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Original Article

# Effect of tamsulosin versus tamsulosin plus tadalafil on renal calculus clearance after shock wave lithotripsy: An open-labelled, randomised, prospective study



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## KEYWORDS

Renal calculus;  
Shock wave  
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Tamsulosin;  
Tadalafil

**Abstract** *Objectives:* To compare the efficacy of tamsulosin versus tamsulosin plus tadalafil in achieving clearance of fragments after shock wave lithotripsy (SWL) to treat renal calculi. *Methods:* Between January 2016 to December 2017, 140 patients with solitary, non-branched, non-lower calyceal renal calculus and measuring less than 20 mm and treated with SWL were randomized to tamsulosin (group A) or tamsulosin plus tadalafil (group B). Therapy was given for a period of 4 weeks. Stone clearance rate, analgesic requirement, occurrence of steinstrasse, need for auxiliary procedures (endoscopic treatment), and adverse effects of drugs were recorded.

*Results:* The overall clearance rate was 72.5% (50/69) in the group A and 90.1% (64/71) in the group B ( $p=0.007$ ). For stones up to 12 mm, the difference in the clearance rate was significant ( $p=0.039$ ) while it was not so for stones larger than 12 mm ( $p=0.151$ ). There was no statistically significant difference between the two groups with regards to analgesic requirement ( $p=0.94$ ), occurrence of steinstrasse ( $p=0.101$ ), need for auxiliary procedures ( $p=0.76$ ), and adverse effects of the drugs ( $p=0.148$ ).

*Conclusion:* Our study shows that adjunctive medical expulsive therapy with tamsulosin and tadalafil achieves better clearance rate than tadalafil alone in patients receiving SWL for renal stones.

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## 1. Introduction

The incidence of urolithiasis is increasing [1]. An estimated 5%–10% of the population in Europe and North America develop urinary tract stones at least once in their life, and about one half develop recurrent disease [1,2]. In India, 12% of the population is expected to suffer from urinary stones, out of which 50% may end up with loss of kidneys or renal damage [3].

Shock wave lithotripsy (SWL) is the first choice of treatment in most patients of urolithiasis, with a reported clearance rate for kidney stones of 66%–99% in patients with stones smaller than 20 mm [4]. SWL can be done in an outpatient setting (with or without anaesthesia), and it carries a low morbidity rate, and high patient compliance as well [4]. The factors that affect the success rate of SWL include the location and composition of the stone, anatomy of the pelvicalyceal system, the lithotripter used and the body mass index of the patient, as well as ureteral status, such as oedema and spasm [5,6]. However, the retreatment rates are high with this procedure and renal colic remains an issue after SWL.

To improve the results of SWL and obtain a better stone-free rate, many institutions have used medical expulsive therapy (MET) as an adjunctive treatment [7]. In the past few years, calcium channel blockers and alpha-1 adrenergic receptor antagonists have been the main established treatments of choice for MET [8]. Both tamsulosin and nifedipine act on the ureteral muscle, causing relaxation and dilation of the ureter and facilitating the elimination of fragments [9]. Recently, tadalafil, a phosphodiesterase-5 (PDE5) inhibitor, which acts by a nitric oxide/cyclic guanosine monophosphate (cGMP)-signaling pathway, has shown to cause smooth muscle relaxation in the ureter [10]. By combining drugs acting through different mechanisms, better ureteric relaxation and reduction in intramural pressure can be achieved, which facilitates stone passage [11].

We conducted a prospective open-labelled study to compare the effect of tamsulosin versus tamsulosin plus tadalafil on stone clearance following SWL. To our knowledge this is the first study assessing the role of tamsulosin plus tadalafil combination as an adjunct medical expulsion therapy after SWL for renal stones.

## 2. Patients and methods

This study was an open-labelled trial conducted in an outpatient setting from January 2016 to December 2017 at our institute after obtaining approval from the institutional ethical committee (approval no. MDC/DOME/391 dated 23-11-2015 by JNMC Institutional Ethics Committee on Human Subjects Research, J. N. Medical College, Belagavi, India). Informed consents were obtained by all subjects when they were enrolled.

Our study included patients aged 18 years and above having solitary renal calculus. Renal ultrasound and plain X-ray of kidney, ureters and bladder were used to diagnose stones and non-contrast enhanced computed tomography scan (NCCT) to determine the exact location, stone size (defined as the longest dimension), and Hounsfield units. Only patients with solitary, non-branched stone with size less

than 20 mm, and not located in the lower calyx were eligible for the study. Patients with solitary kidney, anomalous kidneys, active urinary infection, coagulopathy, morbid obesity, severe scoliosis or kyphosis, pregnancy, uncontrolled hypertension, renal insufficiency, severe cardiopulmonary disease, hypersensitivity to tamsulosin or tadalafil, and also any contraindication for general anaesthesia were not included in the study. Laboratory tests such as complete blood count, blood urea nitrogen, creatinine, electrolytes, coagulation profile, urinalyses, and urine culture were done for all participant patients. Based on visual analog scale (VAS), pain was assessed and scored from 0 to 10.

All lithotripsies were performed in supine position under general anaesthesia using lithotripter (Modularis Variostar; Siemens, AG Healthcare, Germany). All patients received a mean of  $3000 \pm 500$  shocks with an energy level of 50 kV and a frequency of 60 shocks per minute. The patients were adequately hydrated during the procedure. After single-session SWL, patients were alternatively assigned to one of medical treatment groups: Patients in group A were given oral tamsulosin 0.4 mg daily at bed time and those in group B were given a combination drug containing 0.4 mg of tamsulosin and 10 mg of tadalafil at bed time daily. The drug administration was initiated on the day of SWL. In both groups, drugs consumption was continued for 4 weeks. Diclofenac 50 mg twice daily (every 12 h) was given on demand to both groups as analgesic. Patients were instructed to drink at least 2 L of water daily during treatment, to filter their urine to detect stone expulsion, and to record the number of analgesic tablets taken and the side-effect of the drug experienced, if any. They were advised to report to the emergency department if they had severe pain, fever, hematuria, or vomiting. The patients were followed up by history, physical examination, and radiological studies after 4 weeks postoperatively and whenever they would seek medical care. CT scan of kidney ureter bladder region was performed, and stone clearance, stone-free status, steinstrasse formation and outcome, analgesic requirement, and drug side effects were documented.

The study end-points included primary (stone clearance) and secondary (analgesic requirement, incidence of steinstrasse, and the need for auxiliary procedures). Successful clearance was defined as complete clearance or the presence of clinically insignificant residual fragments (asymptomatic nonobstructing renal fragments  $\leq 3$  mm). Steinstrasse was defined as a column of fragments retained in the ureter associated with pain and was managed according to standard practice. Any ureteroscopy, percutaneous nephrostomy, or percutaneous nephrolithotripsy or double-J stenting performed for residual calculi/steinstrasse during the study period were considered auxiliary procedures.

A sample size of 116 patients was calculated using the comparison of two proportion formulas. It was estimated to yield 80% power (type II or beta error of 0.20%) to detect a difference of 20% or more between two groups, allowing 5% of type I error. All data were analyzed using IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY, USA). Nominal variables were taken as counts (or frequencies) and were compared by Chi-square test, while continuous variables with normal distribution were presented as

mean±standard deviation and were compared by independent samples *t*-test and paired *t*-test. All statistical tests were reported based on two tailed probability and a *p*-value <0.05 was considered statistically significant.

### 3. Results

A total of 148 patients with renal calculi and receiving SWL as stone therapy were enrolled for the study. Of these 74 patients were allotted to group A and received tamsulosin 0.4 mg and the other 74 patients of group B received combination of tamsulosin 0.4 mg and tadalafil 10 mg.

Three patients from group A and one patient from group B discontinued the medication, and two patients each from the two groups did not come for follow-up and hence were excluded from the analysis (Fig. 1).

The two groups were comparable in their baseline demographic and clinical characteristics (Table 1). The mean stone size in the group A was 11.75 mm and in the group B was 11.97 mm (range 6 mm–18 mm in both groups). Thirty two patients (14 from group A and 18 from group B) had history of urolithiasis and were managed conservatively. Also, none of the study subjects had prior urological intervention.

The overall clearance rate was 81.4% (114/140). Group A had a stone clearance of 72.5% (50/69) compared with 90%

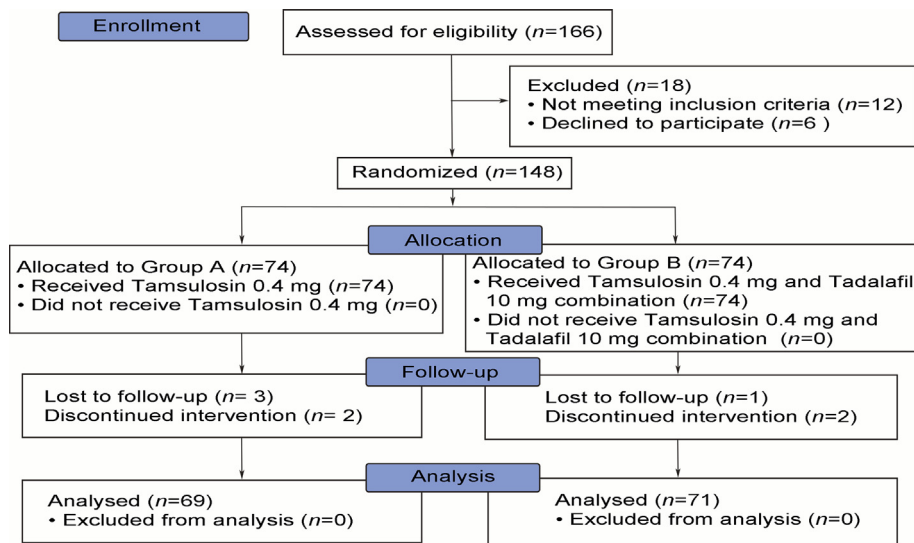


Figure 1 CONSORT diagram.

Table 1 Baseline demographics and clinical characteristics at presentation.

Characteristic	Group A (n=69)	Group B (n=71)	<i>p</i> -Value
Age, mean±SD, year	40.00±10.08	41.32±10.22	0.442
Gender, <i>n</i>			
Male	48	49	0.629
Female	21	22	
BMI, mean±SD, kg/m <sup>2</sup>			
Male	22.40±3.03	22.57±3.49	0.781
Female	23.21±2.62	22.34±2.69	
Side, <i>n</i>			
Right	34	37	0.843
Left	35	34	
Stone location, <i>n</i>			
Upper calyx	12	14	0.923
Mid calyx	25	26	
Renal pelvis	32	31	
Stone size, mean±SD, mm	11.75±2.17	11.97±2.13	0.550
Stone size, <i>n</i> (%)			
6–12 mm	46 (66.7%)	46 (64.7%)	0.550
13–18 mm	23 (33.3%)	25 (35.3%)	
Stone density, mean±SD, HU	854±69	861±71	0.64
Pain score, mean±SD	5.70±1.27	5.72±1.21	0.914

HU, Hounsfield unit; SD, standard deviation.

(64/71) in group B, which was significantly different ( $p=0.007$ ) (Table 2). To facilitate sub-group analysis, stones measuring 12 mm and less were considered as small and stones larger than 12 mm were considered as bigger stones. The mean size of the small stones was 10.3 mm

(standard deviation=1.62); the mean size of bigger stone was 14.6 mm (standard deviation=1.39); and the distribution in both the groups approached normal distribution. Among patients with stones up to 12 mm in size, we found a significant difference in the success rate between the two

**Table 2** Comparison of stone clearance rates.

Stone size	Stone clearance	Treatment group, <i>n</i>		Total, <i>n</i>	<i>p</i> -Value
		Group A (tamsulosin)	Group B (tamsulosin+tadalafil)		
Up to 12 mm	Complete	37	45	82	0.007
	Partial	9	1	10	
	Subtotal	46	46	92	
>12 mm	Complete	13	19	32	0.153
	Partial	10	6	16	
	Subtotal	23	25	48	
Overall	Complete	50	64	114	0.007
	Partial	19	7	26	
	Total	69	71	140	

**Table 3** Comparison of drug side effects.

Drug side effect	Treatment group, <i>n</i>		<i>p</i> -Value
	Group A (tamsulosin)	Group B (tamsulosin+tadalafil)	
None	48	58	0.094
Headache	6	8	0.612
Dizziness	11	3	0.021
Vomiting	1	1	1.000
Nausea	3	1	0.397
Total	69	71	NA

NA, not applicable.

**Table 4** Incidence of steinstrasse.

Stone size	Treatment group, <i>n</i>		Total, <i>n</i>	<i>p</i> -Value
	Group A (tamsulosin)	Group B (tamsulosin+tadalafil)		
Up to 12 mm	Steinstrasse	2	2	0.692
	No steinstrasse	44	44	
	Subtotal	46	46	
>12 mm	Steinstrasse	11	5	0.041
	No steinstrasse	12	20	
	Subtotal	23	25	
Overall	Steinstrasse	13	7	0.101
	No steinstrasse	56	84	
	Subtotal	69	71	

groups (80.4% in group A and 97.8% in group B;  $p=0.039$ ). In contrast, among patients with stones bigger than 12 mm in diameter, no significant increases occurred in the stone clearance rate (68.4% in group A versus 76.0% in group B;  $p=0.151$ ; Table 2).

The stone location did not affect the stone clearance. There was no statistically significant difference in the pain experienced and the analgesic needed in the two groups.

Dizziness was reported by significantly high number of patients in group A (16% vs. 4%;  $p = 0.021$ ), while other side effects were not statistically different amongst the two groups (Table 3).

Twenty patients (13 in group A and seven in group B;  $p=0.101$ ) had steinstrasse (Table 4). The occurrence of steinstrasse was significantly more in patients having stones bigger than 12 mm and belonging to group A ( $p=0.041$ ). Amongst the patients with steinstrasse during the study, 13 patients (eight in group A and five in group B) were successfully managed with conservative measures. Five patients in group A and two patients in group B underwent double-J stenting as they had severe ureteric colic refractory to conservative treatment. Apart from the patients with steinstrasse, three patients in group A and one patient in group B underwent double-J stenting for severe pain caused by fragment impacted in the lower ureter.

#### 4. Discussion

Since the identification of large number of alpha-1D and alpha-1A adrenoceptors in the human ureter, pharmacologic treatment with tamsulosin, a selective alpha-adrenoceptor antagonist, has been established as a potential treatment strategy that may lead to ureteric relaxation and enhanced passage of stone fragments after SWL [9,12–16]. Taher et al. [17] reported the presence of PDE1, 2, 4, and 5 isoenzymes in cytosolic solutions of human ureteral tissue, which suggested nonadrenergic ureteral motility mechanisms and even mechanisms independent of nitric oxide. Similar mechanism is reported to regulate the human detrusor muscle tone [18]. A systemic review by Cardona and García-Perdomo [19] found PDE5 inhibitors were effective as MET for distal ureteric stones. Kumar et al. [11] showed that addition of tadalafil with tamsulosin increases ureteric stone expulsion quite significantly along with significant control of pain, significantly less analgesic requirement, and fewer hospital visits. The present study compared the efficacy of tamsulosin versus tamsulosin plus tadalafil in achieving stone clearance in patients with renal stone after successful SWL.

Though it is logical to assume that longer follow-up of patients after SWL will result in better stone expulsion rates, it has been shown from some studies that stone expulsion rate was not related to the follow-up duration (61.0%, 93.0% and 78.5% in 3, 4 and 12 weeks follow-up) [9,20–22]. In our study, we assessed stone clearance at the end of 4 weeks and found that 140 patients (81%) had achieved complete stone clearance by then. It was observed in our study that group B patients had better stone clearance (72% in group A and 90% in group B) that was statistically significant ( $p=0.007$ ). This finding may possibly due to the combined spasmolytic action of the two

drugs on the ureter. However, in the subgroup analysis based on stone size (stones up to 12 mm and stones larger than 12 mm), there was no significant difference in the stone free rate in patients having stones larger than 12 mm ( $p=0.153$ ), while significant clearance was seen in patients with stones up to 12 mm and receiving tamsulosin and tadalafil ( $p=0.007$ ). Maybe a longer follow-up period could have resulted in better stone clearance rate even in patients with stones larger than 12 mm. Kumar et al. [11] have reported a significantly higher stone expulsion rate in the tamsulosin and tadalafil combination group as compared to tamsulosin group (83.6% vs. 65.5%;  $p=0.031$ ) when used for lower ureteric stones with a follow-up period up to 4 weeks.

Various meta-analyses on the use of alfa-blockers after SWL have reported lower analgesic usage in the tamsulosin group as compared to controls [4, 20–22]. Kumar et al. [11] have also documented lower pain scores and analgesic use in the tamsulosin and tadalafil combination group as compared to tamsulosin group [11]. However, we did not find any difference in the analgesic requirements amongst Group A and group B.

The overall incidence of steinstrasse in our study group was 16% (13 patients in group A and seven patients in group B,  $p=0.101$ ). As expected, the occurrence of steinstrasse (33.3%) was more in patients with stones larger than 12 mm. Bhagat et al. [13] reported 30% incidence of steinstrasse in their series of 60 patients and most were managed conservatively, though the mean clearance time for steinstrasse was higher in placebo group as compared to tamsulosin group. In the present study, 13 patients (eight from group A and five from group B) were managed conservatively while the remaining patients underwent double-J stenting. Addition of tadalafil to tamsulosin did not make any statistically significant difference in the clearance of steinstrasse in our study. The patients in both the groups in the present study tolerated the drugs well although giddiness was reported by significantly higher number of patients of group A. The limitations of the present study include: It being an open-labelled study, the absence of a placebo control group, and not evaluating the stone expulsion percentage between men and women. As the primary end-point of our study was stone clearance rates, which was an objective outcome based on imaging studies, the bias due to the absence of a placebo control might be minimal. Also we have not evaluated the economic implications between the two groups.

#### 5. Conclusion

The results of the present prospective study show that in patients receiving SWL for renal stones, the addition of tadalafil to tamsulosin results in significantly higher stone clearance rate compared with tamsulosin alone. However, larger, double-blinded, randomized, controlled multicenter trials are needed to confirm these results and also assess the economic benefit of using these drugs in after SWL.

#### Conflicts of interest

The authors declare no conflict of interest.

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