

Management of Lower Ureteric Calculi with Alfuzosin, Tamsulosin and Tamsulosin Deflazacort Combination: An Observational Study

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Abstract: ***Study objective:** To observe the efficacy of alfuzosin, tamsulosin and tamsulosin-deflazacort combination in the medical expulsive therapy of lower ureteric calculi. **Methods:** The observational comparison study was done at FATHER MULLER Medical College hospital over a period of 9 months from Jan2016 to Sept 2016, a total sample size of 128 admitted patients was taken. After initial assessment as per the individual consultants choice patients were put on any of the three groups drugs Alfuzosin 10mg, Tamsulosin 0.4mg or Tamsulosin 0.4mg - deflazacort 30mg in conjunction with Medical Expulsive therapy(MET). Each patient was subjected to two sessions of MET and were radiologically assessed for stone passage with NECT-KUB. Those with a persistent calculus were taken up for lithotripsy. **Results:** Of 543 patients considered for the observational study only 128 were found eligible. 68 patients were put on alfuzosin 10mg, 39 were put on tamsulosin 0.4mg and 21 were put on tamsulosin 0.4mg –deflazacort 30mg combination. Due to the non comparative nature of the three groups; no statistically significant conclusions could be drawn. However; In patients with calculi > 7mm; 50% of the patients passed the calculus in the tamsulosin-deflazacort group vs 30% in tamsulosin group and 20% in the alfuzosin group. No difference was noted in efficiency of either of the drugs in clearance of small calculi <5mm. **Conclusion:** Tamsulosin-deflazacort combination could be offered as the first line therapy for lower ureteric calculi in patients with no contraindications to steroids.*

Keywords: ureteric calculi, alfuzosin, tamsulosin and tamsulosin lowere

1. Introduction

Symptomatic Urolithiasis seem to be a common reason for presentation to the Healthcare providers not just in India, but worldwide^[1]; with statistics from the United States accounting to 3 million patients per year^[2]. With the advent of use of alpha blockers for Medical expulsive therapy such as Doxazosine which was used in the 1990's, various selective alpha blockers have been developed with conservative management being a first-line treatment for calculi less than 10mm.

In the recent years selective alpha blockers such as tamsulosin and selective alpha blockers with steroid drug combinations seem to be used in many centres worldwide and have been widely studied for its superiority versus simple analgesics or calcium channel blockers.^[3] Of particular interest is the ability of Tamsulosin being highly effective in the expulsion of lower ureteric calculi measuring (5mm-10mm). Tamsulosin in comparison to other alpha blockers appears to have selective $\alpha 1D$ and $\alpha 1A$ adrenoceptor agonist activity.^[4] It was found that $\alpha 1D$ and $\alpha 1A$ adrenoceptors were expressed in large amounts in the human ureter^[5]. It has been demonstrated that the distal ureter expresses greater amounts of $\alpha 1$ -adrenoceptor mRNA than the proximal and mid ureter, $\alpha 1D$ - adrenoceptor mRNA is more highly expressed than $\alpha 1A$ - adrenoceptor mRNA in each region of the ureter^[6] but ureteral contraction is mediated mainly by $\alpha 1A$ - adrenoceptor, even though $\alpha 1D$ -adrenoceptors were more prevalent^[7].

Tamsulosin also happens to be the most widely studied alpha-blocker used for MET. In a meta-analysis of 20 RCTs across 10 countries done by Fan *et al*^[8] included 799 patients in the tamsulosin arm and 794 patients in the control arm. Expulsion rates for lower and upper ureteral stones were significantly higher in the tamsulosin arm (lower ureteral stones: RR = 1.55, $P < 0.00001$; upper ureteral stones: RR = 1.28; $P = 0.02$)^[36]. Additionally, expulsion time was improved in the tamsulosin group by an average of 2.63 d^[8]. These patients also had fewer colic episodes and underwent fewer surgical interventions. Tamsulosin has been used in most of these studies, probably because of its tolerability and lack of need for dose titration.^[9]

In our hospital experience, alfuzosin which is a selective alpha-1 receptor antagonist has been used for many years for medical expulsive therapy (MET) with a recent preference to use tamsulosin and tamsulosin with steroid (deflazacort) preparations with apparent clinical benefit. This observational study aims to explore the benefits of the use of alpha blocker with steroid combination over plain alpha blockers and drugs based on overall percentage of stone expulsion, time taken for stone expulsion, pain as per visual analogue scale with number of re-visits to the hospital over a period of 3 weeks and to evaluate patients for any adverse drug effects.

The usual protocol in our hospital for IP management of calculi presenting in the emergency with an acute onset of pain is to provide analgesia and start alpha-blockers in conjunction with MET therapy. If two to three sessions fail the position and presence of the ureteric calculi is

ascertained following which patient is taken up for surgical intervention which in our case is mostly ureteroscopic lithotripsy.

2. Aims and Objectives

- 1) To compare the Stone expulsion rate in people with age(18-65yrs) with single distal ureteric calculus ≤ 12 mm using Alfuzosin versus Tamsulosin versus Tamsulosin with deflazacort combination, as medical expulsion therapy.
- 2) In people with single distal ureteric calculus ≤ 12 mm treated by alfuzosin, time taken to stone expulsion compared to those of Tamsulosin and Tamsulosin with deflazacort.
- 3) To compare the surgical intervention rate in patients with single distal ureteric calculus ≤ 12 mm using Alfuzosin versus tamsulosin versus Tamsulosin with deflazacort.

3. Materials and Methods

The observational comparison study was done at FATHER MULLER Medical College hospital over a period of 9 months from Jan 2016 to Sept 2016, a total sample size of 128 admitted patients was taken. Based on other studies, patients on Tamsulosin-deflazacort combination have 84% success in passage of ureteric calculi with no medical therapy.

Inclusion Criteria

- Single distal ureteric calculus less than or equal to 8 mm
- Age 18-65 years
- Patients without contra-indications to steroid use

Exclusion Criteria

- Calculus with moderate or severe hydronephrosis
- Solitary kidney
- Calculus with Urinary tract infection
- Multiple calculi
- Pregnancy and lactation
- h/o previous ureteral surgery or endoscopic procedure
- Renal insufficiency (serum creatinine > 1.5 gms/dl)
- Patients on corticosteroids

4. Methodology and Data Collection

As a part of our routine management each patient were evaluated with the following
 History and clinical examination,
 CBC, Urine analysis
 serum creatinine level,
 urine culture,
 ultrasonography, and

Noncontrast computed tomography- KUB if needed

After initial assessment as per the individual consultants choice patients were put on any of the three groups drugs Alfuzosin 10mg, Tamsulosin 0.4mg or Tamsulosin 0.4mg - deflazacort 30mg in conjunction with Medical Expulsive therapy. Adequate analgesia was provided as required with NSAIDS being administered during an episode of pain. Two sessions of Medical Expulsive therapy were tried per patient. Patients who were symptomatic despite analgesia and in those with a persisting calculus despite the MET therapy as evidenced by imaging- Ultrasonogram of the KUB region were managed surgically. Medical treatment was aborted in case of uncontrolled ureteric colic, fever, infection, severe hydronephrosis and raised serum creatinine and such patients were taken up for surgical intervention.

Patients were assessed by the following parameters:

- Percentage of stone expulsion in each of these groups
- Time taken to stone expulsion in each of these groups
- Rate of surgical intervention in each of these groups
- Analgesic use in each of these groups

5. Results and Discussion

Total sample size = 128 patients

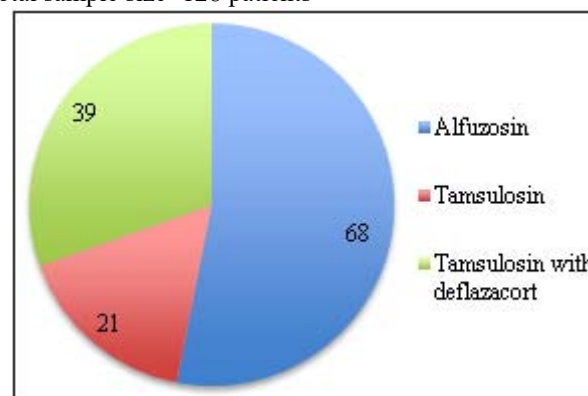


Figure 1

Group A- Patients on alfuzosin 10mg

Group B- Patients on Tamsulosin 0.4mg

Group C- Patients on Tamsulosin 0.4mg + Deflazacort 30mg

The Percentage of passing calculi in the alfuzosin group was 65% with an average calculus size of 5.6mm, Tamsulosin group was 52.3% with an average size of 6.18mm and Tamsulosin- Deflazacort combination was 61.5% with an average calculus size of 6.68mm.

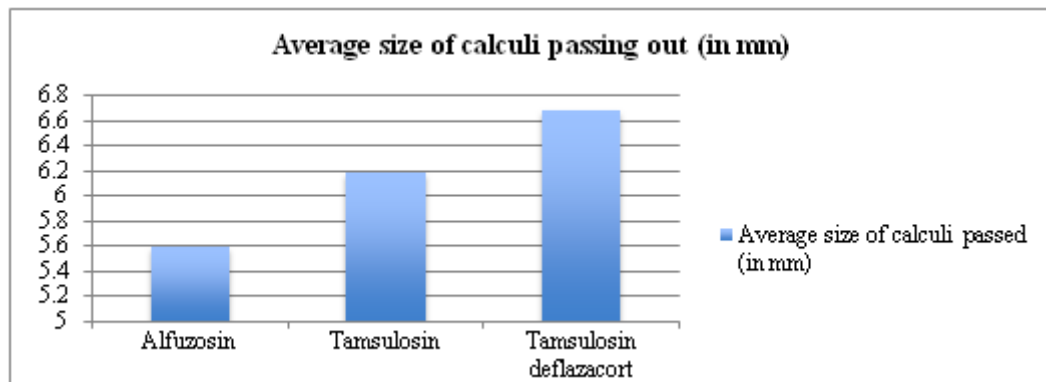


Table 1: Average size of expelled calculi in (mm)

The maximum size of calculus expelled in the alfuzosin group was 8mm, the Tamsulosin group was 10mm and Tamsulosindeflazacort group was 12mm.

In the >5mm subgroup, alfuzosin group 54.3% of the pateints expelled the calculi; in the Tamsulosin group 50% and in the Tamsulosin-deflazacort 58% of patients were able to expel the calculi.

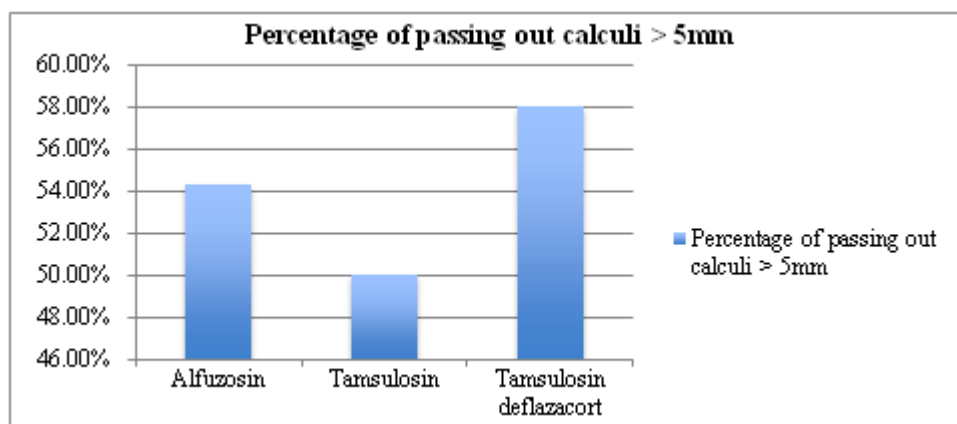


Table 2: Percentage of expulsion in Patients with calculus size >5mm

In those with successful conservative management the average number of days required for passage of calculi in conjunction with MET therapy for the alfuzosin group was

3.16 days, for the Tamsulosin group was 2.8 days and Tamsulosin with deflazacort combination was 2.4 days.

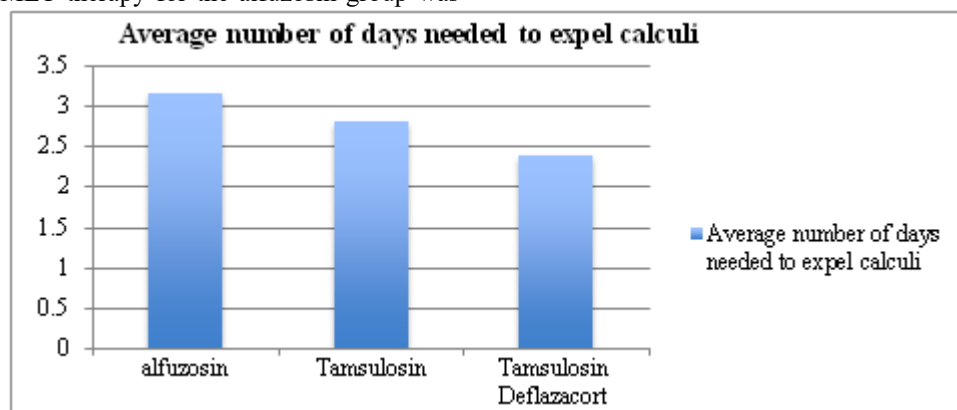


Table 3: Average number of days needed to expel calculi

The process of passage of the calculi was also less painful in our experience in the Tamsulosin-deflazacort group compared with the Tamsulosin group and the alfuzosin group as evidenced in various studies including a multicenter meta-analysis.

The surgical intervention which in our study was lithotripsy was 34% in the alfuzosin group. This could be attributed to the smaller size of calculi on an average in that group. The

tamsulosin group had a 40.9% intervention rate and Tamsulosin with deflazacort group had an intervention rate of 38%. It should also be noted that the average size in both the Tamsulosin and Tamsulosin-deflazacort groups were larger, at 6.18mm and 6.68mm respectively with calculi > than 10mm also expelled in the TamsulosinDeflazacort group.

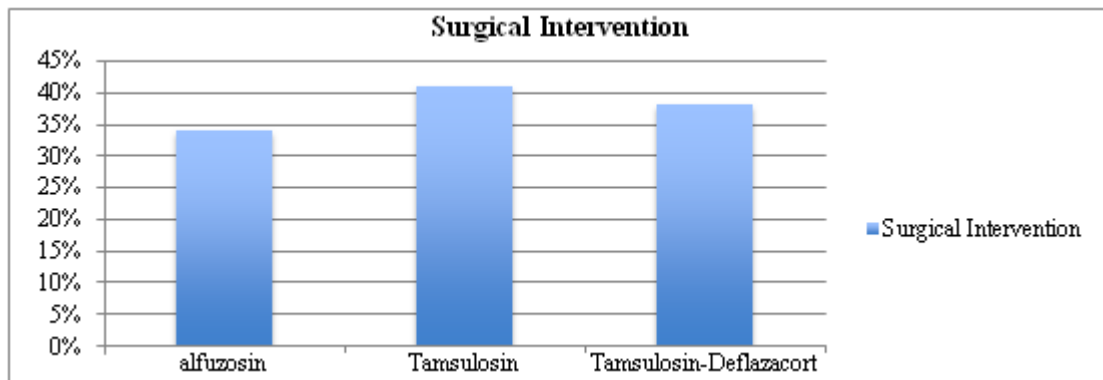


Table 4: Percentage of patients undergoing surgical intervention

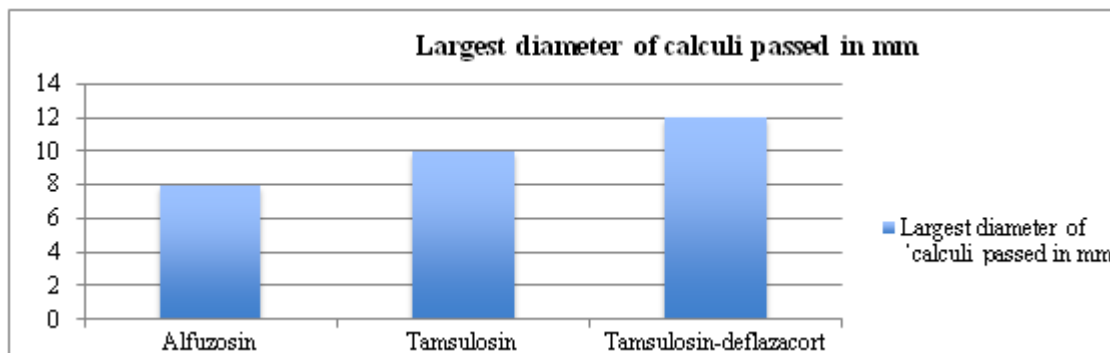
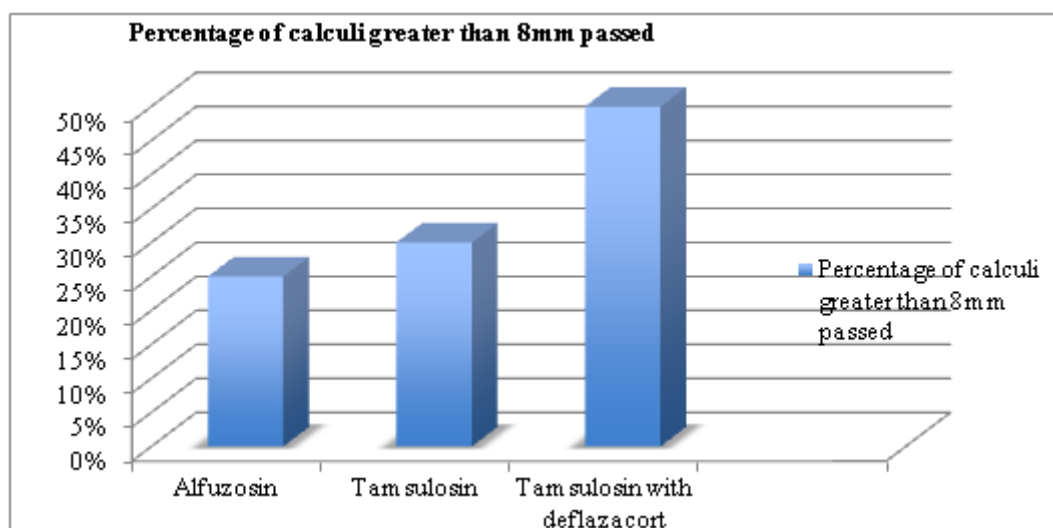


Table 3: Maximum size of calculi passed

The size of the maximum diameter of calculi that was expelled was in the Tamsulosin-deflazacort group with a maximum diameter of 12mm as opposed to 10mm group in the plain tamsulosin group and only 8mm in the alfuzosin group.

On doing a three way ANOVA; there was no statistically significant difference noted in either Tamsulosin-deflazacort combination or Tamsulosin over Alfuzosin in

either the passage of calculi in relationship with size or the number of days taken to expel the calculi in any of the three groups; possibly due to the lack of randomization in our study. However in patients with calculi greater than 8mm; 50% of patients in Tamsulosin-deflazacort group vs 30% of patients with Tamsulosin vs 25% of patients on alfuzosin demonstrated successful passage of calculi.



The analgesics were given on an average of thrice daily doses of NSAIDS in the three groups; however the perceived pain was lower in the Tamsulosin - deflazacort group with lesser frequency of episodic pain noted in these patients thereby limiting the extra analgesic doses.

Adverse effects of postural hypertension and retrograde ejaculation were noted in a few patients treated with tamsulosin-deflazacort and tamsulosin group and neither of these were noted in the alfuzosin group.

6. Conclusion

Despite not able to prove a statistically significant difference due to the inherent limitations of our study such as a small sample size with non comparable groups in terms of diameter of calculi, age and sex distribution, it was observed that the tamsulosin-deflazacort group was more efficient in clearing stones with diameter greater than 8mm when used in conjunction with MET therapy is possible due to the anti-ureteral edema action of the deflazacort(steroid) component.

In a randomized control trial by Furyk et al^[10] more than 400 patients were taken up for the study where Tamsulosin was compared with a placebo in the expulsion of stones at the end of 28 days. No significant benefit was demonstrated 87% tamsulosin vs 81% for placebo; but however in a subset of patients with ureteric calculi diameter between 5mm and 10mm benefit has been demonstrated with the tamsulosin group with expulsion of 83.8% as opposed 60% in the placebo.

In our experience the benefit was best noted in 7mm to 12mm group with an expulsion of calculi in 50% of the patients in the tamsulosin-deflazacort combination vs 30% in the tamsulosin group and only 20% in the alfuzosin group. No benefits are noted in the sub 5mm group which parallels the findings of the aforementioned study.

In a Cochrane review of 32 studies done in various centres with an accumulated pool of 5864 patients; expulsion of calculi was 2.91 days shorter with the use of alpha-blockers as compared to placebo (MD -2.91, 95% CI -4.00 to -1.81). The use of alpha blockers was associated with lower analgesic requirement and shortened hospital duration stay.

The addition of the steroid component to the alpha blocker tamsulosin was demonstrated to show its superiority over plain alpha blockers particularly in larger diameter >7mm calculi. In those patients with contraindication to steroid component; plain tamsulosin can be offered as the therapy. Sitharamaiah et al in their study have also offered Tamsulosin as the first line therapy for lower ureteric calculi.^[12]

Our study offers a peek into daily urological practice in a hospital setting with treatment protocol of stone clearance in the event of failed MET therapy. In a short duration of 2 to 3 days time, the objective was to see which of the three drugs were able to show maximal effect in conjunction with MET therapy. If the MET therapy was not successful then patients in any of the three arms were taken up for ureteroscopic lithotripsy. Finally, Tamsulosin-deflazacort combination could be offered as the first line therapy for lower ureteric calculi in patients with no contraindications to steroids.

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