

The Use of Alpha-Blockers & Hyoscine N-butyl Bromide (HBB) for the Treatment of Nephrolithiasis is most Effective Treatment for lower Uretric Stones

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ABSTRACT

Background: Medical expulsion therapy has been shown to be a useful adjunct to observation in the management of ureteral stones. Alpha-1-adrenergic receptor antagonists have been studied in this role.

Study Design: Experimental Study.

Place and Duration of Study: This study was conducted Urology at GMMMC Hospital Sukkur from January 2008 to December 2010.

Materials and Methods: In this study 480 patients were selected, with stones located in the distal tract of the ureter with stone diameters of 5 to 10mm were enrolled in the present study and were randomized into 4 equal groups. Group 1 received hyoscine N-butyl bromide (HBB), Group 2 received alfuzosin, Group 3 received doxazosin and Group 4 received terazosin. The subjects were prescribed diclofenac injection (75 mg) intramuscularly on demand for pain relief and were followed-up after two weeks with x-rays of the kidneys, ureters, bladder and urinary ultrasonography every week. The number of pain episodes, analgesic dosage and the number of days of spontaneous passage of the calculi through the ureter were also recorded.

Results: The average stone size for groups 1, 2, 3 and 4 was comparable (6.13, 5.83, 5.59 and 5.48 mm respectively). Stone expulsion was observed in 11%, 52.9%, 62%, and 46% in groups 1, 2, 3 and 4 respectively. The average time to expulsion was 10.55 ± 6.21 days in group 1, 7.38 ± 5.55 days in group 2, 7.85 ± 5.11 days in group 3 and 7.45 ± 5.32 days in group 4. Alpha blockers were found to be superior to HBB ($p < 0.05$).

Conclusion: Medical treatment of distal ureteral calculi with alfuzosin, doxazosin and terazosin resulted in a significantly increased stone-expulsion rate and decreased expulsion time when compared with HBB. HBB seems to have a negative effect on stone-expulsion rate.

Key Words: Alpha-Blockers, Hyoscine, N-butyl Bromide (HBB), Nephrolithiasis, Tamsulosin

INTRODUCTION

Medical expulsion therapy has been shown to be a useful adjunct to observation in the management of ureteral stones. Alpha-1-adrenergic receptor antagonists have been studied in this role. Alpha-1 receptors are located in the human ureter, especially the distal ureter. Alpha-blockers have been demonstrated to increase expulsion rates of distal ureteral stones, decrease time to expulsion, and decrease need for analgesia during stone passage. Alpha-blockers promote stone passage in patients receiving shock wave lithotripsy, and may be able to relieve ureteral stent-related symptoms. In the appropriate clinical scenario, the use of α -blockers is recommended in the conservative management of distal ureteral stones.

Anti-spasmodic agents, such as hyoscine -N-butylbromide, are often prescribed by general practitioners or by emergency services as soon as renal colic is diagnosed. HBB may help provide analgesia by inducing smooth muscle relaxation, which decreases ureteral spasm. For this reason, anti-spasmodic agents

are still recommended in the treatment of renal colic, usually as adjuvant therapy to NSAIDs and/or opioids⁵. Tamsulosin has been the most commonly studied alpha-1 blocker in the treatment of ureteral stones with increased spontaneous stone expulsion; however, the efficacy of other alpha-blockers has not been well studied, although many are less costly and more available than tamsulosin. Studies that have assessed anti-spasmodic agents primarily focused on the effect of pain management in renal colic treatment. For this reason, a prospective randomized study was planned to compare the effectiveness of three different types of non-specific alfa1-adrenoreceptor antagonists and HBB for relieving ureteral colic and facilitating the spontaneous expulsion of distal ureteral stones.

MATERIALS AND METHODS

A total of 480 adult patients who were admitted to the Urology ward at GMMMC hospital Sukkur, with complaints of renal colic were prospectively evaluated between January 2008 and December 2010. The study was approved by the local Ethics Committee. Patients

who had radio-opaque stones located in the distal tract of the ureter with stone diameters of 5 to 10 mm were included in the study.

Exclusion criteria were as follows: presence of urinary tract infection, diabetes mellitus, pregnancy, renal insufficiency (serum creatinine greater than 1.8 mg/dL), a solitary kidney, radiolucent stones, multiple stones, a previous history of distal ureter surgery, severe hydronephrosis, current alpha-blocker use or allergic reaction to the study medication.

All patients were evaluated with x-rays of the kidneys, ureters, and bladder as well as ultrasonography of the urinary system. Stone size was recorded for each patient. The treatment was fully explained to patients before obtaining informed consent.

Patients were randomly divided into four groups. Each group initially included 120 patients. Group 1 received HBB (30 mg oral tablet three times a day); Group 2 received alfuzosin (10 mg daily); Group 3 received doxazosin (4mg daily) and Group 4 received terazosin (5 mg daily). Alpha-blocker drugs were administered before going to bed in the evening. The patients receiving terazosin and doxazosin were started on their therapeutic doses upon entering the study rather than being titrated to that dose. All patients were instructed to drink at least 3 L of fluids daily. The patients were prescribed a diclofenac injection (75 mg) intramuscularly on demand for pain relief. The subjects were advised to filter their urine, and those who had passed their stones were asked to stop taking the medication. The patients were followed-up weekly for

up to two weeks with x-rays of the kidney, ureter and bladder region, and urinary ultrasonography and urine analysis were performed to exclude infection. Subjects recorded daily pain using a visual analog pain score (linear 11-point scale from 0, no discomfort, to 10, the most severe pain ever experienced), and they maintained a pain medicine diary that recorded the number of doses of diclofenac medication consumed per day. The date and time of stone passage were recorded. The criteria for treatment discontinuation and the need for hospitalization and/or endoscopic treatment were intolerable pain, fever and/or the development of new severe hydronephrosis or worsening of already present hydronephrosis, or lack of success of stone expulsion after two weeks. Two endpoints were chosen to determine the effect of alpha-blockers and HBB on the treatment of ureter stones, stone expulsion rate and pain score reduction. Statistical analyses were performed with ANOVA and Pearson's chi-square test using the parameters of stone size, expulsion rate, time to expulsion, amount of analgesic compound and number of pain episodes. A value of $P < 0.05$ was statistically significant.

RESULTS

There were no statistically significant differences between the groups with respect to age, sex, stone size, baseline degree of hydronephrosis present and previous stone passage history (Table-1).

Table No.1: Patients Characteristics:

		HBB	Alfuzosin	Doxazosin	Terazosin	p Value
Mean age		45+/-10	45+/-5	30+/-6	36+/-3	0.283
Male-female%		68%-25%	55%-42%	39%-50%	69%-30%	0.065
Stone size(mm)		7.13+/-1.11	6.83+/-1.76	6.59+/-1	6.48+/-1.72	0.626
Hydronephrosis	0	72%	45%	49%	42%	0.477
	1	6%	31%	30%	28%	
	2	16%	15%	14%	25%	
Previous stone passage	yes	32%	25%	16%	34%	0.715
	no	64%	72%	70%	63%	

Table No.2: follow-up Results of the Group:

		Hbb	Alfuzosin	Doxazosin	Terazosin	p Value
Stone expulsion rate%		29%	71%	76%	68.10%	0.05
Mean day to expulsions		10.55 +/- 6.21	7.38 +/- 5.55	7.85 +/- 5.11	7.45 +/- 5.32	0.05
Decrease pain score (VAS)	BL	7.50 +/- 2.4	7.94 +/- 2.1	7.64 +/- 2.8	7.44 +/- 2.3	
	F	3.98 +/- 2.5	4.3+/- 2.4	3.9 +/- 2.3	3.9 +/- 2.6	0.567
Diclofenac requirment (n)		5 +/- 1	7.36 +/- 1.2	6 +/- 2	5.36 +/- 2	0.567

(BL= baseline, F= follow-up, VAS= visual analogue scale)

stone expulsion was observed in 35 of 118 patients in group 1 (29%), 85 of 119 patients in group 2 (71%), 89 of 117 patients in group 3 (76%), and 79 of 116 patients in group 4 (68.1%). In groups 2, 3 and 4, the rate of the spontaneous passage of the calculi was found to be

higher compared with that in group 1 ($P < 0.05$) (Table-2). There was no difference detected between the alpha-blocker groups with respect to the rate of the spontaneous passage of the stones. Average time to expulsion was 10.55 ± 6.21 days in group 1, 7.38 ± 5.55

days in group 2, 7.85 ± 5.11 days in group 3 and 7.45 ± 5.32 days in group 4. Time to expulsion was recorded significantly less often in groups 2, 3 and 4 than in group 1 ($P < 0.05$). However, no significant difference was noted between groups 2, 3 and 4 ($p = 0.756$). Decreases in baseline pain were noted in 53%, 55.6%, 51% and 52% with the use of HBB, alfuzosin, doxazosin and terazosin, respectively. When comparing the improvement in the baseline pain score, there were no significant differences between the groups ($p = 0.567$). Similarly, the mean number of diclofenac administrations was observed to be similar in the groups ($p = 0.567$) (Table-2).

Of the 480 patients, 10 were removed from the study due to urinary tract infection, patient request for intervention and lack of compliance in 5, 2 and 3 patients, respectively. Requiring to stop the medication due to the adverse events was not recorded in the groups.

DISCUSSION

The availability of minimally invasive treatment alternatives and the high success of extracorporeal shockwave lithotripsy (ESWL), emergency ESWL and ureteroscopic extractions have greatly changed the way in which stone treatment is approached⁶. However, urologists are often doubtful about the best form of therapy and should consider the possibility of spontaneous passage of stones or the use of medical therapy. With the introduction of MET, the clinical treatment of ureteral stones has undergone a major evolution. Treatment regimens involving alpha adrenergic drugs are aimed at promoting ureteral smooth muscle relaxation. Alpha-1-adrenergic receptor antagonists have some degree of selectivity for the detrusor muscles and distal ureter and have thus been investigated for their potential to promote stone expulsion and decrease pain^{7,8}. Because there is no need to titrate the dose, tamsulosin has been the most commonly studied alpha-blocker in the treatment of ureteral stones⁹⁻¹¹. Alpha-blockers are still an off-label treatment for ureteral stones. We aimed to evaluate the effectiveness of the other three alpha-blockers, which are less expensive and more available than tamsulosin. Ureteral stones are most prevalent in patients between the ages of 40 and 45¹², and with respect to cardiovascular stability, this population is relatively more stable than patients diagnosed with benign prostatic hyperplasia (BPH). Dose titration with doxazosin and terazosin, which is recommended in the management of BPH, may not be required for this particular population. In this study, patients receiving terazosin and doxazosin were started on their therapeutic doses upon inclusion into the study rather than being titrated to that dose. HBB acts by inhibiting

cholinergic transmission in the abdominal-pelvic parasympathetic ganglia, thus relieving spasm in the smooth muscles of the gastrointestinal, biliary, and urinary tract¹³. In Turkey HBB is the most prescribed agent for the symptomatic treatment of renal colic. To our knowledge, the present study is the first to compare the effectiveness of HBB and nonselective alpha-1 blockers in the treatment of ureteral stones. In complete obstruction, the signs of kidney injury appear within three to four weeks¹⁴. For this reason, clinicians may wait up to four weeks to see if the stones will pass spontaneously, provided that the patient is comfortable. Studies with MET showed that 80-90% of stone expulsion occurs within 15 days¹⁵.

In the current study, intervention was suggested after a two week follow-up. It was determined that the stone expulsion rate for three different alpha-adrenergic blockers was significantly higher when compared to the HBB group (alfuzosin, 71%; doxazosin, 76%; terazosin, 68.1%; HBB, 29%). In addition, alpha-blockers were better than HBB with respect to the time to the spontaneous passage of the stones (7.5 days versus 10.55 days). The pain medicine requirement also decreased significantly with alpha-blockers; however, this difference was not significant when compared with HBB. Yilmaz et al. compared the efficacy of three different alpha-adrenergic blockers¹⁶. The stone expulsion rates of tamsulosin, terazosin, and doxazosin were found to be 79.31%, 78.57%, and 75.86%, respectively. The mean time to passage was significantly lower in the groups receiving alpha-1 blockers compared with the control group. In the present study, the stone-expulsion rates were found to be 62% and 45.1% in the doxazosin and terazosin group, respectively. A meta-analysis of 11 clinical trials that enrolled a total of more than 900 patients suggested that alpha-blockers increase the rate of spontaneous stone passage by 44%¹⁷. Tamsulosin has been the most commonly studied alpha-1 blocker in the treatment of ureteral stones. Direct comparison of alfuzosin and tamsulosin in the management of lower ureteral calculi has shown that both drugs increase the stone-expulsion rate (82.3% vs. 70.5%), decrease expulsion time (12.3 versus 14.5) and reduce the need for analgesics¹⁸. Ukhal et al. found that the rate for the spontaneous passage of distal ureteral stones with doxazosin was 71.1% and demonstrated that the drug decreases the frequency of renal colic¹⁹.

In the present study, the expulsion-rate of stones using alpha-blockers was slightly lower than the literature findings. Our explanations are as follows: 1) Steroids or anti-edema agents have generally been included in medical treatment for their anti-inflammatory action, presumably to reduce local edema; however, in our study, no steroids were used. 2) A factor that might

have affected stone-expulsion rate other than stone size might have been the duration of colic and the degree of impaction and obstruction by the stone, which was not addressed in the current study. 3) Stone sizes < 5 mm were also included in previous reports. 4) The duration of MET was longer in previous reports. In our study, stone sizes < 5 mm were excluded, and the duration of MET was two weeks. Anti-spasmodic agents such as HBB may theoretically help provide analgesia by inducing smooth muscle relaxation, which decreases ureteral spasm. For this reason, anti-spasmodic agents are still recommended in the treatment of renal colic, but with inconsistent clinical benefit²⁰. Most studies administering anti-spasmodic agents focused only on the control of analgesic symptoms for renal colic due to ureteral stone. The current study was performed to assess and compare the expulsive effects of orally administered HBB and alpha-blockers. Dabella et al. evaluated the expulsive effects of orally administered phloroglucinol, tamsulosin and nifedipine for distal ureteral stone³. The expulsion rate was found to be higher for tamsulosin, followed by nifedipine and phloroglucinol; the expulsion rates were 97.1% and 77.1%, 64.3%, respectively. Surprisingly, the expulsion rate in the HBB group was found to be 11% in the current study. The relatively larger stone size and the lack of corticosteroid administration may explain the lower expulsion rate. Pain relief of 53% was noted on the visual analog scale with the use of HBB, which was similar to that of the alpha-blockers. The efficacy of HBB can only be due to a reduction in ureteral hypermotility, as no direct analgesic property of the compound has been documented at the dose used. We speculate that the lower stone-expulsion rate in HBB may be due to its anti-spasmodic effect, resulting in the diminished ureteral activity necessary for stone expulsion. With regard to the two end points of the current trial, alpha-blockers proved to be superior to HBB. Treatment to relieve the pain associated with ureteral colic was found to be similar for all groups.

CONCLUSION

Alpha-1 blockers, regardless of the type, were found to be effective in the treatment of distal ureteral stone in terms of stone expulsion and pain control. HBB was found to be effective at controlling pain; however, the effect of stone expulsion was lower than that of alpha-blockers. HBB seems to have a negative effect on stone expulsion. The major limitation of the current study was the small sample size. Further studies may be needed to evaluate the effect of anti-spasmodic agents and non-tamsulosin alpha-blockers in the treatment of ureteral stones.

REFERENCES

1. Saita A, Bonaccorsi A, Marchese F, Condorelli SV, Motta M. Our experience with nifedipine and prednisolone as expulsive therapy for ureteral stones. *Urol Int* 2004;72 (Suppl 1): 43-5.
2. Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol.* 2004; 172: 568-71.
3. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol* 2005;174: 167-72.
4. Lipkin M, Shah O. The use of alpha-blockers for the treatment of nephrolithiasis. *Rev Urol.* 2006;8 (Suppl 4): S35-42.
5. Maclean A, Dunn R: Renal/Urology. In: R Dunn, editors. *The Emergency Medicine Manual*. West Beach: Venom Publishing;2000.p.437-9.
6. Ghalayini IF, Al-Ghazo MA, Khader YS. Evaluation of emergency extracorporeal shock wave lithotripsy for obstructing ureteral stones. *Int Braz J Urol* 2008;34: 433-40(discussion 441-2).
7. Weiss RM. Physiology and pharmacology of the renal pelvis and ureter. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. *Campbell's Urology*, Philadelphia: Saunders;2002.p.399-400.
8. Sigala S, Dellabella M, Milanese G, Fornari S, Facciolli S, Palazzolo F, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. *Neurourol Urodyn* 2005; 24: 142-8.
9. De Sio M, Autorino R, Di Lorenzo G, Damiano R, Giordano D, Cosentino L, et al. Medical expulsive treatment of distal-ureteral stones using tamsulosin: a single-center experience. *J Endourol* 2006; 20: 12-6.
10. Resim S, Ekerbicer H, Ciftci A. Effect of tamsulosin on the number and intensity of ureteral colic in patients with lower ureteral calculus. *Int J Urol* 2005;12: 615-20.
11. Gravina GL, Costa AM, Ronchi P, Galatioto GP, Angelucci A, Castellani D, et al. Tamsulosin treatment increases clinical success rate of single extracorporeal shock wave lithotripsy of renal stones. *Urol* 2005; 66: 24-8.
12. Scales CD, Curtis LH, Norris RD, Springhart WP, Sur RL, Schulman KA, et al. Changing gender prevalence of stone disease. *J Urol* 2007;177: 979-82.

13. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs* 2007; 67: 1343-57.
14. Menon M, Parulkar BG, Drach GW. Urinary lithiasis: etiology, diagnosis and medical management. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. *Campbell's Urology*, Philadelphia: Saunders;1998;p. 2702-18.
15. Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol* 2004; 172: 568-71.
16. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. *J Urol* 2005; 173: 2010-2.
17. Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of alpha-blockers for the treatment of ureteral stones. *J Urol* 2007; 177:983-7 (discussion 987).
18. Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. *Urology* 2009; 73: 706-9.
19. Ukhal' MI, Malomuzh OI, Strashnyi VV, Shumilin MV: The use of the alpha 1-adrenoblocker doxazosin in the pharmacotherapy of disorders of urine outflow of spastic origin. *Lik Sprava* 1998;8: 118-21.
20. Holdgate A, Oh CM: Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol* 2005;174: 572-5.

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