Original Article

DOI: 10.7860/JCDR/2013/6141.3241

Urology Section

Comparing the Efficacy of Tamsulosin and Silodosin in the Medical Expulsion Therapy for Ureteral Calculi

SANDEEP GUPTA[1], BIJIT LODH[2], AKOIJAM KAKU SINGH[3], KHUMUKCHAM SOMARENDRA[4], KANGJAM SHOLAY MEITEI[5], SINAM RAJENDRA SINGH[6]

ABSTRACT

Background: Urolithiasis is a chronic disease of mankind, which has enormous public health importance and it accounts for a substantial economic burden on our society. Hence, it becomes all the more important to formulate cheaper and easier means for treating this condition. The past few years have seen a number of drugs being introduced and successfully used in the medical expulsion therapy of small, uncomplicated ureteral calculi, with each drug claiming to provide better results than the others. Ours is perhaps the first study which has compared the efficacy of tamsulosin and silodosin in the medical expulsion therapy for ureteral calculi.

Aims: To compare the efficacy of tamsulosin (0.4mg) vs silodosin (8mg), both in terms of the stone expulsion rate and the time to stone expulsion.

Settings and Design: A prospective and a randomized controlled study was conducted in the Department of Urology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India.

Material and Methods: From February to August 2012, 100 patients who were between the age group of 18–50 years, who had unilateral, uncomplicated middle or lower ureteral stones </= 1cm were enrolled and they were divided into two groups. Group 1 received tamsulosin (0.4mg) daily, whereas Group 2 received silodosin (8mg) daily for a maximum period of 4 weeks. The patients were followed up weekly or biweekly with imaging studies. The primary endpoint was the stone expulsion rate and the secondary endpoints were the stone expulsion time, the rate of the interventions and the side effects.

Statistical Analysis: The statistical analysis was performed by using the Student's 't'-test and the Chi–squared test. A p value of < 0.05 was considered to be statistically significant. The SPSS-16 software was used for the statistical analysis of the data.

Results: A spontaneous stone expulsion was observed in 58% of the patients in group 1 and in 82% of the patients in Group 2, which was statistically significant. There was also a significant difference between the groups with regards to the mean stone expulsion time. A lower analgesic use was found in Group 2.

Conclusion: In our study, silodosin was found to be clinically superior to tamsulosin, both in terms of the stone expulsion rate and the stone expulsion time.

Key words: Efficacy, Expulsion time, Expulsion rate

INTRODUCTION

Stone disease is one of the most common afflictions of the modern society and it has been described since antiquity. With the westernization of the global culture, however, the site of stone formation has migrated from the lower to the upper urinary tract. As it has been estimated that 50% of the patients will have a recurrence of colic within 5 years of their first episodes, urolithiasis is a chronic disease with substantial economic consequences and a great public health importance [1,2].

There has been a paradigm shift in the management of the ureteral calculi in the past decade, with the introduction of lesser invasive methods and newer drugs. The alpha1–blockers which were first developed as anti–hypertensive drugs, are now being effectively used in the management of benign prostatic hyperplasia, due to their relaxing properties on the urinary tract. Recent studies have reported excellent results with the medical expulsion therapy for the distal ureteral calculi, with alpha1 blockers. Their use in the treatment of distal ureteral stones arose from the concept that they could induce a selective relaxation of the ureteral smooth muscle, which could inhibit the ureteral spasms and result in dilatation of the ureteral lumen.

There is a large body of published data which have shown the efficacy of such a therapy in increasing the expulsion rate and in decreasing the expulsion time of the stones [3–9]. Their use has thus become an accepted practice. Tamsulosin, an α1-adrenoceptor antagonist, is one of the most popular and effective medical agents, which is used for the expulsive therapy. Silodosin, a recently introduced selective α (1A)-adrenoceptor antagonist, has shown promising results with fewer side effects and a better efficacy.

OBJECTIVES

The objective of this study was to compare the efficacy of tamsulosin (0.4 mg) vs silodosin (8 mg), once daily, both in terms of the stone expulsion rate and the time to stone expulsion.

MATERIAL AND METHODS

Form February 2012 to August 2012, a total of 100 patients (M=38; F=62) who were between age group of 18–50 years, who had unilateral, non–impacted, uncomplicated middle or lower ureteral stones which were </= 1cm, were enrolled in a prospective study and they were randomised into two groups. The sample size of the study was arbitrarily determined and it was not based on the statistical calculations. The patients were evaluated with plain X–ray, ultrasonography and unenhanced computed tomography (CT) scans whenever they were necessary. The stone size was calculated on the first plain X–ray or CT by using a digital ruler and the greatest dimension of the stone was taken into consideration as the stone size.

All the patients provided informed written consents and they were properly informed about the study in which they would be enrolled. The patients were randomly allocated into two treatment groups of 50 patients each, by using a random number table. The patient demographics in the two groups, in terms of the size of the stones in the two groups, their locations in terms of the laterality and their

locations in the ureter have been presented in the form of a table [Table/Fig-1]. Group 1 received tamsulosin (0.4 mg) daily, whereas Group 2 received silodosin (8 mg) daily, for a maximum period of 4 weeks.

All the patients were prescribed the 100 mg diclofenac tablet on demand for pain relief. The patients were advised that on experiencing an episode of unbearable ureteric colic, they should immediately report to us. The patients were followed up weekly or biweekly with X–rays of the abdomen and the pelvis and ultrasonography. The patients were instructed to record the date and time of the stone passage. The follow up continued until the patients were rendered stone-free by intervention or spontaneous stone expulsion, as was confirmed by the patient, for a maximum of 4 weeks. The primary endpoint was the stone expulsion rate and the secondary endpoints were the stone expulsion time, the rates of the interventions such as ureterolithotripsy, extracorporeal shock wave lithotripsy, or ureteral stenting, unbearable ureteric colic and side effects. The expulsion time was defined as the number of days from the random allocation to the stone expulsion.

The statistical analysis was performed by using the Student's t-test and the Chi–squaretest. A p value of < 0.05 was considered to be statistically significant. The SPSS–16 software was used for the statistical analysis of the data.

RESULTS

All the patients in the Groups 1 and 2 completed the study. There was no significant difference between the groups with respect to the patients' ages, the stone sizes and their locations.

A spontaneous stone expulsion was observed in 29 of the 50 patients (58%) in Group 1 and in 41 of the 50 patients (82%) in group 2. The stone expulsion rate was significantly higher in Group 2 than in Group 1(p = 0.008). There was also a significant difference between the groups with regards to the mean stone expulsion time (P=0.01). The mean expulsion time was 19.5 +/- 7.5 days in Group 1 vs. 12.5 +/- 3.5 days in Group 2 [Table/Fig-2].

Two of the male patients who took silodosin experienced a retrograde ejaculation but a lower incidence of the side effects which were related to the peripheral vasodilatation as compared to the patients who took tamsulosin. However, those patients who experienced a retrograde ejaculation were followed-up after the completion of the study and they were found to have been relieved of this problem. No side-effects that required cessation of the treatment were encountered. A lower analgesic use was found in Group 2.

DISCUSSION

Ureteral colic, which is mainly due to ureterolithiasis, represents 1 to 2% of the hospital emergency admissions. There has been a significant improvement in the medical management of the ureteral calculi, with the introduction of effective medical therapeutic agents in the market. The likelihood of a ureteral stone passage is dependent on several factors, which include the stone size and the location and the ureteral conditions. Studies have shown stone passage rates between 71–98% for the distal ureteral stones which are less than 5 mm and from 25–53% for those which are between 5 and 10 mm [10].

The role of adrenergic receptors in the human ureter was first described in 1970 [11]. It was shown later, that the alpha–adrenergic receptors were classified into three different subtypes of a1A, a1B and a1D, of which the distribution in the human ureter was a1D >a1A >a1B [12]. It was also shown that the alpha-adrenergic receptor agonists had a stimulatory effect on the ureteral smooth muscle, whereas the beta-adrenergic receptor agonists had an inhibitory effect [13]. They prevent the uncoordinated muscle activity which is seen in renal colic, while maintaining ureteral peristalsis, which might facilitate a spontaneous stone passage [14]. The alpha blockers mainly produce relaxation of the distal

Characteristics	Group 1 (Tamsulosin)	Group 2 (Silodosin)	p-value
Patients (n)	50	50	_
Sex Male Female	 20 30	 18 32	 0.68
Mean +/- 2 SD stone size(mm)	7.0 +/- 2.3	6.6+/-1.8	0.57
Stone location(n) Right Left	 27 23	 32 18	 0.300
Stone position(n) Mid ureter Lower ureter	 24 26	 21 29	 0.54
None of the differences are statistically significant.			

[Table/Fig 1]: Demographic data of the two study groups

Endpoint	Group 1 (Tamsulosin)	Group 2 (Silodosin)	p-value
Primary endpoint: Stone expulsion rate	29/50 (58%)	41/50 (82%)	0.008
Secondary endpoint: Mean+/- 2SD time to expulsion (days)	19.5+/- 7.5	12.5+/- 3.5	0.01
Both the differences are statistically significant.			

[Table/ Fig 2]: Results according to the treatment

human ureter by reducing the ureteric smooth muscle tone rather than completely ablating its activity. Two meta–analyses provided a high level of evidence for the clinical benefit of the alpha blockers in the patients with distal ureteral calculi, in which the patients who were given alpha blockers had 52% and 44% greater likelihoods of stone passage than those who were not given such treatment [1, 15]. The treatment effect on the expulsion rate was partially lost, as the sizes of the stones decreased, because of the high spontaneous expulsion rate of the small stones [3]. Although most of the studies used tamsulosin, which is a selective a1A/a1D adrenergic receptor antagonist, the efficacies of the other alpha blockers such as doxazosin, terazosin, alfuzosin and naftopidil were also indicated [16–18]. Silodosin was approved for BPH by the US Food and Drug Administration in October 2008. Ours is perhaps the first study of its kind, which has compared the efficacy between silodosin and tamsulosin and our results are also very encouraging. Regarding the incidence of the retrograde ejaculation, there is a consensus among many urologists, that its occurrence should be considered as a sign of the efficacy, rather than an adverse effect of the treatment. Silodosin appears to relax the smooth muscles of the lower urinary tract and the genital tract enough to induce a retrograde ejaculation. This was reflected in the finding that the patients who had the greatest relief from the lower urinary tract symptoms had a higher likelihood of the retrograde ejaculation. This observation suggests that the retrograde ejaculation is actually an indirect indicator of the relaxation of the smooth musculature that silodosin induces. The same was reflected in our study, in which both the patients who had experienced the retrograde ejaculation had successfully passed the stones. The advantage of the medical expulsive therapy is important, because the risks which are related to a surgical intervention are not trivial [19]. Studies have reported the overall complication rates after ureteroscopic lithotripsies to be 10–20%, with major complications such as ureteral perforations, avulsions and strictures occurring during 3–5% of the procedures [19]. Urinomas and sub capsular bleeds have been reported in15–32% of the patients who are treated with shock wave lithotripsy [20].

The medical expulsive therapy should be offered as a cost-effective treatment for the patients with distal ureteral calculi, who are amenable to a waiting management.

CONCLUSION

A conservative approach should be considered as an option in the management of the uncomplicated, small, distal ureteral calculi. Although many such trials are advisable, to come to a definitive conclusion, the findings of our study suggest that the α (1A)-adrenoceptor antagonist, silodosin, was clinically superior to tamsulosin for the stone expulsion in our study.

REFERENCES

[1] Hollingsworth JM, Rogers MA, Kaufman SR et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet.* 2006; 368: 1171-79.

[2] Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G. A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. *J. Urol*. 1999; 162: 27-30.

[3] Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? *Eur Urol.* 2009; 56:455-71.

[4] Autorino R, De Sio M, Damiano R, Di Lorenzo G, Perdonà S, Russo A, et al. The use of tamsulosin in the medical treatment of ureteral calculi: where do we stand? *Urol Res.* 2005; 33:460-64.

[5] Borghi L, Meschi T, Amato F, Novarini A, Giannini A, Quarantelli C, et al. Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. *J Urol.* 1994;152:1095-98.

[6] Cervenàkov I, Fillo J, Mardiak J, Kopecný M, Smirala J, Lepies P. Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker-Tamsulosin. *Int Urol Nephrol.* 2002; 34:25-9.

[7] Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol.* 2003; 170:2202-05.

[8] Küpeli B, Irkilata L, Gürocak S, Tunç L, Kiraç M, Karaoðlan U, et al. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? *Urology.* 2004; 64:1111-15.

[9] Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol.* 2004;172:568-71

[10] Ibrahim AI, Shetty SD, Awad RM, Patel KP. Prognostic factors in the conservative treatment of ureteric stones. *Br. J. Urol*. 1991; 67: 358-61.

[11] Malin JM Jr, Deane RF, Boyarsky S. Characterisation of adrenergic receptors in human ureter. *Br. J. Urol*. 1970; 42: 171-74.

[12] Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. *Int. J. Urol*. 2007; 14: 749-53.

[13] Weiss RM, Bassett AL, Hoffman BF. Adrenergic innervation of the ureter. Invest. *Urol*. 1978; 16: 123–7.

[14] Tzortzis V, Mamoulakis C, Rioja J, Gravas S, Michel MC, de la Rosette JJ. Medical expulsive therapy for distal ureteral stones. *Drugs.* 2009; 69: 677-92.

[15] Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of alpha-blockers for the treatment of ureteral stones. *J. Urol*. 2007; 177: 983-87.

[16] Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J. Urol. 2008; 179: 2244-47.

[17] Wang CJ, Huang SW, Chang CH. Efficacy of an alpha1 blocker in expulsive therapy of lower ureteral stones. *J. Endourol.* 2008; 22: 41-46.

[18] Sun X, He L, Ge W, Lv J. Efficacy of selective alpha1D-blocker naftopidil as medical expulsive therapy for distal ureteral stones. *J. Urol*. 2009; 181: 1716-20.

[19] Daniels GF Jr, Garnett JE, Carter MF. Ureteroscopic results and complications: experience with 130 cases. *J. Urol.* 1988; 139: 710-13.

[20] Lotan Y, Gettman MT, Roehrborn CG, Cadeddu JA, Pearle MS. Management of ureteral calculi: a cost comparison and decision making analysis. *J. Urol*. 2002; 167:1621-29.

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Post Doctoral (Mch) Trainee, Department of Urology, RIMS, Imphal, India.
2. Senior Resident, Post doctoral(Mch) Trainee, Department of Urology, RIMS, Imphal, India.
3. Associate Professor, Department of Urology, RIMS, Imphal, India.
4. Senior Resident, Post Doctoral (Mch) Trainee, Department of Urology, RIMS, Imphal, India.
5. Senior Resident, Post Doctoral (Mch) Trainee, Department of Urology, RIMS, Imphal, India.
6. Professor & Head, Department of Urology, RIMS, Imphal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Sandeep Gupta,
Senior Resident, Post Doctoral (Mch) Trainee, Department of Urology, RIMS, Imphal -795004, India.
Phone: 7308940144, E-mail: drsandeepgupta2009@yahoo.in

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 31, 2013**
Date of Peer Review: **May 22, 2013**
Date of Acceptance: **May 03, 2013**
Date of Publishing: **Aug 01, 2013**