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GENERAL UROLOGY

Original Article

Prospective randomized trial comparing the efficacy of tamsulosin and tamsulosin combined with nifedepine for the management of lower ureteral stones

Alt üreter taşı tedavisinde tamsulosin ile nifedepinle kombine tamsulosininin etkinliğini karşılaştıran prospektif randomize çalışma

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ABSTRACT

Objective: To evaluate the efficacy of tamsulosin compared to the combination of tamsulosin with nifedepine for the management of lower ureteral calculi less than 1 cm in size.

Material and Methods: This study included 150 patients with stones <1 cm in size located in the lower ureter. The patients were divided into three groups. Group 1- Patients (N-50) received 0.4 g tamsulosin once daily. Group 2- Patients (n-50) received 0.4 g tamsulosin once daily with cap. nifedepine (5 mg) twice daily. Group 3- Patients (n-50) received placebo treatment (control group). The patients received an injection of diclofenac/injected hyoscine butyl bromide as necessary. Follow-up was performed at 6 weeks.

Results: The average stone size was similar among the three groups (6.40, 6.75 and 6.25 mm in Groups 1, 2 and 3, respectively). After treatment with medication, stone expulsion was noted in 37 of 50 patients in group 1 (74%), 43 of 50 patients in group 2 (86%), and 15 of 50 patients in group 3 (30%). The average time required for expulsion of the stone in groups 1, 2, and 3 was 28.5 days, 20.5 days, and 37.7 days, respectively. The results were superior in group 1 and group 2 compared to group 3 (placebo). A significantly higher rate of expulsion was noted in group 2 compared to group 1 (12% more expulsion compared to group 1). However, postural hypotension was noted in 3 patients in group 2 but was not so severe as to require dropping these patients from the study.

Conclusion: Study reveals that lower ureteral stones less than 1 cm. can be effectively managed by medical management. We have found that for this purpose combination therapy by tamsulosin with nifedipine is more effective than monotherapy by tamsulosin.

Key words: Lower ureteral calculus; tamsulosin; tamsulosin with nifedepine.

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ÖZET

Amaç: Boyutu 1 cm'den az olan alt üreter taşının tedavisinde tamsulosine kıyasla nifedepin ile tamsulosin kombinasyonunun etkinliğini değerlendirmek

Gereç ve yöntem: Alt üreterinde boyutu <1 cm taşlar bulunan 150 hasta çalışmaya dahil edildi. Hastalar 3 gruba ayrıldı. Grup 1-Hastalara (n=50) günde bir kez 0.4 g tamsulosin verildi. Grup 2-Hastalara (n=50) günde bir kez 0.4 g tamsulosin ile günde iki kez nifedepin kapsül (5 mg) verildi. Grup 3-Hastalara (n=50) plasebo tedavisi uygulandı (kontrol grubu). Gerektiğinde hastalara diklofenak/hiyosin bütilbromür enjeksiyonu yapıldı. 6 haftalık takip yapıldı.

Bulgular: Ortalama taş boyutu, üç grup arasında benzerdi (Grup 1, 2 ve 3'te sırasıyla 6.40, 6.75 ve 6.25 mm). İlaçla tedavinin ardından, Grup 1'deki 50 hastanın 37'sinde (%74), Grup 2'deki 50 hastanın 43'ünde (%86) ve Grup 3'teki 50 hastanın 15'inde (%30) taş düşürme görüldü. Taş düşürme için gereken ortalama zaman Grup 1, 2 ve 3'te sırasıyla 28.5, 20.5, ve 37.7 gün idi. Grup 1 ve 2'deki sonuçlar Grup 3'e (plasebo) kıyasla üstündü. Grup 1 ile karşılaştırıldığında Grup 2'de anlamlı olarak yüksek taş düşürme oranı kaydedildi (Grup 1'e kıyasla %12 daha fazla taş düşürme). Bununla birlikte Grup 2'de 3 hastada postüral hipotansiyon görüldü ancak bu hastaları çalışmadan çıkarmayı gerektirecek kadar ciddi değildi.

Sonuç: Çalışma 1 cm'den küçük alt üreter taşların tıbbi yaklaşım ile etkili bir biçimde tedavi edilebildiğini ortaya koymaktadır. Bu amaçla nifedepin ile tamsulosin kombinasyon tedavisinin tamsulosin ile monoterapiden daha etkili olduğunu bulduk.

Anahtar sözcükler: Alt üreter taşı; tamsulosin; nifedepin ile tamsulosin.

Medical management of lower ureteral stones with tamsulosin and combined treatment with tamsulosin and nifedepine achieves a high rate of stone expulsion, thereby reducing the need for ureteroscopy.

Ureteric colic due to urolithiasis is the most common problem encountered in the emergency department. Interventional (e.g., ESWL and ureteroscopy) and expectant (watchful waiting) treatment are the typical approaches used to manage lower ureteral calculi. Selection of the ideal depends largely on the type of equipment available, the type and size of stone, the needs of the patient and the skill of the surgeon.[1] The two factors that appear to be most useful in facilitating stone passage are an increase in hydrostatic pressure proximal to a calculus and relaxation of the ureter in the region proximal to the stone.

Rationale for the watchful waiting approach has been extended with the use of pharmacologic therapy in the form of α - adrenergic blockers to provide relief from colic and facilitate expulsion.[2-4] As Ca++ is needed for development of the action potential and contraction of the ureter, agents that block the movement of Ca++ in the cell would be expected to depress ureteral function. This phenomenon is known as the spasmolytic effect, and nifedepine is one such agent.

Studies have revealed the presence of α_1 – adrenergic receptors in the ureter. The density of α_1 adrenergic receptor s was significantly greater in lower ureter. α_1 adrenergic antagonists have been shown to inhibit basal tone, peristaltic frequency, and ureteral contractions in the intramural part of the ureter.[4] Recent studies have reported excellent results with the expulsion of distal ureteral calculi and the control of ureteric colic with medical management.

Materials and methods

A prospective randomized trial was conducted in the Department of Urology, North Bengal Medical College, on an Out Patient Department (OPD) basis from January 2006 to December 2010. The study was approved by the institute's ethics committee.

In total, 150 patients who presented with stones <10 mm, located in the distal ureter (in an area extending from the lower border of the S - 1 joint to the ureterovesicular junction) were included in the study. The exclusion criteria included: desire to treat colic, gross back pressure changes, recurrent urinary tract infection, ischemic heart disease, history of previous surgery in the distal ureter, and acute renal failure. Patients were evaluated by performing urinalysis, urine culture and sensitivity, complete hemogram, serum uric acid, USG in the KUB region, and intravenous urography.

In total, 150 symptomatic cases of lower ureteral calculus were divided randomly into study group 1, study group 2 and control group 3.

Group 1-The 50 patients in this group received tamsulosin 0.4 mg OD in the morning after breakfast until expulsion of the stone or for 6 weeks, which ever was earlier. An analgesic (diclofenac tab/injection) and an anti-spasmodic (hyoscine butyl bromide) was administered. Patients were also advised to drink plenty of fluids.

Group 2-The 50 patients in this group received tamsulosin 0.4 mg OD in the morning after breakfast and nifedepine (5 mg) twice daily in the morning and evening. Analgesic and anti-spasmodic treatments were also administered as needed. Patients were also advised to drink plenty of fluids.

Group 3-The 50 patients in this group received analgesic and anti-spasmodic treatment as needed. Patients were also advised to drink plenty of fluids.

Patients were followed up weekly with direct X-ray of the KUB region and ultrasonography of the KUB region. Data regarding time to pass the stone, the size of stone, the need for analgesic and anti-spasmodic treatments, as well as the number of colic episodes experienced were evaluated (Table 1).

Results

In total, 150 patients were included in the study. They were randomized to 3 groups that exhibited no significant difference in terms of age, sex, and stone size (Table 1). Spontaneous stone expulsion was noted in 37 of 50 patients in group 1 (74%), 43 of 50 patients in group 2 (86%), and 15 of 50 patients in group 3 (30%). A significant difference was noted for group 1 and group 2 compared to group 3 with respect to stone expulsion. The rate of spontaneous stone expulsion differed significantly between group 1 and group 2: 74% in group 1 and 86% in group 2. The average time to stone expulsion was 28.5 days in group 1, 20.5 days in Group 2 and 37.7 days in group 3. The time to

Table 1. Profile of the Study

	Group 1 Treated with tamsulosin	Group 2 Treated with tamsulosin with nifedipine	Group 3 Placebo
Patient No.	50	50	50
Sex: Male	39	40	37
Female	11	10	13
Mean Age (years)	32.7	36.4	39.2
Mean Stone Size (mm)	6.40	6.75	6.25
Mean Period for Stone Passage (Days)	28.5	20.5	37.7
Spontaneous Passage of Stone (%)	74%	86%	30%

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stone expulsion was significantly shorter in group 1 and group 2 compared to group 3.

Regarding side-effects of the medication, patients noticed nausea, vertigo, postural hypotension, retrograde ejaculation, headache, and gastritis acidity. These symptoms were noted only in group 1 and group 2. The rates of complication were similar in group 1 and group 2. Only 3 patients in group 2 experienced initial moderate postural hypotension, vertigo and headache. The intensity of these side effects subsequently decreased such that no patient had to drop out of the study. On an average 2-4 episodes of ureteric colic was noted in patients of each of all three groups.

In group 1, 22 out of 50 patients received analgesic diclofenac sodium (injection/tab.). On average, the medication was administered 2.4 times in each patient.

In group 2, 27 out of 50 patients required analgesic diclofenac sodium±anti-spasmodic (hyoscine butyl bromide) (injection/tab) treatment. On average, the medication was administered 2.7 times in each patient.

In group 3, 30 out of 50 patients required analgesic diclofenac sodium/hyoscine butyl bromide. On average, the medication was administered 2.9 times in each patient.

There was no significant difference between group 1 and group 2 regarding the number of episodes of ureteric colic and the need for an analgesic±anti-spasmodic. The requirement was slightly higher in group 3.

Discussion

Factors that affect the spontaneous passage of calculi are[1] the size and shape of stone (Ueno et al., 1977),[2] intrinsic areas of narrowing within the ureter,[3] ureteral peristalsis,[4] hydrostatic pressure of the column of urine proximal to the calculus (Sivula and Lehtonen 1967),[5] edema, inflammation and spasm of the ureter at the site at which the stone is lodged (Holmlund and Hassler 1965).

Two factors that appear to be most useful in facilitating stone passage are an increase in hydrostatic pressure proximal to the calculus and relaxation of the ureter in the region of the stone.

In summarizing the literature, the authors of the 1997 AUA ureteral stone guidelines reported that 71% to 100% of distal ureteral stones less than 5 mm in size passed spontaneously, whereas 25% to 46% of distal ureteral stones from 5 mm to 10 mm in size passed spontaneously.[6] There is a roughly linear relationship between stone size and the likelihood of spontaneous passage, with one study reporting passage rates of 87%, 72%, 47% and 27% for stones measuring 1 mm, 4 mm, 7 mm and 10 mm, respectively, as determined by CT scans.

A recent meta-analysis considered all randomized controlled trials in which calcium channel blockers or alph-blockers were used to treat ureteral stones, with 691 patients in nine clinical trials in the final meta-analysis.[7] Mean stone size ranged from 3.9 to 7.8 mm. In all but one study, calculi were found in the distal ureter. The treatment regimen included an alpha blocker alone in five studies (including tamsulosin in four), tamsulosin with corticosteroids in one, nifedepine alone in one and nifedepine with corticosteroids in three. Typical doses included tamsulosin 0.4 mg daily, terazosin 5 mg daily, doxazosin 4 g daily and nifedepine slow release 30 mg daily.

Overall, there was a 65% greater likelihood of stone passage in the treated patients. In two published comparisons of tamsulosin and nifedepine, tamsulosin tended toward superiority over nifedepine in terms of the rate of stone passage, time to stone passage and reduced narcotic use in one study. The trend was significant with respect to these parameters in the a second study examined. Steroids provide a slight added benefit but do not appear to be as important as the alpha- or calcium channel blocker.[8]

In a comparative study between tamsulosin versus alfuzosin for the treatment of lower ureteral stones, 87 patients were divided in 3 groups. Group 1 received tamsulosin 0.4 mg once daily. Group 2 received alfuzosin (10 mg) once daily. Group 3 received a placebo. Spontaneous expulsion of the stone was observed in 86.2%, 76.6% and 50% of the patients in groups 1, 2, and 3, respectively.[9]

Spontaneous expulsion of lower ureteral stones was noted in 90% of patients treated with naftopedil (50 mg) once daily compared to 26.7% of the patients treated with placebo.[10]

Ureteral calculus can lead to urinary tract infection, hydroureteronephrosis and renal function deterioration. In case of complete ureteral obstruction by calculus, signs of kidney damage will appear within 3-4 weeks. We extended our study to 6 weeks: weekly blood biochemical analysis, USG of the KUB region, and urinalysis were used to monitor renal functional status as well as the progress of stone movement. The likelihood of spontaneous expulsion can be enhanced by extending the trial time slightly.

The rationale for using alpha-blockers is based on the presence of large numbers of alpha-adrenoreceptors in the distal ureter. The stimulation of alpha-receptors increases the force of ureteral contraction and the frequency of ureteral peristalsis, whereas the inhibition of alpha- adrenoreceptors has the opposite effect. These blockers inhibit basal ureteral tone and peristaltic frequency and decrease the intensity of ureteral contraction. The likely mechanism for the effect of alpha-blockers on stone passage is a reduction in the force of ureteral spasm, which

increases pressure proximal to the stone and relaxes the ureter at the site of and distal to the calculus. Ca++ channel blockers help to reduce ureteral spasm at the site of the stone, which facilitates expulsion of the stone.

Conclusion

We investigated uncomplicated distal ureteral calculus before any intervention (URS/ESWL). The results showed that medical management with both tamsulosin and the combination of tamsulosin with a Ca++ channel blocker is significantly superior to placebo in facilitating stone expulsion and providing relief from pain. The combination of tamsulosin with a Ca++ channel blocker was superior to the use of tamsulosin alone.

Conflict of interest

No conflict of interest was declared by the authors.

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