ORIGINAL ARTICLE

ROLE OF ALPHA-1 BLOCKER IN EXPULSION OF STONE FRAGMENTS AFTER EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY FOR RENAL STONES

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Background: Renal stone disease is a significant and worldwide health problem. Recent advances in stone management have allowed kidney stones to be treated using extracorporeal shock wave lithotripsy (ESWL), uretero-renoscopy (URS), and percutaneous nephrostolithotomy (PCNL). Recently, medical expulsion therapy (MET) has been investigated as a supplement to observation in an effort to improve spontaneous stone passage rates. **Patients and Methods:** This study was a randomized, controlled, prospective study to determine whether the administration of Alpha-1-adrenergic receptor antagonists as an adjunctive medical therapy, increases the efficacy of ESWL to treat renal stones. Sixty patients with renal stones of 0.5–1.5 Cm in size (average size 1.2 Cm) were included in this study underwent ESWL followed by administration of Alpha-1-adrenergic receptor antagonists at department of Urology Liaquat National Hospital Karachi from Feb 2008 to Sept 2008. This was a comparative study and patients were divided into two groups. In group A patients received conventional treatment Diclofenac sodium, Anti Spasmodic (Drotverine HCl) as required and Proton Pump inhibitor (Omeprazole 20 mg) once daily after shock wave lithotripsy. In group B patients received alpha-1 blocker, Alfuzosin HCl 5 mg twice daily in addition to conventional treatment. All patients were instructed to drink a minimum of 2 litres water daily. Ultrasound guided Dornier Alpha Impact Lithotripter was utilised for shock wave lithotripsy. **Results:** Of the 60 patients, 76.7% of those receiving Alfuzosin and 46.7% of controls had achieved clinical success at 1 month (p=0.01). The mean cumulative diclofenac dose was 485 mg per patient in the Alfuzosin group and 768 mg per patient in the control group (p=0.002). This difference was statistically significant. **Conclusion:** Alfuzosin therapy as an adjunctive medical therapy after ESWL is more effective than lithotripsy alone for the treatment of patients with large renal stones and is equally safe. It increases the expulsion rates of stones, decreases time to expulsion, and decreases need for analgesia during stone passage.

Keywords: Alpha-blockers, Ureteral stones, Kidney stones, ESWL

INTRODUCTION

Renal stone disease is a significant and world wide health problem. Disease that affects about 8% to 15% of the population in Europe and North America.[1] Morbidity rate due to urinary calculi is 2% to 4%, which is similar to that of diabetes.[2–4] Pakistan is located within the geographical distribution of stone disease. Urolithiasis is the commonest urological problem in Pakistan. The effected population means age group in Pakistan is 40 years.[5] Evidence of Urolithiasis can be traced more then seven thousand years back. Excavations of predynastic era, i.e., 7000–3100 BC in Egypt revealed evidence of urinary bladder calculi among the pelvic bones of a mummy. Urologist can claim the pride of being the pioneers in surgery because they started in 12th century BC.

Recent advances in stone management have allowed kidney stones to be treated using shock wave lithotripsy (SWL), uretero-renoscopy (URS), and percutaneous nephrostolithotomy (PCNL). Dornier, a German aircraft corporation, first developed the ESWL. Now ESWL is the reference treatment for renal stones less than 20 mm in diameter[6] and it is also a favourable choice for proximal ureteric stones.[7] In the stone migration process, the sympathetic nervous system modulates ureteral activity, as demonstrated by the presence of alpha-1 adrenergic receptors, more α1A receptors are found widespread in the proximal urethra, prostate and bladder outflow, α1B receptors are found more densely in the vascular smooth muscles, and α1D are predominantly found in the detrusor. α1D receptors are effective in the relaxation of the detrusor and the spasm of the 1/3 distal part of the ureter (especially the intramural part).[8]

Recently, medical expulsion therapy (MET) has been investigated as a supplement to observation in an effort to improve spontaneous stone passage rates.

Several different medical interventions increase the stone passage rate of ureteral stones, including antispasmodic agents, calcium channel blockers and alpha blockers, which have been used in combination with or without steroids.[9–12]

Alpha-1-Blockers

Alpha blockers (also known as alpha adrenergic blockers or alpha adrenergic antagonists) are medications used primarily in the treatment of high blood pressure & in bladder out flow obstruction. Types

of alpha blockers include dihydroergotamine mesylate, ergotamine, phentolamine mesylate, phenoxybenzamine, prazosin, doxazosin, terazosin, alfuzosin, tamsulosin, and tolazoline.

The most recent application of α-blockers in urological disease has been to facilitate the spontaneous passage of obstructing ureteral calculi. The tension of ureteral smooth muscle is mediated by α_1-adrenoceptors. Several small studies have shown that various α_1-blockers increase both the spontaneous passage rate and the time to spontaneously pass obstructing ureteral calculi. It is likely that the use of α_1-blockers to treat distal ureteral calculi will limit the requirement for instrumentation.[13]

Alpha-1-Blockers and SWL

ESWL has been established as an effective therapy for the treatment of ureteral and renal stones. Tamsulosin has been studied as an adjunct therapy along with ESWL. One study compared the stone-free rate in 48 patients who received ESWL for distal ureteral stones of 6 mm to 15 mm.[14] After the patients underwent ESWL, they were randomised to receive either oral hydration and diclofenac, or oral hydration and diclofenac with tamsulosin 0.4 mg. The stone-free rate was 70.8% for patients who received tamsulosin, compared with 33.3% for those who did not (p=0.019).

Gravina and colleagues studied the efficacy of tamsulosin as an adjunctive therapy after ESWL for renal stones.[15] They included 130 patients who underwent renal stone ESWL, excluding patients with lower pole stones. The stones ranged in size from 4 mm to 20 mm., clinical success was achieved in 78.5% of patients receiving tamsulosin and 60% of patients not receiving tamsulosin (p=0.037). Tamsulosin had a greater effect when compared with the control group for larger stones. In stones 4 mm to 10 mm, the clinical success rates with and without tamsulosin were 75% versus 68% (p=0.05), and for stones 11 mm to 20 mm the success rates were 81% versus 55% (p=0.009). Tamsulosin significantly reduced the amount of diclofenac used and reduced the occurrence of flank pain after SWL. Patients receiving tamsulosin required ureteroscopy or a second SWL less often compared with those who did not receive tamsulosin, but the difference was not statistically significant.

Deliveliotis *et al*[16] has shown that Alfuzosin improves symptoms and quality of life in patients with double-J stents.

MATERIAL AND METHODS

This was a comparative study done at Department of Urology, Liaquat National Hospital Karachi from Feb 2008 to Sep 2008 with the approval of an ethical committee. Sixty patients were included and divided into two groups A and B. Patients with solitary renal stone between 5 mm and 15 mm size located in the renal pelvis, middle or upper pole calices were included in this study. Patients having concomitant stones, solitary lower pole renal stones, previous unsuccessful attempts at ESWL, elevated serum creatinine (>2 mg/dl), urinary tract infection, hydronephrosis, concomitant treatment with calcium antagonist, urinary congenital anomalies or previous pyelouretral surgery, pregnancy, severe obesity, severe skeletal malformations were excluded.

Patients were explained about the research protocol and the study conducted after the informed and written consent of all patients. Patient's safety and comfort was assured. Stone size assessment was done with x-ray and ultrasound. Only those who fulfilled selection criteria underwent shock wave lithotripsy by an ultrasound guided Dornier alpha impact lithotripter. Patients were assigned to either conventional treatment group or alpha-1 blocker administration group, after ESWL by lottery method in OPD. The drug administration was started after ESWL and continued for one month period or until an alternative treatment.

Group A (n=30) received conventional treatment alone (Non-Steroidal inflammatory drugs, Diclofenac sodium) as required by the patients, Anti Spasmodic (Drotverine HCl), and proton Pump inhibitor (Omeprazole 20 mg once daily) and acted as control group. Group B (n=30) received conventional treatment and tablet Alfuzosin HCl 5 mg twice daily. All patients were instructed to drink a minimum of 2 litres water daily. Patients were asked about stone expulsion, use of analgesics, episodes of pain, and side-effects of the medications and complications of treatment in follow-up visits.

The follow-up protocol included plain abdominal x-ray or renal ultrasonography every 2 weeks until complete stone clearance. All follow-up data were collected and analysed within 6 months. Success was defined as absence of residual stones or presence of insignificant gravel of 3 mm or less in diameter. Failure was defined as unsuccessful expulsion after 4 weeks, pain uncontrolled by therapy, fever and patient's desire to remove the stone before day 28.

RESULTS

The mean age of the patients was 36.32±14.8 (Range: 15–75) years. No significant differences between the groups were found in these above mention variables (p>0.05).

Out of 60 patients, 45 (75%) were males and 15 (25%) females with male to female ratio 3:1. Most stones were located in the middle pole. The mean diameter of stones was 12.45±2.7 mm.

Both treatment groups received single shock wave lithotripsy. A mean of 2860±140 shocks per patient was delivered at mean voltage of 13.7±0.5 kV, with no difference between group A and B (p>0.05). Fifty-four

(90%) of the entire cohort had evidence of stone fragmentation one day after the lithotripsy as assessed by Ultrasonography, without any difference between the two groups (p>0.05). No patient was stone free on day 1 after ESWL.

A statistically significant difference was found in the rate of clinical success after four weeks between those receiving Alpha-1 Blocker, tablet Alfuzosin HCl (Group B; 76.7%) and the control group (Group A; 46.7%; p=0.01, Figure-1). Although the percentage of clinical success seemed to increase at each visit in both groups, we observed that statistically relevant difference was achieved only in group B. Alfuzosin HCl was statistically superior to conventional treatment both at 2 and 4 weeks, in terms of clinical success.

Stone size 11 to 15 mm in diameter, we found a relevant difference in the success rate between the two groups (56.7% in group B and 23.3% in group A; p=0.02). In contrast, among patients with stone 5–10 mm in diameter, no significant increase occurred in the success rate (20% in group A versus 23.3% in group B; p>0.05; Figure-2). Certain variables examined related to the efficacy of Alfuzosin HCl. Alfuzosin HCl therapy were more effective for stones greater than 10 mm.

Regarding success rate was obtained according to location, for patients with renal pelvis caliceal stones were not significant between groups (p>0.34) while success rate of patients in middle and upper pool was significant between groups (p=0.006, p=0.003, Figure-3). The mean cumulative doses of diclofenac in the Alfuzosin HCl and conventional treatment groups were 485 and 768 mg respectively, with significant difference between the groups (p=0.002, Figure-4). No difference in side-effects was observed among the groups.

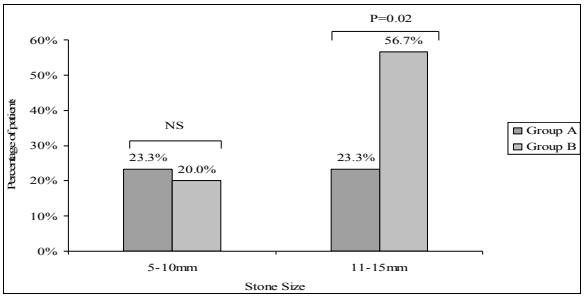

Figure-1

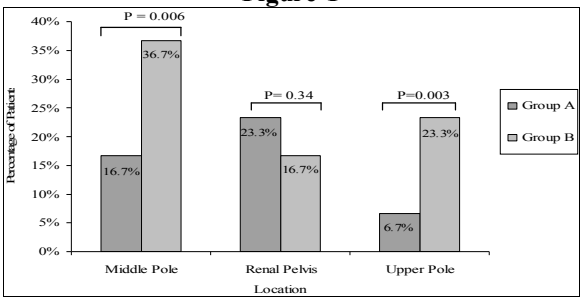

Figure-2

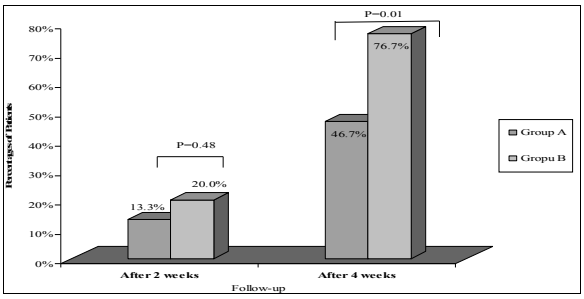

Figure-3

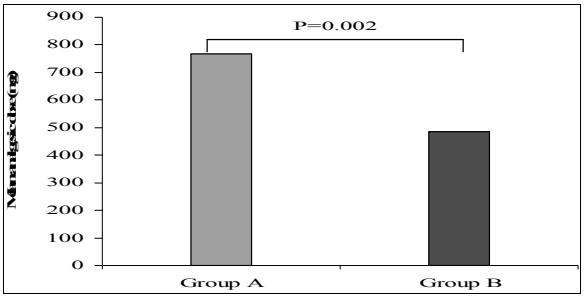

Figure-4

DISCUSSION

Stone fragment expulsion after renal ESWL is probably not dissimilar to spontaneous discharge. Several variables play a fundamental role for the migration process of calculi: stone size; configuration and location, smooth muscle spasm, submucosal oedema, intrinsic areas of narrowing within the ureter; ureteral peristalsis; and infections.[17]

Oedema, infection, spasm, and ureteral peristalsis could be modified by an appropriate medical therapy. Some investigators have reported the effectiveness of different pharmacologic therapies in increasing ureteral stone expulsion by acting primarily on spasm and ureteral peristalsis. Borghi *et al*[18] and Porpiglia *et al*[19] have shown that the association of nifedipine and steroids improved the rate of ureteral stone expulsion and reduced the time for stone passage. Furthermore, alpha$_1$-adrenergic antagonist can cause a decrease in ureteral peristaltic frequency, reducing ureteral spasm.[8]

These changes are accompanied by an increase in the rate of fluid transport.[11] In this regard; several studies have demonstrated that lower tract ureteral stones can be treated efficiently with different types of alpha$_1$ blockers with a few incidences of side effects.[11,19,20] Of the available alpha$_1$ blockers, we chose Alfuzosin because it is much cheaper, easily available and like tamsulosin have comparatively less observed cardiac side effects then other alpha$_1$ blockers like doxazosin or Terazosin. Moreover it is a combined alpha$_{1A}$ and alpha$_{1D}$–selective adrenergic antagonist, and existence of alpha$_{1A}$ and alpha$_{1D}$ adrenoreceptor

subtypes have been demonstrated in the smooth muscle cells of the human ureter.[21]

Alfuzosin was used in addition to conventional medical therapy, which comprises oral analgesic, antispasmodic, proton pump inhibitor and 2 litres of drinking water. The study was performed on carefully selected patients. Patients with lower pole renal stone were excluded because they would probably have realized less benefit from any medical therapy.

By analysing the difference in the stone-free rate of our groups, we observed that 1 month of Alfuzosin therapy had a favourable impact on the clearance of residual fragments after ESWL. However it is possible that prolongation of Alfuzoscin therapy beyond the follow up period could yield an increased stone-free success rate. This assumption originates from the observation that the stone-free status in the control group-A presented with only a little increment between 2 and 4 weeks, but in the treatment group-B, during the same weeks, we observed a continuous increase in the success rate.

The administration of Alfuzosin was particularly effective in the presence of large stones. Stratifying patients according to stone size, we were unable to demonstrate relationship between an original stone diameter up to 10 mm and the success rate. For stones larger then 10 mm, however, success rate was significantly greater in the Alfuzosin group then in the control one.

This result could have been due to the effect of therapy in improving the passage of larger fragments generated after ESWL. During ESWL, larger stone often generate larger stone fragments that migrate less easily. In this occurrence, Alfuzosin could promote the passage of these fragments either by increasing the intra ureteral flow transport above the obstacle or by decreasing the peristalsis above the obstruction.[11]

Gender appeared not to influence the fragment expulsion rate.

Morbidity as measured by pain was significantly lower when ESWL was combined with Alfuzosin, as shown by significant decrease in analgesic use together with easier home patient management. In this regard colic pain is related to ureteral spasm, and Alfuzosin could decrease the algogenic stimuli by decreasing the frequency of peristaltic contractions during expulsion.

The side-effects of Alfuzosin therapy after ESWL were mild, completely reversible, and did not lead any patient to discontinue the drug. On the basis of these results, we propose a simplified algorithm to manage renal stones after ESWL. Patients with a renal stone of 10 mm or less should be primarily treated with ESWL alone. In contrast, patients with a renal stone larger than 10 mm may benefit from adjunctive therapy.

The low clearance rate of lower pole stones after ESWL appear to be due more to retained fragments, relating to the gravity dependant position of the stone and the caliceal anatomy rather than to incomplete stone disintegration.[22]

CONCLUSION

ESWL in association with Alfuzosin is more effective then lithotripsy alone for the treatment patients with renal stones and is equally safe. Alfuzoscin is more useful for stones with large dimension because the larger the original diameter of stone, the greater the number of subjects achieving success. Alfuzosin may decrease the use of analgesic drug after ESWL.

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