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International Journal of Current Research
Vol. 9, Issue, 11, pp.61523-61526, November, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A PROSPECTIVE STUDY ON MEDICAL EXPULSIVE THERAPY FOR DISTAL URETERAL STONES

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ARTICLE INFO

Article History:
Received 23rd August, 2017
Received in revised form
16th September, 2017
Accepted 08th October, 2017
Published online 30th November, 2017

Key words:
Tadalafil;
Tamsulosin;
Ureteral calculi.

ABSTRACT

Urolithiasis is one of the most common diseases of the urinary tract. Ureteral stones account for 20% of the calculi in urolithiasis and about 70% of ureteral stones are present in the distal third of the ureter at the time of presentation. A conservative approach through medical expulsive therapy has now become an established treatment modality that employs various drugs acting on the ureter by different mechanisms.

Aim of the study: To compare the safety and efficacy of tamsulosin and tadalafil as medical expulsive therapy for distal ureteral stones

Materials and Methods: This prospective study was conducted at the Institute of Urology, Rajiv Gandhi government General hospital, Chennai, over a period of 12 months, from October 2016 to September2017 in 100 patients with distal ureteral stones sized 5 to 10 mm. Patients were randomly divided into 2 groups: group A received tamsulosin 0.4 mg and group B received tadalafil 10 mg at night for 10 days. Stone expulsion rate, age group, sex ratio, number of ureteric colic episodes, analgesic requirements, and adverse drug effects were noted in both groups.

Observations and results: Altogether 100 patients, 50 in group A and 50 in group B, were enrolled in the study. The patients' average age was 46.5 years, and the male-to-female ratio was 3.3:1. Demographic profiles, stone size, and baseline investigations were comparable between the 2 groups. Although the stone expulsion rate was significantly higher in the tadalafil group than in the tamsulosin group (53% vs. 47%), this difference was not statistically significant. There were no serious adverse effects.

Conclusion: Tadalafil has a significantly higher stone expulsion rate than tamsulosin when used as a medical expulsive therapy for distal ureteral stones sized 5–10 mm. Both drugs are safe, effective, and well tolerated with minor side effects.

Citation: Hemalatha Krishnasamy, 2017. A prospective study on medical expulsive therapy for distal Ureteral stones", *International Journal of Current Research,* 9, (11), 61523-61526.

INTRODUCTION

Urolithiasis is one of the most common diseases of the urinary tract. The lifetime prevalence of urinary stones is around 1% to 15%, and the peak age of incidence is at 30 years. Men are affected 2 to 3 times more often than women. Ureteral stones account for 20% of the calculi in urolithiasis and about 70% of ureteral stones are present in the distal third of the ureter at the time of presentation. Ureteral stones induce ureteral spasms that interfere with stone expulsion. It has been established that the urinary smooth muscles contain α-adrenergic receptors that facilitate contraction, leading to renal colic and ureteric spasms in the presence of a stone. Stones lead to spasmodic contraction of these smooth muscles, which prevent expulsion due to dis-coordinated contractions and eventually stasis. Furthermore, reactive inflammation caused by the stone will promote mucosal oedema, increasing stasis, which may lead to obstruction.

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Thus, reducing these spasms while maintaining normal peristaltic activity, can facilitate stone expulsion. Almost 50% of ureteral stones will pass spontaneously over time and stone size is the key factor for success. Usually, stones smaller than 5 mm are expected to pass spontaneously. Whereas, only 20% of stones larger than 8 mm will pass. Improvements in minimally invasive procedures in the last few decades have considerably changed the treatment of ureteral stones, but such procedures are not free of risks and are costly as well. A conservative approach through medical expulsive therapy has now become an established treatment modality that employs various drugs acting on the ureter by different mechanisms.

MEDICAL EXPULSIVE THERAPY

Alpha-blockers

Alpha-1A adrenoreceptors are a principal contributor in phenylephrine-induced ureteral contraction in the human isolated ureter. The role of alpha-blockers in medical expulsive therapy has been well described. Current best practice guidelines recommend alpha-blockers for the expulsion of

distal ureteral stones. Meta-analyses have demonstrated that patients treated with alpha-blockers are more likely to pass stones with fewer episodes of colic. Both the European (EAU) and American Urological Associations (AUA) outline the role of alpha-blockers as a viable option in a select patient population who are comfortable with the approach and where there is no role for immediate surgical stone removal. Tamsulosin has been the most studied alpha-blocker in medical expulsive therapy. However, a randomized control trial by Yilmaz and colleagues demonstrated that tamsulosin, terazosin, and doxazosin were equally effective in distal stone expulsion in comparison to the control group. The use of silodosin, as a substitute for tamsulosin, has received increasing attention. The most common side effect reported was transient hypotension at 3.3% to 4.2%.

Calcium channel blockers

Calcium channel blockers and their role in medical expulsive therapy continue to be explored. Nifedipine is the only calcium channel blocker that has shown some benefit in stone expulsion. Studies have indicated that nifedipine can be effective in reducing renal colic, while improvement in stone expulsion rate has been minimal. Alpha-blockers have been described to be significantly better than nifedipine in facilitating stone passage and relieving renal colic. As a result, the most recent EAU guidelines do not recommend calcium channel blockers as a monotherapy for medical expulsive therapy**.** However, it may be safely used in conjunction with alpha-blockers in the appropriate patient population as side effects have been found to be insignificant.

Phosphodiesterase-5 inhibitors

A novel topic in medical expulsive therapy is the utilization of PDE5 inhibitors in stone expulsion. PDE5 inhibitors act by a nitric oxide/cyclic guanosine monophosphate (cGMP)-signaling pathway, resulting in increased levels of cGMP, leading to smooth muscle relaxation in the ureter. Relaxing effects of ureteral muscle tension have been observed in patients receiving vardenafil, sildenafil, and tadalafil. Tadalafil has the longest duration of action (~36 hours) among the current PDE5 inhibitors. Although tadalafil has been used in the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia, its use in for medical expulsive therapy ureteral stones is very limited.

Corticosteroids

The use of corticosteroids as a therapeutic option in distal stone expulsion has been discussed in the literature. A number of studies have found favourable results with the use of steroids in stone treatment, however evidence remains poor. In the studies reviewed, only short-term courses of corticosteroids were prescribed to avoid many of the adverse effects associated with prolonged corticosteroid therapy. In patients with clinical conditions, such as diabetes, gastric ulcers, or steroid intolerance, corticosteroid therapy should be avoided. While corticosteroids have found to be effective as an adjunct to alpha-blockers and calcium channel blockers, evidence remains insufficient to recommend steroids as a monotherapy, as outlined in the most recent EUA and AUA urolithiasis guidelines.

alpha-blockers vs phosphodiesterase-5 inhibitors: The alpha-1 adrenergic blockers are the most commonly used agents for medical expulsive therapy. Tamsulosin has been proved to increase the stone expulsion rate and decrease the expulsion time and thus has been extensively used. Recently, phosphodiesterase-5 inhibitors have shown some benefit in stone expulsion. Phosphodiesterases are key enzymes regulating intracellular cyclic nucleotide metabolism cyclic guanosine monophosphate, cyclic adenosine monophosphate and thus the contraction and relaxation of the muscle. In vitro studies have found that PDE5 inhibitors relax the ureteric muscle. Tadalafil, a PDE5 inhibitor, acts by a nitric oxide/cGMP signaling pathway of smooth muscles, resulting in high levels of cGMP and thus causing relaxation of ureteral muscle. Tadalafil has the longest duration of action (~36 hours) among the current PDE5 inhibitors. Although tadalafil has been used in the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia, its use in medical expulsive therapy for ureteral stones is very limited. On the other hand, tamsulosin has been widely used for ureteral stones in our practice and has been found to be efficacious. This study aimed to analyze the safety and efficacy of tadalafil in distal ureteral stones and also to compare the efficacy of tadalafil with that of tamsulosin.

MATERIALS AND METHODS

This prospective study was performed at the Institute of Urology, Rajiv Gandhi government General hospital, Chennai, over a period of 12 months, from October 2016 to September 2017. Patients aged 18 years or older who presented to the urology outpatient department with ureteral stones 5–10 mm in size and located in the distal ureter (below the sacroiliac joint) were included. Diagnosis was made by noncontrast computed tomography. Patients with urinary tract infection, severe refractory pain, severe hydronephrosis, acute or chronic renal failure, multiple ureteral stones, bilateral ureteral calculus or a single functioning kidney, any history of ureteral surgery or procedure, or urinary tract anomalies were excluded. Similarly, patients receiving concomitant treatment with alpha-blockers, calcium channel blockers, nitrates, steroids, or PDE5 inhibitors; patients having ischemic heart disease, congestive cardiac failure, or complicated hypertension; pregnant or lactating mothers; and patients who demanded urgent stone removal were also not included.

A total of 100 patients who fulfilled the criteria were enrolled in the study. After providing written informed consent, these patients were randomly divided into 2 groups. The patients in group A and those in group B received tamsulosin 0.4 mg or tadalafil 10 mg orally at night, respectively. In both groups, drugs were continued until stone expulsion or for a period of 10days. Patients were asked to drink plenty of fluids and filter their urine with a thin cloth or net to look for stone expulsion. For pain control during colicky episodes, tramadol 100-mg tablets were given on an as-needed basis. The patients were followed up in the urology outpatient department. The stone expulsion time, analgesic use, number of hospital visits for pain, and adverse effects of drugs were noted. Similarly, occurrences of any drug side effects like headache, postural hypotension, gastritis, and backache were recorded. Expulsion of the stone was confirmed by X-ray of the kidneys, ureters, and bladder; ultrasonography; or NCCT. The primary outcome was the stone expulsion rate. The secondary endpoints were stone expulsion time, number of colicky attacks, analgesics required, and drug side effects. Patients who failed to pass the stone after 10 days were subjected to semirigid ureteroscopy for stone removal. Data were collected by filling in pro forma

data sheets, which included the patients' demographic profiles, investigation reports, and the results of primary and secondary outcomes.

RESULTS AND OBSERVATIONS

Of 100 patients, 50 in group A (tamsulosin) and 50 in group B (tadalafil) were analyzed. The patients' mean age was 46.5 years (range, 18–75 years) and the male-to-female ratio was 3.3:1. Variables such as age, sex, symptom duration, presenting symptoms, blood chemistries like creatinine and blood sugar, and stone parameters like stone size and stone laterality were comparable between the 2 groups. The mean stone size was 7.09±1.2 and 7.13±1.5 mm in groups A and B, respectively. Almost two-thirds of the patients had stones on the right side.

PARAMETER – AGE(Y)	TOTAL(N=100)	GROUP A (N=50)	GROUP B (N=50)
<20	2	1	1
20-30	42	22	20
30-40	25	13	12
40-50	17	6	11
50-60	8	4	4
>60	6	4	2

PARAMETER – STONE SIZE(MM)	TOTAL(N=100)	GROUP A (N=50)	GROUP B (N=50)
5	21	8	13
5-7	54	30	24
8-10	25	12	13

PARAMETERS	TOTAL(N=100)	GROUP A (N=50)	GROUP B (N=50)
Sex ratio male:female	77:23	37:13	40:10
Stone laterality right:left	69:31	26:24	33:17
Expulsion time(d)	8.6+/-3.5	9.6+/-3.8	8.08+/-3.3
no of coliky episodes	0.7+/-1.2	0.8+/-1.1	0.6+/-1.4

The overall stone expulsion rate in the study was 85%. The stone expulsion rate was significantly higher in group B than in group A (44% vs. 41%). The mean stone expulsion time was lower in group B (8.08±3.3 days) than in group A (9.64±3.8 days), but this difference was not significant. Forty-eight of 100 patients had no episodes of colicky pain and 52 of 100 patients did not require any analgesics for pain during the study period. The number of episodes of colicky pain, the pain score, and the analgesic requirement were less in group B, but these differences were not significant. The individual side effects were also comparable between the 2 treatment groups. Among the 40 male patients from group B, 18 patients felt a mild degree of penile tumescence (after intake of tadalafil) lasting for 20–30 minutes, but no patients developed priapism. However, all of these side effects were mild and well tolerated, and no patients had to drop out of the study.

DISCUSSION

Urolithiasis is a chronic disease with huge economic consequences and great public health importance, because it affects young people and has a high recurrence rate of approximately 50% within 5 years and 75% at 10 years. Although ureteric stones make up only 20% of urolithiasis, they are the most symptomatic of the calculi. Studies have found that the probability of spontaneous passage of distal ureteral stones is 71% to 98% for stones sized less than 5 mm and 25% to 51% for stones sized 5 to 10 mm. Many factors influence the spontaneous expulsion of stones, such as stone location, stone size, stone number, stone structure, ureteral spasm, mucosal edema or inflammation, and ureteral anatomy. Therefore, the use of medical therapy is justifiable to reduce edema, reduce spasm, and relax the smooth muscles for stone expulsion. Medical expulsive therapy has recently emerged as an alternative strategy for the initial management of selected patients with distal ureteral stones. A better understanding of ureteric function and pathophysiology has helped in employing medical expulsive therapy as a conservative treatment approach. Many randomized controlled trials have supported the role of medical expulsive therapy, especially with alpha-1 blockers. The most common adrenoceptors found in the ureter are alpha-1D and alpha-1A. These are more abundant on the distal ureter. Tamsulosin is an alpha-1A-selective alpha-blocker. Gratzke et al, in their *in vitro* study, showed the ureteral muscle relaxing effect of PDE5 inhibitors. Tadalafil is a PDE5 inhibitor that relaxes the ureteral muscle by increasing the cGMP level. Despite having a well-established role in ED and BPH, the use of tadalafil for medical expulsive therapy is in the preliminary stage.

The stone expulsion rate in the present study was significantly higher in the tadalafil group than in the tamsulosin group. Furthermore, we found that the expulsion rate of both drugs was better than the expulsion rates in historical controls used in earlier studies. Although we could not find studies directly comparing tamsulosin with tadalafil, the expulsion rate of tadalafil was found to be higher in different studies. Kumar et al. and Jayant et al in their studies compared the stone expulsion rate of tamsulosin with the tamsulosin and tadalafil combination. In another study, Hasan et al found that tadalafil had an expulsion rate of 93% compared with 67% for a placebo group. In a randomized study with 285 patients, Kumar et al compared the efficacy of 3 drugs, tamsulosin, silodosin, and tadalafil, as for medical expulsive therapy lower ureteral stones. The expulsion rate was 64.4%, 83.3%, and 66.7%, respectively, but there was no significant difference between the tamsulosin and tadalafil groups.

Subgroup analysis was performed between the patients who passed the stone (medical expulsive therapy success) and those who failed to pass the stone (medical expulsive therapy failure). Patient age and the male-to-female ratio were comparable between the success and failure groups. Similarly, subgroup analysis was also performed among the patients who successfully passed the stones in both the tamsulosin and tadalafil groups. There were no significant differences in age, male-to-female ratio, or stone size between these 2 groups. Medical expulsive therapy not only facilitates stone passage, but also decreases the stone expulsion time, colicky pain episodes, and analgesic requirement. Jayant et al, who had compared tamsulosin with the combination of tamsulosin and tadalafil, demonstrated a significantly decreased expulsion time (16.7±4.8 vs. 14.9±4.4 days, p=0.003), significantly fewer colicky pain episodes (1.60±1.0 vs. 0.45±0.68, p=0.000), and significantly less analgesic use (2.90±0.90 vs. 1.87±0.8, p=0.000). Colicky pain in ureteral stones occurs owing to an increase in intraureteral pressure above the site of ureteral obstruction. Kinnman et al, demonstrated that α-blockade relieves ureteric colic by blocking the C-fibres responsible for mediating pain. Both drugs are thought to decrease the frequency and amplitude of phasic peristaltic contractions that accompany ureteric obstruction and to decrease the need for

analgesia. In the present study, these parameters were lower in group B, but these differences did not reach the level of significance. The incidence of side effects was higher in the tadalafil group, but the difference was not statistically significant. Similar results were demonstrated in studies by Kumar et al and Jayant et a. No serious adverse effects were encountered in either group in our study and all reported side effects were mild and well tolerated. This is probably because the study population was young and lacked significant co morbidities.

Recently, a few studies have questioned the efficacy of medical expulsive therapy for ureteral stones. Bensalah et al in 2008 performed a randomized study in which 129 patients were divided into tamsulosin and placebo groups and treated for 42 days. The expulsion rate was 77.0% and 70.5% for tamsulosin and placebo, respectively. However, mean stone diameter was only 3.1 mm, a stone size that naturally has a high spontaneous expulsion rate. A more recent well designed, randomized, multicenter, placebo-controlled study was reported from 24 hospitals in the United Kingdom in which 1,136 ureteral stone patients were given tamsulosin, nifedipine, and placebo for 4 weeks and followed up until 12 weeks. Their primary outcome, absence of intervention by 4 weeks (which was regarded as equivalent to stone passage), was 81%, 80%, and 80% in the tamsulosin, nifedipine, and placebo groups, respectively, and was not significant (active treatment vs. placebo and tamsulosin vs. nifedipine . However, that study had limitations; first, no imaging was used to document the stone passage, and second, almost 75% of the stones were <5 mm in size. Currently, medical expulsive therapy remains an established treatment option for lower ureteral stones.

Our study was not without limitations. The sample size was small, the treatment duration was short, and there was no placebo group. However, this is one of the few studies that used PDE5 inhibitors as a treatment for distal ureteral stones and thus is still valuable as a pilot study. Further larger, multi-institutional prospective studies will help to establish the role of PDE5 inhibitors as medical expulsive therapy for distal ureteral stones.

Conclusion

Tadalafil has a significantly higher stone expulsion rate than tamsulosin as a medical expulsive therapy for distal ureteral stones of 5–10 mm in size. Tadalafil also provides early stone expulsion, a greater decrease in colicky pain episodes, and a greater decrease in analgesic requirement, although not statistically significant. Both drugs are safe, effective, and well tolerated with minor side effects. The AUA/EAU guidelines suggest medical expulsive therapy as a reasonable treatment choice in select patients. Previous studies have demonstrated a significant benefit in stone expulsion rates with the use of medical expulsive therapy. The use of medical expulsive therapy is not limited to just those patients attempting passage of calculi without other interventions; there is also an advantage to medical expulsive therapy in those subjects treated with other modalities (i.e. SWL and ureteroscopy). Even with multiple studies demonstrating the benefits of medical expulsive therapy, it still is underutilized as a treatment modality. Education in the hospital setting appears to be beneficial in changing practice behaviours. Medical expulsive therapy may reduce medical costs and prevent unnecessary surgeries and the associated risks.

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