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# The efficacy and safety of alpha-adrenergic blockers for medical expulsion therapy in patients with ureteral calculi

## A meta-analysis of placebo-controlled trials

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**Abstract**

**Purpose:** Alpha-adrenergic blockers are commonly used as a medical expulsive therapy (MET) for patients with ureteral calculi. The aim of this meta-analysis was to evaluate the efficacy and safety of alpha-adrenergic blockers compared with a placebo when used as a MET.

**Materials and methods:** We carried out a systematic search of the PubMed, EMBASE, and Web of Science databases, and the Cochrane Library, for relevant articles from inception to November 2020. Our aim was to identify placebo-controlled trails in which patients were randomized to receive either alpha-adrenergic blockers (tamsulosin, alfuzosin, doxazosin, terazosin, naftopidil, or silodosin) or a placebo for the treatment of ureteral calculi.

**Results:** According to strict inclusion criteria, database searches identified 8 placebo-controlled studies that included 2284 patients. Generally, α-blockers had no significant effect on the clearance of stones in the urinary tract (risk ratio [RR] = 1.05; 95% confidence interval [CI] = 1.00–1.11). However, subgroup analysis showed that α-blockers were effective in treating distal urinary tract stones (RR = 1.08; 95% CI = 1.02–1.15). With regards to adverse events, our analysis showed that the combination of MET with α-blockers was likely to cause dizziness (RR = 1.37; 95% CI = 1.06–1.79) and retrograde ejaculation (RR = 3.10; 95% CI = 1.81–5.29).

**Conclusion:** Although α-blockers cannot improve the overall ureteral stone clearance rate, these drugs are still effective for the treatment of stones in the distal urinary tract. However, the application of α-blockers is likely to cause dizziness and/or retrograde ejaculation.

**Abbreviations:** CI = confidence interval, LUTS = lower urinary ract, MET = expulsive therapy, RCT = randomized controlled trial, RR = risk ratio.

**Keywords:** alpha adrenergic blocker, medical expulsion therapy, meta-analysis, ureteral calculi, urolithiasis

## 1. Introduction

Stones in the urinary tract (urolithiasis) are one of the most common diseases of the urinary system and represents a significant public health problem. A previous study reported that the incidence of urinary tract stones is between 1% and 20% worldwide and is increasing.[1,2] And stone disease is rare in only a few geographical areas (e.g., Greenland,coastal areas of Japan).[3] The incidence and prevalence rates of stones may be affected by genetic, nutritional, and environmental factors. One study showed an increase in lifetime prevalence of stone disease ranging from 7.14% to 11.62% over a 10-year period (2000–2010).[4] The incidence of ureteric stones has increased over the last few years and is closely associated with eating habits and the quality of life.[5] This rise could be explained only in part by the increasing prevalence of stone disease, On the other hand, the large-scale application of imaging modalities, such as ultrasound and computed tomography is able to identify many asymptomatic patients with urinary calculi. This disease has begun to attract significant research attention.

Three options are available for urologists when treating patients with ureteral stones <10 mm in size: shock wave lithotripsy, medical expulsive therapy (MET), or ureteroscopy.

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*ZWY and RHW contributed equally to this work.*

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*The datasets generated during and/or analyzed during the current study are publicly available.*

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However, shock wave lithotripsy and ureteroscopy are expensive procedures and can also cause harm to the patient's body. Consequently, the combination of MET and α-blockers has become the most popular form of treatment over recent years. Both the European Association of Urology and the American Urologic Association recommend that patients with ureteral stones <10 mm in size should receive α-adrenoceptor blockers to assist the passage of stones; these recommendations are based on proposals from previous placebo-controlled trials and meta-analyses.[6,7] On the other hand, the European Association of Urology also mentioned that the most of stones <4 mm pass within 40 days. Owing to the high likelihood of spontaneous passage of stones <6 mm, MET is less likely to increase the stone-free rate (SFR) but reduces pain episodes. But if the size of the stones are greater than 6 mm, actively treatment will be necessary.[6]

In 2018, a multicenter, randomized, and placebo-controlled trial conducted by Meltzer et al[8] showed that tamsulosin did not significantly increase the rate of stone passage when compared to a placebo. Although several meta-analysis studies have laid stress on the curative effect of alpha-adrenergic blockers, in previous studies, the methodology of the included literature did not maintain strict consistency. Therefore, there is an urgent need to carry out high-quality meta-analyses of placebo-controlled trials in order to investigate the precise effect of α-blockers for the treatment of ureteral calculi.

## 2. Methods

### 2.1. Literature searches and inclusion/exclusion criteria

This systematic review was performed in accordance with the Cochrane Reviews Guidelines and the PRISMA guidelines for meta-analyzes.[9] We searched a range of databases (PubMed, EMBASE, and Web of Science), and the Cochrane Library, for relevant articles from inception to November 2020. No language restrictions were applied in any of our literature searches. Searches were performed with a number of free words, keywords, and combinations, including "alpha-adrenergic blocker," "tamsulosin," "alfuzosin," "doxazosin," "terazosin," "naftopidil," "silodosin," "urinary calculi," "medical expulsion therapy," and placebo controlled trials". First, we searched the electronic databases for original papers. Then we searched the reference lists of relevant review and original articles by hand to identify additional studies of relevance. Abstract booklets and presentations were also consulted from annual academic conferences. If additional data were required, we contacted the corresponding author of relevant articles by email. If multiple articles had been published using the same study series, only those with the latest or a complete dataset were selected. All analyzes were based on previous published studies, thus no ethical approval and patient consent are required.

The inclusion criteria were as follows:

1. studies must be placebo-controlled trials (featuring an alpha-adrenergic blocker vs a placebo group);
2. all patients had ureteral calculi <10 mm in size;
3. all patients had received imaging of the urinary tract and the stone size reported was the maximum size recorded on plain abdominal film;
4. studies needed to have a sufficient amount of data; studies should have sufficient data; and
5. the modified JADAD score needed to be 7. (Tables 2–3)

The exclusion criteria were as follows:

1. studies containing an incomplete dataset,
2. patients suffered from urinary tract infections, renal insufficiency, high grade hydronephrosis, ureteric strictures, had received previous therapies for stones, or a solitary kidney was involved;
3. patients with a history of ureteral or endoscopic surgery;
4. articles represented a duplication of a previous publication.

The primary outcome for our meta-analysis was the stone expulsion rate. Our secondary outcomes were the different locations for stone expulsion rate and adverse events. If one of these aforementioned outcomes was reported, then trials were deemed to be eligible. The authors evaluated any remaining studies by reviewing the titles, abstracts, and full-texts.

### 2.2. Data extraction and quality assessment

Two authors independently and carefully reviewed all of the identified studies in order to determine compliance with the inclusion criteria. All data was extracted from the included publications and disagreements were resolved by consulting a third author.

Extracted data were recorded in a standardized form, including study characteristics (title, publication year, and the number of patients), patient characteristics (age, the position and size of the stone, control (placebo) treatment, intervention, and methodological factors (blinding, randomization, and loss to follow-up). The methodological quality of the included RCTs was evaluated using the modified JADAD scale.[10]

### 2.3. Data synthesis and analysis

Pooled risk ratios and corresponding 95% confidence intervals (CIs) were used to evaluate the strength of the differences between experimental and control groups (e.g., alpha-adrenergic blockers *vs*. placebo). The verification of heterogeneity was accomplished by performing the Chi-Squared test and *I*-squared test. A random-effects model (DerSimonian-Laird method) was applied in the presence of heterogeneity. Otherwise, a fixed-effects model (Mantel-Haenszel method) was applied. Between study heterogeneity was assessed by the Chi-Squared test, *P* values, and $I^2$ statistics. $I^2$ values of 0, 25, 50, and 75% represented no, low, moderate, and high levels of heterogeneity, respectively.

In addition, sensitivity analysis was performed by omitting an individual study each time; this allowed us to appraise the stability of the results. Funnel plot tests were also applied to investigate publication bias within the included studies. *P* values were all two-sided and *P* values <.05 were considered to be statistically significant. All statistical data were managed by Review Manager software (version 5.3).

## 3. Results

In total, 8 placebo-controlled studies (Cho,[11] Furyk,[12] Hemann,[13] Meltzer,[8] Pedro,[14] Pickard,[15] Sur,[16] Vincendeau[17]), involving a total of 2284 patients, met the inclusion criteria and were enrolled in the present meta-analysis. The characteristics of the included studies are shown in Table 1. The included patients fell into 2 groups: an experimental group (involving alpha-adrenergic blockers) and a control group (involving a placebo).

**Table 1**

**Characteristics of individual studies included in the meta-analysis.**

| Study | Country | Therapy in experimental group | Therapy in control group | Sample size | Included population | Follow-up | Setting |
|---|---|---|---|---|---|---|---|
| Cho | South Korea | Naftopidil 75 mg | Placebo | 124 | Single ureteral stones (3 ± 10 mm) | 90 d | Multi-center |
| Furyk | Australia | Tamsulosin 0.4 mg | Placebo | 393 | Adults with distal ureter stones | 4 wks | Emergency Departments |
| Hemann | Switzerland | Tamsulosin 0.4 mg | Placebo | 90 | Adults with single ureteral stones (≤7 mm) | 3 wks | Single center |
| Meltzer | USA | Tamsulosin 0.4 mg | Placebo | 497 | Adults with largest stone dimension (<9 mm) | 4 wks | Multi-center |
| Pedro | USA | Alfuzosin | Placebo | 69 | Patients with a distal ureteral stone | 4 wks | single center |
| Pickard | UK | Tamsulosin 0.4 mg | Placebo | 757 | Adults with one stone measuring 10 mm or less (at largest dimension) | 4 wks | Multi-center. |
| Sur | USA | Silodosin 8 mg | Placebo | 232 | Adults with a unilateral calculus ≥4 mm and ≤10 mm at any location of the ureter | 4 wks | Multi-center |
| Vincendeau | France | Tamsulosin 0.4 mg | Placebo | 122 | Adults with a radio-opaque distal ureteral stone between 2 and 7 mm | 6 wks | Multi-centre |

When considering all of the included studies, alpha-adrenergic blockers were not associated with a higher expulsion rate (RR = 1.05; 95% CI = 1.00–1.11) than a placebo when treating patients with ureteral stones. In addition, there was no significant heterogeneity among these studies ($P = .81$; $I^2 = 0\%$) (Fig. 1).

Six of the 8 studies, including 1663 participants (831 in the experimental group and 832 in the control group), allowed us to analyze the expulsion rate of patients with ureteral stones in different locations; these analyzes showed that alpha-adrenergic blockers were effective in treating stones in the distal urinary tract (RR = 1.08; 95% CI = 1.02–1.15) (Fig. 2).

Subgroup analysis of 4 studies, including 1149 participants (588 in the experimental group and 561 in the control group), showed that alpha-adrenergic blockers are not likely to cause headache (RR = 0.99; 95% CI = 0.79–1.25) (Fig. 3), nausea, or vomiting (RR = 1.04; 95% CI = 0.85–1.27) (Fig. 4). However, we found that a combination of MET and alpha-adrenergic blockers are likely to cause dizziness (RR = 1.37; 95% CI = 1.06–1.79) (Fig. 5).

Further subgroup analysis, involving 917 participants (473 in the experimental group and 444 in the control group), showed that treatment with alpha-adrenergic blockers are not likely to cause palpitations (RR = 0.87; 95% CI = 0.48–1.57) (Fig. 6).

However, subgroup analysis of 3 studies, involving 761 participants (382 in the experimental group and 361 in the control group), showed that treatment with alpha-adrenergic blockers are likely to cause retrograde ejaculation (RR = 3.10; 95% CI = 1.81–5.29) (Fig. 7).

**Table 2**

**Methodologic quality assessment.**

| The modified JADAD scale |
|---|
| (1) Generation of allocation sequence |
| 2: Computer-generated random numbers |
| 1: Not described |
| (2) Allocation concealment |
| 2: Central randomization |
| 1: Sealed envelopes or similar |
| 0: Not described or inadequate |
| (3) Investigator blindness |
| 2: Identical placebo tablets or similar |
| 1: Inadequate or not described |
| 0: No double-blinding |
| (4) Description of withdrawals and drop-outs |
| 1: Numbers and reasons are described |
| 0: Numbers and reasons are not described |

### 3.1. Publication bias

A funnel plot was used to test for potential publication bias in the data extracted from all of the included studies (Fig. 8). The funnel plot was symmetrical and indicated that there was no publication bias. All of the studies were RCTs and the modified JADAD score of RCTs are 7. Therefore the studies included in this meta-analysis were considered of high quality and low risk of bias. We carried out our literature searches with no language restrictions. However, despite our best efforts, which included contacting the principal investigators of existing studies, it is possible that we may have missed some studies that were published in non-indexed journals.

## 4. Discussion

Alpha-adrenergic blockers include α1A-and α1D-selective adrenergic antagonists; α1A- and α1D-adrenoceptors are mainly expressed in the smooth-muscle cells of the human ureter. These drugs are able to act on the distal end of the ureter and cause relaxation by reducing the tone of the ureteric smooth muscle. Alpha-adrenergic blockers decrease the tension and release the spasm of smooth muscles and thus lessen the obstruction and irritation symptoms in the lower urinary tract (LUTS). They make a faster passing of calculi from the terminal part of the ureters possible.[18] The American Urologic Association and European Association of Urology guidelines recommend that antimuscarinic drugs should be prescribed in men with LUTS with residual storage symptoms after treatment with α-antagonists, if patients with LUTS are planning to undergo surgery.[19]

The predominant finding of the present meta-analysis was that we did not found a higher stone expulsion rate with alpha-adrenergic blockers when compared with a placebo treatment.

**Table 3**

**quality score of selected articles included in the meta-analysis.**

| Study | Generation of allocation sequence | Allocation concealment | Investigator blindness | Description of withdrawals and drop-outs | Total |
|---|---|---|---|---|---|
| Cho | 2 | 2 | 2 | 1 | 7 |
| Furyk | 2 | 2 | 2 | 1 | 7 |
| Hemann | 2 | 2 | 2 | 1 | 7 |
| Meltzer | 2 | 2 | 2 | 1 | 7 |
| Pedro | 2 | 2 | 2 | 1 | 7 |
| Pickard | 2 | 2 | 2 | 1 | 7 |
| Sur | 2 | 2 | 2 | 1 | 7 |
| Vincendeau | 2 | 2 | 2 | 1 | 7 |

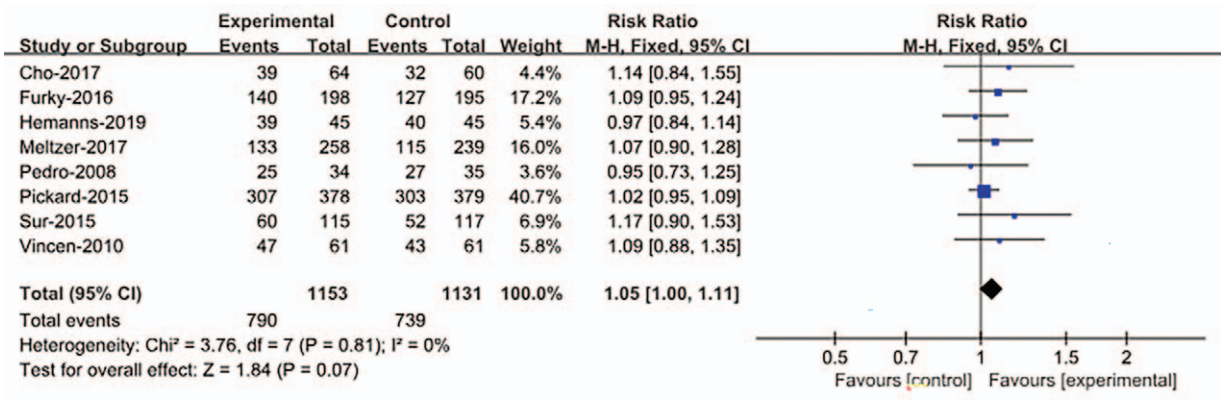


**Figure 1.** Forest plots of the efficacy of α-blockers in the medical expulsion therapy for ureteral calculi.

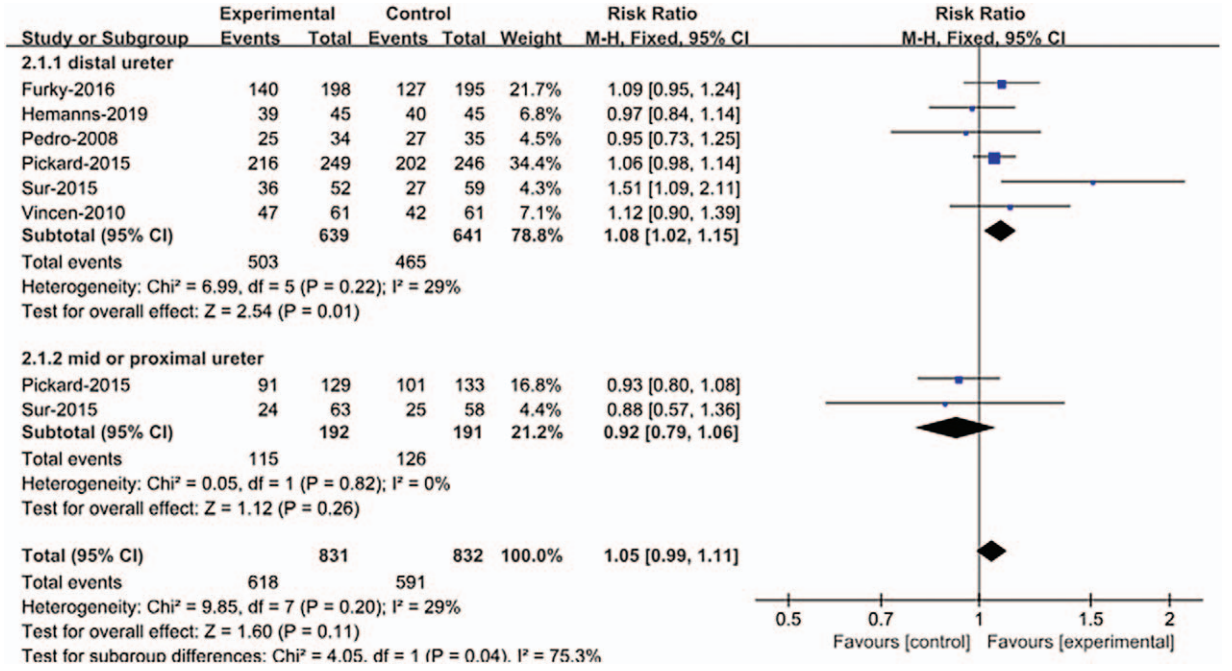


**Figure 2.** Forest plots of the efficacy of α-blockers in the medical expulsion therapy for distal ureteral calculi and mid or proximal ureter.

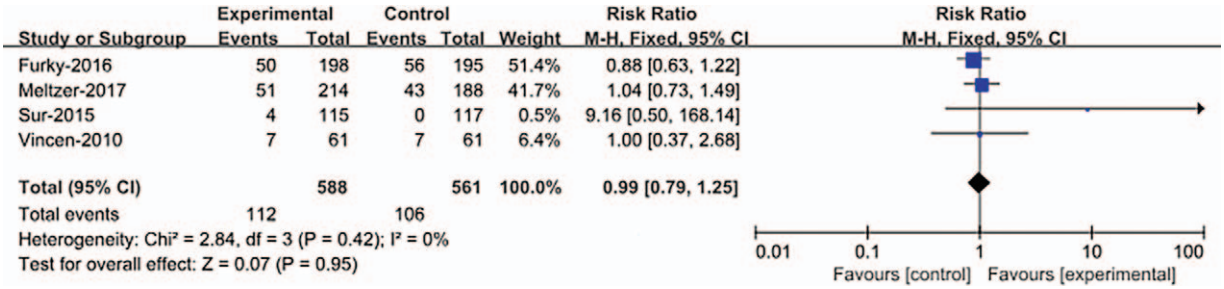


**Figure 3.** Forest plots of the headache complications of α-blockers in the medical expulsion therapy for ureteral calculi.

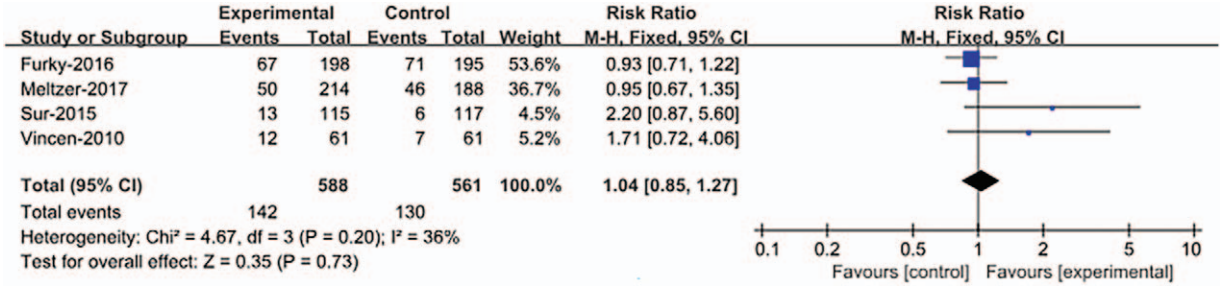


**Figure 4.** Forest plots of the nausea and Vomiting complications of α-blockers in the medical expulsion therapy for ureteral calculi.

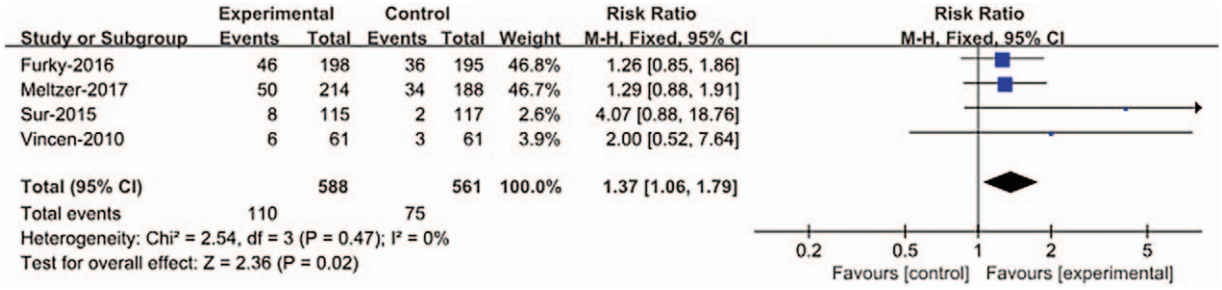


**Figure 5.** Forest plots of the dizziness complications of α-blockers in the medical expulsion therapy for ureteral calculi.

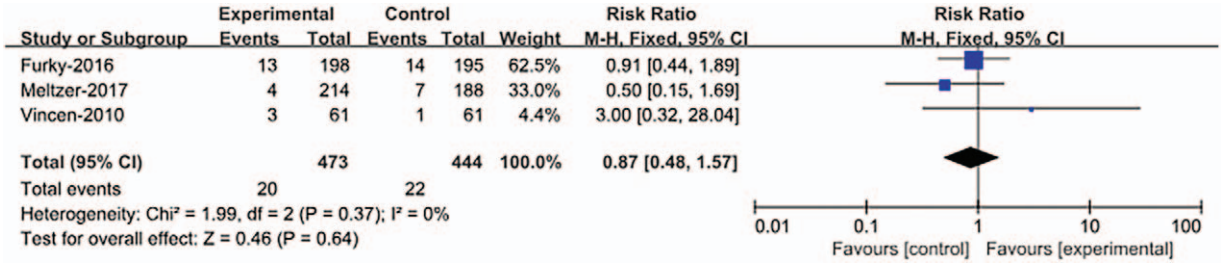


**Figure 6.** Forest plots of the palpitations complications of α-blockers in the medical expulsion therapy for ureteral calculi.

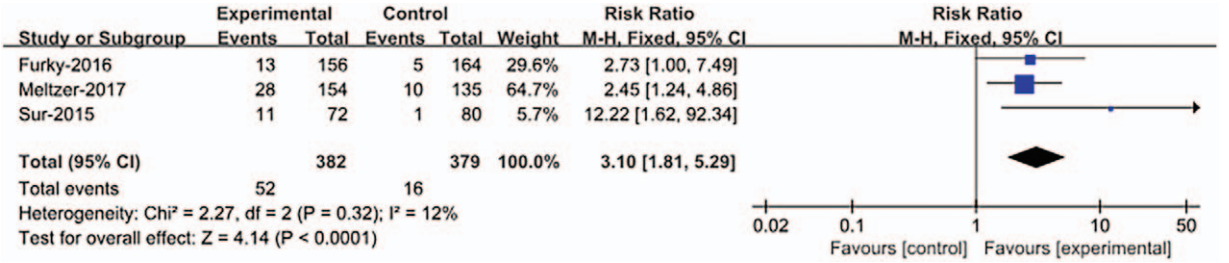


**Figure 7.** Forest plots of the Retrograde ejaculation complications of α-blockers in the medical expulsion therapy for ureteral calculi.

However, we did find that the use of alpha-adrenergic blockers will cause dizziness or retrograde ejaculation. Furthermore, our subgroup analysis identified evidence to support a potential subgroup effect based on the specific location of ureteral stones. It is therefore possible that alpha-adrenergic blockers may provide clinically meaningful improvement in the rate of stone clearance in patients with distal ureteral stones.

Many systematic reviews have investigated the effect of alpha-adrenergic blockers for the treatment of ureteral stones, including reviews by Aboumarzouk et al.[20] Aboumarzouk et al[20] concluded that alpha-adrenergic blockers increase the rate of stone expulsion and that the role of these drugs might be more significant for larger (>5 mm) stones and stones that are located in the lower ureter. However, the conclusions derived from the present study differ from those of Aboumarzouk. In our meta-analysis, we did not identify a higher stone expulsion rate for the application of MET with alpha-adrenergic blockers than with a placebo, although we did identify that the combination of MET with alpha-adrenergic blockers will increase the clearance rate of stones in the distal ureter. Following a randomized controlled trial (RCT), Pickard et al[15] reported that alpha-adrenergic blockers had no beneficial effect on stone clearance rates when compared with placebo treatment, regardless of the size or location of the stone. Another RCT, performed by Furyk et al[12] observed no overall benefit with regards to the daily administration of 0.4 mg of tamsulosin for patients with distal ureteric calculi that were less than or equal to 10 mm in terms of spontaneous passage. Subgroup analysis showed that tamsulosin did increased the passage of large stones (5–10 mm). These studies were all included in our current meta-analysis; however, our conclusions were different. In china,

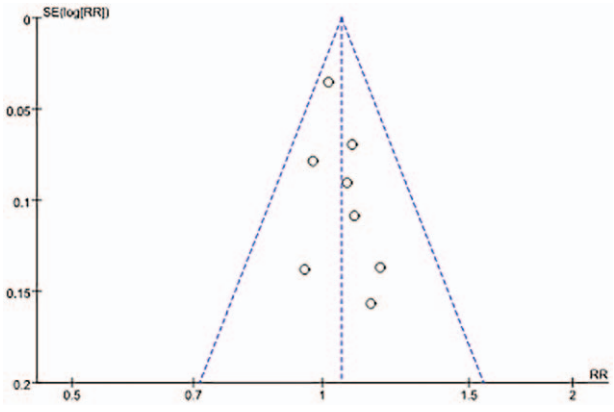


**Figure 8.** funnel plot of publication bias test in the fixed-effects model.

performed by Ye et al[21] concluded that tamsulosin benefits from a higher stone expulsion rate than placebo for distal ureteral and >5 mm stones. But it is no effect on the stone expulsion rate for <5 mm stones. This conclusion was also supported by the meta-analysis which performed by Aboumarzouk et al.[20] But we did not perform specific analysis relating to stone size because the sample size was too small.

Besides, Ye et al also reported that tamsulosin was also associated with a shorter time to expulsion for distal ureteral stones than the placebo and patients treated with tamsulosin reported less recurrent renal colic and required fewer analgesics.

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.[22–24] our meta-analysis showed that the combination of MET with α-blockers was likely to cause dizziness and retrograde ejaculation and no significant difference was detected in the incidence of other side effects. The incidence of dizziness and retrograde ejaculation are 18% (110/588) and 13.6% (52/382) in patients with alpha-adrenergic blockers versus 13.3% (75/561) and 4.2% (18/379) in patients with placebo. But in the 2 groups of patients, the overall incidence of dizziness and retrograde ejaculation is not significant. Besides, alpha-adrenergic blockers was well-tolerated and just mild adverse effects in most patients. And, there are no reports of serious adverse reactions such as death in all patients receiving alpha-adrenergic blockers. Therefore medical expulsive therapy with alpha-adrenergic blockers can be considered safe for patients. It is report that the most recent silodosin has equivalent efficacy compared to tamsulosin, with a lower risk of cardiovascula side effect; it may be considered a good alternative to common non-selective α1-antagonists, especially in the older patients where blood pressure modifications may cause important clinical troubles and ejaculatory dysfunctions are not really relevant.[19] But we did not perform specific analysis relating to types of alpha-adrenergic blockers because the sample size was too small.

Some limitations in our meta-analysis should be acknowledged to a certain extent when interpreting the data. Because the sample size was too small, we did not perform several subgroup analysis including the size of the stones and types of alpha-adrenergic blockers. Therefore it is necessary to conduct multi-center RCTs and placebo-controlled trials for different types of alpha-adrenergic blockers.

## 5. Conclusion

Our current meta-analysis provided evidence alpha-adrenergic blockers provide significant benefit for the treatment of distal

ureteral stones when compared to placebo treatment. Our findings should be validated in future by multi-center RCTs and placebo-controlled trials.

## Author contributions

**Conceptualization:** Ze-Wei Yu, Rui-Hong Wang.
**Data curation:** Ze-Wei Yu, Rui-Hong Wang, Jian-Gang Gao.
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**Resources:** Chang-Cun Zhang.
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**Supervision:** Ze-Wei Yu.
**Validation:** Chang-Cun Zhang.
**Visualization:** Chang-Cun Zhang.
**Writing – original draft:** Ze-Wei Yu, Chang-Cun Zhang.
**Writing – review & editing:** Chang-Cun Zhang, Jian-Gang Gao.

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