Janaki Medical College Journal of Medical Sciences (2018) Vol. 6 (2): 29-36
DOI: https://doi.org/10.3126/jmcjms.v6i02.22058

JMCJMS

**Research Article**

# Outcome of ureteric stone treatment with tamsulocin

**Rakesh Kumar Pandit[1*], Uma Shankar Gupta[2], Subash Thapa Magar[3], Vinay Kumar Jha[4]**

Janaki Medical College Teaching Hospital, Ramdaiya

[1]Associate Professor, Department of Surgery, Janaki Medical College and Teaching Hospital, Janakpur, Nepal
[2,3,4]Assistant Professor, Department of Surgery, Janaki Medical College and Teaching Hospital, Janakpur, Nepal

**ABSTRACT**

**Background and Objectives**: Though medical expulsive therapy for ureteric stones is increasingly used these days, some recent randomized controlled trials have questioned its benefit. This study evaluates the result of treatment of ureteric stones with tamsulosin.

**Materials and Methods:** This prospective study involved ultrasonographically confirmed cases of uncomplicated unilateral ureteric stones. All patients received tamsulocin 0.4 mg daily for 2 to 6 weeks. The primary end point was stone expulsion. The secondary endpoints were the use of analgesics and adverse events.

**Results**: One hundred and sixty two patients completed the study. Ninety seven patients were male and male to female ratio was 3:2. The mean age was 34.9 ± 9.8 (range: 18-71) years. The mean stone size was 6.17 ± 1.68 (range: 3.3-11.2) mm. By the end of 2, 4 and 6 weeks, cumulative stone expulsion rate was 110 (69.1%), 121 (74.7%) and 126 (77.8%) respectively. For the 49 stones of size ≤ 5 mm, the expulsion rate was 47 (95.9%) by the end of 6 weeks. The expulsion rates for stones of size > 5 - 7 mm, > 7 – 9 mm and ≥ 9 mm were 59 (85.5%), 17 (53.1%) and 3 (25%) respectively by the end of 6 weeks. Lower ureteric stones had the highest expulsion rate of 106 (87.6%) by the end of 6 weeks, and the rate was lowest for upper ureteric stones (34.6%). Ten (6.1%) patients required additional analgesics during the course of treatment. Eleven (6.8%) patients complained of mild light-headedness and dizziness which subsided in a few days.

**Conclusion:** Tamsulocin appears to facilitate expulsion of ureteric stones especially the distal ones. The benefit of tamsulocin seems to be maximum for the stones of size up to 9 mm. Further large scale randomized controlled trial should better define the real benefit and more rationale use of tamsulocin in routine clinical practice.

**Key words:** medical expulsive therapy, tamsulocin, ureteric calculi

## INTRODUCTION

Urinary stone is very common and its incidence is increasing [1]. According to the National Health and Nutrition Examination Survey 2007-2010, the prevalence of kidney stones among American adults was 10.6% among men and 7.1% among women [2]. In Saudi Arabia it affects 20% of population [3]. Ureteric stones account for about 20% of urinary calculi. With the advent of minimally invasive techniques like extracorporeal shock wave lithotripsy (ESWL) and ureteroscopic removal, there is increased tendency towards ureteric stone removal using these techniques [4]. However, these techniques are expensive and any invasive treatment has its own risk. Recurrence is another major problem; there is a 50% chance of forming a second stone within 7 years if left untreated after an initial stone treatment [5]. For these reasons, search for effective drug that would expedite spontaneous passage of ureteric stones is compelling.

Medical expulsive therapy (MET) is treatment of ureteric stones using drugs like tamsulocin to relax the smooth muscle of the ureter and facilitate stone expulsion [6]. Several randomized controlled trials and meta-analyses have been published evaluating the efficacy of tamsulosin [6-9]. In general these studies support higher stone expulsion rates after use of tamsulocin. The 2017 European Association of Urology guidelines also recommend the use of $\alpha$-blockers for MET as one of the treatment options, particularly for distal ureteral stones >5mm [10]. However, some recent randomized controlled trials reported unfavorable outcomes of MET [11-13]. These contradictory results have questioned the effectiveness of $\alpha$-blocker in the management of ureteral stones. If MET proves to be effective and safe, it would be of great help to resource poor patients in our context in the management of uncomplicated ureteric stones. There is lake of sufficient studies in Nepalese context. So this study was undertaken with an objective to evaluate the results of treatment of ureteric stones with tamsulosin.

## MATERIALS AND METHODS

This is a prospective observational study conducted at Janaki Medical College Teaching Hospital, Janakpur, Nepal between 11 June 2017 and 10 June 2018. It involved adult patients above 18 years of age with ureteric stones presenting in outpatient clinic of the Department of Surgery. Approval for the study was obtained from the Ethical Review Committee of the college.

Patients presenting in emergency department were managed for pain and investigated by ultrasonography (USG) and urine routine and microscopic examination. After relief of pain, they were referred to surgical outpatient clinic. In the surgical outpatient clinic all patients diagnosed and suspected of ureteric stones were re-evaluated in detail by relevant history and examination, and re-investigated. USG was repeated by a senior radiologist and plain kidney-ureter-bladder radiograph (X-ray KUB) was obtained the next day. Urine routine and microscopic examination, blood sugar and serum creatinine were done.

The study recruited only uncomplicated ureteric stones. Patients excluded were those with abnormal anatomy such as a horseshoe kidney, duplex system or solitary kidney; severe hydronephrosis; urinary tract infection; renal insufficiency, defined by an estimated glomerular filtration rate of <60 ml/min; bilateral ureteric stones; multiple ureteric stones; previous history of ureteric

surgery; diabetes; hypotension; concurrent use of α-adrenoceptor antagonists; known or suspected cases of pregnancy; and lactating mothers. Data recorded included demography, size of stone (maximum diameter in millimeters measured by USG) and location of stone. For the inferential statistics the stones were classified into four categories depending upon size: ≤ 5 mm, > 5 - 7 mm, > 7 – 9 mm and ≥ 9 mm.

The patients recruited for the study received tamsulosin 0.4 mg in the evening for 2 to 6 weeks. It acts by blocking α1-adrenoceptor present in the ureteric smooth muscle; thereby it decreases the force and frequency of ureteral contraction [14]. The relaxation of the ureteric muscle and weight of urine column above the ureter and gravity facilitates passage of stone. In the ureter α1-adrenoceptor has been shown to be present with highest density in the distal ureter and its relative paucity in the mid and upper ureter [15]. By inhibiting ureteral peristalsis, this may also decrease episodes of ureteric colic.

The patients were followed up at least every 2 weeks with USG, and with or without repeat x-ray KUB (depending upon whether the stone was visible in previous X-ray) until the expulsion of stone. They were followed up for maximum of 6 weeks. The stone expulsion was defined by absence of symptoms and signs of ureteric stone, history of passage of stone (if positive), absence of previously visualized stone and hydronephrosis in USG, and absence of previously visible radiopaque shadow in X-ray KUB. The primary end point was stone expulsion. The secondary endpoints were the number of attacks of pain requiring analgesics during the course of treatment, adverse events, progression of hydronephrosis and urosepsis. For the treatment of attacks of pain during MET, ketorolac with or without tramadol was used depending upon the severity of pain. Urosepsis was diagnosed by clinical features (fever with chills and rigor, and increased pain and renal angle tenderness), increase in WBC count and presence of WBC or pus cells in urine microscopic examination. The patients who developed urosepsis were advised for urine culture and sensitivity, intravenous broad spectrum antibiotic (generally ceftriaxone and tazobactum combination) was started and early intervention like ureteric stenting and ureteroscopic removal was suggested. Those who had progression of hydronephrosis and those who failed MET even in 6 weeks were also advised for early stone removal by minimal invasive techniques.

Descriptive analysis of all variables was done in MS Excel 2010. Discrete variables were reported as number (%) and continuous variables like age and stone size as a mean ± standard deviation (range). After initial recording of stone expulsion at 2 weeks, a subsequent rate of expulsion in 4 and 6 weeks was reported as cumulative values.

## RESULTS

Two hundred and thirty six patients of ureteric calculi presented in surgical outpatient clinic during the study period. A hundred and ninety eight patients met the study criteria and were advised tamsulocin. However, some patients did not come for follow up. One patient could not tolerate tamsulocin and had to discontinue the treatment. Another one later developed urosepsis and was found to be diabetic also. So he was also excluded. A hundred and sixty two patients completed the MET and had follow up record for the analysis. Ninety

seven patients were male and male to female ratio was 3:2. The mean age was 34.9 ± 9.8 (range: 18-71) years.

The stone size and location have been detailed in the table. The mean stone size was 6.17 ± 1.68 (range: 3.3-11.2) mm. Forty nine (30.2%) stones were of size ≤ 5 mm while 113 (69.8%) were larger than 5 mm. Among 12 (7.4%) stones bigger than 9 mm, one was of 11.2 mm, one of 10.3mm, two of 10.1 mm and remainders were smaller than 10 mm. Most of the stones (73.5%) were located in the lower ureter. Cumulative stone expulsion rate by the end of 2, 4 and 6 weeks were 110 (69.1%), 121 (74.7%) and 126 (77.8%) respectively.

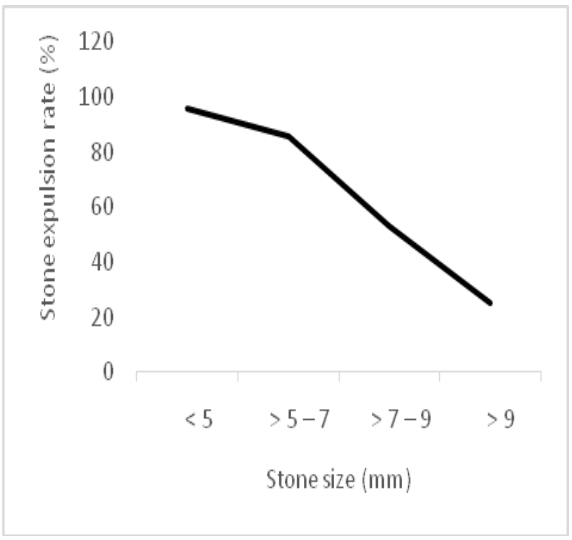


**Figure 1: Stone expulsion rate depending upon size**

**Table: Stone expulsion rate with time stratified by location and size of stone**

| | Total no. | Cumulative no. (%) of stone clearance | | |
|---|---|---|---|---|
| | | 2 weeks | 4 weeks | 6 weeks |
| **Location (ureter)** | | | | |
| **Upper** | 26 (16%) | 5 (19.2%) | 8 (30.8%) | 9 (34.6%) |
| **Mid** | 17 (10.5%) | 8 (47%) | 10 (58.8%) | 11 (64.7%) |
| **Lower** | 119 (73.5%) | 97 (80.1%) | 103 (86.5%) | 106 (87.6%) |
| **Size, average** | | | | |
| **≤ 5 mm** | 49 (30.2%) | 45 (91.8%) | 45 (91.8%) | 47 (95.9%) |
| **> 5 – 7 mm** | 69 (42.6%) | 53 (76.8%) | 57 (82.6%) | 59 (85.5%) |
| **> 7 – 9 mm** | 32 (19.8%) | 12 (37.5%) | 16 (50%) | 17 (53.1%) |
| **> 9 mm** | 12 (7.4%) | 0 | 2 (16.7%) | 3 (25%) |
| **Total** | 162 (100%) | 110 (69.1%) | 121 (74.7%) | 126 (77.8%) |

Figure 1 displays relationship between the stone size and expulsion rate. The rate of stone expulsion decreased as the size increased. Out of 49 stones of size ≤ 5 mm, 47 (95.9%) passed out and majority (91.8%) did so within 2 weeks. Two additional stones passed after 4 weeks of MET. Among 101 stones larger than 5 mm and up to 9 mm, 76 (75.2%) stones passed out by the end of 6 weeks. Among the stones larger than 9 mm, one stone of size 10.1 mm and 2 stones smaller than 10 mm passed out. All these 3 stones passed out after 2 weeks of MET. The smaller stones tended to passed out during the earlier course of MET, while the larger stone tended to pass out during the later course of MET. Figure 2 displays relationship between the location of stone and expulsion rate. The stone expulsion rate increased as

the location of stone moved from upper to lower ureter. Among the lower ureteric stones, 106 (87.6%) passed out while among the upper ureteric stones only 9 (34.6%) passed out. Most of the lower ureteric stones passed out within two weeks of MET. However, in the upper ureter by the end of second week of MET only 5 (19.2%) stone passed out. This rate increased to 9 (34.6%) by the end of 6 weeks.

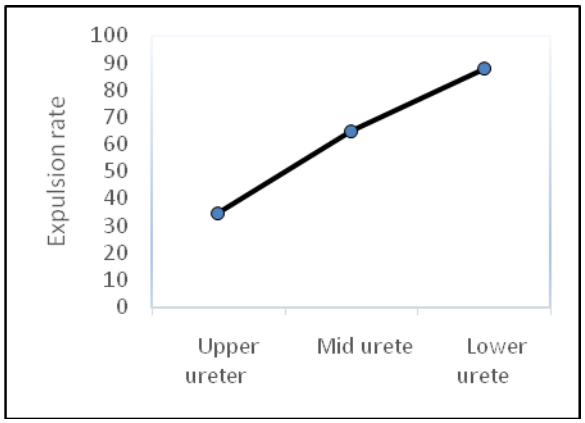


**Figure 2: Stone expulsion rate depending upon location in ureter**

After the management of initial acute attack, 10 (6.1%) patients required analgesic during the course of MET. Eleven (6.8%) patients complained of mild light-headedness and dizziness which subsided after an initial few days. Among the patients who passed stone 11 male patients and one female patient mentioned transient retention of urine followed by spontaneous relief over a few minutes to a few hours. In 3 patients the stone got impacted at fossa navicularis which were removed through the meatus. One patient required cystoscopy stone removal for stone impacted in prostatic urethra.

## DISCUSSION

A ureteric stone may or may not pass out spontaneously. When it does not pass out and obstructs the ureter for long, it can lead to complications like loss of renal function and urosepsis. So these stones need to be out either spontaneously or by using some invasive techniques like ureteroscopy. So far spontaneous expulsion is concerned many factors such as stone size, type, location and anatomy of the urinary tract influence this process. Apart from these factors time is another important factor. Some stones may pass early while the other may take a bit longer. But waiting for long time increases the risk of complications. Additionally failure to pass out spontaneously unnecessarily causes loss of work. Thus came into concept of MET which is intended for early and increased chance of stone expulsion. A recent study by Ye et al demonstrated that use of tamsulocin causes early passage of stone [7]. However, we have not studied this aspect because of less frequent follow up of patients.

An important factor that determines the likelihood of stone expulsion is the size of stone. A small ureteric stone may pass out spontaneously. In a meta-analysis Preminger et al found that spontaneous passage rates were 68 and 47% for ureteral stones less than 5 mm and 5 to 10 mm, respectively. Use of α-1 blockers resulted in 29% absolute increase in stone passage rate which, compared to control, was statistically significant [16]. However, a recent multicenter, randomized, double-blind, placebo-controlled trial by Ye et al revealed no effect of tamsulocin for stones ≤ 5 mm. The Stone expulsion rate was 88% for tamsulocin group and 87% for placebo group, and the difference was not statistically significant ($p = 0.5$) [7]. Compared to the report of Preminger et al, spontaneous passage rate in the report of Ye et al is much higher. All of our patients received tamsulocin and stone expulsion rate for size ≤ 5 mm was comparable to that of Ye

et al by the end of 4 weeks. Higher expulsion rate in our study was noted when tamsulocin was given for longer duration. Jayawardene et al, in a report from Srilanka, revealed that all patients in their study (n=67) with stones less than 5 mm passed out with MET over 12 weeks duration of tamsulocin therapy [17].

As the size of stone increases the expulsion rate decreases. Coll et al in their study did not use MET and reported that ureteral stones of 5 mm had 75% chance of spontaneous expulsion, whereas for 5–7 mm, 7–9 mm, and > 9 mm stones spontaneous expulsion rates were 60%, 48%, and 25%, respectively [18]. These rates were higher for stones in the present study using MET. The difference was more pronounced for smaller stones, and narrows as the size of stone increased. Jayawardene et al reported 98 (90%) percent stone expulsion after 12 weeks of MET for stones ≥ 5 mm [17].

Some studies reported unfavorable outcome of MET [11,12]. A recently published study by Pickard et al reported no benefit of MET on the 28-d expulsion rate of ureteral stones, specifically distal ureteral stones questioning the therapeutic application of MET. They compared the effectiveness of tamsulosin, nifedipine, and placebo and the average stone sizes on the rate of expulsion were 4.6, 4.5, and 4.5 mm for the tamsulosin, nifedipine, and placebo groups, respectively [12].

However, this study was not powered to evaluate the effectiveness of MET for stones > 5 mm. For stones ≤ 5 mm Ye et al also questioned the benefit of MET, but revealed benefit of MET for a stone size of > 5 mm [7]. In our study also the mean stone size was > 5 mm. Another important factor that influence the spontaneous expulsion is the location of stone. Coll et al revealed that the spontaneous expulsion rates, without MET, were 48%, 60%, and 75% depending on whether the stones were located in the proximal, mid or lower ureter respectively [18]. Jayawardene et al revealed that the success of MET significantly improved when the distance to travel along the ureter for the stone was less. Expulsion rate with MET was 47.6%, 82.3% and 94.1% for upper, mid and lower ureteric stones respectively [17].

Our study also demonstrated the increasing expulsion rate with more distal location of the stone. In a double blind, randomized, placebo controlled trial, Ye et al tamsulosin results in a higher stone expulsion rate than the placebo (86% vs 79%; $p < 0.001$) for distal ureteral stones [20]. This is comparable to results of our study (86.5%). The expulsion rate was lowest for the upper ureteric stones. Several other RCTs and meta-analysis have revealed significant increase in stone passage especially of distal ureteric stone with tamsulocin [6-9].

A most plausible explanation for this differential effect of tamsulocin is that highest concentration of $\alpha$1-adrenergic receptors is found in the distal ureter, therefore having the largest potential for tamsulocin in the lower ureteric stones [19]. However the role of $\alpha$1-blocker in the expulsion of upper ureteric stone seems to be less obvious [17]. This might be the reason for the low expulsion rate of the upper ureteric stone.

A noticeable finding in the result of upper ureteric stones is that most stones passed during the later course of MET compared to smaller stones. This finding may have implication that if one waits for longer period, chances of spontaneous expulsion increases. Jayawardene et al also revealed that 25 % of

upper ureteric stones passed in first 6-weeks, while remaining 75% did so in the next 6-weeks [17].

Ye et al reported the rate of side effects in patients receiving tamsulocin to be 6.7%. This rate was higher than placebo in their study however, the difference was not statistically significant [7]. Thus they concluded tamsulocin to be safe in the MET of ureteric stone. The incidence of side effects in patients receiving tamsulocin in this study is comparable to that of our study (6.8%). However, the proportion of patients requiring analgesic is greater in our study (6.1%) compared to that of Ye et al (2.3%).

By the time patients present to hospital most ureteric stones are found in the lower ureter. Erturhan et al reported the proportion of lower ureteric stone to be approximately 70% [20]. Jayawardene et al reported this incidence as 56.3%. Further, in the latter study 82.7% of stone were of size ≤ 10 mm [17]. In our study also, most stones were lower ureteric and 92.6 % were ≤ 9 mm. These findings and the fact that tamsulocin is effective mostly on lower ureteric and medium sized stones has implication on the importance of its benefit in MET.

This study is not without limitations. First, this study does not involve placebo group. So it is difficult to conclude real benefit of tamsulocin based on this study alone. Secondly, the study included only those cases who had USG evidence of ureteric stone. As CT scan was not done in suspected cases of ureteric stone not detected by USG, there is possibility that some mid ureteric stone might have been missed. This might be a reason for lesser number of patients of mid ureteric stone in our study; mid ureteric stones are relatively difficult to be diagnosed by USG. Thirdly, fate of patients after 6 weeks of failed MET, but non-progression of hydronephrosis is not discussed. Forth, we had follow up record of patient at less frequent intervals. So average expulsion time was not calculated. Other studies suggest that the tamsulocin expedites the stone expulsion compared to placebo [Ye et al]. Porpiglia et al [16], Lu et al [17], Islametal [18] and Gandhi et al [19] reported average expulsion times 7.9, 4.0, 7.9 and 9.0 days respectively with tamsulosin.

## CONCLUSION

From our study it appears that the use of tamsulocin facilitates expulsion of ureteric stones especially the distal ones. The benefit of tamsulocin seems to be maximum for the stones up to size 9 mm and less for stones larger than 9 mm. Though smaller stones pass out early, larger stones tend to pass out relatively later. Further large scale randomized controlled trial with further stratification of ureteric stones by location and size, should better define the real benefit and more rationale use of tamsulocin in routine clinical practice.

## ACKNOWLEDGEMENT

Authors would like to thank Department of surgery, JMCTH, Ramdaiya for their consistent support towards this study.

## AUTHOR'S CONTRIBUTION

**RKP-** conception of study design and inscription of first draft and final revision of manuscript; **USG-** patient selection and data acquisition and manuscript writing; **STM-** Data collection and patient selection; **VKJ-** collecting the patient information and data collection

## SOURCE OF SUPPORT

No any financial support or sponsorship.

## CONFLICT OF INTEREST

There is no conflict of interest towards this publication.

## REFERENCES

1. Romero V, Akpinar H, Assimos D. Kidney stones: A global picture of prevalence, incidence, and associated risk factors. Rev Urol 2010; 12:e86–e96.
2. Scales CD Jr, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol 2012; 62:160–5.
3. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. J Nephrol 2000; 13 (Suppl 3):45–50.
4. Drake T, Grivas N, Dabestani S et al. What are the benefits and harms of ureteroscopy compared with shock-wave lithotripsy in the treatment of upper ureteral stones? A systematic review. Eur Urol 2017; 72(5):772-786.
5. Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. Miner Electrolyte Metab 1985; 11:267–9.
6. Somani BK, Aboumarzouk O, Traxer O, Baard J, Kamphuis G, de la Rosette J. Medical expulsive therapy for ureteral stones: where do we go from here? Nat Rev Urol 2016; 13:608–12.
7. Ye Z, Zeng G, Yang H et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. European Urology 2018; 73:385–391.
8. Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol 2009; 56:455–71.
9. Hollingsworth JM, Canales BK, Rogers MA et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ 2016; 355:i6112–23.
10. Turk C, Knoll T, Seitz C et al. Medical expulsive therapy for ureterolithiasis: the EAU recommendations in 2016. Eur Urol 2017; 71:504–7.
11. Hermanns T, Sauermann P, Rufibach K et al. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. Eur Urol 2009; 56:407–12.
12. Pickard R, Starr K, MacLennan G et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo controlled trial. Lancet 2015; 386:341–9.
13. Furyk JS, Chu K, Banks C et al. Distal ureteric stones and tamsulosin: a double-blind, placebo-controlled, randomized, multicenter trial. Ann Emerg Med 2016; 67:86–95e2.
14. Morita T, Wada I, Saeki H et al. Ureteral urine transport: changes in bolus volume, peristaltic frequency, intraluminal pressure and volume of flow resulting from autonomic drugs. J Urol 1987; 137:132–5.
15. Sigala S, Dellabella M, Milanese G et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn 2005; 24:142–8. [3 ] [15]
16. Preminger GM, Tiselius HG, Assimos DG et al. Guideline for the management of ureteral calculi. Eur Urol 2007; 52:1610–31.
17. Jayawardene MD, Balagobi B, Ambegoda ALAMC et al. Outcome of uncomplicated ureteric calculi managed with medical expulsive therapy in the outpatient clinic of a urology unit in Sri Lanka. BMC Res Notes 2017; 10:636. DOI 10.1186/s13104-017-2974-1
18. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. AJR Am J Roentgenol 2002; 178:101–103.
19. Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. Int J Urol 2007; 14:749–53. [32] [19]
20. Erturhan S, Erbagci A, Yagci F, Celik M, Solakhan M, Sarica K. Comparative of efficacy of use of tamsulosin and/or tolterodine for medical treatment of distal ureteral stones. Memorial Hospital, Istanbul, Turkey. Urology 2007; 69:633–636.

***Correspondence to:***
**Dr. Rakesh Kumar Pandit**
Associate Professor,
Department of Surgery,
Janaki Medical College and Teaching Hospital, Janakpur, Nepal
**Email**: rakeshkp1@yahoo.com