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RESEARCH ARTICLE

TO COMPARE THE SAFETY AND EFFICACY OF NAFTOPIDIL AND TAMSULOSIN AS MEDICAL EXPULSIVE THERAPY IN COMBINATION WITH DEFLAZACORT FOR DISTAL URETERAL STONES

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ABSTRACT

Purpose: To compare the safety and efficacy of naftopidil and tamsulosin with deflazacort as medical expulsive therapy for distal ureteric stones.
Methods: This prospective study comprised of 60 patients with distal ureteric stones measuring less than or equal to 10mmThe patients were divided randomly into two groups. Thirty patients in group A received tamsulosin (0.4 mg/daily) orally and deflazacort (6mg/daily) and thirty patients in group B received naftopidil (75mg/daily) orally and deflazacort (6mg/daily) and were observed for two weeks for expulsion rate, expulsion time and analgesic dose required.
Results: In our study we found that the stone expulsion rate was 76.6% in group A and 83.3% in group B. The expulsion rate in the first week was 60% and that in the second week was 40% and in group A, the expulsion rate was 100% in the first week(table 2) in group B which was statistically significant ($p<0.001$). The use of analgesic and the number of episodes of pain was also significantly lower in groups B than in group A ($p<0.001$)
Conclusion: It is found that medical expulsive therapy using either naftopidil or tamsulosin along with deflazacort is safe and effective compared with watchful waiting for distal ureteral stones. There was a trend toward a better expulsion rate of ureteral stones in the group treated with naftopidil, but this needs to be studied further in adequately powered studies.

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INTRODUCTION

Urolithiasis (urinary stones) is an ailment affecting 12% of the world population. (Pak, 1998) Symptomatic urolithiasis represents the most common condition observed by surgeons and urologists in an emergency setting. Seventy percent of urolithiasisare located in the lower third of the ureter. Up to 50% of patients may experience the recurrence of renal stones within 5 years of their first episode, urolithiasis is a chronic disease with substantial economic consequences and great public health importance. (Hollingsworth *et al*., 2006) It is well established that almost 50% of ureteral stones will pass spontaneously over time and that stone size is a critical factor influencing expulsion (only 20% of stones greater than 8 mm will pass spontaneously) (Ueno *et al*., 1977; Carstensen and Hansen, 1973). Alpha-1-adrenergic receptors are present throughout the ureter with a high concentration in the distal third of the ureter. Blockage inhibits basal smooth muscle tone and hyperperistaltic uncoordinated frequency while maintaining tonic propulsive contractions. (Malin *et al*., 1970) Ureteral calculi can induce ureteral spasms that interfere with the expulsion of calculi; thus, reduction of spasm with maintenance of normal peristaltic activity can facilitate expulsion of calculi. It has been shown that ureteral calculi induce inflammatory changes in the ureteral wall and that submucosaloedema around a calculus may worsen ureteral obstruction, thus increasing the risk of impaction and retention (Yamaguchi *et al*., 1999). Thus, steroid drugs can facilitate stone expulsion by reducing the submucosaloedema. On the basis of these observations, medical expulsive therapy using α-1-adrenergic receptor antagonists or calcium channel blockers and steroids has recently emerged as an efficacious and safe option for the initial management of ureteral stones. Tamsulosin has already been proven to increase the stone expulsion rate and to decrease the time to expulsion. (Porpiglia *et al*., 2006) Recently, the newer alpha-blocker naftopidil has been studied in patients with lower urinary tract symptoms due

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to benign prostatic hyperplasia and has been found to be better than tamsulosin for nocturia owing to its α-1D-adrenoceptor blocking action. (Nishino *et al*., 2006) Because the lower ureter and bladder are rich in α-1D-adrenoceptors, there is a theoretical advantage in using naftopidil medical expulsive therapy, because it may reduce the pressure in the intramural part of the ureter, thereby facilitating stone passage. Indeed, naftopidil was shown to increase the spontaneous expulsion rate of distal ureteral stones compared with placebo in a recent study. (Sun *et al*., 2009) The aim of this study was to to compare the safety and efficacy of naftopidil and tamsulosin with deflazacort as medical expulsive therapy for distal ureteric stones.

MATERIALS AND METHODS

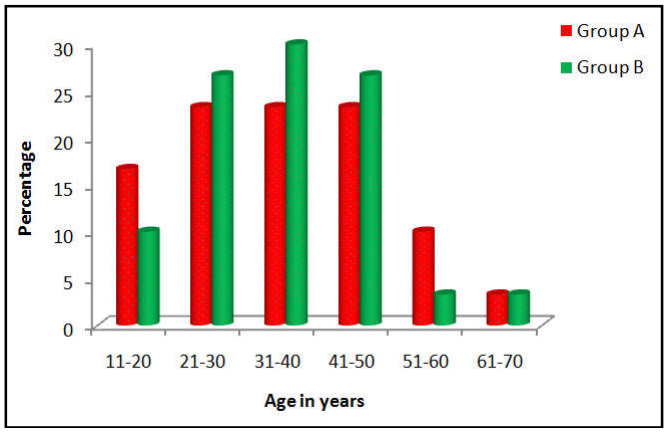
This prospective study comprised of 60 patients with distal ureteric stones measuring less than or equal to 10mm during the period November 2014 and November 2015. The exclusion criteria were urinary tract infections (UTIs), severe hydronephrosis on ultrasound examination (grosspelvicalyceal dilatation with parenchymal thinning), co-morbid conditions such as diabetes, alteration in renalparameters (serum creatinine and blood urea), Previous history or ureteral manipulation and/or surgery, multiple ureteral stones, known sensitivity to alpha blockers and pregnancy. All patients were received and evaluated on outpatient/inpatient basis and underwent a standard evaluation of transabdominal renal utrasonography. The patients were dividedrandomly into two groups. Thirty patients in group A received tamsulosin (0.4 mg/daily) orally and deflazacort (6mg/daily) and thirtypatients in group B received naftopidil (75mg/daily) orally and deflazacort (6mg/daily). The duration of trial was until expulsion of the stone, but no longerthan 2 weeks. The outcome variables measured were expulsion rate, expulsion time and number of times/ cumulative dose of diclofenacadministered. Subjective assessment of stone expulsion was done by patients, who were instructed to filter their urine by using a standard mesh net to detect stone expulsion. Objective documentation of stone expulsion was done based on follow-up renal ultrasonography. Patients who did not pass the stone spontaneously were referred forintervention (Uretrorenoscopy, ureteric stent insertion, Endoscopic Shockwave Lithotripsy).

Statistical analysis

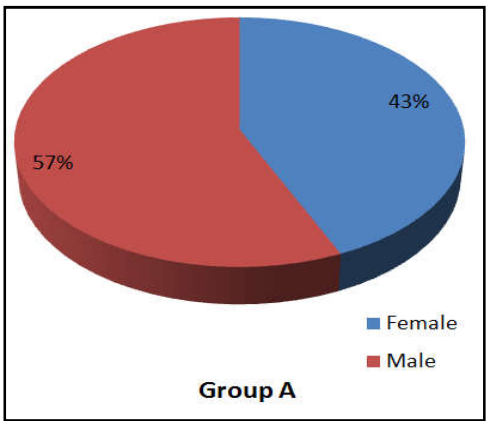
Data will be analysed using the statistical program for social sciences (SPSS) software. Comparison of categorical variables were done using Fischer's test. Comparisons of quantitative variables were done using student t test. A probability value (p value) <0.05 will be considered statistically significant.

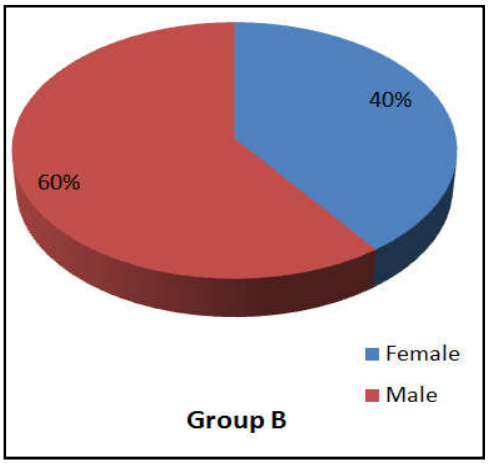
RESULTS

Two groups were comparable with respect to age and sex and the size and side of stones. The stone expulsion rate was 76.6%, 83.3% in group A and group B respectively as shown in Table 1. Although there was a trend toward a higher expulsion rate in group B than in group A, it was not statistically significant. (p=0,424), although in group A, The expulsion rate in the first week was 60% and that in the second week was 40% and in group A, the expulsion rate was 100% in the first week (Table 2) in group B which was statistically significant (p<0.001). The use of analgesic and the number of episodes of pain was also significantly lower in group B than in group A (p<0.001), as in table 3. The average number of hospital visits for pain and follow-up were ranging from 1 to 4 and 0 to 1in groups A and B respectively, which was statistically significant (p<0.001). Five in group A and two in group B did not expel the stones, after 2 weeks these patients underwent ureteroscopic retrieval of stone uneventfully. Dizzziness and headache were noted in one patient in group A.

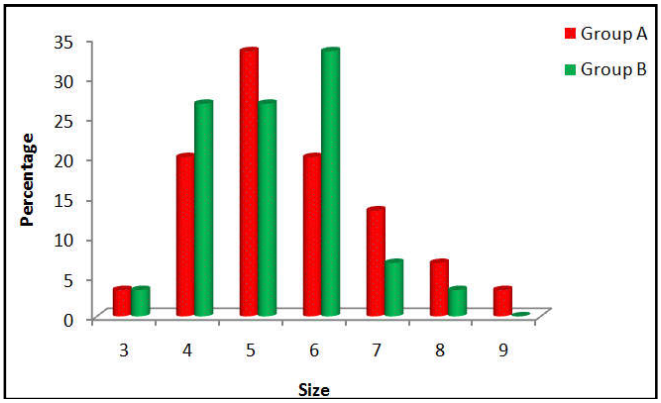


Graph 1. Age distribution of patients studied





Graph 2. Gender distribution of patient studied



Graph 3: Size (mm) distribution in two groups of patients studied

Table 1. Expulsion rate

EXPL	Group A		Group B	
	No	%	No	%
Negative	7	23.4	5	16.7
Positive	23	76.6	25	83.3
Total	30	100.0	30	100.0

P=0.424, Not significant, Chi-Square test

Table 2. Expulsion time

EXPL Time in Days	Group A		Group B	
	No	%	No	%
2-7	15	60.0	28	100.0
8-14	10	40.0	0	0.0
Total	25	100.0	28	100.0

P<0.001**, significant, Chi-Square test

Table 3. Analgesic Dose in two groups of patients studied

ANLG Dose	Group A		Group B	
	No	%	No	%
<500	11	36.7	26	86.7
500-1000	16	53.3	4	13.3
>1000	3	10.0	0	0.0
Total	30	100.0	30	100.0
Mean ± SD	561.67±284.57		288.33±162.25	

P<0.001**, Significant, Student t test

Table 4. Endo-TRT in two groups of patients studied

Endo-TRT	Group A		Group B	
	No	%	No	%
Nil	25	83.3	28	93.3
URS	5	16.7	2	6.7
Total	30	100.0	30	100.0

P=0.424, Not significant, Chi-Square test

DISCUSSION

Among all urinary tract stones, 20% present as ureteral stones, of which 70% are found in the lower third of the ureter. (Wolf, 2007) The factors influencing the spontaneous expulsion of ureteral stones are stone location, size, number, and shape; spasm in the ureteral smooth muscles; mucosal edema or inflammation; and ureteral anatomy. (Wang *et al*., 2008; Segura *et al*., 1997) It has been shown that stones less than 6 mm can be observed for spontaneous expulsion. (Tchey *et al*., 2011) It would seem logical that medical therapy should be used to reduce edema, spasm, and relaxation of smooth muscles. Current therapeutic options for distal ureteral stones include surgical intervention, medical expulsive therapy, and conservative wait and watch approaches. The efficacy of minimally invasive therapies, such as shock wave lithotripsy and ureterorenoscopy, has been proven by several studies. (Wolf, 2007; Segura *et al*., 1997) However, although such procedures are effective, they are not free from risk or inconvenience, and there are consequent implications such as lowering the quality of life, high cost, and suspension of regular activities. (Bensalah *et al*., 2008; Gettman and Segura, 2005) A watchful waiting approach can be used in a large number of cases, as demonstrated by several studies that revealed spontaneous passage rates of up to 85% for distal ureteral stones less than 5 mm. (Hubner *et al*., 1993; Coll *et al*., 2002) Watchful waiting does not always result in stone clearance and may be associated with recurrent uretric colic. (Shokeir, 2001) The rate of spontaneous passage diminishes as stone size increases. (Borghi *et al*., 1994) Thus, to increase the expulsion rate and reduce analgesic consumption, there is a great deal of enthusiasm for adjuvant pharmacological intervention, which can reduce symptoms and facilitate stone expulsion. (Shokeir, 2001; Borghi *et al*., 1994; Porpiglia *et al*., 2000) Malin *et al*. (1970) first described the presence of α- and β-adrenergic receptors throughout the entire length of the human ureter and the physiological response (increase in tone and frequency of contraction) of the ureter when exposed to α-adrenoceptor agonists. Later it was found that α-1D and α-1A-adrenoceptors are expressed in significantly larger amounts than the α-1B-adrenoceptor in the human ureter. (Borghi *et al*., 1994) It was also demonstrated that the distal ureter expresses a greater amount of α-1-adrenoceptor mRNA than do the proximal and middle ureter. Itoh *et al*. (Borghi *et al*., 1994) reported that α-1D-adrenoceptor mRNA is more highly expressed than α-1A-adrenoceptor mRNA in each region of the ureter. According to their results, an α-1D-adrenoceptor antagonist can be expected to be more effective for the expulsion of the ureteral stones than an α-1A-adrenoceptor antagonist.

Numerous clinical trials have been performed to investigate the efficacy of the α-1A-selective α-blocker tamsulosin. Most of these studies were randomized and revealed that tamsulosin treatment significantly improves the expulsion rate of medium-sized (3-10 mm) distal ureteral stones. Thus, tamsulosin represents a noninvasive and cost-effective alternative to interventional approaches. (Malin *et al*., 1970) Although medical expulsive therapy has become a standard treatment option used by urologists, it is still underused by other physicians in emergency departments. (Sigala *et al*., 2005) Although naftopidil acts on both α-1A- and α-1D-receptors, it has approximately three-fold stronger affinity for the α-1D-receptors than for the α-1A. (Itoh *et al*., 2007) Naftopidil has been used in the treatment of benign hyperplasia of the prostate and has been proved to be more effective and safe than tamsulosin. (Itoh *et al*., 2007) Recently, it has shown efficacy in medical expulsive therapy also. (Porpiglia *et al*., 2006) It is possible that the effect of α-1D-receptor antagonist on the obstructed ureter is to induce an increase in the intraureteral pressure gradient around the stone, as well as decreased peristalsis below the ureter. It may also cause a decrease in basal and micturition pressures. For this reason, it induces a strong gradient to expel the stone.

We observed a stone expulsion rate of 83.3% with the use of naftopidil. The expulsion rate of naftopidil in previous studies varied from 61% to 90%. (Porpiglia *et al*., 2006; Itoh *et al*., 2007; Itano *et al*., 2012) The higher dose of naftopidil (75 mg/d) used in our study group as compared to previous studies (Tsuzaka *et al*., 2011; Zhou *et al*., 2011) and the concomitant use of deflazacort could have led to the better expulsion rate in our study than in these previous studies. It was previously shown that the combination of steroid with tamsulosin leads to a higher stone expulsion rate. (Malin *et al*., 1970) The better stone expulsion rate as compared to tamsulosin may be due to the three times higher affinity of naftopidil for the α-1D-adrenoceptor than for the α-1A-adrenoceptor (Takei *et al*., 1999), which allows it to cause relaxation of both detrusor and ureteral muscles more effectively. Because of the simultaneous detrusor and intramural ureteral relaxation, the compression at the intramural part of the ureter, which is the narrowest part of the ureter that the ureteral calculus has to negotiate, is relieved. We believe that this peculiar action of naftopidil is a major reason for its higher stone expulsion rate compared with tamsulosin, although the difference was not statistically significant. In our study, the expulsion rate was 76.6% in patients who received tamsulosin. Tamsulosin has been shown to have a stone expulsion rate varying from 54% to 100% in previous studies. (Seitz *et al*., 2009) The time to expulsion in both the tamsulosin and naftopidil groups was similar to that in previous studies. (Zhou *et al*., 2011; Porpiglia *et al*., 2004) The mean time to expulsion with naftopidilmonotherapy was 7 to 15 days in previous studies. (Tsuzaka *et al*., 2011; Zhou *et al*., 2011) The reported side effects were minimal in our study. This was probably because of the younger study population and the lack of any associated comorbidity. The use of a near physiological dose of deflazacort (Nayak and Acharjya, 2008) and the careful exclusion of patients with contraindications to steroids may explain the lack of significant side effects related to steroid use. Analgesic use was significantly higher in the tamsulosin group thannaftopidil groups. Kinnmen *et al*. (1997) opined that α-blockade may relieve ureteral colic by blocking the C-fibers responsible for mediating pain. Use of α-blockers for expulsion of ureteral stones probably decreases the analgesic requirement in two ways: expulsion of stones, leading to longer stone-free periods, and blockade of C-fibers. It is difficult to assess which of these may be primarily responsible for decreasing the analgesic requirement, because α-blockers are known to be associated with both.

Conclusion

It is found that medical expulsive therapy using either naftopidil or tamsulosin along with deflazacort is safe and effective compared with watchful waiting for distal ureteral stones. There was a trend toward a better expulsion rate of ureteral stones in the group treated with naftopidil, but this needs to be studied further in adequately powered studies.

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