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COMPARATIVE STUDY OF TAMSULOSIN VS SILODOSIN IN MEDICAL EXPULSIVE THERAPY FOR LOWER URETERIC CALCULUS.

Urology

Dr. Girish Kumar Sharma* Associate Professor, Deptt. of Urology, Indira Gandhi Medical College, Shimla, H.P. *Corresponding Author

Dr. Varun Saini Associate Consultant Plastic Surgery, BLK Super Speciality Hospital, New Delhi.

Dr. Puneet Mahajan Professor, Deptt. of Surgery, Indira Gandhi Medical College, Shimla, H.P.,

Dr. Manjeet Kumar Assistant Professor, Deptt. of Urology, Indira Gandhi Medical College, Shimla, H.P

ABSTRACT

The efficacy of ESWL and URSL as the definite management for ureteral stones have been proven, but they are not risk-free and are expensive, so medical expulsive therapy is justified in appropriate patients. We carried out a prospective randomized study in forty patients with symptomatic lower ureteric calculus of size <10mm, who were divided into Group A in whom Tamsulosin and Group B in whom Silodosin was used for expulsive therapy. Patients were followed up weekly for 4 weeks and those who passed stones and confirmed radiologically in less than 4 weeks were considered a success and assessed primarily for expulsion of stone and secondarily for time to expulsion and analgesic use.Using Silodosin as medical expulsive therapy in the management of lower ureteral stones of size <10mm has been shown to be very promising.

KEYWORDS

Silodosin; Tamsulosin; Medical Expulsive Therapy

INTRODUCTION

Urolithiasis is a multifactorial disease that is often experienced in daily practice. About 50% of urolithiasis patients will have a recurrence of renal colic within 10 years of their first episode, making urolithiasis a chronic disease with substantial economic consequences and great public health importance.[1] Ureteral stones of less than 4 mm in diameter have a chance of over 80% to pass spontaneously.[2] Both stone expulsion and time to expulsion of ureteral stones depends heavily on stone size and location.

The efficacy of minimally invasive therapies, such as Extra corporeal shockwave lithotripsy (ESWL) and ureteroscopic lithotrpsy (URSL) as the definite management for ureteral stones have been proven. Nevertheless, they are not risk-free and are expensive, so medical expulsive therapy is justified in appropriate patients.

We carried out a prospective randomized study to evaluate the effectiveness of Tamsulosin, alpha 1 A/D-AR blocker and Silodosin , alpha 1A-AR blocker in the expulsion of lower ureteric stones.Patients were evaluated primarily for expulsion of stones and secondarily for time to expulsion and analgesic use.

MATERIAL AND METHODS

A total of 40 patients with symptomatic lower ureteric calculus of size <10mm on NCCT KUB were recruited for present study and were alternatively divided into Group A, in whom Tamsulosin(0.4mg) & Group B, in whom Silodosin(8mg) was used for medical expulsive therapy & were advised to maintain adequate hydration. In every case a detailed history was taken, thorough clinical examination and urological investigations were done. Patients were asked to document any stone passage and report immediately about it, which was confirmed radiologically and those who had passed their stones were asked to stop taking the medication. All patients were asked to maintain a pain diary and to record the number of doses of analgesic (hyoscine butyl-bromide and paracetamol) medications consumed per day. The patients were followed up weekly for up to 4 weeks with x-ray and ultrasound of the KUB region, complete haemogram, renal function test and urine analysis was performed to exclude infection. Those who passed stone and confirmed radiologically in less than four weeks were considered a success and assessed for stone expulsion time and and analgesics required. The criteria for treatment discontinuation and the need for hospitalisation and/or endoscopic treatment were intolerable pain, fever and/or development of new severe hydronephrosis and worsening of already hydronephrosis or lack of stone expulsion after four weeks.

Student t – test was used to compare the means of normally distributed variables between two treatment Groups. Otherwise the Mann – Whitney u test was used. Nominal parametres were analysed using Fisher exact test. The Cox proportional hazard regression in model was used to evaluate the significance of all factors namely patient age, gender and therapy that could explain the outcome of time related end point. Two sided $p < 0.05$ was considered statistically significant.

RESULTS

Both Groups were comparable with respect to age (mean age of patients in Group A was 38.05±2.47 years, in Group B was 40.50 ±3.00 years; P = 0.09) and sex (Group A had 10 females and 10 males, while Group B had 6 females and 14 males).

Location of stone: All patients included in our study had calculus in lower ureter.

Size of Stone: The mean size of stone in Group A (6.02±1.31 mm) and in Group B (5.93±1.62 mm) was comparable; p = 0.24.

Table 1: Showing distribution of Stone size within each Group

STONE SIZE (NCCT KUB)	Group A	Group B
1-5mm	4	7
5-7mm	11	10
7-10mm	5	3

Expulsion rate of stone: Stone expulsion rate was 75% i.e. 15 out of 20 patients in Group A and 95% i.e.19 out of 20 patients in Group B. Amongst the five failures in Group A, one patient required endoscopic intervention for pain and fever not responding to medical treatment. The expulsion rate in Group B was higher than Group A but it was not statistically significant; P = 0.10.

Time to expulsion: Time to expulsion in Group A (Tamsulosin) was 12.53±4.87 days and Group B (Silodosin) was 8.47±5.00 days.

Table 2: Showing time to expulsion of each stone size sub-group in either Group

	Group A	Group B
1-5mm	10.5 days	6.28 days
5-7mm	12.1 days	7.6 days
7-10mm	25 days	20.5 days

Stone passage occurred within seven days in 57.89% of the patients in Group B, while 73.33% of patients in Group A had expulsion of stone in 7 to 14 days.

Table 3: Expulsion of stone at different time interval in each Group

Expulsion time	Group A	Group B
<7 days	0	11(57.89%)
7-14 days	11(73.33%)	5(26.32%)
14-21 days	3(20%)	2(10.53%)
>21 days	1(6.67%)	1(5.26%)

Analgesics use : Analgesic requirement in Silodosin group (2.10±1.15 times per day) was significantly lower than Tamsulosin group (2.97±0.91 times per day).The difference was statistically significant p = 0.001.

DISCUSSION

Among all urinary tract stones, 20% are ureteral stones, of which 70% are found in the lower third of ureter.[3] The efficacy of minimally invasive therapies, such as extra corporeal shockwave lithotripsy and ureteroscopic lithotripsy, has been proved by several studies.[4,5,6] However, such procedures are effective, they are not free from risk or inconvenience, and there are consequent implications e.g lowering the quality of life, high-cost, suspensions of regular activities.[4,6]

The effectual factors for the spontaneous expulsion of ureteral stones are stone size, location, number, structure, side and ureteral anatomy.[4,7] It would seem logical that medical therapy should be used to reduce spasm and relaxation of smooth muscles of ureter.

The role of watchful waiting approach has been extended as a result of advances in pharmacological therapy, which can reduce symptoms and facilitate stone explosion. The rate of spontaneous passage diminishes as stone size increases.[8] In order to increase the expulsion rate and reduce analgesic consumption, there is a great deal of enthusiasm for adjuvant pharmacological intervention which can reduce symptoms and facilitate stone expulsion.[8,9,10]

Many studies have been published on alpha 1–AR in the human ureter since the first report in 1970. Alpha-1 receptors have been classified into three subtypes (alpha-1 A, alpha-1 B and alpha-1 D)[11-12]. The alpha-1 A receptor predominate in the proximal urethera, prostate and bladder neck, and alpha-1 B receptors are distributed widely in the vascular smooth muscles, while alpha-1 D receptors are found predominantly in the distal ureter where it passes through the detrusor muscles. The frequency of distribution of these receptors in the distal ureter was alpha-1 D> alpha-1 A >alpha-1 B.[11-12]

Sasaki et al reported that alpha1D– AR mRNA expression is highest among Alpha 1-AR subtypes in human ureter. However the Alpha 1–AR subtype which contributed most to contraction was Alpha 1A–AR. Their results suggested that alpha 1A- AR blocker was useful for discharge of ureteral stones[13].

Numerous clinical trials have been performed to investigate the efficacy of alpha 1-A/D selective alpha blocker Tamsulosin. Most of these studies were randomized and revealed that Tamsulosin significantly improves the expulsion rate of medium-sized (3–10 mm) distal ureteral stones. Thus Tamsulosin represents a non-invasive and cost-effective alternative to interventional approaches.[14]

Research has revealed that Silodosin has 56 fold affinities for alpha-1A receptor than for alpha- 1D. Silodosin is a highly selective alpha-1A receptor antagonist, which has been used in the treatment of benign hyperplasia of prostate, and has been proved to be more effective than alpha- 1A/D selective antagonist Tamsulosin.[15]

It is possible that the effect of alpha-1 A receptor antagonist on the obstructed ureter is to induce an increase in the intra ureteral pressure gradient across the stone, as well as decreased peristalsis below the ureter , thus inducing a strong urge to expel the stone.

Table number 4 shows the results of our study in comparison to other studies using Silodosin for medical expulsive therapy.

Table No.4: comparison of studies using Silodosin for Medical Expulsive therapy

	Stone size (mm)	Expulsion rate %	Expulsion time (days)
Group B	5.93	95%	8.47
Tsuzaka et al.[16]	4.2	84%	15
Itoh et al.[17]	5.69	66.3%	10.27

Tsuzaka et al have described an expulsion rate of 84% with Silodosin , though in their study the mean stone size was much less i.e 4.2 ± 1.9 mm.[16] Itoh et al observed an overall expulsion rate of 66.30% with Silodosin use in their patients with mean stone size of 5.69 ± 2.31mm, however they had included patients with proximal and mid ureteric stones also.[17] In patients with ureteric stone sizes ranging 6–9 mm, expulsion rate was 52.20% and in those with distal ureteric stones of size ranging 1–9mm, expulsion rate was 72.70%. The follow-up period in their study was eight weeks. We have observed an expulsion rate of 95% with the mean stone size of 5.93±1.62mm.

Table number 5 shows the results of our study in comparison to other studies using Tamsulosin for medical expulsive therapy.

Table No.5: Comparison of studies using Tamsulosin for Medical Expulsive therapy

	Stone size (mm)	Expulsion rate %	Expulsion time (days)
Group A	6.02	75%	12.53
Zhou et al.[19]	6.54	82.2%	7.7
Propiglia et al.[18]	5.42	85%	7.7

Propiglia et al[18] and Zhou et al[19] have noted expulsion rates of 85% and 82.2% with mean stone sizes of 5.42±1.54mm and 6.54±0.57mm, respectively with Tamsulosin. In our study, expulsion rate was 75% in patients who received Tamsulosin with mean stone size of 6.02±1.31. Expulsion rate of Tamsulosin Group in our study was lower than Silodosin Group but was not statistically significant, p = 0.10.

Time to expulsion in Group A (Tamsulosin) i.e. 12.53±4.87 days was significantly higher than Group B (Silodosin) i.e. 8.47±5.00 days in our study. Propiglia et al[18]and Zhou et al[19] both have reported a mean time to expulsion of 7.7 days with Tamsulosin use. Itoh et al[17] and Tsuzaka et al[16] have reported a mean time to expulsion of 10.27±8.35 days and 15±9 days respectively with Silodosin use, and the mean stone size in their studies (5.69±2.31mm and 4.20±1.9 mm respectively) was less than that in our study (i.e. 5.93 ± 1.62mm). However, Itoh et al[17] included stones of proximal and mid ureter also along with distal ureteric calculus in their study.

Analgesic use in the Silodosin Group (2.10±1.15 times per day) was significantly lower than Tamsulosin Group (2.97±0.90 times per day) p=0.001. Itoh et al[17] noted analgesic use of 0.9±3.8 times in Silodosin Group. Decreased analgesic requirement in Silodosin Group may be due to higher expulsion rate as well as lower expulsion time associated with Silodosin. Silodosin has 56 fold higher affinity for Alpha 1A – AR as compared to Tamsulosin . Studies have reported that Alpha1A– AR is main participant in phenylephrine induced ureteral contraction in isolated human ureter and ureteral contraction is mainly mediated by alpha 1A – AR, therefore Silodosin use may lead to longer pain free periods.

CONCLUSION

Our results indicate that use of Silodosin in patients with lower ureteric stones results in higher expulsion rate with a significantly decreased time to expulsion and analgesic requirement as compared to Tamsulosin . Finally, using Silodosin as medical expulsive therapy in the management of lower ureteral stones has been shown to be very promising, but the major limitation of the current study was its small sample size. Hence, further clinical research in this field is warranted.

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