The Role of Tadalafil in Lower Ureteric Stone Expulsion

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ABSTRACT:

BACKGROUND:

The Recent Studies have reported outstanding results concerning medical expulsive therapy (MET) for distal ureterolithiasis in terms of stone expulsion and control of colic pain. While ureteral intracorporeal lithotripsy and extracorporeal shock wave lithotripsy are recognized to be effective.

OBJECTIVE:

To evaluate the role of phosphodiesterase 5 inhibitor (tadalafil) 10mg in conservative therapy for patients with lower ureteral stones.

PATIENTS AND METHODS:

From December 2009 to October 2010, 60 consecutive symptomatic patients with juxtavesical unilateral lower ureterolithiasis from the urologic consultation department in Baghdad Medical City were enrolled in this randomized prospective placebo controlled study (pilot 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 US 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 7.91mm for treatment group and 7.55mm for placebo group ($p > 0.05$) .The stone expulsion rate was 93% for treatment group and 67% for placebo group ($P<0.05$). Mean expulsion time was 5.5 days for treatment group and 8.84 days for placebo group ($P=0.001$). Mean VAS was 3.9 for treatment group and 7.9 for placebo group ($P<0.0001$). Mean number of indomethacin suppositories used was 1.33 for treatment group and 7.9 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.

INTRODUCTION:

Urinary stones have afflicted humankind since antiquity, with the earliest recorded example being bladder and kidney stones detected in Egyptian mummies dated to 4800 BC. The prevalence of urinary tract stone disease is estimated to be 2% to 3%, and the likelihood that a white man will develop stone disease by age 70 years is about 1 in 8. Until the 1980s, urinary stones were a major health problem, with a significant proportion of patients requiring extensive surgical procedures and a sizable minority losing a kidney. One study showed that about 20% of patients with recurrent stone disease who underwent surgery for obstruction and infection went on to develop mild renal insufficiency. The advent of extracorporeal techniques for stone destruction and the refinements in endoscopic surgery, however, have greatly decreased the morbidity associated with stone surgery, and the disorder is changing from a major health problem to a major nuisance. One unfortunate result of this

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technologic success is that advances in medical management of stone disease and research in prevention have languished. Surgical procedures treat stones but do not prevent them; however, as anyone who has passed a kidney stone can tell, this may be what the majority of patients with stone disease needs.(1)

Ureteral stones occupy an important place in daily urological practice, usually causing an acute episode of ureteral colic by obstructing the urinary tract.(2)

Of all urinary tract stones, 20% are ureteral stones, and 70% of these stones are located in the distal portion of the ureter.(3,4) In the last 20 years the introduction and improvement of new, minimally invasive procedures (extracorporeal shock wave lithotripsy and ureteroscopy) for ureteral stones considerably changed the historical therapy for this disease, determining perhaps a substantial increase in treatment costs, whereas medical therapy (treatment regimens and various therapeutic agents), which is indicated for distal ureteral stones 5mm or smaller according to symptoms, is increasingly less considered (5,7). Some groups have implemented an observational approach based only on the pharmacological control of pain, while others pharmacologically treat the possible causes of stone retention, such as edema, ureteral spasm and infection, trying to favor its expulsion.(8,10)

The majority of ureteral calculi can pass spontaneously and intervention is usually not required. Other published studies provide a variety of results regarding the spontaneous passage of ureteral stones. If the stone diameter is less than 4 mm, spontaneous passage is generally possible. Ureteral calculi >6 mm have a 5% or less chance of spontaneous passage. Ureteral calculi located at the distal ureter have a 50% chance of spontaneous passage with only conservative observation. The majority of stones generally pass spontaneously within a 6-week period after the onset of symptoms.(1,11) Therefore, it is difficult to make a decision between interventional therapy (shock wave lithotripsy or ureteroscopy) and conservative therapy.

The pharmacological relaxation of ureteral smooth muscles would facilitate the treatment of ureteral colic and possibly enhance spontaneous stone passage. In a rabbit in vivo model, rolipram, a phosphodiesterase 4 inhibitor, caused more marked ureteral relaxation than the nonspecific phosphodiesterase inhibitors papaverine and theophylline and without the circulatory side effects seen with the nonspecific phosphodiesterase inhibitors. As the relaxant effect of rolipram was similar in human and rabbit in vitro ureteral segments, it was suggested that rolipram could potentially be of benefit in the treatment of renal colic and in the facilitation of stone passage. (12) Rolipram has also been shown to relax pig intravesical ureteral segments(13) In addition to the phosphodiesterase 4 inhibitor rolipram, phosphodiesterase 5 inhibitors relax in vitro human ureteral segments.(14)Species differences in phosphodiesterase subtypes may exist. Although the nonspecific phosphodiesterase inhibitor papaverine decreased the frequency of ureteral peristalsis in the pig, the phosphodiesterase 4 inhibitor rolipram had no effect.(15)

Tadalafil is a selective phosphodiesterase-5 enzyme inhibitor (PDE5) similar to sildenafil and vardenafil. It is administered orally for the treatment of erectile dysfunction (ED). Similar to vardenafil, tadalafil is also more selective compared to sildenafil for PDE5 than PDE6 receptors, which are present in the retina. This may explain the higher case reports of visual adverse events associated with sildenafil. Tadalafil has the longest duration of action (~36 hours) among the current PDE5 inhibitors, which allows a greater window for sexual activity. It is the only PDE5 inhibitor whose activity is unaffected by meals. Tadalafil was FDA-approved for treatment of ED in 2003.[16,17] Vardenafil has a similar structure to sildenafil's, but the structure of tadalafil is quite different.[18] Figure(1)

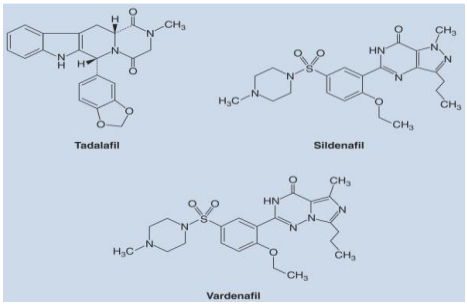

Figure 1: The structure tadalafil, sildenafil and vardenafil.

PATIENTS & METHODS:

From December 2009 to October 2010, we observed 128 patients from the urologic consultation department in Baghdad Medical City with pyeloureteral colic, of whom 78 had unilateral, juxtavesical ureteral lithiasis at lower 5 cm of the ureter of no more than 10 mm in diameter.

Eighteen of the 78 patients with lower ureterolithiasis were not included in the study because of the following conditions: solitary kidney (3), severe refractory pain (2), urinary tract infection (3), multiple stones (2), severe hydronephrosis by obstruction (2), history of ulcer disease (1), history of ureteral surgery for previous stone disease (1), pregnancy(2) and nitrate therapy(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 36 patients and at the right lower ureter in 24 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 indomethacin suppositories on need as a non-steroidal anti-inflammatory drug plus ciprofloxacin tab. 500mg twice daily. All patients were instructed to drink 2 L water daily. Group1 was given the phosphodiesterase 5 inhibitor (tadalafil 10mg) as an accelerator for the passing of the stone in addition to conservative treatment. Group2, 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 the 2-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 visual analog scale (VAS),[19,20] 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 (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 ESWL or ureteroscopy. 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 were 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 ± SD, or as numbers of patients and percentages. Statistical analyses were performed with Student's t test, NPar test, and Mann-Whitney U test as appropriate. Correlation analysis was done using Spearman's rank test. 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 SPSS software, version 9.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS:

Group 1 (tadalafil 10mg group) consisted of 14 males and 16 females with a mean age of 29.8±10.8 years (range 17 to 53), while group 2 (placebo group) included 13 males and 17 females with mean age 30.6±9.3 (range 21 to 51). No statistically significant difference was observed in patients' age between the two groups; (P=0.7), neither with regard to sex difference; (P=0.43).

Mean stone size was 7.91 mm (range 6 to 11) for group 1 and 7.55 mm (range 5 to 10) for group 2 (Figure 2); there was no statistical difference with respect to the average diameter of the stones between the two groups. (P=0.24 p value > 0.05) .Table (1)

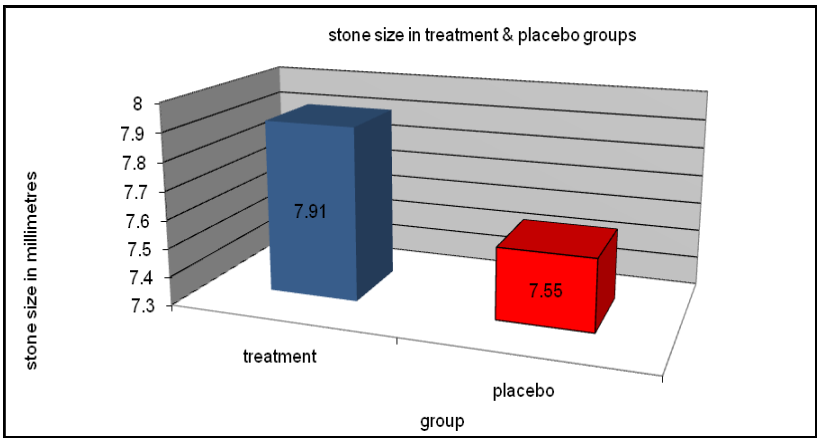

Figure 2: Stone Size in Treatment & Placebo Groups

Table 1: Different Parameters Between the Two Groups.

Parameters	Group (1) Tadalafil (n=30)	Group (2) placebo (n=30)	P value
Mean mm stone size (range)	7.91 (5 - 10) mm	7.55 (6 - 10) mm	0.24*
Percent of expulsion (No. of patients)	93% (28)	63% (19)	0.003
Mean hours for expulsion (range)	5.5 days	8.84 days	0.001
Mean VAS of pain (range)	3.9 (2-6)	7.9 (6- 9)	<0.0001
Mean No. of analgesic use	1.3	7.9	<0.0001
* P value <0.05 considered significant.			

The stone expulsion rate was 93% (28of 30 patients) for group 1 and 63% (19 of 30 patients) for group 2. Figure (3) The expulsion rate is statistically significant for the treatment group (p value **0.003**). Table (1)

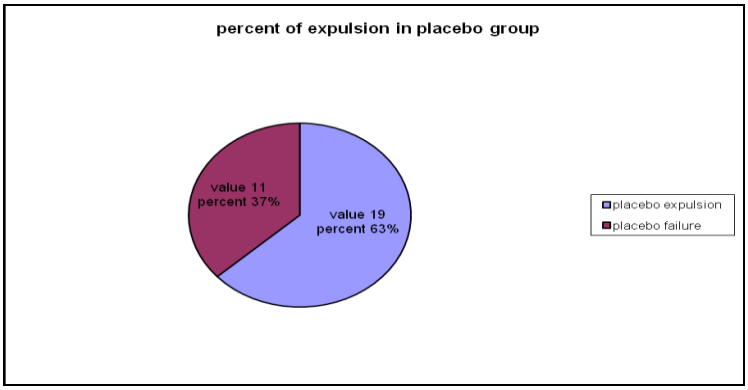

Figure 3 :Percent of Expulsion in Placebo Group.

The mean expulsion time was 5.5 days for group 1 and 8.84 days for group 2. (Figure: 4)

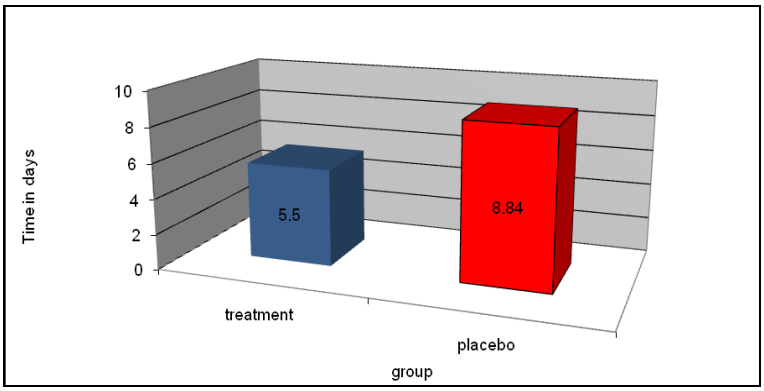

Figure 4 :Time of expulsion in the two groups.

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) 3.9 than 7.9 for patients taking placebo in group 2 (P<0.0001). Table (1)

The mean number of analgesic use during therapy was 1.33 (range 0 to 3) for group 1 and 7.9 (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=0.26). 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)

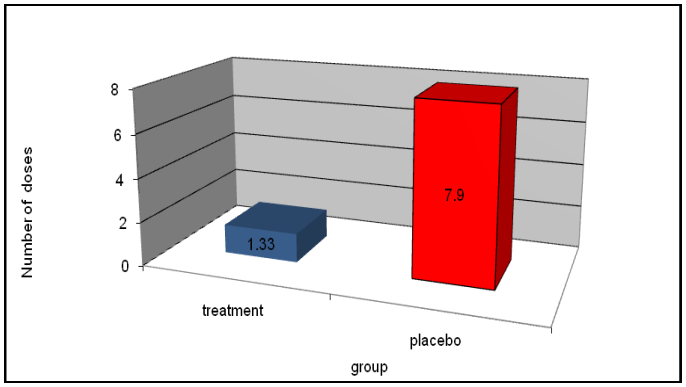

Figure 5 :The analgesia doses in the two groups.

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.

When applying Spearman's rank test, good and strong correlations were observed between the use of tadalafil 10mg and less VAS of pain (rho=0.867; P<0.0001), early expulsion time (P<0.0001), and less analgesic use (P<0.0001). No correlation in both groups was found between stone size and number of acute colic attacks (P=0.614), and between stone size and VAS of pain (P=0.492). Table (2)

Table 2: Spearman's Rank Test Correlations

Spearman's rho	Tadalafil Use		Stone size	
	Correlation Coefficient	Sig. (2-tailed)	Correlation Coefficient	Sig. (2-tailed
VAS of pain	.867**	.000**	.090	.492
Colic attacks	.482**	.000**	.066	.614
Time to expulsion	.728**	.000**	.493**	.000**
Analgesic use	.851**	.000**	.122	.353
Stone size	.124	.344	1.000	.
**: Significance at P<0.0001				

Five patients (16%) in group 2 needed hospitalization because uncontrolled pain. The patients with unsuccessful expulsion after 4 weeks of treatment in both groups underwent ESWL or 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.

DISCUSSION:

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. Pharmacologic data can be interpreted to imply that ureteral relaxation in the region of a concretion could aid in stone passage.[21] Various medications have been utilized to support the passage of ureteral stones.[22] Bajor showed that a β-blocker reduced the time for stone passage from 11 to 5.2 days in 86 patients with lower ureteral stones without encountering any serious side-effects.[15] Borghi et al demonstrated the beneficial effect of calcium antagonist (nifedipine) in reducing time to stone passage and promoting expulsion rates.[8]

In a rabbit in vivo model, rolipram, a phosphodiesterase 4 inhibitor, caused more marked ureteral relaxation than the nonspecific phosphodiesterase inhibitors papaverine and theophylline and without the circulatory side effects seen with the nonspecific phosphodiesterase inhibitors. As the relaxant effect of rolipram was similar in human and rabbit in vitro ureteral segments, it was suggested that rolipram could potentially be of benefit in the treatment of renal colic and in the facilitation of stone passage.[12] Rolipram has also been shown to relax pig intravesical ureteral segments.[13] In addition to the phosphodiesterase 4 inhibitor rolipram, phosphodiesterase 5 inhibitors relax in vitro human ureteral segments.[14]

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.[23,24] The possible causes of stone retention are spasm, edema, and ureteral infections, which are modifiable factors.[10] The goals of medical conservative therapy are to prevent modifiable factors and control painful symptoms until stone expulsion. [9,10] .

In this present study – and to avoid urinary tract infection – all patients were given ciprofloxacin 500mg because of its low cost and excellent activity on urinary tract, in combination with indomethacin suppositories on need to control the pain that arise with ureteric obstruction by stone.

The randomization in this study did not consider any stratification of patients by gender since there is no series in the literature – known to us – have established a dissimilar expulsion capability and different pain tolerance between 2 sexes. Furthermore, the statistical analysis enabled us to figure out any influence of sexual category on our findings. The expulsion rate, expulsion time, and analgesic use were not statistically different between both sexes. In addition according to the Cox proportional hazards regression model only therapy and stone size affected stone expulsion in our patients.

Medical therapy with tadalafil 10mg was significantly more effective (93% of patients) in pushing out lower ureteric stones than in the control group (67% of patients) (p value is < 0.05, so there is statistically significant difference between the two groups), and tadalafil 10mg reduced the mean expulsion time from 8.84 days in control group to 5.5 days in tadalafil 10mg group (P=0.001).

It is worthwhile to mention that all patients who were given tadalafil 10mg and expelled their stones did so within the period of 10 days of treatment initiation and no advantage – expulsion – was observed in continuation of tadalafil 10mg therapy for the end of 2 weeks. The 2 cases of tadalafil 10mg therapy failure can be explicated by the limited water intake, the history of poor compliance to the treatment and increased sexual performance (one of two).

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, non–steroidal anti–inflammatory drugs (NSAIDs) are generally used for relieving the pain caused by acute ureteral obstruction.[2]

Experimental and clinical studies have shown that anti–spasmodic 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.[25,26]

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 (1.3 vs 7.9).

No serious side–effects were encountered in any patient during the study, but it is valuable to point out that the erotogenic effect of tadalafil 10mg seen in most male of group 1. Consequently patient education about this side–effect was deemed important when prescribing tadalafil 10mg.

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. Moreover, if patients with distal ureterolithiasis can carry on their every day activities with their home treatment, without the need for a great number of analgesic usage, it will be likely to advise medical expulsive therapy with tadalafil 10mg to be an alternative to endoscopic treatment in selected patients as patients in our study groups. It is true that the simplification of therapeutic schemes makes patient treatment easier.

CONCLUSION:

Medical Expulsive Therapy (MET) for lower ureterolithiasis with tadalafil 10mg during watchful

waiting period is safe and effective as demonstrated by the absence of serious side effects and increased stone expulsion rate with early time. MET with tadalafil 10mg affords an outstanding control of pain for patients while waiting for stone expulsion.

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