Original Article

Efficacy of Tamsulosin in the Expulsion of Lower Ureteral Calculi

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Abstract: Urolithiasis is the third most common disease of the urinary tract which is surpassed only by urinary tract infections and pathologic conditions of the prostate. It affects up to 5% of the population, with a lifetime risk of passing a kidney stone of about 8-10%.Ureteric calculi of size 4-5 mm have a 40-50% chance of spontaneous passage whereas those> 6 mm size have a <5% chance of spontaneous passage. This study was 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 in our community. All patients with ureteric colic due to radiologically proven distal ureteral stones of size 4-10 mm and planned for conservative management were included and exclusion criteria being, stone larger than 10 mm and less than 4 mm, clinical and laboratory signs of urinary tract infections (UTIs), severe hydronephrosis on ultrasound examination, co-morbid conditions such as diabetes, alteration in renal parameter, previous history of ureteral manipulation and/or surgery, multiple ureteral stones, pregnancy a and radiolucent stones. Minimum sample size was calculated to be N=40 where purposive sampling technique was used and the patients were divided into two groups; control and study groups by a lottery system. Control group were advised for high fluid intake along with analgesic (tablet Diclofenac 50 mg)/spasmolytic (tablet Hyoscine butylbromide 10mg) as on-demand. Study group were given tablet Tamsulosin 0.4mg OD in the morning, a half-hour after breakfast for a maximum period of 14 days or till the spontaneous passage of stone (whichever was earlier). Finding showed our study, 12 out of 20 patients in the control group expelled the distal ureteral stone within 2 weeks of the study, whereas 8 patients did not, with the expulsion rate of 60%. In contrast, 18 out of 20 patients in the tamsulosin group expelled the stone, with an expulsion rate of 90%. The p-value of this parameter was 0.028 which was significant. The p-value was 0.090 which was not significant, a total of 12 out of 40 patients did not use analgesics. Four patients required 200mg of diclofenac (each tablet 50mg) during the trial of 2 weeks. It is concluded that MET can be considered for uncomplicated lower ureteral calculi prior to ureteroscopy or extracorporeal lithotripsy. Tamsulosin has been found to increase the expulsion rate and decrease analgesics dose requirement. However, there is no benefit of tamsulosin in decreasing the time to expulsion. Appropriately used it may have substantial fiscal benefits by reducing the number of interventional procedures. However, this requires larger randomized controlled trials in our developing country like ours before its application in our center.

Keywords: Urolithiasis, analgesia, KUB, UTI

1. INTRODUCTION

Gradually increasing incidence rate of kidney stone is a significant concern of medical world. Genetics and/or life style e.g. stay in hot humid climate accelerate the urolithiasis – the kidney stone formation. Males are at higher risk of incidence than females; a probable impact of endocrinological differentiation. Similarly, likelihood of its occurrence maximizes at the age around 30 years. Sometimes, it is stuck up in ureter especially distal ureter; hence called as lower ureteral stone (LUS) and causes intense flank pain beside urinary obstruction. Stone removal is the only remedial step. However, unlucky sufferers especially children may face the same situation after few years [1]. This poses extra financial burden in the family and pressure on public health sector. A medical practitioner decides type of therapeutic modality for ureteral stone expulsion/removal on clinical manifestations and diagnostic findings. Medical expulsive therapy (MET) is opted for the sufferers agreed to waiting management [2]. Here, patient is free to move for daily functioning without any hindrance like hospitalization. Higher stone expulsion rate, lower health risks, cost-effectiveness, and a chance to avail minimal invasive treatment (on failure) are some of its salient features. Similarly, taking diclophenac Na – the analgesic on colic episode makes the person tension-free [3]. So, the MET successfully covers psycho-physiological dimensions of an undergoing beneficiary. Smooth muscle makes wall of the ureter. Internally, it is lined with alpha-1 adrenergic receptors particularly in lower 1/3rd portion of the ureter also called distal ureter. The receptors detect the stone and stimulate peristalsis for its passage. Otherwise, blockade of receptors (by stone) leads to spasm in stone-surrounding muscle, local edema and inflammation. Colic pain develops when peristalsis attempts to push the stone through the inflamed region. An antagonist of the receptors reverses the mechanism [4]; hence facilitates the stone expulsion. Similarly, analgesic obstructs the transmission of pain stimulus to central nervous system. So, clinicians recommend therapy in the light of stone size as well as controlled symptoms [5]. Tamsulosin is the choice of physicians for two reasons *viz*. high stone expulsion rate and short expulsion time. Many minimally invasive interventional (e.g., ESWL and ureteroscopy) as well as expectant (watchful waiting) treatment exist for the management of lower ureteric calculi. But the choice of the ideal method to be taken up largely depend on the type of equipment available, type and size of stone, needs of the patient and the skills of the surgeon[6]. The stone burden remains the primary factor in deciding the appropriate treatment for a patient with ureteral calculi [7]. Where a failed expectant treatment may well be complicated with hydronephrosis, deranged renal function or urosepsis, interventional techniques are not always free of complications and failures. Recent studies have reported excellent results relating to medical expulsive therapy (MET) for distal ureteral calculi, in terms of stone expulsion and control of ureteral colic pain, using drugs (e.g., nifedipine and prednisolone) that can modulate the function of the ureter obstructed by the stone[8].Recently, a a1A receptor blocker to be used in this regard is tamsulosin. Most of the work on the efficacy of tamsulosin in lower ureteral calculi expulsion has been done in western affluent countries with variable results. The disease spectrum in a developing country like ours, is different from that in developed countries, mainly because of delay in diagnosis, delay in investigations and lack of awareness which tend to modify the outcome in case of ureteral stones or for that matter any disease. More so, advanced interventional facilities in this part of the world are not easily available [9]. A prospective study was thus planned to compare the tamsulosin group with a control group in our setup to evaluate the efficacy of tamsulosin for lower ureteral calculi expulsion within a few days without the need for hospitalization, common endoscopic treatment or shock wave lithotripsy [10]. Urolithiasis is the third most common disease of the urinary tract which is surpassed only by urinary tract infections and pathologic conditions of the prostate. It affects up to 5% of the population, with a lifetime risk of passing a kidney stone of about 8-10%.Ureteric calculi of size 4-5 mm have a 40-50% chance of spontaneous passage whereas those> 6 mm size have a <5% chance of spontaneous passage [11]. Some calculi may arrest in the ureter producing complications such as obstruction, colic, infection, hematuria and acute renal failure. Therefore, urgent relief is to be given to these patients [12]. In the last 20years, the introduction of

new, minimally invasive procedures like percutaneous nephrolithotripsy (PCNL), flexible ureteroscopy, extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS) and laser for ureteral stones have considerably changed the historical therapy for this disease with a substantial increment in treatment costs. Currently, alpha 1-adrenergic receptor antagonists, like Tamsulosin represent the treatment of choice for lower urinary tract symptoms as shown in many randomized controlled clinical trials as well as in several cases studies. Most of the work on the efficacy of tamsulosin in lower ureteral calculi expulsion has been done in western affluent countries with variable results [13]. The disease spectrum in a developing country like ours, is different from that in developed countries, mainly because of delays in diagnosis, delay in investigations and lack of awareness which tend to modify the outcome in case of ureteral stones or for that matter any disease [14].The study was 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 in our community [15,16].

2. MATERIALS & METHODS

All patients with ureteric colic due to radio logically proven distal ureteral stones of size 4-10 mm and planned for conservative management were included and exclusion criteria being, stone larger than 10 mm and less than 4 mm, clinical and laboratory signs of urinary tract infections (UTIs), severe hydronephrosis on ultrasound examination, co-morbid conditions such as diabetes, alteration in renal parameter, previous history of ureteral manipulation and/or surgery, multiple ureteral stones, pregnancy a and radiolucent stones. Minimum sample size was calculated to be 40 using $n = z^2 p * q /d^2$.Purposive sampling technique was used and the .patients were divided into two groups: Control and Study groups by a lottery system. Control group were advised for high fluid intake along with analgesic (tablet Diclofenac 50 mg)/spasmolytic (tablet Oscine butyl bromide 10mg) as on-demand. Study group were given tablet Tamsulosin 0.4mg OD in the morning, a half-hour after breakfast for a maximum period of 14 days or till the spontaneous passage of stone (whichever was earlier).The patients were followed up with a weekly solography KUB and fortnightly X-ray KUB to determine the expulsion rate, time to expulsion and dose of analgesia used. The final evaluation was done after completion of two weeks. Successful results were defined as complete stone passage and failure was considered if the patient failed to pass the stone at the end of 14 days or experienced uncontrolled pain and/or uroseptic fever leading to hospitalization during the study period. Mean stone size, expulsion rate and analgesic dose were calculated. The data was entered into the computer using SPSS-26 and Microsoft Excel software. Collected data were analyzed with Student's t-test and Chi-square test.

3. RESULTS & DISCUSSIONS

The study comprised 40 patients. The mean age of the patient was 36.70. The youngest patient in the study was 18 years and the oldest patient enrolled was 61 years. In the age group of 20-29 years, 12 (30%) patients were noted, the maximum of the age group. The mean age of the patient in the control group was 36.15 years and in tamsulosin group was 37.25 years. The mean age of patients from the control and tamsulosin group was compared using a student t-test ($p = 0.776$) which was not statistically significant. In our study 22 (55%) were male patients and 18 (45%) were female patients. In the control group, 12 (60%) males and 8 (40%) females were involved while in the tamsulosin group 10 (50%) males and 10 (50%) females were involved. P-value was 0.525. No significant difference between the groups for sex. In this study, the mean stone size was 6.025 mm, stone size ranging from 4mm to 9mm. The maximum diameter noted was 9mm and the smallest was 4mm. A stone size of 6mm was noted most which is found in 12 patients and covered 17.5% of the total. The mean stone size in the control group was 6.125mm and in tamsulosin group was 5.900mm. The p-value was 0.603 (not significant).In our study, 45%(18) of the calculi were located in the left ureter and 55%(22) were located in the left ureter. Distribution of the stone side among the control and tamsulosin group was not significant. (p-value

=0.525)In our study, 12 out of 20 patients in the control group expelled the distal ureteral stone within 2 weeks of the study, whereas 8 patients did not, with the expulsion rate of 60%. In contrast, 18 out of 20 patients in the tamsulosin group expelled the stone, with an expulsion rate of 90%. The p-value of this parameter was 0.028 which was significant. 13 patients passed the distal ureteral stone in less than 7 days duration, 17 patients passed within 7-14 days duration while a total of 10 patients did not pass the stone in 2 weeks duration. In the control arm,5 patients passed the distal ureteral calculi in less than 7 days duration, while 7 patients passed the stone in 7-14 days and 8 patients did not pass within 2 weeks duration. In the tamsulosin arm, 8 patients passed stone in less than 7 days, 10 passed within 7-14 days duration while 2 patients in this arm did not pass. The p-value was 0.090 which was not significant. In this study, a total of 12 out of 40 patients did not use analgesics. Four patients required 200mg of diclofenac (each tablet 50mg) during the trial of 2 weeks. Two patients did not use any analgesia in Group I, while 10 patients did not use any analgesia in Group II. The p-value of analgesic requirement among the group was 0.006, chi-square was 7.619 whic0h was stat stoically significant

Table 01: Distribution of patient according to age group

Age group (years)	Frequency	Percent (%)
< 20	2	5%
20 – 29	12	30%
30 – 39	9	22.5%
40 – 49	10	25%
50 – 59	5	12.5%
60+	2	5 %
Total	**40**	**100%**

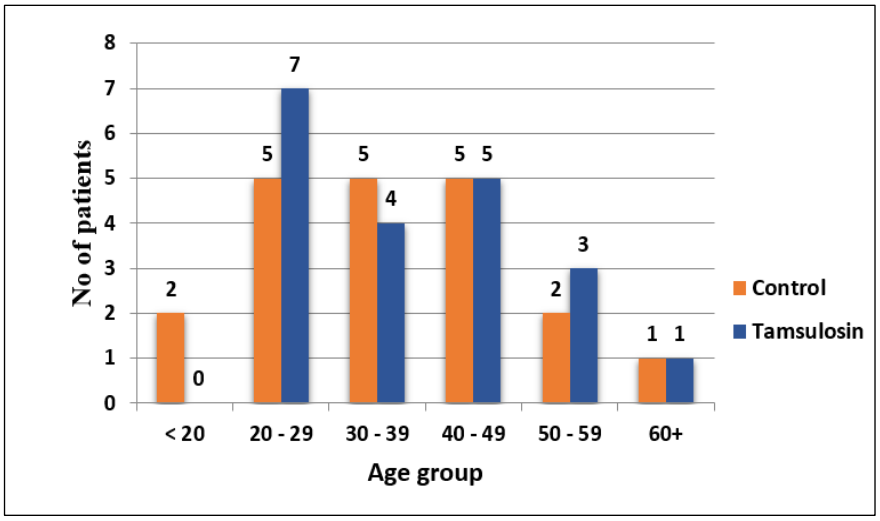

Figure 01: Distribution of patient among control & tamsulosin group

Table 02: Ureteric stone prevalence according to gender

Gender	Frequency	Percent
Male	22	55%
Female	18	45%
Total	**40**	**100%**

Table 03: Distribution of Stone size

Stone size (mm)	Frequency	Percent (%)
4	7	17.5
5	8	20.0
6	12	30.0
7	7	17.5
8	2	5.0
9	4	10.0
10	0	0.0
Total	40	100

Table 04: Mean stone size of Control and Tamsulosin group

Stone size	Control	Tamsulosin
Mean	6.150	5.900
Std. Deviation	1.5313	1.1432

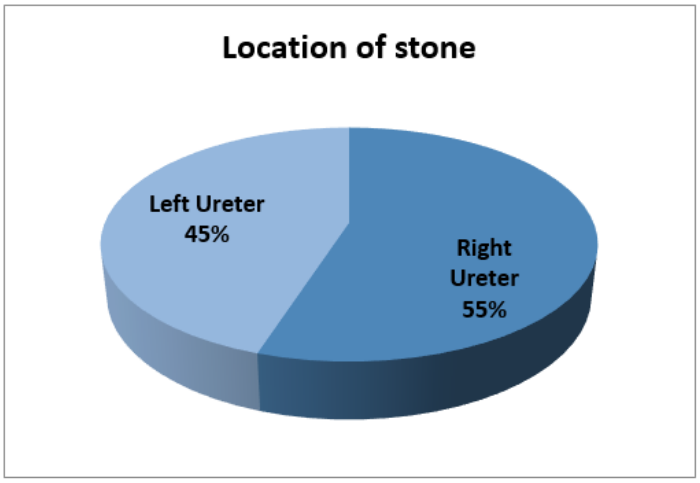

Figure 02: Stone side distribution (Right ureter/left ureter)

Table 05: Comparison of the expulsion of stone among control and tamsulosin group

Stone Expulsion	Control	Tamsulosin	Total
Yes	12 (60%)	18 (90%)	**30**
No	8 (40%)	2 (10%)	**10**
Total	**20**	**20**	**40**

Table 06: Time taken for stone expulsion

Time to Expulsion	Control	Tamsulosin	Total
Less than 7 days	5 (25%)	8 (40%)	**13 (32.5%)**
7-14 days	7 (35%)	10 (50%)	**17 (42.5%)**
Not expelled	8 (40%)	2 (10%)	**10 (25%)**

Table 07: Analgesic Dose requirement

Analgesic status	Control	Tamsulosin	Total
Not needed	2 (10%)	10 (50%)	12
Needed	18 (90%)	10 (50%)	28
Total	20	20	40

DISCUSSION

Recent advances in the urological procedures have largely diverted the management of ureteral stones to either minimal invasive methods like ESWL and ureteroscopy or watchful waiting [17]. Nevertheless, these techniques are not risk-free, are expensive and concentrated at tertiary centers and not widely available in developing countries like ours [18]. The use of a watchful waiting approach has been extended by using pharmacological therapy, which can reduce symptoms and facilitate stone expulsion.α1D receptors are found in abundance in the detrusor and the intramural part of the ureter [19]. α1A and α1D adrenergic receptors are present more densely in the distal 1/3 of the ureter (including intramural part) than other adrenergic receptors. When stimulated, they inhibit the basal tone, peristaltic wave frequency, and the ureteral contractions even in the intramural part of the lower ureter. α1 antagonists have a crucial impact in spontaneous painless elimination of the stones smaller than 8 mm located in the ureter-bladder junction [20]. In this study we used the selective alpha 1a blocker, Tamsulosin to evaluate the efficacy of tamsulosin in the expulsion of distal ureteric calculi of size ranging from 4mm to 10mm, time to expulsion and analgesic dose required over 2 weeks duration. Since there have not been enough studies in Nepal to determine the efficacy of MET using selective alpha-blocker [21], Tamsulosin, which is easily available, cheaper and used for short term duration [22]. No statistically significant difference in the age distribution of patients among the group in our study. The mean age (yrs) of the patient in the control arm was 36.15 (SD 12.270) and in the tamsulosin arm was 37.25 (SD 11.964) (p= 0.776) as shown by most of the studies [23]. Mean patient age in the control group and the tamsulosin group was 36 (SD 12.22) and 34.20 (SD 13.96) respectively (p= 0.597) in the study also observed a similar age distribution among the group. In this study out of 40 patients, 22 were male and 18 were female (55% vs 45%) comprising 12 males and 8 females in the control group and 10 each in the tamsulosin group [24]. Distribution of the patients according to gender among the group was proportional (p= 0.525). Similarly in the study distribution of patients according to gender among the group was not statistically significant (p= 0.786) Distribution of the stone size between the control and the tamsulosin was similar in our study [25]. The mean stone size in control was 6.150 (SD 1.53) and in the tamsulosin group was 5.900 (SD 1.14), (p= 0.603) which was not significant and comparable with the result found by (p = 0.359) in the study. Similar distribution was seen in the study, mean stone size of 6.17mm in the tamsulosin group and 6.03mm in control group with p = 0.724 [26].The distribution of the stone side (right/left ureter) was not significant between the two groups (p= 0.525), although the incidence was higher in the right ureter. Similarly in the study, found no statistical difference in stone location (p= 0.797). Expulsion rate of 60% in the control group and 90% in the tamsulosin group was observed in patients enrolled [27]. This showed tamsulosin significantly facilitates lower ureteral stone expulsion of size 4 to 10mm in diameter (p = 0.028) in our study. Similarly, a study conducted observed the expulsion rate of 70% in control group and 90% in the tamsulosin group statistically significant (p=0.04) [28], A study, showed the stone expulsion rate was 100% in tamsulosin group vs. 70% in the control group (statistically significant p= 0.001) might be due to use of steroid (Deflazacort) in both groups [29]. Comparing the results with the study the expulsion rate was 54.54% in the tamsulosin group and 43.75% in the control group. Here the use of tamsulosin was not significantly associated with a higher expulsion rate (p=0.384)[10]. Also in the study showed the stone

expulsion rate was not significantly different between the tamsulosin arm (86.7%) and the placebo arm (88.9%; p = 1.0) contrast to our study [30].

4. CONCLUSIONS

In our study tamsulosin showed no benefit in decreasing time to stone expulsion. Time to expulsion was less in patients in the tamsulosin group than in the control group however the difference is not statistically significant (p=0.090). Similarly in another study done by Thomas Hermans, Peter Sauermann and Kasper Rucibach the time to stone passage was not significant, the median time to stone passage was 7 days in the tamsulosin arm and 10 days in the placebo arm (log-rank test, p = 0.36). In contrary to our result in the study done by Griwan the time to stone expulsion was statistically significant in the tamsulosin group (p= 0.01).Similarly, the time to stone expulsion in the study done by Autorino et al was statistically significant (p= 0.005) in tamsulosin group. The time to expulsion was significantly higher in the tamsulosin group (p= 0.020) in the study done by Dellabella .In our study, 50% of the patients in tamsulosin did not require analgesia while 90% of patient in the control group required analgesia. The frequency of analgesic requirement was significantly higher in the control group (p = 0.006) which was concurrence with other studies done by Ye Z and Chandawat. This study found that tamsulosin was able to reduce the amount of analgesia requirement significantly (p=0.001). The mean analgesic dose (mg) used in the control group was 82.50 and in tamsulosin group mean analgesic dose used was 35.00. Griwan found the mean analgesic (mg) used in the control group of 63.33 and 30.00 in the tamsulosin group, statistically significant (p = 0.007) which is similar to our result. The mean number of diclofenac injections was 2.83 for control and 0.13 for tamsulosin group (p = 0.001) in the study conducted by Dellabella . Similar results were found in the study done by Chandawat . An average dose of analgesics in the study group was 63.7mg and in the control group was 109.2mg with statistical significance (p=0.019) in the study done by Nuraj P and Hyseni N which is comparable to our result.However in the study done by Pradhan the mean amount of analgesic (tablet diclofenac) used was 563.32mg in the tamsulosin group and 637.5mg in control group (p= 0.121), no statistical difference in analgesic requirement in tamsulosin group . Cervenakov concluded that the treatment by alpha-blockers not only lower urinary tract symptoms but also suggested that alpha-blockers potentiate the spasmoanalgesic action of drugs in standard methods of treatment. Analgesic requirement in study group in our study is due to the spasmoanalgesic action of tamsulosin. Although the time to stone expulsion was less in the tamsulosin group than that of the control group but was not found significant like most of the studies have shown, it might have been since we have taken the time to expulsion in terms of duration rather than days. Also, most of the studies were carried for 4 weeks duration.However, we see the findings of our study are similar to most other studies in that tamsulosin was found to significantly increase the expulsion rate of stone for the distal ureteric stone of size ranging from 4 to 10mm as compared to the control group. Similarly, the mean analgesic dose requirement was significantly lower in the tamsulosin group as supported by most studies. It is concluded that MET can be considered for uncomplicated lower ureteral calculi prior to ureteroscopy or extracorporeal lithotripsy. Tamsulosin has been found to increase the expulsion rate and decrease analgesics dose requirement. However, there is no benefit of tamsulosin in decreasing the time to expulsion. Appropriately used it may have substantial fiscal benefits by reducing the number of interventional procedures. However, this requires larger randomized controlled trials in our developing country like ours before its application in our center. This study found the status of adolescent friendly health service delivery in Kaski district was below the certification criteria of adolescent friendliness except indicators of organizing effective services, making conducive environment, addressing the sexual and reproductive health rights of adolescents but other standards set by ASRH implementation guideline were below the set benchmark. Most of the adolescents observed that the health facilities were located in convenient location and had conducive environment. Though adolescents perceived that

confidentiality was maintained and privacy was protected by the service providers in the facility majority of the adolescents did not have trust on providers regarding the assurance of confidentiality. The AFHFs in Kaski had conducive environment, friendly and respectful service providers but the service providers were not trained on AFHS. Almost all the health facilities had established IEC corner but community outreach programs regarding the adolescent friendly sexual and reproductive health services had not been conducted by health facilities. There was no specific clinic hours allocated to adolescents in Kaski district and the involvement of adolescents in planning and implementation of AFHS is lacking. This Study's key conclusion was that donors who have given blood five or more times have significantly lower MCV, MCH, and MCHC and much greater RDW. According to the Study's data, a significant risk of iron deficiency exists for these recurrent donors because of the prevalence of subclinical anaemia.

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