Running Head: The treatment of tamsulosin for distal ureteral calculi.

**Efficacy and safety of tamsulosin in the medical expulsion therapy for distal ureteral calculi: a systematic review and meta-analysis of a placebo-controlled trial**

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Abstract

Purpose: Tamsulosin, a medical expulsive therapy (MET), was always recommended for patients with distal ureteral calculi less than 10 mm. The aim of the systematic review was to assess the efficacy and safety of tamsulosin in MET compared with placebo.

Materials and Methods: A comprehensive search was conducted in the databases PubMed, EMBASE and Web of Science for relevant articles, covering all the literatures published until April 2018. All placebo controlled trials were identified in which patients were randomized to receive either tamsulosin or placebo for distal ureteral calculi.

Results: A total of seven placebo controlled studies including 4135 patients met the inclusion criteria and were involved in the review. We found that tamsulosin was associated with a significantly higher expulsion rate (ESR) [odds ratio (OR) = 1.10, 95% confidence interval (CI) = 1.00-1.21] than placebo in patients with distal ureteral stones less than 7 mm. The ESR ranged from 67.0%-90.7%. But the significant difference was better seen in patients with distal ureteral stones less than 10 mm (OR = 1.11, 95% CI = 1.01-1.21). Even though tamsulosin has a higher incidence of retrograde ejaculation than placebo, no significant difference was observed in the incidence of other adverse events.

Conclusion: The results of the current meta-analysis indicated that tamsulosin was superior to placebo in its efficacy for distal ureteral stones though retrograde ejaculation was worse with tamsulosin use. It should be a safe and effective medical expulsive therapy choice for distal ureteral stones when stone sizes are less than 10 mm.

Key words Tamsulosin, Distal ureteral calculi, Medical expulsion therapy, Urolithiasis, Meta-analysis
1 Introduction

Urolithiasis, ranks as the third most common affliction in the urinary system, is a well-known disease affecting public health problem \(^{[1]}\). It is reported that 1 of 11 persons in the United States suffers from stone disease, and the lifetime recurrence rate is approximately 50\% \(^{[2,3]}\). Meanwhile, the increasing incidence of ureteric stones, which has close associations with the improved quality of life, has been paid greater attentions in this era \(^{[4]}\). Preminger et al. revealed that most ureteral stones are sited in the distal ureter, and it is estimated that 68\% of ureteral stones have the size of 5 mm and 47\% of stones that between 5-10 mm are expelled spontaneously \(^{[5]}\).

When it comes to the patients getting a diagnosis of distal ureteral stones less than 10 mm, the most common treatment approaches include shock wave lithotripsy (SWL), medical expulsive therapy (MET), as well as ureteroscopy (URS). Due to the high healthcare expenditures and invasive procedures associated with SWL and URS, the \(\alpha\)-blockers and calcium channel antagonists, the two types of MET, is preferred by patients for the promotion of the spontaneous expulsion of distal ureteral stones. Both the European Association of Urology (EAU) and the American Urologic Association (AUA) have recommended that the patients with ureteral stones less than 10 mm should receive \(\alpha\)-adrenoceptor blockers therapy for stone passage in accordance with the proposals of numerous placebo-controlled trials and meta-analyses \(^{[5,6]}\).

Tamsulosin, an \(\alpha_{1A/1D}\)-adrenoceptor blockers, is the most frequently used drug to facilitate the ureteral stones expulsion, prominently in distal ureteral stones \(^{[7,8]}\). A recent double-blind and placebo-controlled study regarding 3296 patients suggested that the stone expulsion rate of tamsulosin (86\%) is higher than the placebo (79\%; \(P < 0.001\)) for distal ureteral stones \(^{[9]}\). Although several meta-analysis studies have laid stress on the curative effect of tamsulosin, the majority of trails were not placebo controlled and blinded \(^{[10,11]}\). Therefore, a systematic review and meta-analyses from placebo-controlled trials were urgently needed to conduct in order to assess the functions of tamsulosin in the treatment of distal ureteral calculi.

2 Methods
2.1 Search strategy and study selection

The systematic review was performed in accordance with the Cochrane reviews guidelines as well as the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines \(^{[12]}\). The databases, such as PubMed, EMBASE and Web of Science, have been comprehensively searched for relevant eligible articles, which cover all the studies published until April 2018. There were no language restrictions for these studies. The literature retrieval was carried out with the combinations of free words and keywords: “tamsulosin”, “ureteral calculi” or “urolithiasis” or “stone”, “medical expulsion therapy” and “placebo controlled trials”. Except for searching the original papers from electronic databases, other relevant review articles were searched by hand from reference lists of original articles or reviews so as to further seek additional eligible studies. In addition, abstract booklets and presentations were also consulted from the annual academic conferences. Besides, if more data was needed, we contacted the corresponding author for obtaining desired information by sending emails. Except that, we would also ask the person involved in the trial to see if the study was not retrieved in the trial. Last but not least, if multiple articles were published using the same study series, only those with the latest or complete data were selected. The estimation of the level of evidence (LE) for each included study was performed in accordance with the criteria provided by the Oxford Centre for Evidence-based Medicine \(^{[13]}\).

The inclusion criteria for eligible articles were as follows: (1) studies should be placebo controlled trials; (2) The patients in this study were limited to patients with the stone size of 10 mm or smaller of ureteral calculi.; (3) All patients underwent preliminary diagnosis of kidney, ureter, and bladder (KUB) by abdominal ultrasound and plain abdominal X-ray. An unenhanced CT scan was implemented if it was necessary. The maximum diameter that measured on a plain abdominal film was recorded as the stone size; (4) The included studies should have sufficient data. The exclusion criteria were presented as follows: (1) The studies without available information or complete data; (2) Patients in the studies suffered from urinary tract infections, renal insufficiency, high grade hydronephrosis, ureteric strictures, previous
therapies for the stone, or solitary kidney; (3) Patients in the studies had a history of ureteral surgery or endoscopic surgery; (4) Duplicates of previous publication.

The most important outcome for this present study was the stone expulsion rate. The secondary outcomes were the stone expulsion time (hours) and complications. Complications were defined as one of the following symptoms: self-reported dizziness, headache, fatigue and retrograde ejaculation. If one of these aforementioned outcomes was reported, the trials were deemed to be eligible. The reviewers appraised the qualifications of the remaining studies by gradually reviewing the titles, abstracts, as well as full texts.

2.2 Data extraction and quality assessment

Two co-authors (Rong-zhen Tao and Zhi-qiang Qin) independently and carefully reviewed all the identified studies in order to determine the compliance of individual studies with inclusion criteria. All data was extracted from the qualified publications and any disagreement appearing in this process was resolved by consulting a third reviewer. All the data selected from the included articles, were recorded in a standardized form, and the extracted information included study characteristics (title, publication year and the number of patients), patient characteristics (age, the location and size of the stone, control (placebo), intervention, method (blinding, randomization and loss to follow-up) as well as outcomes (expulsion rate, expulsion time, and some relevant complications). Furthermore, the Cochrane Collaboration’s tool was utilized for the evaluation of the risk of selection, performance, detection, attrition, and reporting biases among the included studies [14]. If high risk of bias was found among studies, meta-analyses stratified by study quality could be performed.

2.3 Data synthesis and analysis

The pooled odds ratios (ORs) with its corresponding 95% confidence intervals (CIs) were implemented for the assessment of the strength of differences between the experimental and the control groups (tamsulosin vs. placebo). The verification of the heterogeneity assumption was accomplished by the calculation of the Chi-square test and I-square test. The random-effects model (DerSimonian-Laird method) was conducted with the presence of heterogeneity. Otherwise, the fixed-effects model
(Mantel-Haenszel method) was used. Between-study heterogeneity was assessed by the \( \chi^2 \) test, P values and \( I^2 \) statistics. \( I^2 \) values of 0, 25, 50, and 75% represent no, low, moderate, and high heterogeneity, respectively. Besides, if significant heterogeneity was detected among studies, the sources of heterogeneity were discussed. Based on which, subgroup analysis was further conducted by different complications between the experimental and the control groups. In addition, sensitivity analysis was performed by omitting an individual study each time, with the purpose of appraising the stability of results. Moreover, Begg’s funnel plot and Egger’s linear regression test were applied for the examination of publication bias among all the enrolled studies. P values were all two-sided, and the values less than 0.05 were considered statistically significant[^15]. All statistical data in this present meta-analysis were conducted by using Stata software (version 12.0; StataCorp LP, College Station, TX).

### 3 Results

#### The baseline characteristics for the included studies

In total, seven placebo controlled studies with total 4,135 patients who had met the inclusion criteria were enrolled in the present meta-analysis[^9,16-21], which had accrued between September 2009 and April 2018 [Figure 1]. The baseline characteristics of all the included studies are comprehensively displayed in Table 1. In this current meta-analysis, these articles consisted of two groups: the experimental group (Tamsulosin 0.4 mg) and the control group (Placebo). Five trials provided Tamsulosin for 4 weeks, one provided the drug for 3 weeks, and the remaining one provided for 6 weeks.

#### Expulsion rate in all cases

In these included studies, tamsulosin presented an obviously higher expulsion rate (OR = 1.11, 95% CI = 1.01-1.21) than placebo in treating the patients with distal ureteral stones less than 10 mm, and there was no heterogeneity among these studies (\( P = 0.935; I^2 = 0.0% \)). Additionally, the expulsion rate for those patients with distal ureteral stones that received tamsulosin ranged from 69.0%-87.0% [Figure 2A]. Moreover, a total of five studies including 3,678 participants (1,833 in the experimental group and 1,845 in the control group) made it possible for analyzing the
expulsion rate of patients with distal ureteral stones less than 7 mm. within contrast to placebo, tamsulosin showed a remarkably higher expulsion rate (OR = 1.10, 95% CI = 1.00-1.21), and no heterogeneity was detected among these studies (P = 0.964; I² = 0.0%). The expulsion rate for those patients with distal ureteral stones less than 7 mm that treated with tamsulosin was ranged from 67.0%-90.7% [Figure 2B].

**Expulsion time (hours) of distal ureteral stones**

A total of four studies concerning 3,579 participants (1,785 in the experimental group and 1,794 in the control group) made it possible for analyzing the expulsion time (hours) of distal ureteral stones less than 10 mm. According to the obtained results, no significant differences were found in terms of the expulsion time of the experimental group versus the control group [Standardized mean difference (SMD) = -0.77, 95% CI = -1.97-0.42], and significant heterogeneity was discovered among these studies (P < 0.001; I² = 98.4%) [Figure 3].

**Complications**

**Dizziness**

A total of four studies including 3,557 participants (1,769 in the experimental group and 1,788 in the control group) helped to bring about the analysis of the dizziness. No significant results were detected between the experimental group and the control group (OR = 1.00, 95% CI = 0.69-1.47), and no heterogeneity was detected among these studies (P = 0.814; I² = 0.0%) [Figure 4A].

**Headache**

A total of three studies regarding 3,514 participants (1,753 in the experimental group and 1,761 in the control group) helped to bring about the analysis of the headache. The results still showed no significant differences (OR = 0.91, 95% CI = 0.62-1.35), and no heterogeneity was found among these studies (P = 0.984; I² = 0.0%) [Figure 4B].

**Retrograde ejaculation**

A total of five studies concerning 3,669 participants (1,830 in the experimental group and 1,839 in the control group) was conductive to the analysis of the retrograde ejaculation. The meta-analysis indicated that tamsulosin was related to a significantly
higher rate of retrograde ejaculation than placebo  (OR = 1.57, 95% CI = 1.09-2.25), and no heterogeneity was discovered among these studies (P = 0.571; I² = 0.0%) [Figure 4C].

**Fatigue**

A total of three studies including 3,514 participants (1,753 in the experimental group and 1,761 in the control group) was conductive to the analysis of the fatigue. There were no significant differences detected between the experimental group and the control group  (OR = 1.21, 95% CI = 0.74-1.97), and no heterogeneity was detected among these studies (P = 0.940; I² = 0.0%) [Figure 4D].

**Test of heterogeneity**

Under the fixed-effects model, a Galbraith radial plot was utilized for the heterogeneity of all the included studies [Figure 5]. The obtained results elucidated that no significant heterogeneity was observed between studies.

**Publication bias**

Sensitivity analysis was implemented to evaluate whether the deletion of each individual study functions on the pooled ORs. Figure 6 showed the sensitivity analysis with respect to the efficacy of tamsulosin in the treatment of distal ureteral calculi under the fixed-effects model, which implied the reliability of our results.

The Begg’s funnel plot along with the Egger’s test was applied for the evaluation of the potential publication bias for the data in all the enrolled eligible studies. Based on the funnel plot analysis, we found that the shape of the funnel plot was symmetrical[Figure 7]. The results demonstrated that no publication bias was found in the Begg’s test and Egger’s test under the fixed-effects model (P = 0.881; P = 0.630).

4 Discussion

In 2001, the latest print versions of the EAU guidelines regarding the treatment of urolithiasis were published [22]. In the next year, the tamsulosin was firstly reported for the promotion of the spontaneous passage of distal ureteral stones [23]. From then on, the publications of several meta-analyses were mainly used to discuss the curative
effect of tamsulosin in treating those patients with distal ureteral stones less than 10 mm \cite{11, 24-25}. However, our systematic review and meta-analysis involving in 7 randomized, double-blind, and placebo-controlled trials was directly used for the evaluation of the efficacy between tamsulosin and placebo. The obtained results in our study fully showed that tamsulosin could significantly improve the stone expulsion rate (SER), shorten the expulsion time and reduce the complications except for retrograde ejaculation. Additionally, the results of our meta-analysis also presented that tamsulosin was superior to placebo for the treatment of distal ureteral stones, especially a strong trend towards the stone size less than 10 mm, which was inconsistent with the findings in previous meta-analyses \cite{11, 24-25}.

Tamsulosin, acting as an $\alpha$-blocker, consists of $\alpha_{1A}$- and $\alpha_{1D}$-selective adrenergic antagonist, while $\alpha_{1A}$- and $\alpha_{1D}$-adrenoceptors were mainly expressed in smooth-muscle cells of the human ureter \cite{26}. The produce of the related reactions were realized for the distal end of the ureter could be relaxed by reducing the ureteric smooth muscle tone. A systematic review with a combined of 1384 participants showed that tamsulosin significantly improved stone passage in patients with ureteral stones 5-10 mm (risk difference = 22%; 95% confidence interval 12% to 33%; number needed to treat = 5) \cite{11}. Seitz et al. also performed a meta-analysis, and the findings revealed that there were higher and faster stone expulsion rate in patients after receiving $\alpha$-blocker therapy (RR = 1.45 vs. 1.49) \cite{27}. Meanwhile, a recent multicenter, randomized, double-blind and placebo-controlled trial demonstrated that subgroup analysis identified a specific benefit of tamsulosin when patients with large distal ureteral stones (6-7 mm) had been treated, but no effect for stones $\leq$ 5 mm \cite{9}. Therefore, it could be concluded that stone size was an important parameter for the prediction of MET-success in patients with distal ureteral stones. Besides, several studies have suggested that approximately 68%-98% of stones less than 5 mm are expected to pass spontaneously for patients with distal ureteral stones \cite{5, 28}. However, the ESR was unfortunately decreased to 60.3% with stone size increasing (ranging from 5 to 10 mm). In this meta-analysis, a significantly higher ESR was found in tamsulosin (OR = 1.10, 95% CI = 1.00-1.21) in contrast to placebo in distal ureteral
stones patients with the stone size less than 7 mm. The ESR ranged from 67.0%-90.7%. Except that, this kind of significantly difference was better presented in distal ureteral stones patients with the stone size less than 10 mm (OR = 1.11, 95% CI = 1.01-1.21). These findings confirmed the results of previous reviews, and the meaningful functions of tamsulosin on stone expulsion in distal ureteral stone would be also observed when the stone size was 8-10 mm.

It was reported that different α1-adrenoceptor blockers commonly presented with various side effects, including dizziness, headache, rhinitis, syncope, retrograde ejaculation as well as fatigue [29-31]. Except for a higher incidence of retrograde ejaculation in tamsulosin in comparison to placebo, no other significant difference was detected in the incidence of other side effects. Besides, tamsulosin was well-tolerated and just mild adverse effects in most patients. In these trials, retrograde ejaculation was the most commonly reported adverse effects for tamsulosin.

Since the standard daily dose of tamsulosin was 0.4 mg, the 0.4 mg daily was selected as an effective and well tolerated treatment dose for tamsulosin for distal ureteral stones. Moreover, MET should be an economical and effective treatment for those patients with ureteral calculi who had a stone size of 10 mm or smaller, and these patients are willing to a waiting management.

Some limitations in our meta-analysis should be acknowledged to a certain extent when interpreting the data. Firstly, the results were more or less based on unadjusted estimates due to the small numbers of published studies and small sample size of patients. As a consequence, the inclusion criteria for each patient in previous articles vary greatly, which can reduce heterogeneity through subgroup analysis. Secondly, many factors could affect ESR, such as compliance of MET, exercise volume and different follow-up periods, but these factors were not been taken into consideration in our subgroup analysis. In addition, the patients with high grade hydronephrosis were excluded from our meta-analysis, which may introduce a bias to patient selection. Last but not least, most of the studies were conducted in Australian and Asian populations, suggesting that there may be some merit in the analysis. Hence, more researches should attach great importance on the influence of different factors in
subsequent articles to guaranty reliability of our meta-analysis. Silodosin, as a kind of selective \(\alpha\)-1A adrenergic receptors’ antagonist, has also been proved to be safe and effective in the medical expulsive therapy for symptomatic distal ureteral stones. in multiple studies\[^{32,33}\]. Further studies could been conducted to compare the efficacy and safety between tamsulosin and silodosin in MET of ureteral stones.

5 Conclusions

In summary, the results of the current meta-analysis provided evidence that tamsulosin was still superior to placebo in terms of its efficacy for the treatment of distal ureteral stones even if retrograde ejaculation was worse with the application of tamsulosin. Tamsulosin should be a safe and effective choice in treating distal ureteral stones when stone sizes are less than 10 mm. In the future, high-quality multicenter randomized controlled trial (RCTs) and placebo-controlled trials are necessary to thoroughly evaluate the outcome.

6 Compliance with Ethical standards

All procedures conducted in studies with participants involved complied with the 1964 Helsinki declaration and its later comparable or amendments ethical standards, and with the ethical standards of Affiliated Jiangning Hospital with Nanjing Medical University.

7 Competing financial interests

The authors declare no financial interests competing.

8 Funding

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9 Author's Contribution

JL Lv and RZ Tao conceived protocol/ project development. FD Liu and ZQ Qin performed data collection or management. RZ Tao and ZQ Qin performed data analysis. RZ Tao and ZQ Qin drafted the initial manuscript. All authors read and approved the final version of the manuscript.

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### Table 1. Characteristics of individual studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Therapy in experimental group</th>
<th>Therapy in control group</th>
<th>Sample size (E/C)</th>
<th>Inclusion population</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ye et al. 2017 [9]</td>
<td>China</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>1642/1654</td>
<td>Adults, 18-60 years; With renal colic: Presence of a single distal ureteral stone (range 4-7 mm in size).</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Jeremy et al. 2015 [16]</td>
<td>Australia</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>161/155</td>
<td>With symptoms suggestive of ureteric colic and a distal ureteral stone of less than 10 mm in diameter.</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Sebastien et al. 2015 [17]</td>
<td>France</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>61/61</td>
<td>Patients older than 18 years, with acute renal colic and distal ureteral stone (range 2-7 mm in size).</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Taha et al. 2010 [18]</td>
<td>Arabia</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>75/75</td>
<td>Patients older than 18 years, distal ureteral stone (range 4-10 mm in size).</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Abdulla et al. 2009 [19]</td>
<td>Arabia</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>50/46</td>
<td>Patients presented with acute flank pain and none received SWL. Lower ureteral stone less than 10 mm in diameter.</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Thomas et al. 2009 [20]</td>
<td>Switzerland</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>45/45</td>
<td>Patients older than 18 years presenting with acute renal colic. Distal ureteral stone≤7 mm.</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Raul et al. 2011[21]</td>
<td>Mexico</td>
<td>Tamsulosin 0.4 mg</td>
<td>Placebo</td>
<td>32/33</td>
<td>Patients older than 18 years and presented with reno-ureteral stones less than 7 mm in diameter.</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

E/C: experimental group/control group.
Figure 1. Flow diagram of the study selection process.

Records identified through database searching (n=317)

Additional records identified through other sources (n=48)

Records after duplicates removed (n=341)

Removal of publications with titles not relevant to this analysis (n=313)

Full-text articles assessed for eligibility (n=28)

Articles excluded for one of the reasons:
- Not placebo control trial (n=4);
- No original available data (n=6);
- Meta-analysis (n=3);
- Review article (n=3);
- Overlapping articles (n=5).

Studies included meet criteria for meta-analysis (n=7)
**Figure 2.** (A). Forest plots of the efficacy of tamsulosin in the medical expulsion therapy for distal ureteral calculi; (B). Forest plots of the efficacy of tamsulosin in the medical expulsion therapy for distal ureteral calculi when distal ureteral stones < 7 mm.
Figure 3. Forest plots of the expulsion time (hours) of distal ureteral stones in the medical expulsion therapy.
Figure 4. Forest plots of all complications of tamsulosin in the medical expulsion therapy for distal ureteral calculi. (A). Dizziness; (B). Headache; (C). Retrograde ejaculation; (D). Fatigue.
Figure 5. Galbraith plot of the efficacy of tamsulosin in the medical expulsion therapy for distal ureteral calculi in the fixed-effects model.
Figure 6. Sensitivity analysis in the fixed-effects model.
**Figure 7.** Begg’s funnel plot of publication bias test in the fixed-effects model.