IMPACT OF TAMSULOSIN ON CLEARANCE OF RENAL CALCULI AFTER EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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Aim of the work: Is to investigate the role and effect of tamsulosin as adjuvant therapy in treatment of symptomatic renal calculi after extracorporeal shock wave lithotripsy (ESWL).

Patients and Methods: A total 120 patients with single renal pelvic stone <20mm subjected for ESWL. The patients subdivided randomly by the closed envelop technique into 2 equal groups (n=60) according to tamsulosin administration after ESWL. Group I (control group) received no specific treatment while group II received tamsulosin orally (0.4 mg/day). Follow-up was performed at 2, 4 and 6 weeks including history taking, clinical examination, urinalysis, serum creatinine, plain X-ray of urinary tract and abdominal ultrasonography and/or non contrast spiral CT. Definition of success was stone-free state or presence of insignificant asymptomatic residual fragments <4 mm at 6 weeks or earlier. The efficacy of treatment was determined by analysis of stone clearance rate and time, steinstrasse formation, frequency of pain episodes, number and dose of analgesia, side effects of medications and report of admission for severe pain, hematuria or fever.

Results: Out of 120 patients, 113 had a full data and enrolled in the study. Group I included 55 patients and 58 in group II. The overall clearance rate was 95% (55 of 58) in the tamsulosin group and 78% (43 of 55) in the control group (p< 0.05). With larger stones (11 to <20 mm) the difference in the clearance rate was significant (p<0.05) but not with smaller stones (p>0.05). The average dose of analgesic requirment was less with tamsulosin than with controls but with no statistical significance. Steinstrasse resolved spontaneously in tamsulosin group whereas 29% (2 of 7) required intervention in the control group. No significance was detected between both groups for age, sex and stone size.

Conclusions: Shock wave lithotripsy plays a pivotal important role as non-invasive modality in management of renal calculi. Tamsulosin use appear to augment the outcome of ESWL by improving the overall stone clearance rate and time, especially with the larger calculi. Also, it seems to improve the outcome of steinstrasse as it reduce the need of re-admission and intervention. However, further researches are needed to confirm these findings and evaluate tamsulosin as cost effectiveness therapy in stone expulsion.

Key words: ESWL, renal calculi, Tamsulosin, alpha adrenergic blocker.

INTRODUCTION

Revolution in the management of urinary calculi is achieved since the introduction of extracorporeal shock wave lithotripsy at 1982.1 From that date, ESWL become the 1st line of treatment for renal calculi due to its non-invasiveness and high success rate.2 Eighty percent of urinary tract calculi are treated with ESWL with success rate varies from 70% - 90%.2,3 The ESWL outcome depends on proper fragmentation and clearance rate of fragmented stones. Also, there are different variables that affect the efficacy and outcome of ESWL either related to lithotripter as type or design, energy setting, electrode consumption and shock delivery rate or related to stone size, site, number and chemical composition.4 Once the calculus bulk is disintegrated into smaller fragments to pass within the ureter, various factors like ureteral lumen, edema, infection and fragments size determine their spontaneous descent through the ureter. It means that management at this stage is similar to conservative treatment of ureteral calculi. However, use of some drugs can control symptoms and facilitate stone expulsion like anti-inflammatory and anti-edematous, alpha adrenergic blockers or calcium channel blockers.5,6 It is evidenced that blockage of ureteral &amp; #945;1 adrenoceptors, resulting in multiple physiological events as reduction of basal tone of smooth muscle, amplitude and frequency of peristalsis and intra-ureteral pressure with increase of frequency of urine transport and the pressure gradient around the stone that enhances stone expulsion.7 Tamsulosin is a famous alpha blocker used as medical expulsive therapy (MET) due to its good tolerability; no need for dose titration and its uroselectivity for &amp; #945;1a and &amp; #945;1d receptors.8,9,10 The aim of the current study is to investigate the role and effect of tamsulosin as adjuvant therapy in treatment of symptomatic, uncomplicated renal calculi after ESWL.

PATIENTS AND METHODS
This prospective randomized clinical study that included 120 patients with renal pelvic stone subjected for extracorporeal shock wave lithotripsy at a period from January 2009 to June 2010. The inclusion criteria were age above 18 years old, single symptomatic radio-opaque pelvic renal calculi with normal contra-lateral kidney and stone size <20 mm. The exclusion criteria were patients with pregnancy, uncontrolled coagulopathy, severe hydronephrosis, history of previous surgery on ipsilateral lower ureter, multiplicity or bilaterality of stones, renal insufficiency, urinary tract infection and patients on therapy as &\#945; blockers, calcium channel blockers and known allergy to tamsulosin. An informed consent was obtained from all patients. All patients had complete history taking, physical examination, laboratory tests including complete urinalysis and culture, urinary pH, serum creatinine. Diagnosis of stones was based on plain X-ray of urinary tract (PUT), abdominopelvic ultrasonography (US) and non-contrast helical computed tomography (CT).

All patients were divided randomly by the closed envelop technique into 2 equal groups (n=60) according to tamsulosin administration after ESWL. Patients in group I (control group) received no specific treatment, in the form of increase daily fluid intake (>2.5 liters /day), ciprofloxacin 500 mg twice daily and diclofenac sodium orally to relieve pain episodes. Patients in group II received the same previous measures plus oral dose of tamsulosin (0.4 mg/day).

ESWL was performed by electromagnetic Dornier U/30 lithotripter (Dornier Medical Systems-Munich, Germany). The procedure was done in outpatient basis under local infiltration anaesthesia and intravenous analgesia. The procedure began at 10% intensity and increased by 10% every 100 shocks till reach 50%. Then, intensity increased regularly by 5% every 250 shocks to a maximum 70% at a rate of 70 shock / minute depending on stone fragmentation and patient pain tolerance. ESWL was terminated if stone fragmented or 3000 shocks were reached. Few hours later, the patients were discharged after clinical evaluation and post- procedure US to examine for perinephric or subcapsular hematomas. Repeat ESWL was done in cases of incomplete stone fragmentation or presence of residual fragments (>4 mm). Patients allowed for maximum 3 sessions with 2 weeks apart.

The study medications were given for 6 weeks and stopped after spontaneous stone expulsion or at intervention due to complications as hydronephrosis or steinstrasse. Follow-up of the patients was performed at 2, 4 and 6 weeks from enrolling in the study. In every visit, patients evaluated by history taking, clinical examination, urinalysis, serum creatinine, PUT and abdominal US.

Definition of success was stone-free state or appearance of insignificant asymptomatic residual fragments <4 mm at 6 weeks or earlier. On the other hand, failed cases considered as failure of stone expulsion at the end of study, severe hydronephrosis, uncontrollable attacks of renal colic or febrile UTIs were in need of further appropriate management. Those were excluded from final analysis.

The efficacy of treatment was determined by analysis of stone clearance rate and time, steinstrasse formation, frequency of pain episodes, number and dose of analgesia, side effects of medications and report of admission for severe pain, hematuria, vomiting or fever. Statistical analysis was performed using SPSS software ?version 12?. Continuous variables were expressed as mean and SD between the treatment groups. The unpaired Student-t test or Mann-Whitney U test was used to compare the continuous variables between tamsulosin and placebo group, and the chi-square test was used for categorical variables with differences considered statistically significant if p values <0.05.

RESULTS
A total of 120 patients were enrolled in the study, 7 patients excluded during follow up (5 and 2 from group I and II respectively). So 113 patients completed the study. Group I (55 patients) included 33 men and 22 women (mean age; 37.6±11.9 years), group II (58 patients) included 37 men and 21 women (mean age; 39.3±14.7 years). The mean stone size was 10.17±3.17 mm, and 11.52±2.51 mm for group I and group II respectively. The data of patients characteristics of both groups were illustrated in table I and showed no statistical significance for sex, age, or stone size (p> 0.05).

The overall success rate was 92% (101 of 110) with better success rate was in tamsulosin group (97%) versus 82% in the control (p< 0.05). It was noted that there was statistical significance only with large calculi (11-<20 mm) (p< 0.05), not in smaller calculi (5-10 mm) (p> 0.05).

There was a statistical significant difference in the overall stone clearance rate between both groups, it was reported as 80% in group I and 95% in group II (p<0.05). In patients with calculi dimensions from 6 to 10 mm, the difference was statistically insignificant (p>0.05). With larger calculus dimension from 11 to <20 mm, the clearance was 64% (14 of 22) in group I and 89% (25 of 28) in group II, and the difference was statistically significant (p<0.05).

At the end of follow up, residual ureteral fragments were seen in 6 patients in the control group and none in the tamsulosin group. Residual renal fragments were seen in 2 patients in each groups. Steinstrasse was determined in 7 patients in the control group and 5 patients in the tamsulosin group. All patients with steinstrasse cleared spontaneously on follow up except 2 in the control group.
required intervention with ureteroscopy and placement of Double-J stent (excluded from study). The mean clearance time for steinstrasse was 18.3±8.6 vs 12.4±8.1 days in both groups and seems that patients in group II take a longer time for stone clearance. The average dose of analgesia used in group I was higher (median 7) than in group II (median 4), but was not statistically significant (p>0.05). Re-hospitalization was reported to relief pain for 6 patients in group I and 1 patient in group II. They received injectable diclofenac sodium or pethidine hydrochloride.

Perinephric and subcapsular hematoma showed by US in 2 patients in each groups. Dizziness (2 patients) and anejaculation (1 patient) were reported in group II and no other complication related to tamsulosin.

Table (1): Patients characteristics

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>p-value</th>
<th>n.s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>37.6±11.9 y</td>
<td>39.3±14.7</td>
<td>n.s</td>
</tr>
</tbody>
</table>
- Male to female

33

37

n.s

- Rt Sided stones

30

38

n.s

- Mean stone size (mm)
  No. of stones 5-10mm
  No. of stones 11-<20mm

10.17±3.17

33

22

11.52±2.51

30

28

n.s
- n.s = not significant  - HN = hydronephrosis

Table (2): Follow up results at 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall success rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For stones 5-10mm</td>
<td>44 (80%)</td>
<td>43 (78%)</td>
</tr>
<tr>
<td>For stones 11-&lt;20mm</td>
<td>30 (91%)</td>
<td>29 (88%)</td>
</tr>
<tr>
<td>Overall stone free rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For stones 5-10 mm</td>
<td>56 (97%)</td>
<td>55 (95%)</td>
</tr>
<tr>
<td>For stones 11-&lt;20 mm</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td></td>
<td>26 (93%)</td>
<td>25 (89%)</td>
</tr>
</tbody>
</table>

(x2 = 6.09, p< 0.05)*

p > 0.05
(x2= 4.78, p< 0.05)*

(x2= 5.43, p< 0.05)*
p> 0.05
(x2= 8.44, p< 0.05)*

Mean clearance time

17.3 ± 8.6

10.4 ± 7.3

p< 0.05*

Median analgesic use

7

2

p> 0.05

Re-admission rate

6

1

p> 0.05
DISCUSSION

The scenario and rules of descent of renal stone fragments within the ureter after disintegration by ESWL is similar to that controlling spontaneous expulsion of ureteral calculi. Many authors assessed the different factors that control spontaneous expulsion rate of ureteral calculi by clinical studies. Some authors stated that fragment size and location are the most important ones as expulsion rate for stones ≤5 mm is 71% to 94% and 25% to 53% for stone size 5 to 10 mm.11,12 Spasm, edema or infection are other associated factors that may prevent stone passage.13

From the pathophysiological point, impaction of calculous or fragment during its journey within the ureter particularly in narrow parts as ureterovesical junction results in increase intraluminal pressure and spasm of ureteral smooth muscle.14 The aim of conservative therapy is to enhance stone expulsion by increased oral hydration and increased urine output, plus medications that reduce ureteral spasm and relieve the pain of colic. Calcium channel blockers and nitrates are investigated to reduce the spasm.5,15

On studying the distribution of Alpha adrenergic receptors in the lower third of the ureter, a predominance of α1A and α1D receptor subtypes was found.8 As we know, the Urologists are familiar with the use of tamsulosin in treatment of bladder outflow obstruction and this encouraging them to be used in clinical trials. This mean that use of tamsulosin in management of ureteral calculi support the concept of use of a drug with receptor selectivity is better than organ selectivity. Tamsulosin is a selective α1A receptor blocker especially and α1D receptor subtypes of the ureter. The mechanism of action of tamsulosin is to increase urine flow by reduction of the frequency and intensity of peristaltic waves and prevents spasm by relaxing the smooth muscle of the ureter.16 Also, it acts on the C fibers blocking pain conduction.17

In our series, the overall stone clearance is significantly increased with tamsulosin compared to the control group that in agreement with others.4,18 This results are explained by an increase in the intra-ureteral flow due to decreased frequency and amplitude of peristalsis with diminished intra-ureteral pressure above the stone.

As regards to the relation between the effect of tamsulosin on stone clearance and size, it was found that with smaller stones, the difference in clearance between the 2 groups was not significant (p>0.05). With larger stones (11 to <20 mm), the clearance was statistically significant between tamsulosin and control groups (p<0.05). These data are in proportional to others and suggesting that tamsulosin may have a role as an adjunctive to ESWL for larger stones.4,19

The incidence of steinstrasse after ESWL was 2% to 20% with spontaneous passage in 65%. Intervention is limited to patients with obstruction or infection. In a previous trial comparing spontaneous clearance of steinstrasse in placebo and tamsulosin, clearance occurred in 65% in placebo and 75% in tamsulosin group. (20) In our series, 12 patients developed steinstrasse, 5 were in the tamsulosin group and 7 in the control group. Spontaneous clearance was observed in 5 patients (100%) of study group compared to 5 (71%) in the control group. In the tamsulosin group, no residual ureteral fragments noticed in comparison to 6 in the control group suggesting that tamsulosin induce ureteral relaxation to facilitate fragments expulsion.

One of the distressing symptoms of ureteral stones is the ureteral colic. Our results showed that the number of colic episodes and average analgesic requirements showed marked decrease in pain attacks and analgesic use with tamsulosin but of no statistical significance as Bhagat et al (4) and in contrary to others reported statistical significance in their studies.16,20

Different medications were tried clinically to decrease the time of stone passage and pain episodes as corticosteroids and calcium channel blockers aiming to reduce the edema and inflammation by steroids that associated with uretral stone descent and after ESWL. Nifedipine reduces phasic contractions of the ureter and decrease the spasms.15 On comparison between effect of nifedipine and tamsulosin on clearance of ureteral stones, the outcome was not statistically significant between them.14 In another study, it was concluded that expulsion rate was significantly higher in combination of tamsulosin and steroid than steroid alone.21 Moreover, the continuation of tamsulosin intake beyond 3 months after a single session of lithotripsy allowed stone clearance to continue in the tamsulosin group. While in the control group, there was only initial improvement.18

In our study, dizziness in 2 patients and anejaculation in 1 patient are the reported side effects in tamsulosin group. The explanation of limited side effects in our study is that most of the adverse effects occurred beyond 13 weeks of therapy.22

CONCLUSION

Shock wave lithotripsy plays a pivotal important role as noninvasive modality in management of renal calculi. Tamsulosin use appear to augment the outcome of ESWL by improving the overall stone clearance rate and time, especially with the larger calculi.
Also, it seems to improve the outcome of steinstrasse as it reduce the need of re-admission and intervention. However, further researches are needed to confirm these findings and evaluate tamsulosin as cost effectiveness therapy in stone expulsion.

ABBREVIATIONS
ESWL= extracorporeal shock wave lithotripsy; UTIs= urinary tract infections; PUT= plain X-ray to urinary tract; US= ultrasonography; CT= computerized tomography

REFERENCES


