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ORIGINAL ARTICLE

RANDOMIZED TRIAL OF THE SAFETY AND EFFICACY OF TAMSULOSIN AND SILODOSIN IN MEDICAL EXPULSIVE THERAPY FOR DISTAL THIRD URETERIC CALCULI

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ABSTRACT: INTRODUCTION: Urolithiasis is a common condition that affects approximately 5% to 10% of the population and the incidence of Urolithiasis is rising. Ureteric stones account for 20% of urinary tract stones and about 70% of them are found in the lower third of the ureter at presentation. Recent literatures show the efficacy of various drugs and minimally invasive procedures for the management of lower third ureteral stones. We performed a randomized, prospective study to assess and compare the efficacy of tamsulosin and silodosin as medical expulsive therapy for lower third ureteral stones. **SETTING AND DURATION:** Department of Surgery, Hassan Institute of Medical Sciences/ Teaching Hospital, Hassan. from August 2013 to August 2014. **MATERIALS AND METHODS:** The prospective data of 60 symptomatic patients with unilateral, lower third ureteral calculi of less than ≤10 mm were randomly allocated for out- patient treatment with tamsulosin and silodosin groups Patients aged ≥ 18 years with a single, unilateral, symptomatic, radio-opaque ureteric stone of 10 mm or smaller in the largest dimension located between the lower border of the sacroiliac joint and vesico-ureteric junction were included. For Group I tamsulosin a daily single dose of 0.4 mg for 28days and for Group II a daily single dose of silodosin 8mg was given. Nonsteroidal anti-inflammatory drugs were used on demand for both the groups. All the patients were told to observe passage of stone by filtering urine stream. The primary end point was the expulsion of the stone and the secondary end points were expulsion time, analgesic use, socioeconomic status, need for hospitalization, endoscopic treatment and drug side effects were documented. **RESULTS:** The stone expulsion rates in patients treated with tamsulosin and silodosin were 83.3% and 86.6% respectively. Mean stone expulsion times in tamsulosin group and silodosin group were 6.8 and 6.2 days respectively. Mean number of pain episodes were 1.5 and 1.4 in the tamsulosin and silodosin group respectively. The mean number of analgesic requirement was 1.0 and 0.8 for the tamsulosin and silodosin group, respectively with no significant difference. Overall, incidence of side effects was similar in both groups. Patients taking silodosin experienced a higher incidence of retrograde ejaculation but a lower incidence of side effects related to peripheral vasodilation when compared to patients taking tamsulosin. Sub-group analysis shows, higher expulsion rates but lower mean expulsion time and pain episodes for stones ≤ 5 mm with both tamsulosin and silodosin groups. The total number of patients from lower socioeconomic status was more than 50% in this study and expulsion rates were better than with patients of higher socio-economic status with tamsulosin is 89 % and silodosin is 94%. There was higher expulsion rates in patients with stones ≤ 5 mm and this was true for both patients treated with tamsulosin 13(92.8%) and silodosin 14(93.3%). However the difference was not statistically significant. Most trials on MET for lower ureteric stones with tamsulosin demonstrated significant lower mean number of pain episodes with respect to placebo (1, 9, 21-23). Results from the present study in terms of mean number of pain episodes and need for

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analgesics are within the published ranges for tamsulosin 1.5(0-4) and 1.0(0-3) and similar data have also emerged for silodosin 1.4(0-4) and 0.8 (0-3) respectively. **CONCLUSION:** MET for suitable cases could effectively increase calculi expulsion rate and decrease expulsion time, complications, cost of treatment, and hospitalization rate. Our study shows a lower incidence of side effects related to peripheral vasodilation and a higher incidence of retrograde ejaculation with silodosin thus making this drug mainly suitable for older patients. There was no significant correlation between expulsion rate and socio-economic status.

KEYWORDS: Silodosin; Tamsulosin; Medical expulsive therapy (MET); ureteric stones; a-1 adrenoceptor blockers.

INTRODUCTION: Urolithiasis is a common condition that affects approximately 5% to 10% of the population and the incidence of urolithiasis is rising. Ureteric stones account for 20% of urinary tract stones and about 70% of them are found in the lower third of the ureter at presentation.[1]

Ureteric colic is one of the most common painful conditions that are often caused by stone in the distal portion of the ureter.[2,3]

A watchful waiting approach for spontaneous stone expulsion may be up to 50% of cases but some complications, such as urinary infection, hydronephrosis and repeat colic events, may occur.[4,5] Minimally invasive procedure may allow distal ureteral calculi to resolve in almost all cases.[5]

However, these procedures are not risk-free and they require some experience and imply high costs. [6,7] The expectant approach by using alpha adrenergic receptor antagonist for management of distal ureteric stones used as adjuvant medical expulsive therapy (MET), and be able to reduce symptoms and facilitate stone expulsion due to the presence of alpha and beta adrenergic receptors (AR) in the human ureter.[8]

Antagonists of these receptors have been proved to decrease ureteric basal tone, peristaltic activity and contractions thus decreasing intra-ureteric pressure and increasing urine transport. [9]

Three meta analyses have confirmed a positive effect of alpha-blocker therapy on the stone expulsion rates. [10-13]

Alpha blockade using tamsulosin has been proved to improve the likelihood of spontaneous stone passage, and to decrease both the time to stone passage and analgesic requirements.[14] The selective alpha1A adrenergic receptor antagonist, silodosin, was more effective than other drugs used MET.[15,16]

However there are few clinical studies that compared silodosin to tamsulosin as MET for lower ureteric stones. We aimed to compare the efficacy of tamsulosin and silodosin as MET for symptomatic, uncomplicated distal ureteric stones.

MATERIALS AND METHODS: We performed a prospective randomized study of 60 consecutive patients in to two equal groups, 30(50%) patients who received tamsulosin or silodosin as MET from August 2013 to August 2014.

Inclusion Criteria: Patients aged ≥ 18 years with a single, unilateral, symptomatic, radio opaque ureteric stone of 10 mm or smaller in the largest dimension located between the lower border of the sacroiliac joint and the vesicoureteric junction as assessed on computerized tomography of kidney ureter and bladder.

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Exclusion Criteria:

1. UTI.
2. Radiolucent stones.
3. Hydronephrosis (grades 2 and 3) in sonography.
4. Diabetes (FBS greater than 125 mg/ dl).
5. Patients with a history of peptic ulcer disease.
6. Systolic blood pressure less than 100.
7. Consumers of calcium antagonist drugs.
8. Patients with a history of surgery on the distal ureter.
9. Single renal patients.
10. Creatinine over 1.4 for males and 1.2 in females.
11. Pain resistant to conservative treatment (non-tolerant patients).
12. Patients with NSAID drug intolerance or adverse effects of Tamsulosin/ Silodosin during study.
13. Patient withdrew from the study at any time.
14. Pregnancy.

In this study, data from a total of 60 patients who fulfilled both inclusion and exclusion criteria were collected from August 2013 to August 2014. These 60 patients were randomized into two equal groups, 30 (50%) patients received a daily single dose of tamsulosin 0.4 mg for 28 days and 30 (50%) patients received a daily single dose of silodosin 8 mg for 28 days.

Both the group of patients were strictly instructed to drink a minimum of 2 L of water daily and to use symptomatic treatment with injection of 75 mg diclofenac on demand. All patients were advised to filter/ strain their urine stream to detect stone passage and to stop the medications when the stone was expulsed and report for confirmation. Patients were followed up weekly with x-ray of the kidney, ureter, and bladder region and with ultrasonography.

RESULTS: The following data were recorded and compared in terms of patients demographics, socio-economic status, stone size and side, type of MET, stone expulsion rate, stone expulsion time, number of pain episodes, need for analgesics use, incidence of side effects. Patients who experienced stone expulsion before first medication, or who were lost to follow-up were excluded from the analysis. Statistical analysis of mean values was carried out with the Student ' t' test and the chi square test. Subgroup analysis was performed according to stone size ≤ or > 5 mm.

Any minimally invasive procedures like ureteroscopy, stenting, ESWL or discontinuation of MET during treatment period due to uncontrollable pain, adverse events, urinary tract infections, acute renal failure, or the patient's decision for stone removal were considered failed therapy. Absence of stone expulsion after 28 days was considered failed therapy. Demographic data of both tamsulosin and silodosin groups were recorded separately & mentioned in Table 1.

	Tamsulosin[n=30]	**Silodosin[n=30]**	**P value**
Mean age[years]	38.5[18-75]	37.8[21-75]	n.s
Gender M/F	18/12	17/13	n.s
Low socio- economic status. n [%]	18[60%]	17[56.6%]	n.s

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Ureteric stone side Left Right	 13[43.3%] 17[56.6%]	 14[46.6%] 16[43.3%]	 n.s n.s
Mean stone size in mm[range] ≤5 mm >5 mm	14[46.6%] 16[53.3%]	15[50%] 15[50%]	n.s n.s

Table 1: Demographic data of both treatment groups

In both the groups parameters related to mean age, sex, socio-economic status, mean stone size, stone side were comparable. Also, the number of patients with smaller stones (≤ 5 mm) and larger (> 5 mm) stones were also comparable in both groups.

Spontaneous stone expulsion rate within 28 days was observed in 25[83.3%] patients in the tamsulosin group and in 26[86.6%] patients in the silodosin group without statistically significant differences (Table 2). During study period hospitalization and ureteroscopy were required in 2 patients belonging to the tamsulosin arm and in 1 patients belonging to the silodosin arm.

Unsuccessful expulsion after 4 weeks of treatment was observed in 3 patients from each group and they underwent ureteroscopic procedure electively. There were no statistically significant differences observed in terms of mean expulsion time, mean number of pain episodes and need for analgesics. The incidence of side effects tamsulosin and silodosin were similar, mild and did not require cessation of MET in any patient. The incidence of retrograde ejaculation was significantly higher in the silodosin arm while the incidence of side effects related to peripheral vasodilation dizziness, Postural hypotension, headache, nasal congestion) were significantly higher in the tamsulosin arm (Table 2).

	Tamsulosin	**Silodosin**	**P value**
Expulsion rate. n [%]	25[83-3%]	26[86.6%]	n.s
Expulsion time days mean (range)	6.8[2-12]	6.2[2-10]	n.s
Pain episodes mean(range)	1.5[0-4]	1.4[0-4]	n.s
Need for analgesics	1.0[0-3]	0.8[0-3]	n.s
SIDE EFFECTS (n %) Retrograde ejaculation	Nil	4 [13.3]	<0.05
Side effects related to peripheral vasodilatation dizziness nasal congestion postural hypotension head ache	 3[10%] 3[10%] 1[3.3%] 3[10%]	 1[3.3%] 1[3.3%] 1[3.3%] 1[3.3%]	 n.s n.s n.s n.s
Total	10[33.3%]	4[13.3%]	<0.05

Table: 2 Final results

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	Tamsulosin - % of expulsion	Silodosin- % of expulsion
Low socioeconomic status	16/ 18 (89%)	16/ 17 (94%)
Higher socioeconomic status	9/ 12 (75%)	10/13 (77%)

Table 2A: Comparing expulsion rate to socioeconomic status

The subgroup analysis according to stone size from both groups are reported in Table 3. The mean expulsion times and the mean number of pain episodes were significantly lower in patients with smaller stones, of both treatment arms.

	Tamsulosin ≤ 5mm >5mm p value	Silodosin ≤ 5mm >5mm p value
Expulsion rate n [%]	13(92.8) 12(75) n.s	14(93.3) 12(80) n.s
Expulsion time days mean (range)	5.5(2-10) 8.2(6-12) <0.05	5.8(3-9) 8.9(5-11) <0.05
Pain episodes mean(range)	1.2(0-3) 2.5(0-5) <0.05	1.1(0-4) 1.9(0-4) <0.05
Need for analgesics	0.7(0-3) 0.9(0-3) n.s	0.6(0-2) 0.8(0-8) n.s

Table 3: RESULTS OF SUBGROUP ANALYSIS

DISCUSSION: Currently, the predominant therapy for distal ureteric calculi is minimally invasive treatment, which could reduce injury to patients while enhancing the success rate, compared to traditional open surgery.

Minimally invasive treatments in distal ureteric calculi include extracorporeal shock wave lithotripsy (ESWL), ureteroscopic lithotripsy (URSL), laparoscopy, and so on. Despite the relative small injury, however, minimally invasive treatment is more expensive and has some potential risks.[7,17] Therefore, small calculi that could be expulsed spontaneously and without clear surgical indications can be treated with conservative strategy. MET that is effective, safe, non-invasive, and suitable for outpatients.[18]

MET is recently emerged as an alternative strategy for the initial management of selected patients with distal ureteric stones.[19] Blockade of alpha1 Adrenergic Receptor inhibits basal tone, reduces peristaltic amplitude and frequency, and decreases intraluminal pressure while increasing the rate of fluid transport and the chances of stone expulsion. Alpha1A and alpha1D are the Adrenergic Receptor subtypes that are more densely expressed in the distal ureter.[20] Tamsulosin has been widely studied in the context of MET for patients with distal ureteric stones smaller than 10 mm. It has been proved that tamsulosin increases stone expulsion rates, decreases pain, reduces mean time to stone expulsion and decreases analgesic usage when compared to placebo.[1,8,21-23]

Various trials demonstrated increased stone expulsion rates using tamsulosin, doxazosin, terazosin, alfuzosin, and naftopidil.[9,24] Itoh performed the first prospective randomized study evaluating the use of silodosin in the management of ureteric stones ≤ 10 mm.[25] Tsuzaka compared the efficacy of the selective alpha1D AR antagonist naftopidil and the selective alpha1A AR antagonist silodosin in the management of symptomatic ≤ 10 mm ureteral stones.[26] Vittorio Imperatore, et al, compared for the first time tamsulosin and silodosin in the context of MET for distal ureteric stones.[27]

Spontaneous stone expulsion rates without MET in patients with distal ureteric stones ≤ 10 mm have been reported to vary between 35.2% to 61% with mean expulsion times ranging from 9.87 to 24.5 days.[1,5,19-21] Tamsulosin enhances stone expulsion rates and decrease mean expulsion time in this subset of patients with reported values ranging from 79.31% to 89.5% and from 6.31 to 12.3 days, respectively.[1,9,21-23] Stone expulsion rate in patients with distal ureteric stones treated with silodosin has been reported to be 72.7%with mean expulsion time of 9.29 days.[25]

Results from our study, demonstrate stone expulsion rates and stone expulsion times in patients treated with tamsulosin that are within the published ranges. Patients treated with silodosin exhibit stone expulsion rates and mean expulsion times that are comparable to those reported in the tamsulosin group. However, stone expulsion rates and times with silodosin in the our study are better than that reported by other authors.[25]

Studies on MET with sub analysis according to stone size demonstrated higher expulsion rates for stones ≤ 5 mm with respect to larger stones[21] and this was true for both patients treated with tamsulosin 13(92.8%) and silodosin 14(93.3%). Stone expulsion rate of 92.8% and 75% in patients treated with tamsulosin with stone size ≤ 5mm and > 5 mm respectively, 93.3% and 80% for silodosin group for similar calculi. However these differences were not statistically significant.

Most trials on MET for lower ureteric stones with tamsulosin demonstrated significant lower mean number of pain episodes with respect to placebo (1, 9, 21-23). Results from the present study in terms of mean number of pain episodes and need for analgesics are within the published ranges for tamsulosin 1.5(0-4) and 1.0(0-3) and similar data have also emerged for silodosin 1.4(0-4) and 0.8 (0-3) respectively.

In our study the percentage of expulsion in lower socioeconomic status patients with tamsulosin is 89% and silodosin is 77%. The expulsion rate for distal ureteric calculi was better in lower economic status compare to higher economic status as given in Table 2A.

Safety issues and adverse events spectra differ considerably between the available alpha-blockers. Adverse side effects commonly reported with different alpha1 AR blockers include dizziness, headache, asthenia, postural hypotension, syncope, rhinitis, sexual dysfunction.[28,29]

Tamsulosin preferentially blocks alpha1A and alpha1D AR, with a 10-fold greater affinity than for alpha1B AR. In contrast, silodosin is highly selective for alpha1A AR, with a 162-fold greater affinity than alpha1B AR and about a 50-foldgreater affinity than for alpha1D AR.[30]

Studies conducted recently have suggested that silodosin as a consequence of its high subtype selectivity is less likely than tamsulosin to have significant cardiovascular side effects either when used alone or in combination with other agents, which may affect blood pressure.[28]

In a study by Yu HG et al., tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure relative to the negligible change of silodosin.[31] The incidence of orthostatic hypotension with silodosin has been reported to be < 3%.[32]

Results from our study shows retrograde ejaculation in 4 (13.3%) patients treated with silodosin and none in tamsulosin group. The incidence of side effects related to peripheral vasodilation in tamsulosin group is 10(33.3%) and silodosin group is 4 (13.3%) which is similar to Vittorio Imperatore et al, and none of our patients discontinued the treatment. The incidence of side effects is similar to that reported by other authors.[29] The lower incidence of side effects related to peripheral vasodilation associated with silodosin use make it more suitable for older patients.[28]

CONCLUSION: In summary, MET using Tamsulosin or Silodosin for suitable cases could effectively increase calculi expulsion rate and decrease expulsion time, complications, cost of treatment, and hospitalization rate.

Our study shows a lower incidence of side effects related to peripheral vasodilation and a higher incidence of retrograde ejaculation with silodosin thus making this drug mainly suitable for older patients.

There was no significant correlation between expulsion rate and socio-economic status.

Although medical expulsion therapy for distal ureteric calculi is encouraging, further studies with double-blind and placebo remain to be performed to evaluate the current medicines and to develop other medicines.

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