

Comparative Study of Tamsulosin versus Placebo in the Management of Lower Ureteric Stone

Bhim Bala¹, Pushpendra Kumar Shukla², Rachna Gupta³

¹Post Graduate Student, Department of Surgery, Shyam Shah Medical College and Associated Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India, ²Assistant Professor, Department of Surgery, Shyam Shah Medical College and Associated Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India, ³Associate Professor and Head, Department of Surgery, Shyam Shah Medical College and Associated Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India

Abstract

Aim: This study aims to compare the effect of tamsulosin versus placebo in the management of lower ureteric stones.

Material and Methods: A total of 100 diagnosed patients of lower ureteric stone from the period of June 1, 2018, to May 31, 2019 (12 months), were taken for the study. The study group was divided into three groups, Group A taken tamsulosin 0.4 mg + steroids (deflozacort 6 mg), Group B taken tamsulosin 0.4 mg + dicyclomine 20 mg, and Group C dicyclomine 20 mg alone. The results of three group were compared by expulsion rate and expulsion time of stones. Chi-square test was used for calculating the effect.

Results: The mean age of Group A was 38.46 ± 10.68 years, Group B was 33.87 ± 9.62 years, and in Group C 32.94 ± 7.07 years. There was no significant relation between ages in stone expulsion. The mean calculus size in Group A was 5.93 ± 2.12 mm, Group B was 6.00 ± 2.03 mm, and Group C was 5.00 ± 2.01 mm. $P = 0.784$ was not statistically significant. In Group A, 40% of stones were on the left side and 29.7% on the right side, in Group B, 20% of stones were on the left side and 40% on the right side, and in Group C, 40% of stones were on the left side and 30.7% on the right side. $P = 0.126$ is not statistically significant. The mean time taken for stone expulsion in Group A was 5.39 ± 1.94 days, Group B was 4.75 ± 2.03 days, and Group C was 6.76 ± 1.90 days. $P = 0.006$ (<0.05) is highly statistically significant. Hence, in the present study, in Group A, 29 patients out of 33 patients, in Group B, 28 patients out of 33, and in Group C, 22 patients out of 34 patients, the stone was expelled out. $P = 0.040$ (<0.05) is highly statistically significant. There was no statistically significant difference which was found between the three groups in age, size, and side of stone.

Conclusion: The results of this study have shown a potentially important role of tamsulosin for conservative expulsive therapy of distal ureteral stones, broadening pharmacological indications rather than endoscopic treatments for the resolution of this disease. Obviously, further studies with larger number of cases are necessary to validate these promising and statistically significant results. The comparison with minimally invasive procedures in terms of cost and efficacy was useful, highlighting a predominant role of first-line pharmacological treatment, which can be easily be provided in an outpatient setting and not only at large, technologically advanced, centers. The drug tamsulosin proved to be safe and effective as demonstrated by the low incidence of side effects and the increased stone expulsion rate and reduced expulsion time. Moreover, medical expulsive therapy with tamsulosin considerably decreased the analgesic use, thereby reducing additional need for pain relief and served as an effective bridge between watch-and-wait management and surgical intervention.

Key words: Patients, Therapy, Ureteric stone

INTRODUCTION

The incidence of nephrolithiasis in industrialized country is increasing. Indeed, the number of ER admission for

ureteral colic increased 55% from 1994 to 2000.^[1] Most visit to the emergency room are secondary to distal ureteral stones smaller than 5 mm, which would be ideal candidates for the conservative management or stone expulsion therapy. The clinical management of distal ureter stone has benefited from an increased understanding of the molecular aspects of ureteral muscle. Identification of alpha-1a-adrenergic receptor as the specific subtype responsible for the muscular tone and contraction of the ureter directed the evaluation of a new line of pharmacological interventions aimed at promoting stone passage.^[2]

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Corresponding Author: Dr. Pushpendra Kumar Shukla, Department of Surgery, Shyam Shah Medical College and Associated Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India.

Pain is the main cause for hospital admissions and the site, size, and other renal factors are the key to determine further management. Smaller stones are liable to pass spontaneously with stones <5 mm having 68% chance of passing without treatment.^[3]

The transport of stones from the kidney into the bladder and their movement through the ureter is accompanied by three basic factors;

1. Spasm of smooth muscles
2. Submucosal edema and
3. Associated pain.

Determining factors for spontaneous passage of stones are their size, their configuration, and the smooth muscle activity of the ureters. In the transport of stones, the greatest obstacle is usually the terminal part of the ureters in the intramural “detrusor tunnel.” Usually, stones are 4 mm or smaller pass spontaneously, although with discomfort to the patient. Ureteral calculi of any size are often associated with renal obstruction, and care must be taken to prevent irreversible damage to the kidney whether choosing expectant or active management. In the past 20 years, the introduction of new, minimally invasive procedures such as percutaneous nephrolithotripsy, flexible ureteroscopy, extracorporeal shock wave lithotripsy, ureterorenoscopy, and laser for ureteral stones have considerably changed the historical therapy for this disease with a substantial decrease in morbidity. Pharmacologically, it is possible to treat the causes of ureteric stone retention such as edema, ureteral spasm, and infection, favoring its expulsion using drugs such as steroids, calcium antagonists, and glyceryl trinitrate. At present, alpha-1-adrenergic receptor antagonists represent the treatment of choice for lower urinary tract symptoms as shown in many randomized controlled clinical trials as well as in several case studies.^[2] Studies have also revealed that alpha-1-adrenergic receptors in ureteral smooth muscle cells are significantly higher than other adrenergic receptors. Alpha-1-adrenergic antagonists have proved to inhibit basal tone of the ureters, their peristaltic frequency, and the ureteral contractions even in the intramural tract. The study is taken up to assess the possible role of the combined alpha-1a and alpha-1d selective antagonist tamsulosin for facilitating the spontaneous expulsion of distal ureteral stones.^[2,4-11]

MATERIALS AND METHODS

The study was a prospective study and conducted in the Department of Surgery, Shyam Shah Medical College and Associated Sanjay Gandhi Memorial Hospital Rewa (Madhya Pradesh) from the period of June 1, 2018, to May 31, 2019 (12 months).

Inclusion Criteria

The following criteria were included in the study:

1. Acute ureteric colic patients of all age and gender groups
2. Suspected and diagnosed patients of lower ureteric stones
3. Ureteric stones size <10 mm in lower ureter.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with ureteral stones associated with urinary tract infection (UTI), severe and refractory pain, severe hydronephrosis, and acute or chronic renal failure
2. Patients with ureteral stones associated with a history of ureteral surgery, ureteral procedure, or urinary tract anomalies
3. Patients with ureteral stones associated with renal calculus, vesical calculus, BPH, bladder outlet obstruction, urethral calculus, and ureteric calculi size more than 10 mm
4. All ureteral stones in upper and mid ureter
5. Pregnancy associated with ureteric calculi.

All patients were received and evaluated on outpatient basis and underwent a standard evaluation by abdominal renal ultrasonography.

RESULTS

The mean age of Group A was 38.46 ± 10.68 years, Group B was 33.87 ± 9.62 years, and in Group C 32.94 ± 7.07 years. There was no significant relation between ages in stone expulsion. The mean calculus size in Group A was 5.93 ± 2.12 mm, Group B was 6.00 ± 2.03 mm, and Group C was 5.00 ± 2.01 mm. $P = 0.784$ was not statistically significant. In Group A, 40% of stones were on the left side and 29.7% on the right side, in Group B, 20% of stones were on the left side and 40% on the right side, and in Group C, 40% of stones were on the left side and 30.7% on the right side. $P = 0.126$ is not statistically significant. The mean time taken for stone expulsion in Group A was 5.39 ± 1.94 days, Group B was 4.75 ± 2.03 days, and Group C was 6.76 ± 1.90 days. $P = 0.006 (<0.05)$ is highly statistically significant. Hence, in the present study, in Group A, 29 patients out of 33 patients, in Group B, 28 patients out of 33, and in Group C, 22 patients out of 34 patients, the stone was expelled out. P value was $0.040 (<0.05)$ is highly statistically significant. There was no statistically significant difference which was found between the three groups in age, size, and side of stone [Tables 1-3].^[12,13-16]

DISCUSSION

Ureteric stones are the third most common condition of urinary system exceeded only by the UTI and pathological

Table 1: Tamsulosin arms in randomized studies on treatment of ureteral stone

| Study | Mean stone size (mm) | Expulsion rate (%) | Expulsion time | Pharmacologic regime: (tamsulosin 0.4 mg plus) | Follow-up | Side effect |
|--|----------------------|--------------------|----------------|---|-----------|-------------|
| Cervenakov <i>et al.</i> ^[14] | 5.8 | 80.1 | 3.9 days | Tramadol (50 mg), diazepam (5 mg), veral (150 mg), yellow (120 mg) | 1 week | Nil |
| Dellabella <i>et al.</i> ^[16] | 7.2 | 90 | 4.4 days | Deflazacort (30 mg), cotrimoxazole (640 mg), diclofenac (75 mg on demand) | 4 weeks | Nil |
| Autorino <i>et al.</i> ^[17] | 6.1 | 88 | 4.8 days | Tamsulosin 0.4 mg versus control | 2 weeks | Low |
| Porpiglia <i>et al.</i> ^[18] | 5.4 | 60 | 7.7 days | Deflazacort (30 mg), diclofenac (75 mg on demand) | 4 weeks | 2 |
| Yilmaz <i>et al.</i> ^[19] | 6.0 | 79.3 | 6.3 days | Diclofenac (75 mg) on demand | 4 weeks | Nil |
| Present study | | | | | | |
| Group A | 5.93 | 87.87 | 5.39 days | Tamsulosin (0.4 mg), deflazacort 6 mg), diclofenac (50 mg) on demand | 3 weeks | 2 |
| Group B | 6.0 | 84.84 | 4.75 days | Tamsulosin (0.4 mg), dicyclomine (20 mg), diclofenac (50 mg) on demand | 3 weeks | 3 |

Table 2: Expulsion rate

| Expulsion | Group A (n=33) | Group B (n=33) | Group C (n=34) | P-value |
|-----------|----------------|----------------|----------------|---------|
| Yes | 29 | 28 | 22 | 0.040 |
| No | 4 | 5 | 12 | |
| Total | 33 | 33 | 34 | |
| Rate | 87.87 | 84.84 | 64% | |

$\chi^2=6.435$, $P=0.040$ ($P<0.05$), HS

Table 3: Expulsion time

| Expulsion | Group | n | Mean time of stone expulsion (days) | Std. deviation | P-value |
|-----------|-------|-----|-------------------------------------|----------------|-----------|
| Yes | A | 33 | 5.39 | 1.94 | $P=0.006$ |
| | B | 33 | 4.75 | 2.03 | |
| | C | 34 | 6.76 | 1.90 | |
| Total | | 100 | | | |

condition of the prostate. Ureteric stones have affected humans since the earliest record of civilization. The etiology of stones remains speculative. Even after extensive research on various aspect, no definite etiological factor is known. Recurrence and its management are still a great problem, although in the past 20 years due to the development of newer method of treatment for urinary stones, it has now become possible to treat urinary stones endoscopically. Medication is available that can help to prevent recurrence of calculi to some extent. The urine routine and microscopy examination and urine culture give the information regarding the urinary tract infection in causation of calculus formation.

In the present study, the incidence of radiologically confirmed cases of ureteric stones was 6.83% from the total patients reporting in surgical outpatient department. The incidence of ureteric stones observed by Singh *et al.*^[17]

was 11.4%; Shakya *et al.*^[18] from Rewa was 2.26%, and Hughes^[19] was 6–9%. Moreover, these results were similar to the present study.

Several authors have reported that 30–50 years of age period were maximum incidence of ureteric stones occur. In a study by Shakhssalim *et al.*^[5] the mean age of ureteric stone at presentation was 41.5 years \pm 16.3 and peak incidence range was between 55 and 65 years. In the present study, the most common age group affected was between 30 and 40 years. Shakhssalim *et al.*^[5] reported in his study that male-to-female ratio was 1.38 (male: 58% and female: 42%). In the present study, male-to-female ratio was 1.6:1.4.

In a study by Jeevaraman *et al.*^[10] the incidence of lower ureteric stones is more as compared to upper ureteric stones. Moreover, these results were similar to the present study.

The symptoms of ureteric stones are burning micturition and increased frequency of urination suggestive of urinary tract infection. Pain in abdomen has a typical, intermittent, and colicky in nature with specific radiation which is diagnostic of site of stone.^[6] In the present study, most of the patient presented with flank pain (74.39%) and 33.33% presented with burning micturition (lower urinary tract symptoms).

Dellabella *et al.*^[13] found greater efficacy with tamsulosin, which was compared with phloroglucinol, a spasmolytic drug very popular in Italy. Interestingly, these authors explained the positive effect of tamsulosin, it should induce an increase in the intraureteral pressure gradient around the stone as well as decrease the frequency of peristaltic contraction in the obstructed ureter and therefore a reduction of the allogeneic stimulus. Porpiglia *et al.*^[15] compared the safety and effectiveness of nifedipine and deflazacort with those of tamsulosin and deflazacort for the treatment of distal ureteral stones. They concluded

that medical, particularly with tamsulosin, could reduce expulsion time. Yilmaz *et al.*^[16] were the first to perform a randomized comparison of three alpha-1-blocker in the treatment of distal ureteral stones. They enrolled 114 patients who received nothing, tamsulosin, terazosin, or doxazosin for as long as 1 month. All three were equally efficacious.

In the present study, the expulsion rate in the tamsulosin group was 87.87% in Group A and 84.84% in Group B which was in concurrence with other studies. In Group C, the expulsion rate was 64%. In the present study, only five cases were complaining side effects in tamsulosin group which confirms the safety and tolerability of the drug and seven cases lost follow-up. The mean stone expulsion time in Group A was 5.39 ± 1.94 days, Group B was 4.75 ± 2.03 days, and in Group C, it was 6.76 ± 1.90 days.

Diclofenac sodium is nonsteroidal anti-inflammatory drug (NSAID) drug advocate for use in painful conditions. It possesses potent analgesic properties with a fast onset and longer duration. It has already been proposed that pain relief, together with spasmolysis of the ureter supporting stone passage, can be achieved by application of an NSAID such as diclofenac.

It is our belief from above study that a conservative approach to distal ureteral stones up to 10 mm should not be proposed for longer than 2 weeks to avoid renal impairment, urosepsis, and intractable pain.

CONCLUSION

Therefore, it is possible to suggest that the effect of tamsulosin on the obstructed ureter is to induce an increase in the intraureteral pressure gradient around the stone that is an increase in the urine bolus above the stone (and consequently an increase in intraureteral pressure above the stone) as well as decreased peristalsis below the ureter (and consequently a decrease in intraureteral pressure below the stone) in association with the decrease in basal and micturition pressures even at the bladder neck.^[13] For these reasons, there would be a stronger urge to expel the stone. Furthermore, the decreased frequency of phasic peristaltic

contractions in the obstructed ureteral tract induced by tamsulosin might determine a decrease in or the absence of the algogenic stimulus, as in our study.

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