The Role Of Tamsulosine And Deflazacort In The Expulsion Of Up To 6 Mid And Lower Ureteric Calculi

R Ranjan, P Kumari, M Mundu, R Baxla

Citation
R Ranjan, P Kumari, M Mundu, R Baxla. The Role Of Tamsulosine And Deflazacort In The Expulsion Of Up To 6 Mid And Lower Ureteric Calculi. The Internet Journal of Urology. 2013 Volume 11 Number 1.

Abstract
Introduction
Pharmacologically it is possible to treat the possible causes of stone retention such as oedema, ureteral spasm and infection, trying to favour its expulsion by using drugs such as steroids, calcium antagonists and glyceryl trinitrate. Currently alpha 1-adrenergic receptor antagonists represent the treatment of choice for lower urinary tract symptoms as shown in many randomized controlled clinical trials as well as in several case studies.

Aim of the study
To evaluate the efficacy of tamsulosin and deflazacort in the expulsion rate and expulsion time of stone and frequency of analgesic use for relief of ureteral

MATERIALS AND METHODS
This study included consecutive one hundred patients in Rajendra Institute of Medical Science with symptoms suggestive of ureteral calculi between September 2011 and September 2012.

Inclusion criteria: All patients evaluated in Rajendra Institute of Medical Science with ureteral colic due to radiologically proven mid and distal ureteral stones less than or equal to 6 mm and who are managed conservatively

Study type: Experimental study
The study included 100 patients who were selected using purposive sampling technique. The patients were divided into two groups.

• Patients with ureteral colic requiring diclofenac (50/75mg) orally/ parenterally as needed for pain.
• Analgesic therapy plus tamsulosin (0.4 mg/daily) orally and deflazacort (30 mg) for 10 days

The duration of trial was until expulsion of the stone, but no longer than 4 weeks.

Result
Mean stone size was 5.157 mm which was in the similar range found in most studies. The expulsion rate in the tamsulosin and deflazacort group in the present study was 92% which was in concurrence with other studies. The mean time to expulsion in the tamsulosin group in the present study was 7.95 days which was in comparable with and shorter than in other study (7.9 days).

Conclusion
Medical expulsive therapy with tamsulosin and deflazacort considerably decreased the analgesic use thereby reducing additional need for pain relief and served as an effective bridge between watch-and-wait management and surgical intervention

LIST OF ABBREVIATIONS
ESWL/SWL : Extracorporeal Shockwave Lithotripsy
PCNL/PNL : Percutaneous Nephrolithotomy
URS : Ureterorenoscopy
UTI : Urinary Tract Infection
NANC : Noradrenergic Noncholinergic Components
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AR : Androgen Receptor
PLC : Phospholipase C
IP3 : Inositol Triphosphate
DAG : Diacylglycerol
SS : Spersaturation
Ksp : Thermodynamic solubility product
CaOx : Calcium Oxalate
CaP : Calcium Phosphate
Kfp : Formation product
ULM : Upper Limit of Metastability
THP : Tamm-Horsfall Protein
RNA : Ribonucleic Acid
DNA : Deoxyribonucleic Acid
ROS : Reactive Oxygen Species
NC : Nephrocalcin
NB : Nanobacteria
UPJO : Uretero-pelvic Junction Obstruction
CD : Calyceal Diverticulum
AUA : American Urology Association
LUTS : Lower Urinary Tract Symptoms

INTRODUCTION

Urolithiasis (urinary stones) is an ailment affecting 12% of the world population. Symptomatic urolithiasis represents the most common condition observed by surgeons and urologists in an emergency setting. 70% of urolithiasis are located in the lower third of the ureter. The transport of stones from the kidney into the bladder and their movement through the ureter is accompanied by three basic factors; 1) spasm of smooth muscles, 2) submucoal oedema and 3) pain. Determining factors for spontaneous passage of stones are their size, their configuration, and the smooth muscle activity of the ureters. In the transport of stones, the greatest obstacle is usually the terminal part of the ureters, mainly in the intramural 'detrusor tunnel'. Most stones are 4 mm or smaller and pass spontaneously, although this is not without discomfort and expense to the patient. Ureteral calculi of any size are often associated with renal obstruction, and care must be taken to prevent irreversible damage to the kidney whether choosing expectant or active management.

In the last 20 years, the introduction of new, minimally invasive procedures like percutaneous nephrolithotripsy (PCNL), flexible ureteroscopy, extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS) and laser for ureteral stones have considerably changed the historical therapy for this disease with a substantial increment in treatment costs.

Pharmacologically it is possible to treat the possible causes of stone retention such as oedema, ureteral spasm and infection, trying to favour its expulsion by using drugs such as steroids, calcium antagonists and glyceryl trinitrate. Currently alpha 1-adrenergic receptor antagonists represent the treatment of choice for lower urinary tract symptoms as shown in many randomized controlled clinical trials as well as in several case studies. Studies have revealed that presence of alpha 1-adrenergic receptors are significantly higher in ureteral smooth muscle cells than other adrenergic receptors. Furthermore, alpha 1-adrenergic antagonists have proved to inhibit basal tone, peristaltic frequency and ureteral contractions even in the intramural tract. The study is taken up to assess the possible role of the combined alpha 1a and alpha 1d selective antagonist tamsulosin and corticosteroid deflazacort for facilitating spontaneous expulsion of mid and distal ureteral stones.

OBJECTIVES OF THE STUDY

1. To evaluate the efficacy of tamsulosin and deflazacort in the expulsion rate and expulsion time of the stone.
2. To evaluate the effect of tamsulosin and deflazacort administration on frequency of analgesic use for relief of ureteral colic due to mid and lower ureteral calculi.

MATERIALS AND METHODS

This study included consecutive one hundred patients in Rajendra Institute of Medical Science with symptoms suggestive of ureteral calculi between September 2011 and September 2012. All patients were evaluated on outpatient basis and underwent a standard evaluation of transabdominal renal ultrasonography. In this study only such patient had been considered who had stones in the mid and lower third ureter.

Inclusion criteria:
• All patients evaluated in Rajendra Institute of Medical Science with ureteral colic due to radiologically proven mid and distal ureteral stones less than or equal to 6 mm and who are managed conservatively.

Exclusion criteria:
• Stone larger than 6 mm
• Clinical and laboratory signs of urinary tract infections (UTIs)
• Severe hydronephrosis on ultrasound examination (gross pelvicalyceal dilatation with parenchymal thinning).
• Co-morbid conditions such as diabetes, alteration in renal parameters (serum creatinine and blood urea).
• Previous history or ureteral manipulation and/or surgery.
• Multiple ureteral stones.
• Known sensitivity to alpha blockers.
• Pregnancy.
• Urethral stricture

Study type:
Experimental study
The study included 100 patients who were selected using purposive sampling technique. The patients were divided into two groups.

• Patients with ureteral colic requiring diclofenac (50/75mg) orally/parenterally as needed for pain.
• Analgesic therapy plus tamsulosin(0.4 mg/daily) orally and deflazacort (30mg) for 10 days.

The duration of trial was until expulsion of the stone, but no longer than 4 weeks.

Outcome measures:

• Expulsion rate: Stone expelled or not.
• Expulsion time: time to expulsion from the commencement of therapy.
• Number of times/ cumulative dose of diclofenac administered.
• Objective documentation of stone expulsion was done based on follow-up renal ultrasonography.

Patients who did not pass the stone spontaneously were referred for intervention (URS, ureteric stent insertion, ESWL).

Collected data was analyzed with Student’s t test and Chi-square.

RESULTS
There is no significant difference in control and test group according to age incidence.

Table 1
AGE DISTRIBUTION

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>CONTROL GROUP</th>
<th>TAMSULOSINE+DEFLAZACORT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>20-30</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>31-40</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>41-50</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>&gt;51</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Chi-square=0.328 p value=0.9875 (non-significant)

Figure 1
AGE DISTRIBUTION

There is no significant difference in control and test group according to calculus size distribution.

MEAN CALCULUS SIZE = 5.123 (CONTROL GROUP)
MEAN CALCULUS SIZE = 5.203 (TAMSULOSINE+DEFLAZACORT)

Table 2
CALCULUS SIZE DISTRIBUTION

<table>
<thead>
<tr>
<th>CALCULUS SIZE IN mm</th>
<th>NUMBER</th>
<th>PERCENTAGE</th>
<th>NUMBER</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>6</td>
<td>12</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>4.5</td>
<td>18</td>
<td>36</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>5-6</td>
<td>26</td>
<td>52</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>100</td>
<td>50</td>
<td>100</td>
</tr>
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</table>

Chi-square = 0.194 P value = 0.9078 (non-significant)
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Table 3
CALCULUS SIDE DISTRIBUTION

<table>
<thead>
<tr>
<th>CALCULUS SIDE</th>
<th>CONTROL GROUP</th>
<th>TAMSULOSINE+DEFLAZACORT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER</td>
<td>PERCENTAGE</td>
<td>NUMBER</td>
</tr>
<tr>
<td>LEFT</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>RIGHT</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Chi-square = 0.100  P value = 0.6891 (non-significant)

The mean analgesic dose consumed by a patient in the control arm was 903 mg, while it was 285 mg by a patient in the tamsulosin arm. The p value was 0.000 (<0.001) which is highly significant.

Table 5
ANALGESIC DOSE

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NUMBER</th>
<th>MEDIA</th>
<th>STANDARD DEVIATION</th>
<th>MEAN</th>
<th>p VALUE</th>
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</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>50</td>
<td>1000</td>
<td>803.00</td>
<td>491.1</td>
<td>51</td>
</tr>
<tr>
<td>TAMSULOSINE + DEFLAZACORT</td>
<td>50</td>
<td>200</td>
<td>195.00</td>
<td>227.386</td>
<td>0.00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>500</td>
<td>540.00</td>
<td>268.3</td>
<td>36</td>
</tr>
</tbody>
</table>

Figure 5
ANALGESIC DOSE

Figure 2
CALCULUS SIZE DISTRIBUTION

Figure 4
EXPULSION RATE

Chi-square = 13.653  P value = 0.0002 (significant)
Expulsion rate in tamsulosin + deflazacort group is significantly affected. The p value is 0.0002.

Table 4
EXPULSION RATE

<table>
<thead>
<tr>
<th>EXPULSION</th>
<th>CONTROL GROUP</th>
<th>TAMSULOSINE+DEFLAZACORT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER</td>
<td>PERCENTAGE</td>
<td>NUMBER</td>
</tr>
<tr>
<td>NO</td>
<td>29</td>
<td>58</td>
</tr>
<tr>
<td>YES</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

DISCUSSION
In this study, we used the selective alpha-1a blocker, tamsulosin and deflazacort to evaluate the efficacy of medical expulsive therapy in mid and distal ureteral calculi less than 6 mm.

There was no statistical significant difference in the age
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distribution or the size of the calculus in the two groups. Mean stone size was 5.157 mm which was in the similar range found in most studies. The expulsion rate in the tamsulosin and deflazacort group in the present study was 92% which was in concurrence with other studies. The mean time to expulsion in the tamsulosin group in the present study was 7.95 days which was in comparable with and shorter than in Porpigilia study (7.9 days).

The frequency of analgesic use was significantly reduced in the tamsulosin and deflazacort group in the present study (285 v 903 mg) which was in concurrence with other studies. However, there is considerable variation in the absolute value of the analgesic dose which may be due to various factors like difference in the standard dose available and patient's threshold for pain.

There were no significant side effects in either group which confirmed. The clinical profile of tamsulosin and deflazacort and diclofenac as considerably safe and convenient.

Table 6
Comparison of outcome parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>Expulsion Rate</th>
<th>Expulsion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervosier</td>
<td>63.7%</td>
<td></td>
</tr>
<tr>
<td>Cellabellu</td>
<td>68%</td>
<td>4.4 days</td>
</tr>
<tr>
<td>Antonio</td>
<td>68%</td>
<td>4.8 days</td>
</tr>
<tr>
<td>Porpigilia</td>
<td>68%</td>
<td>7.7 days</td>
</tr>
<tr>
<td>Our study</td>
<td>92%</td>
<td>7.95 days</td>
</tr>
</tbody>
</table>

There were no significant side effects in either group which confirmed. The clinical profile of tamsulosin and deflazacort and diclofenac as considerably safe and convenient.

Therefore, it is possible to suggest that the effect of tamsulosin on the obstructed ureter is to induce an increase in the intraureteral pressure gradient around the stone, that is an increase in the urine bolus above the stone (and consequently an increase in intraureteral pressure above the stone) as well as decreased peristalsis below the ureter (and consequently a decrease in intraureteral pressure below the stone) in association with the decrease in basal and micturition pressures even at the bladder neck. For these reasons there would be a stronger urge to expel the stone. Furthermore, the decreased frequency of phasic peristaltic contractions in the obstructed ureteral tract induced by tamsulosin might determine a decrease in or the absence of the algogenic stimulus, as in our study. Steroids have also been used to aid stone passage. The rationale for this treatment is that it reduces stone-induced oedema and hence allows a calculus to pass. Steroids combined with an alpha blocker proved more efficacious than either a steroid or alpha blocker alone. Porpiglia et al. Compared tamsulosin; deflazocort; a combination of tamsulosin and deflazocort; and analgesics (taken when required). The groups were comparable in terms of age, sex, and stone size and location of the stone.

Figure 6
USG showing stone of 5.8 cm at right Ureterovesical Junction

Figure 7
USG of same patient after treatment with Tamsulosine and Deflazacort

SUMMARY

• The majority of patients in our study were in the age group between 20-40 years.
• There was no statistical significant difference in age and calculus size distribution in the two groups.
• The expulsion rate was significantly higher in the tamsulosin and deflazacort group.
• The expulsion time was significantly less in the tamsulosin and deflazacort group.

• The analgesic dose used by patient in the tamsulosin and deflazacort group was significantly lower.

CONCLUSION

The results of this study have shown a potentially important role of tamsulosin for conservative expulsive therapy of juxtavesical ureteral stones, broadening pharmacological indications rather than endoscopic treatments for the resolution of this disease. Obviously further studies with larger number of cases are necessary to validate these promising and statistically significant results. The comparison with minimally invasive procedures in terms of cost and efficacy was useful, highlighting a predominant role of first line pharmacological treatment, which can be easily be provided in an outpatient setting and not only at large, technologically advanced, special centers. The drug, tamsulosin proved to be safe and effective as demonstrated by the low incidence of side effects and the increased stone expulsion rate and reduced expulsion time. Moreover, medical expulsive therapy with tamsulosin and deflazacort considerably decreased the analgesic use thereby reducing additional need for pain relief and served as an effective bridge between watch-and-wait management and surgical intervention.

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Author Information

Rajeev Ranjan, Dr, M.B.B.S, J.R.A III
Department Of Surgery, Rajendra Institute Of Medical Sciences
Ranchi, India
drrajeevsingh1982@gmail.com

Puja Kumari, Dr, M.B.B.S, J.R.A III
Department of obstetrics and gynaecology, N.E.I.G.H.R.I.M.S.
Shillong, India

M. Mundu, Dr, M.B.B.S, M.S, Assistant Professor
Department Of Surgery, Rajendra Institute Of Medical Sciences
Ranchi, India

R.G. Baxla, M.B.B.S, M.S, Professor
Department Of Surgery, Rajendra Institute Of Medical Sciences
Ranchi, India