



## COMPARATIVE PROSPECTIVE STUDY OF TADALAFIL, SILODOSIN ALFUZOSIN AND TAMSULOSIN AS THE MEDICAL EXPULSIVE THERAPY IN LOWER URETERIC STONE OF SIZE UP TO 10 MM

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### ABSTRACT

**Aim-** To compare safety and efficacy of tadalafil, silodosin, tamsulosin and alfuzosin as medical expulsive therapy for distal ureteral stone of size up to 10 mm.

**Material and methods:** Comparative prospective study conducted in department of surgery, L.L.R.H, Kanpur, for period of 24 months in patients with distal ureteral stones of size up to 10 mm. Patients were randomly divided into 4 groups: group A received tadalafil 10 mg and group B received silodosin 8 mg, group C received tamsulosin 0.4 mg and group D received alfuzosin 10 mg bed time for 4 weeks. Stone expulsion rate, pain relieved or not, analgesic requirements and side effects were noted in all four groups. Statistical analysis was performed using student t test and chi square test.

**Results:** Total patients enrolled in the study initially was 218, but few were lost to follow up. Finally, altogether 200 patients, 50 in each group were analysed in the study. 58.3 % of patients belonged to age group 20 to 30 yr. Male to female ratio 3.61:1. Mean stone size was 5.65±2.13. Demographic profile and baseline investigation were comparable in all 4 groups. Stone expulsion rate was significantly higher in silodosin (within 1 week) followed by tadalafil, tamsulosin and alfuzosin (within 2). Although occurrence of side effect, headache, flu like symptoms and postural hypotension were non-significant. Silodosin was more acceptable in patients because of earlier pain relief among tadalafil, tamsulosin, alfuzosin despite of retrograde ejaculation in few young patients as side effects.

**Conclusion:** Silodosin has significantly higher stone expulsion rate followed by tadalafil, tamsulosin and alfuzosin. All four drugs are safe, effective and well tolerated with minor side effects.

**KEYWORDS :** Tadalafil; Tamsulosin; Silodosin; Alfuzosin; Ureteral calculi

### INTRODUCTION:

Ureteric stone are increasingly common these days. Medical expulsive therapy (MET) for stone expulsion, has become routine in the treatment of obstructive ureteral calculi in recent few years. Ureteral stones induce ureteral spasms that interfere with stone expulsion. Thus, reducing these spasms while maintaining normal peristaltic activity can facilitate stone expulsion. Almost 50% of ureteral stones will pass spontaneously over time and stone size is the key factor for success. Usually, stones smaller than 5 mm are expected to pass spontaneously. Improvements in minimally invasive procedures in the last few decades have considerably changed the treatment of ureteral stones, but such procedures are not free of risks and are costly as well. A conservative approach through medical expulsive therapy (MET) has now become an established treatment modality that employs various drugs acting on the ureter by different mechanisms. Alpha-1 and particularly subtype alpha-1D are the most commonly observed adrenergic receptor subtypes in the ureteral smooth muscle cells. Alpha blockade has been proven to decrease peristaltic activity, contraction and intraureteral pressure and to improve spontaneous stone passage and decrease both the time to stone passage and analgesic requirements. According to European association of urology on urolithiasis 2017 by C. Turk (Chair) et al, alpha-blockers are recommended for MET.

Tadalafil, a PDE5 inhibitor, acts by a nitric oxide/cGMP signalling pathway of smooth muscles, resulting in high levels of cGMP and thus causing relaxation of ureteral muscle and expulsion of ureteric stone

### AIM AND OBJECTIVES:

to find out the drug with higher expulsion rate and shorter expulsion time & to compare the safety and efficacy of tadalafil, silodosin, alfuzosin and tamsulosin as medical expulsive therapies for lower ureteric stones.

### MATERIAL AND METHODS:

This study was conducted out on a prospective basis in LLR and Associated Hospitals in the Department of Surgery with help of

department of pathology, microbiology and Radiology, GSVM Medical College, Kanpur in those patients who presented in surgery OPD in LLR Hospital with symptoms and signs and diagnosis of the lower ureteric diseases and subjected to medical therapy.

Four drugs were compared with 50 patients in each group: Group A were given tadalafil, Group B were given silodosin, Group C were given tamsulosin, Group D were given alfuzosin

### Inclusion Criteria:

- Patient >18 and <60 years with radio-opaque ureteric stone <10 mm

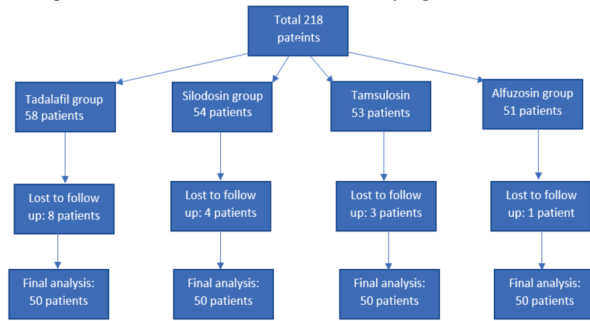
### Exclusion Criteria

- Solitary kidney, Bilateral kidney disease, Renal failure
- Severe comorbid conditions like diabetes mellitus, Hypertension, COPD, Tuberculosis, Coagulopathy, Patient not willing to participate, Radio lucent stone.

Detailed history of patient was taken in reference to pain during micturition, burning micturition, pain in inguino-scrotal region and medial side of thigh. Patients' urine routine/microscopy and culture/sensitivity was done. Hemogram and renal function tests were done. USG and X-ray and NCCT KUB region was done.

Patients were followed at weekly interval and were enquired about pain during micturition, inguino-scrotal region and medial side of thigh and side effects. Expulsion of stone was confirmed by digital x-ray KUB and ultrasonography on weekly interval till 4 weeks. Patient who failed to pass stone after 4 weeks were subjected to semirigid ureteroscopy for stone removal. primary outcome of study was stone expulsion rate and secondary end points were side effects and pain relieved or not. Data were collected by filling in proforma data sheets, which included the patients' demographic profiles, investigation reports, and the results of primary and secondary outcomes. Data were analyzed by using the SPSS, ver. 21.0. Discrete variables were evaluated by chi-square test and continuous variables by unpaired

Student t-test. All statistical tests were based on two-tailed probability, and a p-value <0.05 was considered statistically significant



**Observations:**

In the study maximum number of patients (58.3 %) belong to age group 20 to 30 years. Maximum patients in the study were males. In the study after 4 weeks of treatment, stone was expelled in 45 patients in group A out of 50 and in group B, stone was expelled in 48 patients out of 50 and in group C, stone was expelled in 44 out of 50 and group D, stone was expelled in 44 out of 50. In the study mean stone expulsion time was minimum in group B silodosin (within 1 week).it was maximum for group D Alfuzosin (within 2 week).

**Efficacy of drug**

| Group | Stone expelled | Stone not expelled |
|-------|----------------|--------------------|
| A     | 45             | 05                 |
| B     | 48             | 02                 |
| C     | 44             | 06                 |
| D     | 44             | 06                 |

**Stone expulsion rate of tadalafil, silodosin, tamsulosin and alfuzosin for distal ureteral stones in various studies**

| Study                        | tadalafil | silodosin | tamsulosin | Tamsulosin + tadalafil | alfuzosin | placebo |
|------------------------------|-----------|-----------|------------|------------------------|-----------|---------|
| Present study                | 90        | 96        | 88         | -                      | 88        | -       |
| Hari bahadur K C et al, 2016 | 84.1      | -         | 61         | -                      | -         | -       |
| Kumar et al, 2015            | 66.7      | 83.3      | 64.4       | -                      | -         | -       |
| Kumar et al, 2014            | -         | -         | 74.2       | 83.9                   | -         | -       |
| Jayant et al, 2014           | -         | -         | 65.5       | 83.6                   | -         | -       |
| Hasan et al, 2011            | 93        | -         | -          | -                      | -         | 67      |
| Al-Ansari et al, 2010        | -         | -         | 82         | -                      | -         | 61      |

**DISCUSSION:**

- In the study maximum number of patients (58.3 %) belong to age group 20 to 30 years. **Chand RB et al 2012** in a study in Nepal found that ureteric stone were more in patients of productive age group (71.8 % belong to 20 to 60-year age group). They also concluded that distal ureter is most common site for ureteric stone.
- Maximum patients in the study were males. **Scales CD Jr et al 2007** also suggest male predominance of nephrolithiasis. Male to female ratio 1.3:1.
- In the study after 4 weeks of treatment, stone was expelled in 45 patients in group A and 48 patients in group B and stone was expelled in 44 patients in group C and 44 patients in group D out of 50. **Suresh Kumar Goel et al 2018** found in a study of 123 patients that stone was expelled 73.7 % in group A (61 Patients given tamsulosin) and stone was expelled in 69.35 % patients in group B (62 patients were given tadalafil). It showed that although tamsulosin more effective in stone clearance than tadalafil, no statistical difference was found in stone expulsion rate in both groups. **Sandeep Puvada 2016** studied 200 patients randomly allocated assigned 2 groups. Stone expulsion rate was 84 % in group A tadalafil which was significantly higher than group B (68%) tamsulosin.
- The stone expulsion rate in the present study was significantly higher in the silodosin (96%) group than in the tadalafil (90%) group followed by tamsulosin (88%) and alfuzosin (88%) group. Kumar et al. and Jayant et al. in their studies compared the stone expulsion rate of tamsulosin with the tamsulosin and tadalafil combination. The expulsion rate was 74.2% versus 83.9% (p=0.349) and 65.5% versus 83.6% (p=0.031), respectively. In another study, Hasan et al. [22] found that tadalafil had an expulsion rate of 93% compared with 67% for a placebo group. In a randomized study with 285 patients, Kumar et al. [23] compared the efficacy of 3 drugs, tamsulosin, silodosin, and tadalafil, as MET for lower ureteral stones. The expulsion rate was 64.4%, 83.3%, and 66.7%, respectively, but there was no significant

|            |                                |
|------------|--------------------------------|
| Chi square | 2.50                           |
| d.o. f     | 3                              |
| P value    | 0.4752, p>0.05 non-significant |

**Potency of drug**

| Group      | Stone expelled in less than 1 week | Stone expelled in 1-2 weeks | Stone expelled in 2-3 weeks | Stone expelled in 3-4 weeks | Stone not expelled |
|------------|------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------|
| A          | 30                                 | 7                           | 5                           | 3                           | 5                  |
| B          | 35                                 | 10                          | 3                           | 0                           | 2                  |
| C          | 26                                 | 8                           | 7                           | 3                           | 6                  |
| D          | 28                                 | 6                           | 3                           | 7                           | 6                  |
| Chi square | 34.22                              |                             |                             |                             |                    |
| d.o. f     | 12                                 |                             |                             |                             |                    |
| P value    | <0.0006222= significant            |                             |                             |                             |                    |

**Side effects in different groups**

| Group | Retrograde ejaculation |    | Postural hypotension |    | Flu like symptoms |    | Headache |    |
|-------|------------------------|----|----------------------|----|-------------------|----|----------|----|
|       | No.                    | %  | No.                  | %  | No.               | %  | No.      | %  |
| A     | 0                      | 0  | 12                   | 24 | 02                | 4  | 10       | 20 |
| B     | 15                     | 30 | 6                    | 12 | 4                 | 8  | 4        | 8  |
| C     | 4                      | 8  | 4                    | 8  | 3                 | 6  | 4        | 8  |
| D     | 2                      | 4  | 3                    | 6  | 6                 | 12 | 6        | 12 |

**Mean expulsion time**

| Group | Mean stone expulsion time  |
|-------|----------------------------|
| A     | 0.77 week (within 1 weeks) |
| B     | 0.55 week (within 1 week)  |
| C     | 1.20week (within 2 weeks)  |
| D     | 1.25week (within 2 weeks)  |

difference between the tamsulosin and tadalafil groups (p=0.875).

**Sandeep Puvada 2016** studied 200 patients randomly allocated assigned 2 groups. Stone expulsion rate was 84 % in group A tadalafil which was significantly higher than group B (68%) tamsulosin. **Celik et al 2018** concluded that stone was expelled in 71.8 % for alfuzosin and 75 % for doxazosin and 76.5 % for tamsulosin and 88.6 % for silodosin and it was 90 % for tadalafil. Expulsion rate was highest in tadalafil and silodosin for distal ureteral stone.

- In the study, Flu like symptom more commonly seen in 12% patients in alfuzosin group. Group D. Retrograde ejaculation was reported maximum in silodosin group in 30 % of patient taking silodosin. Headache and postural hypotension were reported maximum in patients taking tadalafil. All side effects were minor and well tolerable by patients. **Kumar S, et al (2015)** observed in a Randomized control trial study that medical expulsive therapy for the distal ureteric stones using tamsulosin, silodosin, and tadalafil is safe, efficacious, and well tolerated.

**RESULTS:**

- In the study mean stone size was 5.65 ± 2.13mm.
- Maximum patients of our study belong to lower socioeconomic status and most of them are male. Maximum number of patients (58.3 %) belong to age group 20 to 30 years.
- In the study mean stone expulsion time was minimum in group B silodosin (0.55Weeks).it was maximum for group D Alfuzosin (2 weeks).
- In the study, patient given with drug Tadalafil had an expulsion of stone within first week and the most common side effect observed were headache and postural hypotension.
- While with Silodosin, very high expulsion rate was observed. Most of the patients had expulsion of stone within first week and the most common side effect observed was retrograde ejaculation while some of the patients also presented with headache and postural hypotension.

- While with Tamsulosin, in most of the patients expulsion of stone was within second week with side effect of postural hypotension while some of the patients also presented with headache, and flu like symptoms.
- While with Alfuzosin, in most of the patient expulsion of stone within second week with side effect of postural hypotension while some of the patients also presented with headache, flu like symptoms and retrograde ejaculation.

### CONCLUSION:

Silodosin has significantly higher stone expulsion rate than tadalafil, tamsulosin and alfuzosin as MET for distal ureter stone of size upto 10mm. Silodosin was more acceptable in patients because of earlier pain relief with few side effects like retrograde ejaculation, headache and postural hypotension. All four drugs are safe, effective and well tolerated with minor side effects.

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