



A comparative study for the effectiveness of Tamsulosin alone versus Tamsulosin plus Tadalafil combination as an expulsive medical treatment in the management of lower ureteric calculous in Al-Diwaniyah teaching hospital

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Article History:

Received on: 13.11.2018

Revised on: 09.01.2019

Accepted on: 15.01.2019

Keywords:

Urinary calculi,
Tamsulosin,
Tadalafil

ABSTRACT

To evaluate the efficacy & safety of tamsulosin alone versus tamsulosin plus tadalafil combination as expulsive medical treatment of distal ureteric calculus. From March 2015 until March 2017, two hundred patients (one hundred thirty males and seventy females), who attended the outpatient urology clinic and presented with stones size 5 to 10 mm in distal ureteric part, have been randomly allocated into two equal treatment groups. Group A treated with tamsulosin alone, and group B treated with tamsulosin plus tadalafil. Both treatments were given for a maximum of six weeks' duration. The rate and time to the calculous passage, type of analgesic use, adverse effects of the drugs, number of outpatient urology clinic visits for pain, and follow-up were noted. Both treatment groups have higher expulsion rate with a lower time to expulsion with no statistically significant differences between them ($p=0.350$, $p=0.074$, respectively). Group B showed a significantly lower rate in admission to the hospital for pain and need for analgesia than in group A. No dangerous adverse events had been observed in both groups. Additional benefit seen in group B was the improvement in erectile function regarding male patients. Using tamsulosin and tadalafil as an expulsive medical treatment for distal ureteric calculous is safe and efficacious. Such combination therapy may provide additional advantages in cases of erectile dysfunction co-exist with distal ureteric calculi.



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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v10i2.875>

Production and Hosted by

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INTRODUCTION

Increase in the prevalence and incidence of nephrolithiasis among the population render it as a major healthcare problem. The urinary stone is very

common among both sexes; male form stones two times more as often as female with approximated 2-3% prevalence and an expected 12% lifetime risk for white men and 5-6% for white women. Urinary stones have a high rate of recurrence about 50% and variable recurrence interval and frequency, with approximately ten percent within one year, thirty-five percent within five years, and fifty percent within ten years. Urinary calculus formation usually started in the kidney and then passed through the renal calyces into the renal pelvis and then the stone passes to the ureter. Stones primarily formed in the ureter need an already existing obstructed urinary flow. Although modern understanding of the mechanisms of stone formation is pretty remarkable, ureteral calculi are still a medical issue bothering a huge number of patients worldwide (Stefanos *et al.*, 2006).

The ureter consists of three main parts; the upper part of the ureter lying above the sacroiliac joint, while its lower part lying below the level at which the ureter crosses the common iliac artery bifurcation, and the middle part is the portion connects the upper and the lower parts. However, on the bases of treatment outcomes analysis, the ureter divided into proximal and distal parts, the proximal ureter includes the upper and middle thirds, as mentioned above (Whitfield, 1999).

Most of the ureteral stones pass passively and do not need intervention depending on their size, shape, site, and presence of ureteral wall edema (that likely depends on the duration a stone has not moved) (Ueno *et al.*, 1977).

The stone size is highly related to the rate of spontaneous passage, those stones with size lesser than 4 mm, 4-6 mm, and greater than 6 mm showed rates of spontaneous passage of 79%, 59% and 21% respectively. Additionally, sites of the stones affecting the spontaneous passage rates whether from the upper (25%), middle (45%), or lower (70%) ureter. Usually, most of the ureteric stones will pass in an average time of four to six weeks after the starting of symptoms. However, it is not necessarily mean that a 10 mm calculus will not pass or that a 1-2 mm calculus will always pass smoothly (Miller and Kane, 1999).

For ureteric stone with a size of a 6 mm and less, the conservative therapy strategy of an ultrasound follows up is the preferable and effective approach. Therefore, conservative treatment for four to six weeks may be reasonable for such stones sizes if the patient continues to be symptoms free. Conservative therapy includes analgesia (non-steroidal anti-inflammatory drugs like ketorolac and narcotic analgesia like morphine), anti-inflammatory drugs (methylprednisolone), calcium channel blockers (nifedipine), and alpha-adrenoceptor antagonist such as tamsulosin. However, associated acute urinary tract infection, impairment of renal function or pain persistence in spite of strong analgesic drugs could be among the contraindications for such approach (Porpiglia *et al.*, 2006).

The ureter, especially in the distal third, is lined by smooth muscle cells with alpha-1 adrenergic receptors. Intervention with these receptors activity will inhibit both basal smooth muscle tone and uncoordinated hyperperistaltic frequency providing tonic propulsive contractions. Ureteric stones can lead to ureteric smooth muscle spasms that interfere with expulsion; therefore, the stone passage may be facilitated by inducing relaxation of the smooth muscle of the ureter while maintaining normal peristaltic activity. Such a scenario can be achieved by alpha-1 adrenergic receptor antagonists, e.g. tamsulosin, through making an increased

pressure gradient above the calculi, which pushes lower ureteral calculi out of the ureter thereby increasing the calculi passage rate and in lowering the passing time (Becker *et al.*, 1998).

Furthermore, ureteral stones have been found to be associated with high inflammatory changes and edema in the ureteric mucosa in the area nearby a stone which may deteriorate obstruction of the ureter and increasing the risk of impaction. Therefore, drugs with anti-inflammatory properties such as steroids may facilitate calculous passage by improving the ureteric mucosal wall edema. Lately, (PDE5) inhibitor, tadalafil, was found to act through nitric oxide/cyclic guanosine monophosphate (cGMP)-signaling pathway, causing increased levels of cGMP and subsequent relaxation of the smooth muscle of the ureter (Kloner *et al.*, 2004).

In this study, we use a combination of tadalafil with tamsulosin as those drugs acting through different mechanisms. We assumed that this achieves better relaxation of ureteric smooth muscle and decrease in intramural pressure, which will increase the chance of calculous passage.

PATIENTS AND METHODS

From March 2015 to March 2017, two hundred patients (one hundred thirty males and seventy females) with ureteric stones were enrolled in this study at the urology unit in Al-Diwaniyah teaching hospital and the mean age of our patients was 30±35 years ranging from twenty to sixty years.

The size, site, of the stone and degree of hydronephrosis, were assessed by radiological studies, in the form of Kidney Ureter Bladder (KUB) X-ray, ultrasonography and CT scan.

This study, including patients with ureteric stones size 5-10 mm located below the common iliac arteries bifurcation as confirmed by non-contrast CT scan and their pain was subsiding with ketorolac injection through 24 hours.

Patients presented with fever, multiple ureteral stones, high degree of hydronephrosis, impairment of renal function, previous open or endoscopic operations in the urinary system, pregnant and lactating mothers, severe, intractable pain not subside by analgesia, concomitant using of calcium channel antagonists, β -blockers, or nitrates drugs, and patients who wished immediate stone removal were excluded from this study.

Patients were allocated into two equal groups of one hundred patients. In the first group (group A) patients were given (0.4 mg tamsulosin) per day, and those in the second group (group B) were given tamsulosin 0.4 mg and tadalafil 5 mg per day. The maximum duration of treatment was six

weeks or until stone passing. Patients who had ureteric colic received intravenous ketorolac for pain relief.

The expulsion time, adverse effects of drugs, need for analgesia, a number of outpatient urology clinic visits for pain, follow-up, were noted. After 6 weeks' duration of treatment, for stones that were not expelled, patients underwent semi-rigid ureterorenoscopy to remove those stones.

The outcomes observed in this study were the passing stone rate, stone passing time, analgesic use and the number of pain attacks that need a hospital visit. Stone passing was confirmed by radiological studies in the form of KUB, Ultrasound and non-contrast CT scan.

RESULTS

All of our patients completed the study. Our results showed that group A has a stone expulsion rate of 75%, while group B has a rate of 91%. Although the rate was higher in group B, the difference was not statistically significant ($p=0.350$). Furthermore, we found that the mean time that needed to stone expulsion was a lower value in group B (11.5 ± 5.3 days) than in group A (18.6 ± 5.2 days), but again this variance was statistically insignificant ($p=0.350$) as shown in table 1.

On the other hand, group B has a comparatively fewer number of outpatient urology clinic visits for colicky pain (0.23 ± 0.50) than group A (4.88 ± 0.95), and this variance was highly significant ($p\text{-value}=0.000$). Similarly, the mean analgesic need was considerably less in group B (1.02 ± 1.32 times) than in group A (4.95 ± 0.95 times) ($p\text{-value}<0.0001$) as shown in the following table.

Generally speaking, drug combination is commonly associated with an increased rate of drug side effects. In our study, patients treated with tamsulosin and tadalafil have more frequent drug side effects such as dizziness, headache and postural hypotension. However, these side effects were not substantial enough to eliminate the patients from the study ($p>0.05$). Retrograde ejaculation, usually caused by α -1 adrenergic receptor antagonists, was observed at a higher rate in group A patient (20.4%) than in group B patients (12.9%), but the difference was not significant ($p=0.489$). Finally, an important finding regarding the improvement in erectile dysfunction was seen in group B patients (24%) while no patients in group A showed progress in erectile dysfunction.

DISCUSSION

Conservative treatment in the form of Medical expulsive treatment (MET) is an excellent and encouraging choice for the management of ureteric

calculous with increasing published results concerning spontaneous ureteric calculous passage. Pharmacological intervention can be directed toward relaxation of the ureteric smooth muscle in the area of a concretion which will aid in stone expulsion. The probability of spontaneous passage of ureteric calculi mostly depends on the size, site of the calculus, and the structural anatomy of the ureter and those factors are unmodifiable factors (Becker *et al.*, 1998).

Many types of medications have been utilized for lower ureteric stone management and to support the ureteric calculous expulsion.

The most likely and reasonable causes for ureteric calculous retention and impaction are ureteric smooth muscle spasm and increasing of the edema at the ureteral wall lumen, and the infection and those factors are modifiable factors and can be managed and treated.

The purpose of conservative treatment of the ureteric calculus is targeted toward the treatment of these modifiable factors and relieving of the painful episode until complete passing of the stone happens. Factors that inducing spontaneous passing of the calculus are location, size, number, and chemical composition; ureteral muscle contraction; edema of the mucosal wall the or inflammation; and structural anatomy of the ureter. Hence, the usage of drug treatment is reasonable to decrease edema, contraction, and relax the ureteral smooth muscles for calculous passing (Singh *et al.*, 2011).

Regarding literature data, in the watchful waiting approach the passing rate for lower ureteric stone, even for stones less than 4 mm is 25% to 54% and the mean passing time is greater than 10 days, and there is a considerable analgesic requirement. There is a large agreement of interest for adjuvant pharmacological interventions to raise the passing rate and diminish the analgesic requirement. While expulsive medical treatment has become a typical treatment choice, it is still not commonly used by doctors in emergency units (Coll *et al.*, 2002).

α -1A and α -1D receptors are founded in larger amounts than α -1B receptors in the ureteric smooth muscle of the human ureter (Sigala *et al.*, 2005).

Because tamsulosin has combined selective α -1A and α -1D blocker, many clinical articles have been focused on the effect of this drug in aiding in the passing of lower ureteral stone by acting on blocking of these receptors. These articles explained that tamsulosin treatment increases the passing rate of average-sized (3–10 mm) stones.

Table 1: characteristic features of the patients

Parameter	Group A	Group B	p-value
Sex			
Male/female	72/28	65/35	0.350
Age (years)	32.45±9.36	34.25±10.50	0.090
Stone size (mm)	7.15±1.62	7.75±1.30	0.350
Passaging rate (%)	75	91	0.350
Passaging time (days)	18.6±5.2	11.5±5.3	0.075
Analgesia required	4.95±0.95	1.02±1.32	<0.0001
No. of outpatient clinic visits	4.88±0.95	0.23±0.50	0.000

Table 2: Drugs adverse effects

Parameter	Group A	Group B	p-value
Headache	14%	16.1%	0.720
Dizziness	13.9%	17.1%	0.720
Postural hypotension	2.0%	5.4%	0.425
retrograde ejaculation	21.2%	13.1%	0.450
Progression in erectile dysfunction	0%	30%	0.005

Additionally, tamsulosin found to have a passaging rate of 75%, which was superior to the passaging rates in other controls used in other articles of 43% and 30.2%. Consequently, tamsulosin denotes a cost-effective none invasive treatment substitute to other interventional choices (Parsons *et al.*, 2007).

The role of PDE inhibitors in ureteric muscles relaxation as explained by Gratzke *et al.* (Gratzke *et al.*, 2007) in the vigorous order of vardenafil is more than sildenafil and both of them more than tadalafil.

Comparing to sildenafil, tadalafil is highly selective for PDE5 receptors that have inhibitory activity for PDE6 also, which are found in the retina, so the visual complications are fewer. Among the current PDE5 inhibitors, tadalafil has the longest duration of action (thirty-six hrs. with a half-life time of 17.5 hrs.), and its action is not affected by food. Vardenafil has a configuration similar to that of sildenafil, but the configuration of tadalafil is completely different (Taher *et al.*, 1994).

We utilized tadalafil in small doses (5 mg) to keep side effects to a minimum. Kloner *et al.* (13) explained that the combination of tamsulosin and tadalafil did not show significant hemodynamic changes.

As demonstrated by Oelke M. *et al.* such combination had successfully being used for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia and has led to a relaxation of the bladder, urethra, and prostate and this lead to a substantial reduction in pain (Oelke *et al.*, 2012).

Both treatment groups in this study were confirmed superior to the previous approaches which were managed by the watchful waiting. Our data

show a higher rate and lower time in stone expulsion in group B than in group A; nevertheless, these results were statistically insignificant (91%, 11.5±5.3 days compared with 75%, 18.6±5.2 days, p-value =0.350 and p-value =0.075).

Combined spasmolytic effect on the ureter by medications used in group B might be the possible explanation for these better results. The reduction in the frequency and amplitude of the phasic peristaltic spasms on the ureter were possibly due to the effects of the combined use of tamsulosin and tadalafil.

Colicky pain induced by ureteral stones develops due to an increase in the intraluminal ureteral pressure above the site of ureteric obstruction. Kuhn *et al.* establish that blocking of α -adrenoceptors may relieve ureteric colic via blocking the C-fibers accountable for arbitrating sensation of pain (Kuhn *et al.*, 2000).

In this study, the need for analgesia was significantly less in group B than in group A (p-value =0.001). Expulsion of ureteric stones by using α -blockers probably decreases the need for analgesia in two approaches: blockade of C-fibers and expulsion of stones. However, it is difficult to know which of these mechanisms may be primarily leading to lowering the rate for the need for the analgesia. In group B, brilliant pain control might be explained by the fewer need for an outpatient clinic visit for colic throughout our study.

The retrograde ejaculation was noted in 21.2%, 13.1% of patients in group A and group B respectively, however, this difference was also statistically insignificant (p-value =0.450) similarly we noted progression in erectile function in 30% of patients in group B, whereas no patient showed somewhat changes in group A

CONCLUSION

tamsulosin and tadalafil when used together in combination initiate increment in the rate of ureteric calculous expulsion and had a substantial reduction in pain experience and need for using of analgesic medication.

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