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Original Research Article

Role of tamsulosin in patients undergoing ESWL for renal and ureteric stones

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ABSTRACT

Background: To determine the effect of tamsulosin, as adjunctive medical therapy on the outcome of extracorporeal shock wave lithotripsy (ESWL) for solitary renal and ureteric calculi.
Methods: From January 2017 onwards, a prospective, randomized controlled study was conducted in patients with solitary renal or ureteral calculus measuring less than 20 mm undergoing ESWL. The study group (n=62) received 0.4 mg of tamsulosin daily till stone clearance or a maximum period of 12 weeks and control group (n=58) received ESWL only. Parameters assessed were stone size, composition, location, stone clearance, mean time to clearance, analgesic requirement, steinstrasse, need for hospitalization and/or auxiliary procedures.
Results: There was no difference between the 2 groups with regards to age, stone size, location or composition. The complete clearance rate for renal stones was 62.7% and 36.5% (p=0.004) and for ureteric stone was 89.4% and 58.8% (p=0.03) in study and control groups, respectively. The control group had a higher rate of clinically insignificant residual fragments (CISF i.e. <3 mm), 12.9% versus 35.4% (p=0.002). There was no significant difference in the mean time to stone clearance (p=0.07) or in the incidence of steinstrasse formation (p=0.12). The mean analgesic requirement (p=0.01), need for auxiliary procedures and hospitalization (p=0.03) was significantly was higher in the control group.
Conclusions: Tamsulosin increase the complete clearance rate and decrease the incidence of CISF. It also reduces analgesic requirement, need of additional procedures and hospitalization rate and might be useful as a routine adjunctive therapy following ESWL.

Keywords: CISF, ESWL, Tamsulosin, Ureteric stone

INTRODUCTION

Urinary stone disease is a significant and worldwide health problem. Since its introduction in 1981, extracorporeal shockwave lithotripsy (ESWL) has revolutionized the management of urinary stones. It is now considered as the standard of care for most renal and ureteric calculi less than 20 mm. The major goal of ESWL is to achieve a stone-free status. The success of this procedure is determined by 2 factors, fragmentation and clearance. Fragmentation is dependent on the type of lithotripter and the nature of the calculus. Once fragmented, both renal and ureteric stones behave similarly with conservative treatment. Their clearance from the urinary tract depends upon several factors such as fragment size (the expulsion rate for stone fragments less than 5 mm is up to 98% and 53% for size 5 to 10 mm), calyceal configuration, smooth muscle spasm, sub mucosal edema, peristaltic activity and ureteral anatomy.[1] Various methods have been used to promote spontaneous stone passage such as hydration, analgesics, anti-inflammatory agents.[2,3] Ureterovesical junction (UVJ) is the narrowest part of the ureter where most of the stone fragments get impacted. The concept of relaxation of UVJ, thereby facilitating passage of stone fragments led to use of various relaxants like calcium channel blockers, nitrates, anticholinergics, antihistamines and alpha-blockers.[4-6] The rationale of using Alpha blockers is that

Alpha adrenergic receptors have been detected in the human ureter with a predominance of Alpha 1A and Alpha 1D receptor subtypes in the lower ureter, especially near UVJ.[7] Alpha 1-adrenergic antagonists inhibit basal tone, peristaltic activity, and spontaneous ureteral contractions, may affect stone passage.[8] tamsulosin, an alpha blocker that is commonly used in the treatment of BPH, was chosen for this study as it acts on alpha 1A receptor subtypes of the ureter. It prevents ureteral spasm by relaxing the smooth muscle of the ureter and decreases the pain by acting on the C fibers, thereby blocking pain conduction. Current available literature suggests that tamsulosin is a safe and effective expulsive therapy for the management of small distal ureteral stones. Role of tamsulosin as an adjunctive therapy following ESWL is emerging. In this regard, few studies have evaluated the role of tamsulosin after ESWL, but still data remain limited while in addition a discrepancy is observed in the reported efficacy. For this reason, we felt need of conducting a prospective, randomized study to evaluate the efficacy of tamsulosin as adjunctive treatment in patients undergoing ESWL for renal and ureteric stones.

Aim and objectives

To determine the effect of tamsulosin, as adjunctive medical therapy on the outcome of extracorporeal shock wave lithotripsy (ESWL) for solitary renal and ureteric calculi.

METHODS

After obtaining Institute's ethical committee approval, a prospective, randomized controlled study was conducted in the Department of Urology, SCB Medical College, Cuttack from January 2017 to December 2019.

Inclusion criteria

Patients with solitary radiopaque renal/ureteric calculus less than 20 mm in size.

Exclusion criteria

Previous unsuccessful attempts at ESWL; age <18 years; in-situ DJs; radiolucent stones; elevated serum creatinine (greater than 2 mg/dl); urinary tract infection; coagulopathy, urinary tract anomalies; and previous pyeloureteral surgery.

Brief procedure

From all patients enrolled in the study, informed consent was obtained after they read a summary of the protocol and agreed to comply with the follow-up schedule. The possibility of side effects and undesired events during the study period was discussed. Patients were evaluated before treatment with x-ray KUB, intravenous urography, renal ultrasonography, clinical (history and brief physical examination) and laboratory (complete blood count, urine culture, renal profile, coagulation screening, and pregnancy test) examinations were conducted. An additional x-ray KUB was done 1 day before lithotripsy. Patients were then randomized into 2 groups (study and control) based upon the last digit (even/odd) of their hospital registration number. Both groups were subjected to Dornier-M3 compact Delta electromagnetic lithotripter at 60 shockwaves per minute with a total of with 3000 shockwaves per session. In study group, in addition to the standard treatment (hydration, analgesics, potassium citrate), tamsulosin was started immediately after the ESWL at a dose of 0.4 mg once daily and continued till the study end point is reached or till a maximum of 12 weeks. Control group received only standard treatment following ESWL. Shockwave sessions were repeated as needed. Follow-up was done with clinical examination and x-ray /USG KUB at 2, 4, 6, 9 and 12 weeks.

Factors analyzed during each follow-up include; success rate (defined as the percentage of patients who either rendered stone free or had clinically insignificant residual fragments (CIRF) i.e. fragments less than or equal to 3 mm in diameter, complete stone-free rate (percentage of patients having complete clearance on x-ray/USG), mean time to stone clearance, number of shockwave sessions, dose of analgesic required [calculated as total amount (mg) of diclofennac required for pain relief], incidence of steinstrasse formation and need for hospitalization and or auxiliary procedures.

Study end point

Complete stone-free status, presence of clinically insignificant residual fragments and 3 month follow-up.

Statistical analysis

A sample size of 130 patients (65 in each group) was chosen using "PS power and sample size" software, version 2.1.30. It was estimated to yield 80% power (type II or beta error of 0.2%) to detect a difference of 22% or more between the two groups, allowing a two-side type I error rate of 5%. Statistical analysis was performed using the Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, Ill) software. All p values less than 0.05 were considered to indicate significance. All statistical tests were two-tailed. Differences in the success rate between treatments were compared with the chi-square test for 2×2 tables or Fisher's exact test when the tables were too sparse. Continuous variables were analyzed using the Student t test or Wilcoxon rank sum test, as appropriate.

RESULTS

Baseline demographic and clinical characteristics

A total of 140 patients were included in study, out of which 72 patients in tamsulosin group and 68 patients in

the control group. The 2 groups were comparable in their baseline demographic and clinical characteristics (Table 1). There were no significant differences in age, sex, stone size, location or composition.

Table 1: Baseline clinical characteristics.

Characteristics	Group 1 (n=71)	Group 2 (n=68)	P value
Mean age (years) (range)	37.7 (20-75)	37 (19-82)	0.87
Sex			
Male	41	36	0.30
Female	30	32	
Stone size (mm)			
<10 mm	25	26	0.61
10-20 mm	46	42	
Stone location			
Pelvic	25	22	0.65
Calyceal	26	27	
Ureteric	20	19	
Stone composition			
Ca oxalate (mono +dihydrate)	93.3%	91.2%	0.45
Triple phosphate	6.7%	8.8%	

Stone clearance

Results are shown in Table 2. The overall complete stone free rate in study and control group were 48 (67.6%) and 27 (39.7%) respectively (p=0.005). The complete clearance rate for renal stones was 62.7% and 36.5% (p=0.004) and for ureteric stone was 89.4% and 58.8% (p=0.03) in study and control groups, respectively.

Table 2: Stone clearance.

Characteristics	Group 1 (n=71)	Group 2 (n=68)	P value
Complete clearance (CC)	48 (67.6%)	27 (39.7%)	0.005
Renal	62.7%	38.7%	0.004
Ureteric	85.0%	63.1%	0.03
CISF	11 (15.5%)	29 (42.6%)	0.002
Success rate (CC+CISF)	59 (83.1%)	56 (82.3%)	0.67
Partial clearance	10	11	0.65
No fragmentation	2	1	0.43
Mean time to stone clearance (weeks)	5.3 (2-12)	6.5 (2-12)	0.06
No. of shockwave session needed	2.3 (1-5)	2.7 (1-5)	0.09

Incidence of clinically insignificant residual fragments (CISF i.e. <3 mm) was significantly higher in control group 29 (42.6%) than in study group 11 (15.5%) (p=0.002). If success rate (often defined as percentage of patients who either rendered stone free or had CISF) is considered, then there was no significant difference (p=0.67) in success rate between the study 59 (83.1%) and control group 56 (82.3%). There were no significant difference with regards to mean time to stone clearance, number of shockwave session needed to achieve clearance.

Stone clearance by size

Results are shown in Table 3. For convenience, stones were stratified into 2 groups, <10 mm and 10-20 mm. There were no significant difference in average stone size between the 2 groups (p=0.932). Patients in tamsulosin group had significantly higher stone free rate (p=0.03) irrespective of stone size.

Table 3: Stone clearance by size.

Characteristics	Group 1 (n=71)	Group 2 (n=68)	P value
Smaller stones (<10 mm)	21 (84%)	11 (42.3%)	0.03
Complete clearance (CC) CISF	3 (12%)	6 (23.1%)	0.04
Larger stones (10-20 mm)	29 (63.1%)	18 (42.8%)	0.04
Complete clearance (CC) CISF	6 (13.1%)	21 (50%)	0.005

Stone clearance by location

Results are shown in Table 4. Irrespective of stone location (pelvic, calyceal, ureteric) use of tamsulosin resulted in significantly higher rate of complete clearance.

Table 4: Stone clearance by location.

Characteristics	Group 1 (n=71)	Group 2 (n=68)	P value
Pelvic	**N=25**	**N=22**	
Complete clearance (CC)	18	11	0.03
CISF	3	7	0.04
Calyceal	**N=26**	**N=27**	
Complete clearance (CC)	14	8	0.04
CISF	6	13	0.003
Ureteric	**N=20**	**N=19**	
Complete clearance (CC)	17	12	0.02
CISF	2	6	0.004

Other parameters

These are shown in Table 5. Mean analgesic requirement in tamsulosin group was 493 (150-1100) mg and it was significantly lower than in control group 681 (200-1400) mg (p=0.001). The incidence of steinstrasse was 9 (12.5%) and 7 (10.2%) in tamsulosin and control groups, respectively (p=0.67). 9 (13.2%) patients in control group required either in patient hospitalization for pain relief or

underwent auxiliary procedures like PCN (percutaneous nephrostomy), DJ stenting, URS (ureteroscopy), whereas patients in tamsulosin group had significantly less need for hospitalization or auxiliary procedures 4 (5.5%) (p=0.006).

Table 5: Other parameters.

Characteristics	Group 1 (n=71)	Group 2 (n=68)	P value
Mean analgesic Requirement (mg)	493 (150-1100)	681 (200-1400)	0.001
Steinstrasse	9 (12.5%)	8 (11.7%)	0.67
Need for ancillary procedures or hospitalization	4 (5.5%) Casualty=2 In patient=2	9 (13.2%) DJS=1 URS=3 Casualty=4 In patient=1	0.006

DISCUSSION

Following the initial phase of stone disintegration in ESWL, the final clearance of the fragments from the ureter is similar to the spontaneous passage of ureteral calculi. The expulsion rate for stones less than 5 mm is up to 98% and up to 53% for size 5 to 10 mm.[1] Therefore, fragment size is an important factor that determines the passage of stone through the ureterovesical junction, the narrowest part of the ureter. Spasm, edema or infection may hinder stone passage.[2,3] Ureteral colic, associated with stone, is the manifestation of the visceral pain that is referred to the somatic region corresponding to the spinal segments of the sympathetic supply of the ureter.[3] Increased intraluminal pressure due to calculus obstruction and the increased lactic acid production resulting from smooth muscle spasm may have a part in this event.[4] Conservative therapy attempts to facilitate stone expulsion and has traditionally been achieved by improving oral hydration. In addition, various drugs have been used to reduce ureteral spasm and relieve the pain of colic until the calculus is passed. Calcium channel blockers and nitrates have been used to help reduce the spasm.[5,6]

Alpha adrenergic receptors have been detected in the human ureter with a predominance of alpha 1A and alpha 1D receptor subtypes in the lower ureter.[7] Alpha 1-adrenergic inhibition reduces the frequency and intensity of peristalsis of the ureter with an increase in the flow of urine.[8] Tamsulosin, an alpha 1-receptor blocker that is commonly used in the treatment of bladder outflow obstruction, was chosen for this study as it acts on alpha 1A and alpha 1D receptor subtypes of the ureter. It also prevents spasm by relaxing the smooth muscle of the ureter and acts on the C fibers blocking pain conduction.[9,10]

In ESWL, the management of the ureteral fragments is not different from conservative therapy of ureteral stones. Drugs that have been used to enhance the passage include calcium channel blockers, steroids and alpha blockers. Studies have shown that the initial stone location has not been shown to make a difference in their passage.[11] Contrary to other studies, our study did not show any difference in the success rate (i.e. percentage of patients who either rendered stone free or had CISF) between the 2 groups.[11-13] But in our series, complete stone clearance rate was significantly higher in tamsulosin group. The mechanisms cited are an increase in the intraureteral flow resulting from the decreased frequency and amplitude of the ureteral peristalsis with a loss of intraureteral pressure above the stone.[8,11,14] When comparing the effect of tamsulosin on stone size in our study, it was found that irrespective of stone size, use of tamsulosin made a significant difference in stone free rate between study and control group, suggesting that the drug may have a role as an adjunct to ESWL for all stones less than 20 mm size. The interpretation of these findings in the clinical setting has to be tempered with the knowledge that the sample size in the subgroups was small. Following ESWL, incidence of steinstrasse was observed on 2% to 20% of plain x-rays with spontaneous passage in 65%.[15] Intervention is indicated only in the presence of obstruction or infection. In a trial comparing placebo and tamsulosin for steinstrasse, spontaneous clearance occurred in 65% in the former and 75% in the latter.[13] In our study, steinstrasse developed 9 (12.5%) patients in the study group and in 8 (11.7%) patients in the control group. All 9 (100%) in the study group cleared spontaneously compared to 6 (75%) in the control group. Rest 2 patients had to undergo intervention (one underwent DJS and other required URS for clearance of fragments. The fact that no residual fragments remained in the ureter in the study group compared to 2 in the control group suggests that ureteral relaxation induced by tamsulosin may have facilitated the expulsion of the fragments.

One of the most distressing symptoms of ureteral stones is the pain of colic. The number of colic episodes and the analgesic requirements have been reported to be significantly lower with the use of tamsulosin.[8,13,16] Similarly, in our series the average analgesic requirement in tamsulosin group was 493 (150-1100) mg and it was significantly lower than in control group 681 (200-1400) mg (p=0.001). In another trial nifedipine, a calcium channel blocker and corticosteroid, proved to be useful in reducing the time taken for stone passage and reducing colic.[12] The steroids had a part in controlling the edema due to inflammation. Nifedipine reduced phasic contractions of the ureter without influencing the tonic activity of the ureter, thereby decreasing the spasms.[16] When nifedipine and tamsulosin were compared in the conservative management of lower ureteral stones, the outcome was similar and not statistically significant.[17] In yet another trial when steroids alone were compared to a combination with tamsulosin, the expulsion rate was significantly higher with the latter.[17]

The common side effects of tamsulosin are headache, abnormal ejaculation, dizziness and diarrhea. In our study the only adverse effect was dizziness in 1 patient and it was not severe enough to warrant interruption of therapy. Additionally, the total duration of therapy was only for a maximum of 1 month. The majority of the side effects recorded in the literature occurred after at least 13 weeks of therapy for benign prostatic hyperplasia.[18]

Another interesting observation in our study is that patients in the control group had a significantly higher incidence of CISF i.e. 29 (42.6%) versus 11 (15.5%) in study group (p=0.002). Most of the previous studies on adjuvant effect of tamsulosin on ESWL have considered success rate as the percentage of patients who either became stone free or had CISF, thereby ignoring the significance of CISF. CISF is usually defined as post-ESWL, nonobstructive, noninfectious, asymptomatic (absence of pain, hematuria, and pyuria), residual fragments 4 mm or less in size.[19] Various studies have followed up the patients having CISF to ascertain their significance. In an earlier study from our department by Gupta et al in which 81 patients with post ESWL CISF were followed up for a mean of 15 months (6-60), fragments became clinically significant in 44 patients, particularly in patients with calyceal CISF.[20] Similarly, another study by Beck et al found that re-growth of CISF occurs in 21-70% cases and patients require close follow-up and timely adjuvant therapy.[21] In a 5 year follow-up of CISF by Osman et al found that 80% of the CIRF after ESWL pass spontaneously without any complications.[22] But considering that one fifth of the patients developed new stones at the side of residual fragments, he recommended that close follow-up is required.

From the above all studies, it is prudent to closely observe patients with CISF and intervene as required. Any adjuvant drugs, particularly tamsulosin which can clear these residual fragments is definitely desirable.

Limitations of this study are: small sample size, other alfa blockers like silodosin and alfuzosin were not compared and single institutional study.

CONCLUSION

Shock wave lithotripsy is an important component of the treatment modalities available in the noninvasive management of renal and ureteral stones. The use of tamsulosin, an alpha 1A and alpha 1D receptor antagonist concurrently with ESWL improved complete stone clearance. It also reduces the analgesic requirement and reduces the need for intervention/hospitalization. We believe that tamsulosin may have a potential role in routine shock wave lithotripsy. However, further trials with a larger sample size are required to confirm these findings before planning specific treatment guidelines.

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