

**Research Article****Tadalafil versus Tamsulosin: As an Expulsive Therapy for Ureteric Calculus after Extracorporeal Shock Wave Lithotripsy**

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Mob no: 9437050270, Email: drbmishra@gmail.com**Abstract**

Background and Aims: Tamsulosin has been used widely for smaller (< 10mm) Ureteric stone in our practice and found to be efficacious. On the other hand the use of Tadalafil in medical expulsive therapy for ureteric stone is very limited .Therefore, we conducted a study to evaluate the efficacy and safety of Tadalafil in comparison with Tamsulosin for ureteric stone after one session of extracorporeal shock wave lithotripsy.

Materials and Methods: This prospective randomized study was conducted at the Department of Urology of VSS Institute of Medical science and Research, Burla over a period of 18months in patients with ureteric stones of size 5 to 15 mm after one session of extracorporeal shock wave lithotripsy. Patients were divided into 2 groups by lottery method: Group A received Tadalafil 10mg and Group B received tamsulosin 0.4 mg at bedtime for 4 weeks. Stone expulsion rate, number of uretericcolic episodes and pain score, analgesic requirements, and adverse drug effects were noted in both groups. Statistical analysis were performed by using Student t-test and chi-square test.

Result: A statistically significant expulsion rate of 73.8% in Group A compared with 85.3% in Group B (P value = 0.0120), and shorter stone expulsion time in Group B (14.2 ± 3.4) in comparison to Group A (15.6 ± 3.8) was observed. Although the adverse effects were more in case of Tadalafil, dose of analgesic requirements was lower and patient having erectile dysfunction were significantly benefited by using this drug.No serious adverse effects were noted in both group.

Conclusions: This study showed that Tamsulosin is having better expulsion rate with shorter expulsion time than Tadalafil. Both drugs are safe and well tolerated. Patients having erectile dysfunction are significantly benefited by Tadalafil but it's efficacy is lower than Tamsulosin.

Introduction

Urolithiasis is one of the most common disorders of the urinary tract and the prevalence of stone disease has been estimated at 15% to 20% worldwide^[1]. The probability of having a stone also varies according to age, gender, race, and geographic location. Renal stones are most prevalent between the age of 20 and 40 years and are 2-3 times more common in men than

women^[2]. Twenty two percent of all urinary tract stones are found in the ureter, of which 70% are seen in the mid and lower ureter^[3]. The best treatment modality depends upon various factors such as size, location and composition of the stone, severity of obstruction, and anatomy of the urinary system.In the presence of normal renal function and absence of infection, observation is generally preferred for ureteric calculi measuring

a maximum of 5 mm. However, the spontaneous expulsion rate of distal ureteric stone is about 25% if their size is between 4-6 mm, 5% if greater than 6 mm and calculi over 8 mm are very rarely eliminated spontaneously^[4]. Extra corporeal shock wave lithotripsy (ESWL) or retrograde endoscopic stone removal comprises the next line of management depending on stone location, size and urgency of clearance.

In recent years, medical expulsive therapy (MET) has been used in the management of distal ureteric stones as well as fragmented stones after ESWL as a supplement to conservative treatment. The ureter is lined by α -1 adrenergic receptors, particularly the subtype α -1D, which are more concentrated in its distal third section and they play an important role in the lower ureteric physiology through its effect on detrusor and ureteric smooth muscle contraction. Blocking these receptors subsequently induces selective relaxation of the ureteric smooth muscles, which will result in ureteric lumen dilatation, facilitating antrograde stone propagation^[5]. Tamsulosin, a selective alpha-blocker with equal affinity for both α -1A and α -1D receptors, has a proven role in MET in increasing the stone expulsion rate and decreasing expulsion time.

A newly launched phosphodiesterase-5 (PDE-5) inhibitor, Tadalafil has emerged which acts on the NO/cGMP-signaling pathway of smooth muscles, resulting in increased levels of cyclic guanosine monophosphate, causing ureteric relaxation. Tadalafil has the longest duration of action(36 hours) among the current PDE-5 inhibitors^[6]. Due to its smooth muscle relaxation property, Tadalafil is approved by the FDA for use in lower urinary tract symptoms in patients with benign prostatic hyperplasia and erectile dysfunction. But its role as MET for ureteric stones is very limited. Therefore, we conducted a study to evaluate the efficacy and safety of Tadalafil in comparison with Tamsulosin for ureteric stone after one session of extracorporeal shock wave lithotripsy. By doing this study the role and efficiency of Tadalafil can be established in ureteric stone so

that the young patients having erectile dysfunction and elderly having BHP simultaneously suffering from ureteric stone will benefit by using tadalafil. As both the drugs act through different mechanisms, there is a potential chance of using these two drugs as combined therapy for rapid expulsion of ureteric stone after ESWL.

Material and Methods

This study was conducted in Department of Urology, VSS Institute of Medical science and Research, Burla, after receiving clearance from the institutional ethical committee. It was conducted over a period of 18 months from September 2016 to March 2018. After obtaining written informed consent, patients aged ≥ 18 years with a ureteral stone size of 5-15 mm in its greatest dimension as diagnosed by non-contrast computed tomography of the kidney, ureter and bladder (KUB), Digital X-Ray KUB, IVU, were included in this study. Patients with fever, hydronephrosis, acute or chronic renal insufficiency, multiple ureteral stones, open surgery or endoscopic interventions, diabetes, peptic ulcer or on concomitant treatment with β -blockers, calcium antagonists, or nitrates, pregnant or lactating mothers; or patients who demanded immediate intervention were excluded. Detailed history about lower ureteric symptoms and erectile dysfunction were taken.

A total of 100 patients who fulfilled the criteria were enrolled in the study. After getting written informed consent, these patients were divided into 2 groups after randomly drawing out coupons from a closed box bearing number 1 to 100. A patient with even number grouped as GroupA and odd numbers as GroupB. All the patients in study group had undergone a single session of ESWL. The patients in group A and those in group B received Tadalafil 10 mg and tamsulosin 0.4 mg orally at bedtime, respectively. In both the groups, drugs were continued until expulsion of the stone or for a period of 3 weeks. The drugs were used for 3 weeks because there is no strong evidence that a longer duration will increase the expulsion

rate or that the deleterious effect of obstruction on kidney function will be minimized. Patients were asked to drink plenty of fluids and filter their urine with a thin cloth or net to look for stone expulsion. For pain control during colicky episodes, Diclofenac 50-mg tablets were given on need basis. The patients were followed up every week in the Urology OPD. The stone expulsion time, analgesic use, number of hospital visits for pain, and adverse effects of drugs were noted. Occurrences of any drug side effects like headache, postural hypotension, gastritis, and backache were recorded. Expulsion of the stone was confirmed by X-ray of the kidneys, ureters and bladder; Ultrasonography; or NCCT. The

primary outcome was the stone expulsion rate. The secondary endpoints were stone expulsion time, number of colicky attacks, analgesics required, and drug side effects. Patients who failed to pass the stone after 4 weeks were subjected to another session of ESWL or Ureteroscopy for stone removal.

Data were collected by filling in pro forma datasheets, which included the patients' demographic profiles, investigation reports, and the results of primary and secondary outcomes. Data were analyzed. Discrete variables were evaluated by chi-square test and continuous variables by unpaired Student t-test. Difference were considered significant at a p-value <0.05.



DIGITAL X-RAY SHOWING LEFT
UPPER URETERIC STONE



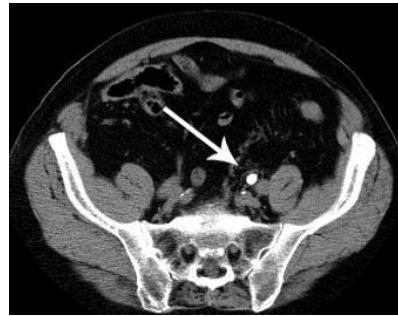
IVP PICTURE OF LEFT UPPER URE-
TERIC STONE



X-RAY SHOWING CLEARANCE OF
LEFT UPPER URETERIC STONE AFTER
TREATMENT



DIGITAL X-RAY SHOWING LEFT MID
URETERIC STONE OF PATIENT



NCCT Picture of Left Upper Ureteric Stone



IVP PICTURE OF LEFT MID URETERIC STONE



CLEARANCE OF LEFT MID URETERIC STONE

PATIENT UNDERGOING ESWL (DORNIER COMPACT DELTA 2) IN
OUR INSTITUTE VIMSAR,BURLA

Results

100 patients are included out of which 11 were lost to follow up in Urology opd. Thus, 89 patients completed the study. 45 were from Group A (Tadalafil) and 44 were from Group B (Tamsulosin). No statistically significant differences were observed regarding patients' age, gender, stone size. The mean stone size was 9.32 ± 1.7 in group A and 9.48 ± 1.6 in group B. The stone clearance was 85.3% in Group B and 73.8%

in Group A. Group B showed a significantly higher stone expulsion rate compared with Group A (P value = 0.0120). The mean stone expulsion time was lower in group B (14.2 ± 3.4 days) than in group A (15.6 ± 3.8 days) but this difference was less significant ($p=0.058$). The average colicky pain episodes were significantly less in Group A (0.52 ± 0.61) compared with Group B (1.2 ± 0.9) with P value 0.045 and the mean requirement of analgesia was significantly less in Group A

(0.4±0.2) than in Group B(0.9±0.2) with P value 0.021

The incidence of side-effects were higher in Group A than in Group B. But this difference was not significant. The Headache, postural Hypotension and backache episodes were more in case on Group A than Group B. Dizziness and rate of abnormal ejaculation were more in case of Group B as compare to Group A .

7 patients in (Tadalafil) Group A and 6 patients in Group B (Tamsulosin) were having erectile dysfunction. All 7 patients from Group A showed improvement from these symptoms but no improvement in symptoms in Group B.

Six patients (3 from each group) did not responded to expulsive therapy after one session of ESWL. out of which 4 patients has undergone second session of ESWL and 2 patients undergone ureteroscopy removal of stone.

Table: 1 Demographic Information

Parameter	Group A	Group B	P value
Mean age (years)	32.85±11.92	33.15±11.83	0.815
No. male/female	32/13	30/14	0.681
Mean stone size (mm)	9.32±1.7	9.48±1.6	0.539
Stone Laterality,R/L	27/18	29/15	0.257

Table: 2 Patients having erectile dysfunction

Total No. of patients	Group A	Group B
13/62	7/32	6/30

Table: 3 Results

Parameter	Group A	Group B	P value
Expulsion rate (%)	73.8(31/42)	85.3(35/41)	0.0120
Mean expulsion time (days)	(15.6 ±3.8)	(14.2±3.4)	0.058
Mean analgesic use	(0.5±0.1)	(0.7±0.2)	0.021
Mean no. colic episodes	(0.52±0.61)	(1.85±0.7)	0.045

Table: 4 Adverse Effects

Parameter	Group A	Group B	P value
Headache (%)	13	7	0.152
Dizziness (%)	6	8	0.421
Backache (%)	11	5	0.065
Orthostatic hypotension (%)	8	4	0.528
Rate of abnormal ejaculation (%)	3	10	0.072
Gastritis (%)	9	5	0.086

Table: 5 Effect on erectile dysfunction

Parameter	Group A	Group B
No. of patients	7	
Significant Improvement in Symptoms	7	-

Discussion

Ureteric calculus is a common problem in young adults affecting day to day normal activity. It has a high recurrence rate of approximately 50% within 5 years and 75% at 10 years^[7]. Although ureteric stones make up only 20% of urolithiasis, they are the most symptomatic of the calculi. Ureteral calculi 5 mm in size have a 70-80 % chance of spontaneous passage. In contrast,

calculi > 6 mm have a less than 50% chance of spontaneous passage^[8]. Many Factors influence the spontaneous expulsion of stones, such as stone location, stone size, stone number, stone structure, ureteral spasm, mucosal edema or inflammation, and ureteral anatomy.

Revolution in the treatment of urolithiasis is achieved since the introduction of extracorporeal shock wave lithotripsy at 1982. From that time,

ESWL has been used as the modality for treatment for renal calculi because of its non-invasiveness and high success rate. Eighty percent of urinary tract calculi is treated with ESWL with success rate varies from 70% – 90%^[9]. Once the calculus bulk is disintegrated into smaller fragments to pass within the ureter, various factors like ureteral lumen, edema, infection and fragments size determine their spontaneous descent through the ureter. Many studies shows use of some drugs can control symptoms and facilitate stone expulsion like anti-inflammatory and anti-edematous, alpha adrenergic blockers, calcium channel blockers or 5PDE inhibitors combination. Many studies have done to compare efficacy of Tamsulosin as an expulsive therapy with placebo group. Some studies compare the efficacy of Tamsulosin, Tadalafil and other calcium channel blocker.

Micali et al,^[10] reported that medical therapy with nifedipine or tamsulosin following ESWL to facilitate ureteral stone expulsion results in increase in stone-free rates and lower the percentage of those needing re-treatment. Kumar et al. and Jayant et al^[6,11]. in their studies compared the stone expulsion rate of tamsulosin with the tamsulosin and tadalafil combination in distal ureteric calculus. The expulsion rate was 74.2% versus 83.9% ($p=0.349$) and 65.5% versus 83.6% ($p=0.031$), respectively. Hari Bahadur KC et al^[12] in their studies compared the stone expulsion rate of tamsulosin with tadalafil in distal ureteric stones. The expulsion rate was 84.1% versus 61% respectively. Sandeep Puvvada et al^[13] in their studies compared the stone expulsion rate of tamsulosin with tadalafil. The expulsion rate was 84% versus 68% respectively with expulsion time (14.7 ± 3.8) and (16.8 ± 4.5) respectively. Santoshkumar et al^[14] compare the efficacy of Tamsulosin with a placebo group for lower ureteric calculus after ESWL and found clearance rate of 93 % in Tamsulosin group as compare to 90% in control group.

The incidence of adverse effects was higher in the tadalafil group, but the difference was not

statistically significant. Similar results were demonstrated in studies by Kumar et al. and Jayant et al^[6,11], Hari Bahadur KC et al^[12] and Sandeep Puvvada et al. Episode of pain and dose analgesic requirement was lower in Tadalafil group.

There was not much information regarding comparative efficacy of Tamsulosin vs Tadalafil in Ureteric stone after single session of ESWL. Our study was designed to compare efficacy, safety and benefits of both the drug in Ureteric calculus after single session of ESWL.

Conclusion

This study shows Tamsulosin has higher stone expulsion rate than Tadalafil as an expulsive therapy for ureteric stones of size 5–15mm with shorter expulsion time. Both drugs are safe, effective and well tolerated. Patients having erectile dysfunction and young patients apprehensive for erectile dysfunction were significantly benefited with Tadalafil. As both the drugs act through different mechanisms, there is a potential chance of using these two drugs as a combined therapy for rapid expulsion of ureteric stone after ESWL.

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