Does Tamsulosin Promote the Passage of Distal Ureteric Stones? A Systematic Review and Meta-analysis

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Abstract

**Background:** Ureteric colic is a common presentation to the emergency department, usually managed by conservative and medical expulsive treatments. The objective of this meta-analysis was to assess whether tamsulosin is effective in promoting stone passage in adult patients presenting with ureteric colic.

**Methods:** We searched several electronic databases for randomized controlled trials (RCTs), investigating the efficacy of tamsulosin in ureteric stone expulsion. Data were extracted from eligible trials and pooled using Comprehensive Meta-analysis software as Odds ratios (OR) and respective 95% confidence interval (CI).

**Results:** Our search retrieved 14 studies (n= 4877 patients) that met our inclusion criteria. Analysis under the random effects model showed that tamsulosin was significantly superior to control groups in eliminating stones (OR=2.96; 95% CI: 2.02, 4.34; p < 0.01). However, we noted significant heterogeneity (p <0.001; I² = 65.9%) and publication bias in this outcome. Data of individual studies showed reduced stone expulsion time (in most studies), improved expulsion rate with stone size < 5 mm and mild reported adverse events, including dizziness, hypotension and retrograde ejaculation.

**Conclusion:** The current published data suggest that tamsulosin is safe and effective in increasing the expulsion rate of distal ureteric stones especially in the subgroup of <5 mm calculi. Future multicentre studies with longer follow-up periods should use more standardized protocols and consider stratification based on calculus size.

**Keywords:** Alpha-blockers; Meta-analysis; Tamsulosin; Ureteric stones

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INTRODUCTION

Urinary stones are a common urological problem worldwide whose incidence has increased in the recent years probably due to dietary changes. An average of 12% of the global population has a history of urinary stones and the overall recurrence rate is approximately 50% (1). The peak age of incidence is between 20 and 50 years (2). Ureteric colic is a common presentation to the emergency department, usually caused by a stone stuck in the ureter (3). The mainstay of emergency management is analgesia, bloods tests, imaging to confirm the position of stone and rule out complications and then follow up in the Urology outpatient clinic. A small number of patients require inpatient management for pain relief and dealing with any complications (4).

Current treatment options for ureteral stones include conservative management, as well as active procedures, such as extracorporeal shock wave lithotripsy and ureteroscopy (3). Because of technological advances, the success rates of stone-related procedures have increased while complication rates have decreased (4). Despite the benefits of active interventions, they are expensive and still pose a greater than minimal risk in terms of anaesthetic and surgical risks (5). As long as the patient is not suffering from stone-related complications, conservative management or medical expulsive treatment is an appealing, low-cost approach (6). Several receptors were found in the ureteral tissue, including α adrenergic receptors and blocking them inhibits the peristaltic activity and ureteral contractions (7). This explains why some α-blockers were found effective in promoting stone expulsion (8). However, there is debate in the literature over the efficacy of α-blockers in ureteral stone expulsion with positive and negative results in different studies.

The objective of this meta-analysis was to assess whether tamsulosin is effective in promoting stone passage in adult patients presenting with ureteric colic.

METHODS

Literature search

Before commencing literature search, the inclusion and exclusion criteria were set and are illustrated fully in table 1. The following keywords were used with different combinations (Ureteric OR Urinary AND Stone OR Calculus AND Tamsulosin OR alpha blocker OR alpha 1 adrenergic receptor antagonist AND expulsion). The following databases were searched: MEDLINE (via PubMed), EMBASE and CINAHL from their inception till March 2018. The full search strategies in all three databases are illustrated in supplementary file 1. We ran an additional search of Google Scholar, Clinicaltrials.gov and Cochrane register of clinical trials. Moreover, we searched the bibliography of relevant studies for any missed eligible trials. The Grey literature was searched to find any other articles missing from the main search engines.

Data extraction and quality assessment

Data were extracted from all eligible studies in a standardized Microsoft Excel sheet. The extracted data included the study criteria as for sample size, methods, results and strength points/limitations. Quantitative data on the stone expulsion rate were extracted for meta-analysis. The quality of included studies was evaluated using the JADAD score which assesses the quality of randomization and blinding as well as the rates of drop-outs or withdrawals.
Table 1 shows the criteria for including studies in this review

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<tr>
<th>Domain</th>
<th>Inclusion Criteria</th>
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<tr>
<td>Population</td>
<td>Adult patients presenting with distal ureteric colic</td>
<td>Proximal ureteric stones</td>
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<tr>
<td>Intervention</td>
<td>Tamsulosin</td>
<td>Other alpha blockers, use of multiple drugs and muscle relaxants</td>
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<tr>
<td>Comparison</td>
<td>Conventional treatment, Placebo</td>
<td>Operative treatments and shock wave lithotripsy</td>
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<tr>
<td>Outcome Measures</td>
<td>1ry: Expulsion rate of the stone</td>
<td></td>
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<td></td>
<td>2ry: Expulsion time and complications</td>
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<tr>
<td>Study Design</td>
<td>Randomised Controlled Trials</td>
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<td>Case Series</td>
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<td>Conference presentations</td>
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**Meta-analysis**

Data from eligible studies was subjected to meta-analysis to test whether Tamsulosin is better than control in expelling distal ureteral stones. For this review, Odds Ratio (OR) with 95% confidence interval was chosen as the effect size. The Cochran Q, a Chi square based test was used to assess the heterogeneity (between study variability) in this meta-analysis. A significance level of p<0.1 was used for statistical test of heterogeneity. While ‘Q’ statistic provided the qualitative information on the existence of heterogeneity, ‘I2’ that is calculated as the percentage of the total variability in a set of effect sizes due to true heterogeneity, was used to quantify the degree of heterogeneity. In case of multiple dosage groups within a study, the groups were considered as separate data sets.

High resolution forest plots were derived to represent the comparison of effects of the interventions corresponding to 95% confidence interval and the p value. The Random effects model was used in the current meta-analysis because heterogeneity was significant.

Publication bias was investigated using the funnel plots constructed based on standard error by log odds ratio. The classic fail-safe N test was used to quantify the degree of publication bias. Comprehensive Meta-analysis, Version 2 was used for all the meta-analysis procedures.

**RESULTS**

**Literature search results**

The literature and manual searches combined retrieved 285 records. After duplicate removal, the titles and abstracts of 222 articles were scrutinized for relevance and 21 were selected for full-text review (Figure 1: PRISMA Flow diagram). Of these, seven articles were excluded, and the remaining 14 (4877 patients) were selected for inclusion in this analysis (9-22). The design and findings of all included trials, as well as the quality scoring are illustrated in Table 2.

**Findings of individual studies**

The primary outcome in included studies was the stone expulsion rate, defined as stone
expulsion, confirmed by negative findings on imaging-X-ray, Ultrasound scan (USS), intravenous urogram or computed tomography (CT). While most studies showed improvement in the stone expulsion rate in the tamsulosin group, compared to control groups, some authors (21) reported no overall benefit. Most studies completed the follow-up period for 28 days. However, the follow up periods in the studies by Herman et al (12) and Ferre et al (11) were 21 and 14 days, respectively. A low dose of tamsulosin (200 mcg) was used in two studies (9, 14) and showed increase in stone expulsion rate compared to control groups.

The secondary outcomes in the included trials were expulsion time and complication rates. Most studies showed reduce expulsion time in the Tamsulosin group. Some authors showed no difference in the expulsion time (14). In the study done by Hermanns et al, the exact time of passing the stone was missing in a significant number of patients (12). In terms of pain and complications, most included studies showed reduce use of analgesia in the tamsulosin group and no significant side effects which would warrant stopping tamsulosin. The reported adverse events were dizziness, hypotension and retrograde ejaculation.

The size of the calculi was <10 mm in all studies, but the size limit varied, as well as the radiological methods used to measure it. Some studies enrolled patients with intermediate stone size of 4-7 mm (17, 22), while others enrolled patients with stone sizes between 5 and 10 mm (10, 15). The X-ray of kidney, ureter and bladder (KUB) was used to measure the size of the calculus in the study by Lojanapiwat et al. (9), while others used a combination of X-ray and CT (22) or USS only (17). There had been no mention of Kappa scoring for these measurements. Subgroup analysis of different calculi sizes was done in a study by Al-Ansari et al. (13) and showed more benefit with stone size <5 mm.
<table>
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<tr>
<th>Study ID and quality score</th>
<th>Design, Population group</th>
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<tr>
<td>Ye et al⁹, 2017 (JADAD score = 5)</td>
<td>China, Outpatients, Sep 2011-Aug 2013</td>
<td>N=3450 Tamsulosin 400 mcg vs. Placebo for 4 weeks.</td>
<td>T group had higher stone expulsion than placebo (86% vs 79%; p&lt;0.001)</td>
<td>-T treatment increase stone expulsion and reduce pain. -Subgroup analysis for T group showed increased expulsion rate for stones &gt; 5 mm.</td>
<td>-Large, Multicentre, Randomized, double-blind, placebo-controlled trial. -Inclusion/exclusion criteria given. -Intention-to-treat analysis used. -Power calculation done.</td>
<td>Stone size only 4-7 mm was included in the trial.</td>
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<td>Hermanns et al¹³, 2009 (JADAD score = 5)</td>
<td>Switzerland outpatients Sep 2006 – Sep 2008</td>
<td>N= 90 Tamsulosin 400 mcg for 21 days vs. placebo</td>
<td>-Stone expulsion rate in T = 86.7% and 88.9% in C (p=1.0). -Expulsion time in T = 7 (3-10) and 10 (3-20) in C (p=0.36).</td>
<td>No improvement in stone expulsion rate in patients with stones &lt; 7 mm.</td>
<td>-Double blinded -Placebo controlled and allocation concealment -Inclusion/exclusion criteria given. -Power calculation done.</td>
<td>Stone size &lt; 7 mm included in this study - Metamizole used as second-line analgesic. -Follow up is 21 days -Exact time of stone expulsion missing in 32% patients. -No intention-to-treat analysis</td>
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<td>Al-Ansari et al.¹⁰, 2010 (JADAD score = 4)</td>
<td>Egypt, Outpatients Recruitment May 2007 – May 2009</td>
<td>N=96 Tamsulosin 400 mcg vs. placebo for 4 weeks</td>
<td>-Stone expulsion in T = 82% (41/50) and 61% (28/46) in C (p&lt;0.02). -Expulsion time in T = 6.4±2.77 days vs. 9.87±5.4 in C</td>
<td>Tamsulosin enhances stone (&lt;10 mm) expulsion in the distal ureter and is safe.</td>
<td>-Power calculation done -Inclusion/exclusion criteria given -Double blinded -Allocation concealment</td>
<td>No overall benefit with 400 mcg of Tamsulosin. In the subgroup with large stones (5-10 mm), T increased the stone passage. -Randomized, double-blind, placebo-controlled multicentre trial -Inclusion/exclusion criteria given -Intention-to-treat analysis -Pragmatic-done in ED -Large number of patients assessed but not included in the trial-selection bias. -Attrition bias as patients lost to follow-up. -Poor compliance. -Measurement and recall bias.</td>
</tr>
<tr>
<td>Furyk et al²², 2015 (JADAD score = 4)</td>
<td>Australia, Emergency Department, October 2010-March 2014</td>
<td>N=403 Tamsulosin 400 mcg vs. placebo for 28 days.</td>
<td>Stone expulsion 140/161 (87%) in T and 127/155 (81.9%) in C: Difference of 5% (95% CI 3.1%-41.6%)</td>
<td>No overall benefit with 400 mcg of Tamsulosin. In the subgroup with large stones (5-10 mm), T increased the stone passage.</td>
<td>-Randomized, double-blind, placebo-controlled multicentre trial -Inclusion/exclusion criteria given -Intention-to-treat analysis -Pragmatic-done in ED</td>
<td>-Large number of patients assessed but not included in the trial-selection bias. -Attrition bias as patients lost to follow-up. -Poor compliance. -Measurement and recall bias.</td>
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| Ferre et al\(^\text{19}, \ 2009\) | USA Emergency Department Aug 2006-Nov 2007 | N=80 Tamsulosin 400 mcg for 10 days vs. analgesics only. | Stone expulsion in T=27/39 (77.1%) and in C=24/41 (64.9%); p =0.504 | No overall benefit with the addition of Tamsulosin | -Emergency department study  
-Intention-to-treat analysis  
-Inclusion/exclusion criteria given  
-Allocation concealment. | -Tamsulosin given only for 10 days and early follow up at 14 days.  
-Small, single centre study.  
-No placebo in the control group. Not double blinded  
-Incomplete data for 5 subjects.  
-Stone size < 6 mm. |
| Gomez et al\(^\text{16} \ 2010\) | Mexico Emergency Department Jun 2006-Dec 2007 | N=65 Tamsulosin 400 mcg for 4 weeks vs. Placebo (starch tablets) | Stone expulsion 69%(22/32) in T group and 70%(23/33) in control group. P=0.9 | No significant difference in mean expulsion time between the 2 groups. | -Double blinded  
-Inclusion/exclusion criteria given  
-Power calculation done | -Stone size 5-10mm  
-No pain follow-up carried.  
-No description of randomization and blinding.  
-No intention-to-treat analysis |
| Lojanapiwat et al\(^\text{5}, \ 2008\) | Thailand, outpatients Recruitment Jan 2006-Jul 2006 | N=75 200mcg and 400mcg of Tamsulosin (maximum 28 day) vs. Diclofenac only | Expulsion rate in Tamsulosin (400mcg) = 68%(17/25), P<0.001  
Expulsion time= 10.76 days  
Expulsion rate in Tamsulosin(200mcg) = 40%(10/25)  
Expulsion time 9.3  
Expulsion rate in control= 4%(1/25)  
P< 0.001  
Expulsion time = 23 | Both low dose and standard dose Tamsulosin are effective in Asian patients and can be used as first-line treatment for stone size of 4-10mm | -Block randomization  
-Power calculation  
-Compared 2 doses of Tamsulosin  
-Inclusion/exclusion criteria given | -Calculi measurement on KUB and included only 4-10mm.  
-Randomized by assistant nurse and lack of allocation concealment  
-No blinding  
-Small, single centre study |
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| Sayed et al\(^9\), 2008   | Egypt, Outpatient        | N=90    | Expulsion rate in T = 88.9% (40/45) and 51.1% (23/45) in C group; \(p=0.001\) | Tamsulosin should be added to the standard medical treatment of patients with distal ureteric stones. | -No dropouts  
-No complications  
-Data on analgesic use and pain episodes  
-Inclusion/exclusion criteria given | -No mention of randomization or blinding  
-No power calculation  
-Radio-opaque calculi 5 - 10 mm only  
-Small single-center study |
| (JADAD score = 2)          | Recruitment Oct 2005 – Jul 2006 | Tamsulosin 400 mcg for 4 weeks vs. conventional treatment | Expulsion time in T = 7.32±0.78 and 12.53±2.12 in C group; \(p=0.04\) | | |
| Bajwa et al\(^8\) 2011    | Pakistan, Urology        | N=60    | T group stone expulsion 23/30 compared to C group 11/30, \(p=0.0026\) | Tamsulosin increases spontaneous expulsion of small distal ureteral stones. | -Inclusion/exclusion criteria given | -Simple randomization  
-Small, single centre study  
-No mention of blinding  
-Follow up not explained  
-No power calculation |
| (JADAD score = 2)          | outpatient, Mar 2011-Sep 2011 | Tamsulosin 400 mcg vs. control (diclofenac) for 4 weeks | | | |
| Mustafa et al\(^11\) 2016 | Bangladesh, Urology      | N=120   | Stone expulsion in T group 51/60 (85%) and 32/60 (53.3%) in C group; \(P<0.05\) | Tamsulosin supplemental conventional therapy is more effective. | -Parallel, double blinded.  
-Randomization by computer.  
-Inclusion and exclusion criteria given. | -Single centre  
-Stone size<8mm  
-No intention to treat analysis  
-No explanation given for the drop outs. |
| (JADAD score = 2)          | outpatients Jul 2007-Jun 2008 | Tamsulosin 400 mcg vs. control (hydrotherapy) for 4 weeks | | | |
| Rahim et al\(^8\) 2012    | Pakistan Urology         | N=90    | T group stone expulsion 37/45 and C group 22/45, \(P=0.001\) | Tamsulosin increases spontaneous stone expulsion in the distal ureter. | Inclusion/exclusion criteria given. | -Stone size 4-7mm  
-Confusion as which treatment given Tamsulosin or Terazosin.  
-Single centre and small study |
<p>| (JADAD score = 2)          | outpatients, Nov 2008-May 2009 | Tamsulosin 400 mcg for 4 weeks vs. control diclofenac | | | |</p>
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<tr>
<td>Kaneko et al, 2010 (JADAD score = 2)</td>
<td>Japan, urology Nov 2005 - Aug 2006</td>
<td>N=65 Tamsulosin 200mcg for 28 days vs. control</td>
<td>Expulsion rate in T = 24/31 (77%) and 17/34 (50%) in C p=0.002</td>
<td>Low dose Tamsulosin showed increase in the spontaneous passage of stones</td>
<td>-Inclusion/exclusion criteria given</td>
<td>-Small, single centre study, restricted to Japanese males -Used lower dose of Tamsulosin (200 mcg/day) -No power calculation -Randomization not explained -No mention of blinding</td>
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<tr>
<td>Ahmad et al, 2015 (JADAD score = 1)</td>
<td>Pakistan, Jan 2010-Oct 2010</td>
<td>N=97 Tamsulosin 400mcg for 4 weeks vs. placebo</td>
<td>Stone expulsion rate of 85.71% (42/49) in T group and 54.20% (26/48) in C group; P=0.032</td>
<td>Increase stone expulsion rate in T group</td>
<td></td>
<td>-Small, single centre study -Stone size&lt;8mm -No intention-to-treat analysis -Randomization not explained -No description of blinding</td>
</tr>
<tr>
<td>Alizadeh et al, 2014 (JADAD score = 1)</td>
<td>Iran Urology outpatients, (Jun 2007-Jul 2008)</td>
<td>N=96 Tamsulosin 400mcg vs. control for 4 weeks.</td>
<td>Stone expulsion 82% (41/50) in T group compared to 62.5% (30/46) in control; p&gt;0.05</td>
<td>No significant difference between the 2 groups in spontaneous stone expulsion but reduction in the duration of expulsion in the T group.</td>
<td></td>
<td>-Small, single centre study -Stone size 3-6mm and age&lt;60 years. -No intention-to-treat analysis -No description of randomization and blinding</td>
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</table>
**Meta-analysis results**

Analysis under the random effects model showed that tamsulosin was significantly superior to control groups in eliminating the stone (OR=2.96; 95% CI: 2.02, 4.34; p < 0.01). The Cochran Q was 41.12, which was statistically highly significant (p < 0.001). The included studies were highly heterogeneous (I² = 65.96%); Figure 2. Sensitivity analysis conducted by removal of each study showed that none of the studies had a greater impact on the overall OR as the statistical significance was unchanged; Figure 3.

The funnel plot of expulsion rate showed that publication bias exists in the included set of studies as more studies were plotted on the right side of the plot; Figure 4. Further, imputation plotted 5 studies on left side that are possibly missing. The fail-safe N was 338. This means that we would need to locate and include 338 'null' studies for the combined 2-tailed p-value to exceed 0.05. Put another way, 22.5 missing studies are needed for every observed study for the effect to be nullified.

**Figure 2** shows the Forest plot of expulsion rate comparing tamsulosin and control groups.

**Figure 3** shows the results of sensitivity analysis of expulsion rate outcome.
DISCUSSION

The results of this meta-analysis, as well as most included studies showed that tamsulosin is safe and effective when used at doses of 200 to 400 mcg in patients with distal ureteric stones. Moreover, data from individual studies showed reduced ureteric colic with tamsulosin treatment which may occur through two mechanisms 1) relieving the ureteric spasm by blocking α-receptors and 2) acting on the C fibres to block pain propagation. It worth noting that the efficacy of tamsulosin can be affected by several factors, such as stone size (most important), spasm and presence of oedema (23). Subgroup analysis in some included studies showed that tamsulosin is more effective with stone size < 5 mm because at this size, there is a high probability for spontaneous stone passage (13).

A previous meta-analysis by Liu et al. (2012) pooled data of 1067 patients and showed a significant improvement in stone expulsion rate with tamsulosin (RR=1.41, 95% CI: 1.18, 1.70), compared to control group (24). Our findings are in agreement with such findings; however, our meta-analysis pooled data of a remarkably higher number of patients (n=4877) and therefore is more powered to investigate the intended objective. The reason for such difference in sample size is primarily due to the inclusion of the study by Ye et al. (2018) in our analysis which enrolled 3450 patients (22). To confirm the robustness of our analysis, we performed a sensitivity analysis that showed that our effect estimate was not controlled by the inclusion of any individual study.

Limitations

Our inclusion criteria limited the range of included studies as several published studies had one or more of our exclusion criteria. The observed heterogeneity in the primary outcome could be explained by the different control groups, stone size or follow-up period in the included studies. Most included studies achieved low scores on the JADAD scale, which affects the reliability of our evidence. Moreover, the observed publication bias in the funnel plot refers to the possibility of absence of considerable data from the literature, even in the Grey one which we searched thoroughly.
Recommendations for clinical practice

Based on our findings, emergency medicine physicians are advised to 1) Prescribe adequate analgesia and tamsulosin 400 mcg orally for 28 days to promote stone expulsion, 2) Seek advice from the urology registrar regarding tamsulosin use if any contraindications to tamsulosin or stone in the proximal ureter, and 3) Give written advice to patient noting the appointment details, tamsulosin use and when to return to the Emergency department.

Conclusion

The current published data indicate that tamsulosin is safe and effective in increasing the expulsion rate of distal ureteric stones especially in the subgroup of <5 mm sized calculi. Future studies should be multicentre RCTs that are adequately powered with strict methodology and long follow-up periods. Future studies should consider stratifying for size of the calculi.

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References


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