.3) days ($P < 0.001$). In the Jayant et al. study¹¹, the mean expulsion time was 14.9 (± 4.4) days with the tadalafil and tamsulosin combination compared to 16.7

(4.8) days for tamsulosin alone ($P = 0.003$). In Rahman et al.⁹ study, tadalafil and tamsulosin Group had significantly fewer pain episodes than Silodosin alone Group ($P < 0.001$).

Jayant et al.¹¹ also showed significant lower pain episodes with a tadalafil and tamsulosin combination compared to tamsulosin alone. This may be due to two drugs with different actions on the ureter. The stone expulsion rate was 79.0% in Group A and 62.5% in Group B (P value = 0.025). The mean time for stone expulsion in Group A was 1.66 vs. 2.32 weeks in Group B (P value = 0.001). Combination of tamsulosin and tadalafil was found to be safe by Kloner et al.¹² Bechara et al.¹³ showed effectiveness of combination when they used for LUTS.¹⁴

While comparing the efficacy of drugs in Gnyawali et al.¹ study, they found Group A (tamsulosin plus tadalafil) patients had higher expulsion rate than Group B (tamsulosin) 79.01% vs. 62.50% (P value 0.025) respectively. Hari Bahadur KC et al.¹⁰ reported that the overall stone expulsion rate in the study was 72.9% (62 of 85). The stone expulsion rate was significantly higher in group B than in group A (84.1% vs. 61.0%, $p = 0.017$). The mean stone expulsion time was lower in group B (8.08 \pm 3.3 days) than in group A (9.64 \pm 3.8 days), but this difference was not significant ($p = 0.094$).

Regarding adverse effects, such as headache, dizziness, backache, orthostatic hypotension and retrograde ejaculation were a little bit higher in Silodosin plus Tadalafil Group than Silodosin alone; however, it was not statistically significant ($P > 0.05$). No serious side-effects were encountered in the Rahman et al.⁹ study. In Gnyawali et al.¹ study shows drug-related adverse effects such as headache, dizziness, postural hypotension, backache, and runny nose were comparable between two groups and not statistically significant.

Conclusion

The present study concludes that combination of silodosin and tadalafil increases the ureteric stone expulsion rate, decreases stone expulsion time and reduces episode of pain significantly than silodosin alone without any serious side-effects.

Limitation

Small group study and not randomized.

Recommendation

Large number of sample and multi-centered double blind randomized control trial should be taken.

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