

*Research Article***Tadalafil versus Tamsulosin as a medical expulsive therapy for solitary unilateral lower ureteric stone less than 1 cm: a prospective randomized study.****Amr M. Abdel Rahim, Mamdouh A. Abdel-Raheem, Mohammed G. Sayed and Al-Ayman F. Hussein**

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Abstract

Introduction: In up to 50 percent of cases, expectant treatment may result in spontaneous stone expulsion. The therapeutic potential of α -adrenergic blockers for ureteral stone disease was investigated, prompted by α -receptor detection in ureteral smooth muscle cells improves the passage of larger ureteric stones (5-10 mm). A newly launched phosphodiesterase-5 (PDE-5) inhibitor, tadalafil, has emerged that acts on the smooth muscle NO / cGMP and can be used as expulsive therapy. **Aim of the work:** To assess the impact of Tadalafil vs. Tamsulosin, as medical expulsive therapy of solitary unilateral lower ureteric stone less than 1 cm. **Patients and Methods:** Our prospective, randomized, placebo-controlled, comparative clinical study at Nephrology and Urology Minia University Hospital, included 99 patients who randomized into 3 equal groups, 33 patients in each group. First group received Tadalafil 5 mg, second group received Tamsulosin 0.4mg, third group was control group (placebo). **Results:** The stone expulsion rate was 78.8%, 81.8% and 54.5% respectively, with a significant difference between group (A,B) and group (C). Mean days till stone passed was (11.17 \pm 5.1), (10.27 \pm 4.17) and (15.7 \pm 3.66) respectively, the difference is statistically significant.

Key Word: PDE-5: phosphodiesterase-5.**Introduction**

Urolithiasis affects 4-15% of the world's population and this disease's prevalence is growing day by day. For all the urinary stones, 20% are ureteral stones, and 70% are located in the distal portion of the ureters.⁽¹⁾ Non-invasive treatment with extracorporeal shockwave lithotripsy and minimal invasive ureteroscopy method allows ureterolithiasis to be resolved in almost all cases, although these techniques are not risk-free and involve experience and may not in some cases be cost-effective.⁽²⁾

The therapeutic potential of α -adrenergic blockers for ureteral stone disease was investigated, prompted by α -receptor detection in ureteral smooth muscle cells.⁽³⁾ The usage of tamsulosin improves the spontaneous passage of distal ureteral stones, which is correlated with a reduced need for analgesics which improved

patient satisfaction. These data support its use in conservative management of distal ureteral stones.⁽⁴⁾

A newly launched phosphodiesterase-5 (PDE-5) inhibitor, tadalafil, has emerged that acts on the smooth muscle NO / cGMP signaling pathway, leading to increased levels of cyclic guanosine monophosphate, resulting in ureteric relaxation. Tadalafil has been approved by the FDA for use in the lower urinary tract symptoms in patients with benign prostatic hyperplasia and erectile dysfunction due to its smooth muscle relaxation property.⁽⁵⁾

Patients and Methods**Study design:***

This is a prospective, randomized, placebo-controlled, comparative study including 99 patients in the period from June 2019 to March 2020.

Target Population:*

All adults symptomatic patients aged above 18 years old present to Minia Urology and Nephrology University Hospital with symptomatic lower third ureteric stones less than 1 cm confirmed by non-contrast computed tomography of kidney, ureters, bladder (CTKUB).

***Inclusion criteria: The study included patients with:**

1. Symptomatic single lower third ureteric stone.
2. Stone size less than 1 cm.
3. Either sex ≥ 18 years of age.
4. Unilateral lower ureteric stone.
5. Newly diagnosed patients with ureteric stones within 1 month.
6. Women not expected to get pregnant during the next 2 months.

***Exclusion criteria: The study excluded patients with:**

1. Patients of age less than 18 years.
2. Bilateral ureteric stones.
3. Multiple lower ureteric stones.
4. Lower ureteric stone more than 1 cm
5. Ureteric stone in solitary kidney.
6. Pregnant and lactating women.
7. Presence of ipsilateral renal stones.
8. Patients with abnormal renal tract anatomy such as duplex system.
9. Febrile urinary tract infections.
10. Patients who have infected hydronephrosis or any degree more than minimal hydronephrosis, renal insufficiency, previous ureteral surgery.
11. Desire of the patient for immediate stone removal.
12. Any contraindication or allergy to the drug.

Study Intervention:

A. Initially, all patients are evaluated by means of physical examination, urine analysis, abdominal ultrasonography (US), KUB x-ray, blood urea, serum creatinine and CTKUB.

B. Patients divided into 3 groups:-

Group A:

Patients who received daily oral dose of Tadalafil 5 mg.

Group B:

Patients who received daily oral dose of Tamsulosin hydrochloride 0.4 mg.

Group C (Control group):

It included the control cases and patients in this group received placebo which is an expectant treatment. Patients in this group did not suffer any additional adverse effects or complications of the drug used in the study.

In each group patient will receive the expectant treatment which include:

1. Adequate hydration (at least 3 liters of water per day).
2. Oral diclofenac 50 mg for 1 week then on demand.
3. On demand parenteral ketorolac 30 mg ampoules.
4. On demand parenteral antiemetic; Ondansetron hydrochloride 4 mg ampoules.
5. Dietary sodium restriction.

C. Follow-up continued until stone expulsion or for a maximum of 4 weeks then intervention by means of ureteroscopy.

The criteria for treatment discontinuation as well as intervention were; uncontrollable pain, fever, change in degree of hydronephrosis, lack of stone expulsion after 4 weeks and a desire by the patient for the stone to be removed by means of another form of therapy.

Follow-up included determination of the stone expulsion rate, time of expulsion, pain episodes and total analgesic dosage.

D. Radiological follow up of the cases:

Follow up by ultrasonography for observation any change in degree of hydronephrosis, KUB for radiopaque stones and CT KUB for confirmation of complete clearance of stone.

Results

The study group composed of 99 newly diagnosed patients with lower ureteric stone in 3 groups each group contains (33 patients)

- **(Group 1)** received a daily oral dose of Tadalafil 5 mg.

- **(Group 2)** received a daily oral dose of tamsulosin hydrochloride 0.4 mg.

- **(Group 3)** Control group received (placebo)

Table (1): Age of patients in the study groups:

| Variable | All Cases | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|-------------------------------|-----------------|-------------------|-------------------|-------------------|---------------|
| Age (mean \pm SD) | 32.06 \pm 8.1 | 32.09 \pm 8.2 | 31.91 \pm 7.9 | 32.18 \pm 8.2 | P=0.99 |

ANOVA test was used to compare means

In table (1) mean age of patients in study group was (32.09 \pm 8.2), (31.91 \pm 7.9), (32.18 \pm 8.2) respectively, there is no statistically significant difference between three groups (P=0.99).

Table (2): Stone characteristics in each study group.

| Variable | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|---|------------------------------------|------------------------------------|------------------------------------|----------------|
| Stone length(mm) (mean \pm SD) | 5.48 \pm 1.5 | 5.88 \pm 1.9 | 4.73 \pm 1.4 | P=0.01* |
| Stone width(mm) (mean \pm SD) | 4.76 \pm 1.5 | 5.21 \pm 1.8 | 4.64 \pm 1.1 | P=0.26 |
| Stone outline Smooth irregular total | 27(81.8%) 6 (18.2%) 33(100%) | 25(75.8%) 8 (24.2%) 33(100%) | 24(72.7%) 9 (27.3%) 33(100%) | P=0.67 |
| Stone side Right Left Total | 17(51.5%) 16(48.5%) 33(100%) | 13(39.4%) 20(60.6%) 33(100%) | 15(45.5%) 18(54.5%) 33(100%) | P=0.61 |
| Stone density(HU) (mean \pm SD) | 381.67 \pm 211.5 | 358.58 \pm 182.7 | 485.64 \pm 244.7 | P=0.04* |

ANOVA test was used to compare quantitative data**Qui square test was used to compare qualitative data**

There was no statistically significant difference between groups regarding stone width, outline and side. Mean stone length was (5.48 \pm 1.5) mm in group (1) compared to (5.88 \pm 1.9) mm in second group and (4.73 \pm 1.4) mm in group (3), the difference was significant (P=0.01)

Table (3) :Stone expulsion rate in the groups :

| Item | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|-----------------------|-------------------|-------------------|-------------------|---|
| Expulsion rate | 26 (78.8%) | 27 (81.8%) | 18 (54.5%) | Group (1&2) P=0.76 Group (2&3) P=0.02* Group (1&3) P=0.04* |

There was no statistically significant difference regarding stone expulsion rate between group (1&2) . But there was statistically significant diff. between group (1&3) AND (2&3).

Table (4): Time till stone passed:

| Item | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|--|-------------------|-------------------|-------------------|----------------|
| Time till stone passed (days) (mean \pm SD) | 11.17 \pm 5.1 | 10.27 \pm 4.17 | 15.7 \pm 3.66 | P=0.02* |

Mean days till stone passed was (11.17 \pm 5.1), (10.27 \pm 4.17) and (15.7 \pm 3.66) respectively, the difference was statistically significant (**P=0.02**)

Table (5): orthostatic hypotension in both groups:

| Item | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|--------------------------------|-------------------|-------------------|-------------------|--------------|
| Orthostatic hypotension | | | | 0.04* |
| Positive | 5 (15.2%) | 6 (18.2%) | 0 (0%) | |
| Negative | 28(84.4%) | 27(81.8%) | 33(100%) | |
| Total | 33(100%) | 33(100%) | 33(100%) | |

Qui square test was used to compare variables

Orthostatic hypotension was higher among group (2) where (18.2%) of cases had orthostatic hypotension, while (15.2%) of cases in group (1) had orthostatic hypotension, no cases in group(3) had orthostatic hypotension . The difference is statistically significant (P= 0.04)

Table (6) :retrograde ejaculation in study groups:

| Item | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|-------------------------------|-------------------|-------------------|-------------------|---------------|
| Retrograde ejaculation | | | | 0.003* |
| Positive | 1 (3%) | 7 (21.2%) | 0 (0%) | |
| Negative | 32(97%) | 26(78.8%) | 33 (100%) | |

Qui square test was used to compare variables

Retrograde ejaculation occurred most frequent (21.2%) in group (2) than group (1) (3%) . The difference is statistically significant (P=0.003)

Table (7); Complications during treatment :

| Complication | Group (1) n=33 | Group (2) n=33 | Group (3) n=33 | Significance |
|--------------------------------|-------------------|-------------------|-------------------|---------------|
| Nil | 22(66.7%) | 24 (72.7%) | 27 (81.8%) | 0.001* |
| Headache | 9 (27.3%) | 1 (3%) | 6(18.2%) | |
| Penile tumescence | 7 (21.2%) | 0 (0%) | 0 (0%) | |
| flushing | 2 (6.1%) | 0 (0%) | 0(0%) | |
| Penile tumescence and flushing | 1(3%) | 0(0%) | 0(0%) | |
| Total | 33(100%) | 33(100%) | 33(100%) | |

Qui square test was used to compare variables

Headache occurred most frequently (27.3%) in group (1) than group (3) (18.2%). Penile tumescence and flushing mostly occurred among group (1). The difference is statistically significant(P=0.001)

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. Hence, observation has been advised for small ureteral stones, which have a high probability to pass spontaneously.

The use of the expectant approach for distal ureteric stones can be extended with the use of adjuvant medical expulsive therapy (MET), which is able to reduce symptoms and facilitate stone expulsion. The factors influencing expulsion of calculi include stone size, shape, and location, ureteric edema, and ureteric convolutions. Of these, the location of the calculus and its size are the most important factors. The management of patients with ureteral calculi has changed dramatically in the current era, with the conservative approach being the primary focus, its main benefit being minimum patient morbidity. Conservative nonsurgical approaches are usually implemented in the treatment plan of distal ureteral stones of size 5–10 mm as these are less likely to pass spontaneously.^(6,7)

The majority of ureteral calculi can pass spontaneously and intervention is usually not required. It is estimated that 95% of stones up to 4 mm pass spontaneously within 40 days.⁽⁸⁾

A meta-analysis by the AUA guidelines panel determined that ureteral stones with a diameter of <5 mm will pass in up to 98% of cases. For stones with diameters >7 mm, the overall chance of spontaneous passage is low⁽⁹⁻¹¹⁾. A wide range of spontaneous passage rates have been reported, ranging from 71% to 98% for distal ureteral stones <5 mm and 25%–53% for stones measuring 5–10 mm with a mean expulsion time of >10 days and is associated with high analgesic requirement even for stones <5 mm. To improve the expulsion rate and reduce analgesic require-

ment, medical therapy is considered for distal ureteral stones^(7,8).

In a study conducted by Suresh Kumar Goyal et al., 2018, about Comparative efficacy of tamsulosin versus tadalafil as medical expulsive therapy for distal ureteric stones, randomized non placebo controlled study of 124 patients divided in two groups. The stone expulsion rate was 73.77% in Group Tamsulosin (A) and 69.35% in Group Tadalafil (B). Although this was on the higher side in Group A, but the difference was not significant ($P = 0.69$). The mean expulsion time from the starting of MET was lower for tamsulosin group (9.38 ± 6.66 days) than for tadalafil group (9.61 ± 7.47 days), but this difference was also not significant ($P = 0.78$).⁽¹²⁾

A number of colic episodes and analgesic use (NSAIDs) were significantly higher in tadalafil group than in tamsulosin group (0.96 ± 0.74 , 0.62 ± 0.83 , 0.010 ; 11.82 ± 3.34 , 9.15 ± 3.80 , 0.020), but the number of hospital visits was higher in tadalafil group ($P = 0.15$).⁽¹²⁾

Adverse effects such as headache and dizziness occurred more often in tadalafil group ($P > 0.05$), these were not significant enough to exclude the patients from the study. Incidence of orthostatic hypotension and backache was almost equal in both groups. Abnormal ejaculation was observed in 9.8% of patients in tamsulosin group and 1.6% of patients in tadalafil group with a highly significant difference ($P < 0.001$).⁽¹²⁾

In our study, placebo controlled, shows no significant difference in stone expulsion rate between tadalafil, tamsulosin but statistically different than control group with 78.8%, 81.8% and 54.5% respectively. Mean days till stone passed was (11.17 ± 5.1), (10.27 ± 4.17) and (15.7 ± 3.66) respectively, the difference was statistically significant. Also orthostatic hypotension and retrograde ejaculation were noticed to be significantly higher in first two groups than control group. No other serious side effects were detected

Also in another study conducted by Sandeep Puvvada et al., 2016, comparing efficacy of tadalafil vs. tamsulosin in expulsion of lower

third ureteric stone. The stone expulsion rate was 84.0% in Group tadalafil (A) and 68.0% in Group tamsulosin (B); Group A showed a significantly higher stone expulsion rate compared with Group B (P value = 0.0130). The mean time for stone expulsion in (Group A) was 14.7 ± 3.8 days, and in Group B was 16.8 ± 4.5 days. The time was significantly less in (Group A) than Group B (P value = 0.0021).⁽¹³⁾

The average number of episodes of colicky pain were significantly less in Group A (0.45 ± 0.68 ; P value = .0002). Additionally, the mean requirement of analgesia was significantly less in Group A (1.88 ± 0.60) than in Group B (2.6 ± 0.8).⁽¹³⁾

Drug-related adverse effects such as headache, dizziness, orthostatic hypotension, and backache were more frequent in Group B patients (P value >0.05), but not significantly enough to exclude them from the study. Abnormal ejaculation was seen in 6% of patients in Group A, and 12% in Group B, which was again not statistically significant.⁽¹³⁾

The results of this study indicate that tadalafil significantly increases ureteric stone expulsion and simultaneously provides better pain control and significantly lowers analgesic requirement unlikely to our study.⁽¹³⁾

In our study retrograde ejaculation occurred most frequent (21.2%) in group tamsulosin than group tadalafil (3%). The difference is statistically significant (P=0.003).

Headache occurred most frequently (27.3%) in group tadalafil than group placebo (18.2%). Penile tumescence and flushing mostly occurred among group tadalafil. The difference is statistically significant (P=0.001).

In 2019, Abhishek Laddha et al., conducted a Comparison study of Tadalafil and Tamsulosin in Medical Expulsive Therapy for Ureteric Calculus: Prospective, randomized, placebo controlled study. Each group contains 50 patients. They found that The stone expulsion rate was 58% (36 of 50 patients) for the placebo group, 80% (40 of 50 patients) for tadalafil group and 74% for the

tamsulosin group (37 of 50 patients). Tadalafil was superior to placebo in terms of stone expulsion rate (p-value: 0.017) but comparable to tamsulosin (p: 0.139). Patients in the tadalafil group had significantly less pain scores at 1 and 2 weeks follow up in comparison to the other two groups. Mean analgesic requirement for placebo, tadalafil and tamsulosin was 331, 132.93 and 277.08 mg of diclofenac respectively.⁽¹⁴⁾

In 2020, K A H teama et al., at Ain Shams university conducted a Comparative Study between Tadalafil versus Tamsulosin versus Halphabarol with Terpenes Mixture as a Medical Expulsive Therapy for Lower Ureteric Stones. Each group contains 20 patients. The results of this study indicate that the stone expulsion rate was significantly higher in tadalafil group and tamsulosin group than Proxamol with Rowatinex group (75% vs. 75% vs. 40%, P value = 0.030). Also, the mean stone expulsion time was significantly shorter in tadalafil group and tamsulosin group than Proxamol with Rowatinex group (10.20 ± 3.91 days vs. 10.80 ± 3.64 days vs. 14.25 ± 3.28 days, P value = 0.046).

The number of patients who experienced renal colic episodes, the number of colic episodes and the number of injectable analgesic uses were significantly lower in tadalafil group and tamsulosin group than Proxamol with Rowatinex group (P value < 0.05). The number of follow up ureteroscopic procedures was significantly lower in tadalafil group and tamsulosin group than Proxamol with Rowatinex group (25% vs. 25% vs. 60%, P value = 0.030). Also, the drugs are safe with mild few side effects.⁽¹⁵⁾

Another study by Hari Bahadur KC et al, about Tamsulosin versus tadalafil as a medical expulsive therapy for distal ureteral stones: A prospective randomized study. Altogether 85 patients, 41 in group tamsulosin and 44 in group tadalafil, were enrolled in the study. The patients' average age was 31.72 ± 12.63 years, and the male-to-female ratio was 1.5:1. Demographic profiles, stone size, and baseline investigations were comparable between the 2 groups. The stone expulsion rate was significantly higher in the tadalafil group than in the tamsulosin group

(84.1% vs. 61.0%, $p=0.017$). Although the occurrence of side effects was higher with tadalafil, this difference was not significant ($p=0.099$). There were no serious adverse effects.⁽¹⁶⁾

A comparative study made by Chirag Parikh et al., in 2019 about Tamsulosin versus tadalafil as medical expulsive therapy of distal ureteric stones. Each group contain 30 patients. Mean expulsion of calculi was significantly earlier in patients managed by tadalafil as compared to tamsulosin (13.1 vs 16.92 days; $p<0.05$). Complete expulsion was seen in 86.7% cases on tadalafil as compared to only 63.3% cases on tamsulosin ($p<0.05$). Mean analgesic use (2.69 vs 1.81; $p<0.05$) and episodes of colicky pain (1.41 vs 0.43; $p<0.05$) were significantly higher in patients managed by tamsulosin. The number of hospital visits required during treatment was also more with tamsulosin, but the difference did not reach significance levels (2.56 vs 2.02 days; $p=0.06$). No difference was seen in the adverse effect profile of both drugs.⁽¹⁷⁾

Conclusion

PDE5 inhibitors (tadalafil) are equally efficacious to alpha-1 adrenergic antagonists (tamsulosin) in expulsion of lower ureteric stones less than 1 cm without any serious side effects. Comparing to placebo, both tadalafil and tamsulosin increase significantly the stone expulsion rate and decrease significantly the stone expulsion time.

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