

## The Role of Tadalafil in expulsion of Lower Ureteric Stone

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**Abstract: Background:** The Recent Studies Have Reported Outstanding Results Concerning Medical Expulsive Therapy (MET) For Lower Ureteric Stone In Terms Of Stone Expulsion And Control Of Colic Pain. Therefore We Conducted A Prospective Randomized Controlled Study To Evaluate The Role Of Tadalafil In Comparison Of Placebo In Lower Ureteric Stone Expulsion. **Objective:** To Evaluate The Role Of Phosphodiesterase 5 Inhibitor (Tadalafil) 10mg In Conservative Therapy For Patients With Lower Ureteral Stones. **Patients And Methods:** From September 2016 To August 2017, 60 Consecutive Symptomatic Patients With Unilateral Lower Ureteric Stone From The Urology And Nephrology Department In Pgims Rohtak Were Enrolled In This Randomized Prospective Placebo Controlled Study. Patients Were Randomly Divided Into Two Groups, Group 1 (N=30) And Group 2 (N=30). Group 1 Was Given Tadalafil 10mg. Group 2 Was Given Placebo. Tadalafil 10mg Or Placebo Was Administered Once Daily. The Treatment Duration Was Until Stone Expulsion Or 14 Days. During This Period, All Patients Were Evaluated Weekly By USG And Serum Creatinine Level And Were Asked Whether They Experienced Acute Colic Pain, To Score The Intensity Of Pain According To A Visual Analog Scale, Whether The Calculus Passed Spontaneously, The Day And Time Of Stone Expulsion, Number Of Analgesic Use, And Any Drug Side Effects **Results:** The Mean Stone Size Was 7.41mm For Treatment Group And 7.15mm For Placebo Group ( $P > 0.05$ ). The Stone Expulsion Rate Was 90% For Treatment Group And 60% For Placebo Group ( $P < 0.05$ ). Mean Expulsion Time Was 5.4 Days For Treatment Group And 9.54 Days For Placebo Group ( $P = 0.001$ ). Mean VAS Was 2.9 For Treatment Group And 6.9 For Placebo Group ( $P < 0.0001$ ). Mean Number Of Tablet Diclofenac Used Was 1.87 For Treatment Group And 7.11 For Placebo Group ( $P < 0.05$ ). The Univariate Analysis Using Cox Proportional Hazard Model Revealed That Only Therapy And Stone Size Proved To Be Significantly Predictive Factors Of Stone Expulsion ( $P < 0.0001$  And  $0.001$ ) Respectively, While Gender And Age Did Not Have Any Predictive Value. Although Side-Effects Occurred More In Patients Who Were Given Tadalafil 10mg, No Significant Side-Effect Was Detected So As To Require Exclusion Of A Patient From The Study **Conclusion:** Medical Expulsive Therapy (MET) For Lower Ureterolithiasis With Tadalafil During Conservative Treatment Period Is Safe And Effective As Demonstrated By The Absence Of Serious Side Effects And Increased Stone Expulsion Rate With Early Time. Also MET With Tadalafil 10mg Affords An Outstanding Control Of Pain For Patients While Waiting For Stone Expulsion.

**Keywords:** Tadalafil, Lower Ureteric Stone, Medical Expulsive Therapy.

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### I. Introduction

Urolithiasis is one of the most common pathology of the urinary tract and the prevalence of stone disease has been estimated at 10% to 15% in the United States [1]. The probability of having a stone varies according to age, race, gender, and geographic location. Renal stones are most prevalent between the ages of 20 and 40 years and are 3 times more common in men than women [2]. Women excrete more citrate and less calcium than men, which partially explains the higher incidence of stone disease in men. Twenty-two percent of all urinary tract stones are found in the ureter, of which 68% are seen in the distal ureter [3]. The treatment depends upon various factors such as size, localization and composition of the stone, severity of obstruction, symptoms, and anatomy of the urinary system. The watchful waiting approach can result in complications, such as infection of the urinary tract, hydronephrosis, and deranged renal function. Ureteric stones have been treated traditionally with interventional techniques like ureteroscopy or open surgery. In recent years, medical expulsive therapy (MET) has been used in the management of distal ureteric stones as a supplement to conservative treatment. The ureter is lined by alpha -1 adrenergic receptors, particularly the subtype alpha -1D, which are more concentrated in its distal third section, and they play an important role in the lower ureteric physiology through an effect on detrusor and ureteric smooth muscle contraction. Blocking these receptors subsequently induces selective relaxation of the ureteric smooth muscle, which will result in ureteric lumen dilatation facilitating antegrade stone propagation [4, 5]. Tamsulosin, a selective alpha-blocker with equal  $\alpha$  -1A and  $\alpha$  -1D receptors,

has a proven role in MET in increasing the stone expulsion rate and decreasing expulsion time [6, 7]. A newly launched phosphodiesterase-5 (PDE-5) inhibitor tadalafil has emerged which acts on NO/cGMP-signaling pathway of smooth muscles, resulting in increased levels of cyclic guanosine monophosphate, causing ureteric relaxation. Due to its smooth muscle relaxation property, tadalafil was approved by the FDA for use in lower urinary tract symptoms in patients with benign prostatic hyperplasia and erectile dysfunction. It also received FDA approval for use in pulmonary arterial hyper-tension for both men and women [8]. Therefore, we conducted a prospective randomized controlled study to evaluate the role of phosphodiesterase 5 inhibitor (tadalafil) 10mg in conservative therapy for patients with lower ureteral stones.

## **II. Materials And Methods**

This study was conducted in Pgims rohtak after receiving clearance from the institutional ethics committee. It was conducted over a period of 12 months from september 2016 to august 2017. We observed 88 patients from the urology department with ureteric colic, of whom 28 were not included in the study because of the following conditions: solitary kidney (3), severe refractory pain (5), urinary tract infection (3) multiple stones (5), severe hydronephrosis by obstruction (2), history of ulcer disease (1), history of ureter surgery for previous stone disease (7), pregnancy (2).

Sixty patients suffering from ureterolithiasis of the lower part of the ureter were included in this randomized prospective placebo controlled study. The stone was at the left lower ureter in 35 patients and at the right lower ureter in 25 patients. No patients had a history of ipsilateral ureteric surgery endoscopy, systemic disease or medication. Stone presence and characteristics were diagnosed with abdominal ultrasonography and stone size was measured along its longest axis in millimeters. Radiological evaluation was done for all patients at initial visit.

The patients were prospectively randomized into two groups of 30 patients. The two patient groups used diclofenac tablet on need as a non-steroidal anti-inflammatory drug 75mg. All patients were instructed to drink 3 L water daily. Group 1 was given the phosphodiesterase 5 inhibitor (tadalafil 10mg) as an accelerator for the passing of the stone in addition to conservative treatment. Group 2, served as the control group, was given placebo. Patients were instructed to ingest study medication at the same time every day without regard to meal timing. The participants of both groups read and signed an informed consent form.

Both groups were followed up for 2 weeks because the probability of spontaneous passage of the stone was higher during this period. The treatment duration was until stone expulsion or 14 days, whichever came first during this period. The treatment was until stone expulsion or 14 days which ever came first. During the two week period all patients enrolled were evaluated weekly by urinary tract ultrasonography and serum creatinine level, and were asked whether they experienced acute colic pain, to score the intensity of pain according to a analog scale (VAS), [9,10] whether the calculus passed spontaneously, the day and time of stone expulsion, number of analgesic usage, and finally any drug side effects

In the VAS, we asked patients to express their perception of the intensity of the pain. Patients were requested to define the colicky pain they experienced as a number between 0 and 10 by comparing the pain with the most severe pain they had ever experienced and (0, no pain; 10, the most severe pain perceived)

An explanation was given to the patients, including the reason why we gave them tadalafil 10 mg, and their approval was taken. Patients who failed to expel the stone within 2 weeks underwent ureteroscopy and stone removal. To highlight possible stone expulsion, all patients were required to filter the urine. Patients who expelled their stones underwent ultrasound examination to confirm stone passage. The criteria for treatment discontinuation as well as the need of hospitalization and/or intervention pain uncontrolled by therapy, uroseptic fever and/or severe hydronephrosis, increased serum creatinine (greater than 2 mg/dl), unsuccessful expulsion after 2 weeks and patient desire to remove the stone before day 14. All variables were expressed as mean values  $\pm$  SD, as numbers of patients and percentages. Statistical analysis was done using student t test, Npar test and Mann-Whitney U test as appropriate. Cox proportional hazard regression module was used to determine the predictive factors for expulsion. A p value of more than 0.05 was considered significant. Analyses were performed using recent SPSS software.

## **III. Results**

Group 1 (tadalafil 10mg group) consisted of 13 males and 17 females with a mean age of 29.8 $\pm$ 10.8 years (range 17 to 53), while group 2 (placebo group) included 14 males and 16 females with mean age 32.6 $\pm$ 9.3 (range 21 to 51). No statistically significant difference was observed in patient's age between the two groups; (P=0.6), neither with regard to sex difference; (P=0.33). Mean stone size was 7.41 mm (range 6 to 11) for group 1 and 7.15 mm (range 5 to 10) for group 2 ; there was no statistical difference with respect to the average diameter of the stones between the two groups. (P=0.29 p value > 0.05). Table (1) The stone expulsion rate was 90% (27 of 30 patients) for group 1 and 60% (18 of 30 patients) for group 2 (figure 2). The expulsion rate is statistically significant for the treatment group (p value **0.002**). Table (1)

Parameters	Group (1) Tadalafil (n=30)	Group (2) Placebo (30)	P value
Mean stone size	7.41	7.15	0.290
Expulsion rate (no of patients)	90%(27)	60%(18)	0.002
Mean time for expulsion (days)	5.40	9.54	0.001
Mean VAS of pain (range)	2.90	6.90	<0.0001
Mean no of analgesic use	1.87	7.11	<0.0001

\* P value <0.05 considered significant

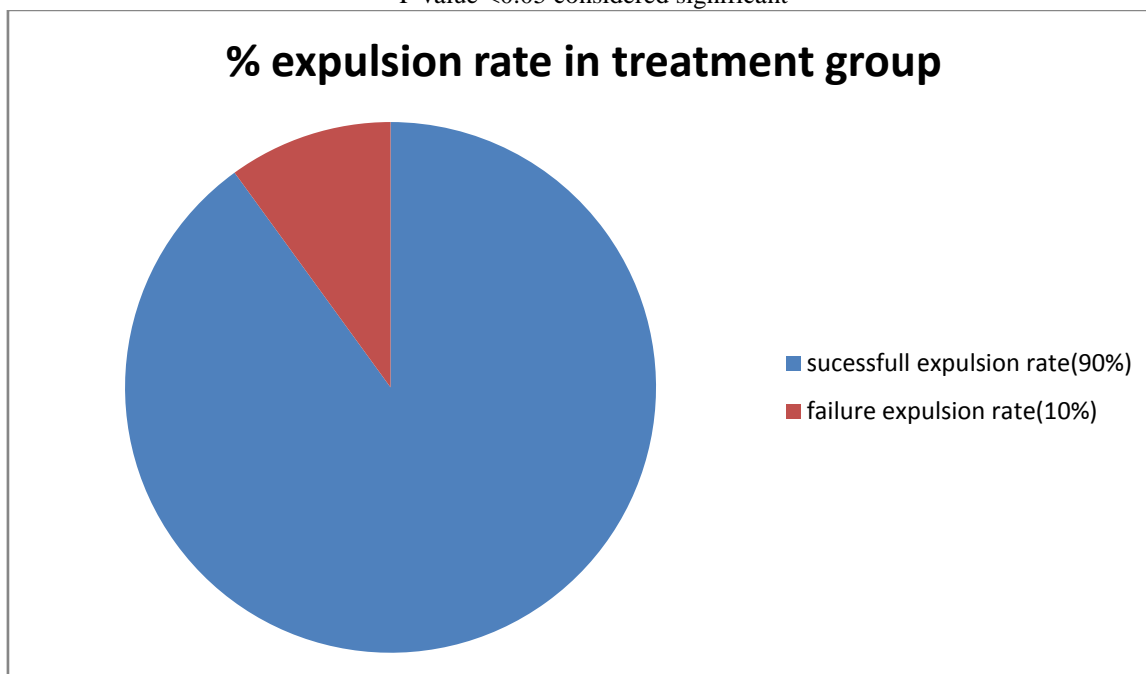


Figure 2 :Percent of Expulsion in treatment Group.

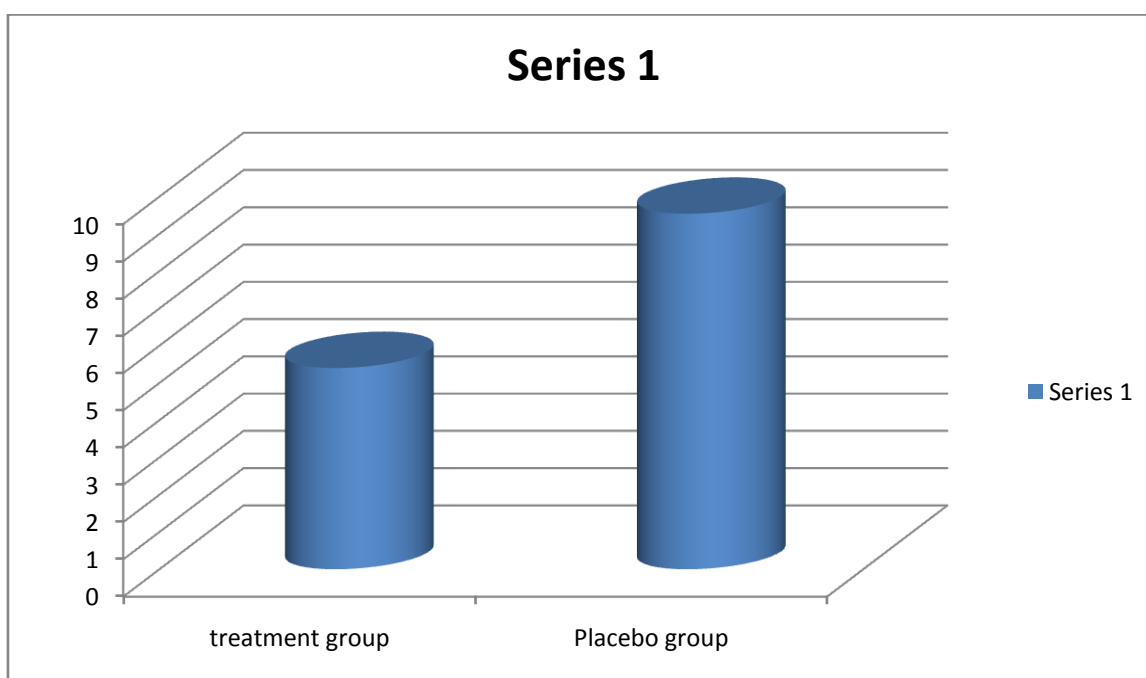


Figure 3: Time of expulsion in the two groups.

Group 1 showed a statistically significant advantage in term of the stone expulsion rate ( p value < 0.05 so there is statistically significant difference between the two groups) and expulsion time (P=0.001 i.e. p value < 0.05 so there is statistically significant difference between the two groups) Table (1). No significant difference was observed in the distribution of expulsion by male and female gender and median expulsion time was not different between both genders. It was identified that all patients whom expelled their stones did that within 10 days of oral tadalafil 10mg treatment start. Patients in group 1 had lower mean VAS (Visual Analogue Scale) 2.9 than 6.9 for patients taking placebo in group 2 (P<0.0001). Table (1). The mean expulsion time was 5.4 days for group 1 and 9.54 days for group 2.

The mean number of analgesic use during therapy was 1.87 (range 0 to 3) for group 1 and 7.11 (range 3 to 12) for group 2 (figure 5), showing significantly less analgesic use in group 1, (P<0.0001). No difference in median analgesic use was observed between males and females, (P=0.23). In addition, when excluding from analysis the patients in group 2 who didn't expel the stones, the difference in mean analgesic use between the two groups was still significant (P<0.0001). Table (1)

The univariate analysis using Cox proportional; hazard model revealed that only therapy and stone size proved to be significantly predictive factors of stone expulsion (P<0.0001 and 0.001) respectively, while gender and age did not have any predictive value. Six patients (20%) in group 2 needed hospitalization because uncontrolled pain. The patients with unsuccessful expulsion after 4 weeks of treatment in both groups underwent ureteroscopy for their stones. The mean stone size and age of the 2 patients who failed to expel their stones were not statistically different from other patients in group 1 . Although side-effects such as backache, improved erection, and myalgia occurred more in patients who were given tadalafil 10mg (P value< 0.05), no significant side-effects was detected so as to require exclusion of a patient from the study and medical intervention was not performed in any of the patients because of side-effects.

#### **IV. Discussion**

The advances in minimally invasive techniques have led to a decrease in the treatment related morbidity associated with management of ureteric calculi. These advances include shock wave lithotripsy and ureteroscopic lithotripsy. Although these approaches are less invasive than traditional open surgical methods, they are expensive and have inherent risks. Pharmacologic data can be interpreted to imply that ureteral relaxation in the region of a concretion could aid in stone passage(11). Various medications have been utilized to support the passage of ureteral stones. (12)

The likelihood of ureteral stone spontaneous passage fundamentally depends on stone size, site, and the internal anatomical structure of the ureter, which are unmodifiable factors. [13,14] The possible causes of stone retention are spasm, edema, and ureteral infections, which are modifiable factors. (15) The goals of medical conservative therapy are to prevent modifiable factors and control painful symptoms until stone expulsion. (16) .

Medical expulsive therapy (MET) is an appealing and encouraging approach for treatment of ureteric stone. The literature provides a variety of results concerning spontaneous ureteral stone passage. A newly launched phosphodiesterase-5 (PDE-5) inhibitor Tadalafil has emerged which acts on NO/cGMP-signaling pathway of smooth muscles, resulting in increased levels of cyclic guanosine monophosphate, causing ureteric relaxation.

According to earlier studies, the expulsion rate of distal ureteric stone by watchful waiting is 25–54% with mean expulsion time >10 days and is associated with high analgesic requirement even for stones <5 mm. To improve the expulsion rate and reduce analgesic requirement, medical therapy is considered for distal ureteral stones [17,18] A ureteral stone usually causes severe colicky pain as a result of an increase in intraureteral pressure above the site of ureteral obstruction. The goals in the treatment of renal and ureteric colic are to alleviate the pain and release the obstruction. Although morphine and pethidine have been the traditional agents, today nonsteroidal antiinflammatory drugs (NSAIDs) are generally used for relieving the pain caused by acute ureteral obstruction. (19) Experimental and clinical studies have shown that antispasmodic drugs are effective for the relief of ureteral colic and possibly for the promotion of stone passage, but such drugs are generally considered unsatisfactory in term of efficacy and safety. (4, 20)

The expulsion rate, expulsion time, and analgesic use were not statistically different between both sexes. Medical therapy with tadalafil 10mg was significantly more effective (90% of patients) in pushing out lower ureteric stones than in the control group (60% of patients) ( p value is < 0.05, so there is statistically significant difference between the two groups ), and reduced the mean expulsion time from 9.54 days in control group to 5.4 days in tadalafil 10mg group (P=0.001). All patients who were given tadalafil 10mg expelled their stones did so within the period of 10 days of treatment initiation.

We observed that patients who were given tadalafil 10mg had significantly better outcome in that they had less VAS (Visual Analogue Scale) scores, less attacks of acute colic, and they used less NSAIDs during therapy (P<0.0001, P<0.0001, and P<0.0001 respectively). These findings made obvious that the effect of

tadalafil 10mg on the ureter was probably to decrease the frequency and amplitude of phasic peristaltic contractions that accompanying ureteric obstruction and decrease need to analgesia. No serious side effects were encountered in any patient during the study. Patients get benefit from therapeutic option of tadalafil 10mg for ureterolithiasis since it encourages early stone expulsion without the requirement of hospitalization or ordinary endoscopic treatments, which, although available and accessible, result in considerable expenditures to the health care system.

## V. Conclusion

Medical Expulsive Therapy (MET) for lower ureterolithiasis with tadalafil 10mg is safe and effective as demonstrated by the absence of serious side effects and increased stone expulsion rate with early time. Also, MET with tadalafil 10mg have an outstanding control of pain for patients while waiting for stone expulsion.

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