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TITLE PAGE

Efficacy and Safety of Muscarinic Antagonists Combined with Adrenergic alpha-Antagonists in the Medical Expulsion Therapy for Distal Ureteral Stone: A Meta-Analysis

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Abstract

Introduction: Lower ureteral stones, due to their proximity to the bladder, frequently cause irritation symptoms and voiding disturbances. The efficacy of combining adrenergic alpha-antagonists with muscarinic antagonists in improving stone expulsion and alleviating lower urinary tract symptoms (LUTS) remains uncertain. This meta-analysis aims to evaluate the clinical benefit of such combination therapy for distal ureteral calculi.

Methods: A comprehensive literature search was conducted across PubMed, Embase, Cochrane Library, Web of Science, and major Chinese databases through October 2024. Only randomized controlled trials comparing combination therapy with monotherapy were included. The quality of evidence was assessed using the GRADE framework, and meta-analyses were performed using RevMan 5.3 software.

Results: Eight RCTs comprising 800 patients were included. Combination therapy significantly improved stone expulsion rates compared to either alpha-blockers alone (RR = 1.13; p = 0.04) or muscarinic antagonists alone (RR = 1.53; p <0.00001). It also reduced pain episodes (MD = –0.75; p <0.0001) and severity (VAS), and improved urgency symptoms (USS) at 3 and 7 days. No significant difference in stone expulsion time was observed. Constipation and dry mouth were more common in the combination group.

Conclusion: Combination therapy with alpha-blockers and muscarinic antagonists improves stone expulsion and symptomatic relief in patients with lower ureteral stones <10 mm, without significantly affecting stone passage time, but at the cost of more anticholinergic side effects.

Word count：3608

Introduction

Urinary calculi is one of the most common diseases of the urinary system and is more common in men than in women. It has an estimated total prevalence rate as high as 15%[1, 2] and a recurrence rate of 50% within 5 years after initial onset[3]. The high incidence rate of urinary calculi increases the medical burden annually. In fact, expenditure in the United States is estimated to exceed USD 4 billion by 2030[4–6]. Three treatments are commonly used for patients with stones <10 mm: shock wave lithotripsy, medical expulsive therapy (MET) and ureteroscopy. Spontaneous or medicated stone removal is generally recommended for patients without severe clinical symptoms or complete urinary tract obstruction[7]. However, the larger

stones make spontaneous passage more difficult and may even cause renal colic. Some studies have suggested that recurrent renal colic may be related to spontaneous stone expulsion[8].
Alpha 1A- and 1D-adrenergic receptors are mainly expressed in the smooth muscle cells of the ureter. Alpha-blockers can reduce urinary tract obstruction by relieving ureteral smooth muscle tension and spasm and are currently one of the standard drugs for the treatment of urinary calculi[9]. The intramural ureter is the narrowest part of the ureter, and the most important obstacle to stone expulsion is at the end of the ureter[10]. Therefore, nearly 70% of urinary tract stones are distal ureteral stones[11]. Due to their proximity to the bladder, lower urinary tract stones often cause bladder irritation and urinary stream interruption. Muscarinic antagonists selectively block M2 and M3 receptors at the level of bladder detrusor muscle cells and reduce bladder afferent nerve activity to reduce involuntary bladder contraction or change contraction threshold, thereby, increasing bladder capacity and improving urination urgency[12].
For the treatment of lower ureteral stones, does the combination of alpha-blocker and muscarinic antagonist alleviate lower urinary tract discomfort during stone expulsion? The objectives of this study were to compare the efficacy and safety of a combination of alpha-blocker and muscarinic antagonist with alpha-blocker alone for the removal of lower ureteral calculi and to investigate the capability of this combination in alleviating lower urinary tract symptoms (LUTS) based on existing clinical trials.

Materials and Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (suppl.material PRISMA Checklist) and was registered at PROSPERO (CRD42024598671).

Search Strategy and Selection Criteria

We performed a systematic search of the PubMed, Embase, Cochrane Library, Web of Science and Chinese databases to identify clinical studies on the use of alpha-blockers combined with muscarinic antagonists for the treatment of patients with lower ureteral stones published from database inception to October 2024. When multiple publications of the same study were found, the latest published data were used. The references included in the studies were manually reviewed. Only randomised controlled trials were included.
We defined study eligibility using the patient population, intervention, comparator, outcomes approach and study design criteria. Studies comparing the efficacy and safety between muscarinic antagonists combined with alpha-blockers and alpha-blockers or muscarinic antagonists alone in medical expulsion therapy for distal ureteral stones were included. The specific inclusion criteria were as follows: (1) studies on humans, (2) original research, (3) enrolled patients with distal ureteric stone measuring ≤10 mm in diameter and (4) use of alpha-blockers and/or muscarinic antagonists. The exclusion criteria were (1) age <18 years, (2) patients who were pregnant and lactating, (3) urinary tract infection, (4) renal colic more than 24 h, (5) renal insufficiency, (6) single kidney, (7) ureteral stricture, (8) ureteral tumour, (9) history of distal ureter surgery, (10) bilateral ureteral calculi, (11) concomitant upper urinary tract stones, (12) moderate or severe hydronephrosis and (13) allergic reaction to alpha-blockers and/or muscarinic antagonists.

Data Extraction

Data were independently extracted by two authors (CJ Chen and ZY Ning). Any disagreement between the two authors was resolved by a third author (H Ding). The following data were extracted from the included trials: first author, year of publication, intervention group, control group, total number of patients, enrolled patients, treatment duration and outcome data.

Outcomes

The outcome measures of the included studies were (1) stone excretion rate (SER), which was defined as the percentage of patients with stone excretion at the end of follow-up; (2) stone excretion time (SET), which was defined as the time when the patients self-reported stone expulsion and was accurately confirmed by imaging studies; (3) pain episodes (PE), which was defined as the frequency of pain attacks during stone removal; (4) Visual Analogue Scale (VAS), which recorded patients' subjective description of pain [13, 14] and (5) urine sensation scale (USS), which assessed the urgency of each urination.

Assessment of Certainty of Evidence

Two investigators independently assessed the quality level of the included studies using the Cochrane Collaboration tool[15]. Aspects, such as randomisation, allocation and blinding processes, outcome reporting and other types of bias were assessed and assigned a grade of low, high or uncertain risk based on quality evaluation. Any disagreement was resolved by discussion with a third reviewer until a consensus was

reached. Using the GRADE system, each unique pooled analysis was evaluated and categorised as high, moderate, low or very low quality of evidence[16].

Statistical Analysis

All statistical analyses were conducted using the Cochrane Collaboration Review Manager software (RevMan 5.3). In the summary analysis, risk ratio (RR) was used to evaluate dichotomous data, such as SER and adverse effects, and weighted mean difference (MD) was used to evaluate continuous data, such as SET, PE, USS and VAS. We selected two-sided tests, and P <0.05 was considered to indicate statistical significance. Inconsistency was quantified using the I^2 statistic. When I^2 was >50% or P was ≤0.1, which suggested substantial heterogeneity, the random effects model (DerSimonian–Laird method)[17] was used; otherwise, the fixed effects model (Mantel–Haenszel method)[18] was applied. Sensitivity analyses were conducted by sequentially excluding each study to validate the reliability of the results and analyse heterogeneity. The presence of possible publication bias was investigated using a funnel plot; if possible, sub-analysis was performed to control this bias.

Results

Study Selection and Characteristics

The database search for Medical Subject Headings and free terms retrieved 42 articles. After removing duplicates, 36 studies were retained; another 12 were removed after reviewing titles and abstracts. Finally, after screening the full text of the remaining 24 articles, 8 clinical trials were included in the systematic review (Figure 1). Eight trials [13, 14, 19-24] involving 800 patients compared alpha-blockers in combination with muscarinic antagonists and alpha-blockers or muscarinic antagonists alone. The studies included in our meta-analysis are summarised in Table 1, and their efficacy results are summarised in Table 2.

Risk of Bias and GRADE Quality Assessment

As shown in Figure 2, the study randomisation method[24] was in order of precedence rather than strict randomisation, and there was a risk of bias in sequence generation. One study[13] described the method for allocation concealment, but other studies did not. Four studies[13, 14, 19, 24] did not clearly explain whether participants were informed, and three studies[14, 19, 24] did not clearly explain whether subjects were informed, so there were unclear performance and detection biases. All studies reported loss to follow-up, withdrawal and all outcomes, thereby, avoiding attrition and reporting biases. All studies were adequately described to exclude other sources of bias. Based on the GRADE system, each unique pooled analysis was categorised as either low or very low quality evidence (Supplementary Table 1).

Meta-analysis

Stone Expulsion Rate

Pooled meta-analysis (Figure 3) showed a significant benefit in SER among patients treated with a combination of muscarinic antagonists and alpha-blockers than among those treated with alpha-blockers alone (RR = 1.13, 95% CI 1.00 to 1.27; P = 0.04, I^2 = 51%).

Four studies compared SER between combination therapy and muscarinic antagonists. Pooled results showed significantly higher SER with combination therapy than with muscarinic antagonist alone (RR = 1.53, 95% CI 1.26 to 1.87; P < 0.0001, I^2 = 0%). Four studies compared SER between alpha-blockers and muscarinic antagonists. Pooled results showed significantly higher SER with alpha-blockers alone than with muscarinic antagonist alone (RR = 1.55, 95% CI 1.27 to 1.88; P < 0.0001, I^2 = 0%).

Stone Excretion Time

Seven studies reported SET. In Erturhan 2007, only the mean value and stone removal time range were given. Using the estimation formula[25], the average ± standard deviation (SD) SETs were 7.5 ± 2.75 and 6.4 ± 2.08 days for the experimental (combination therapy) and control (alpha-blocker monotherapy) groups, respectively. The pooled meta-analysis (Figure 4) showed no reduction in SET after combination therapy with alpha-blockers and muscarinic antagonists, compared with that after alpha-blocker monotherapy (MD = −1.01, 95% CI −2.62 to 0.59; P = 0.22, I^2 = 95%).

Renal Colic

Among the four studies that reported renal colic occurrence, one study reported on the incidence and significantly reduced pain frequency with alpha-adrenergic antagonist monotherapy than with combination therapy (13.2% vs. 27.9%)[24]; the other three studies reported the average frequency of renal colic[13,14,20]. The pooled results (Figure 5) showed that compared with alpha-blocker monotherapy, combination therapy significantly reduced the number of PEs (MD = −0.75, 95% CI −1.10 to −0.4, P <0.0001).

Visual Analogue Scale

In four studies[13,14,19,23], VAS was used to record the pain descriptions of all patients. A score of 0 indicated no pain, and a score of 10 indicated the most severe and unbearable pain. The SD data of the VAS were not reported in Erturhan 2007[23]; therefore, this meta-analysis included only the VAS of the remaining three studies. The pooled results showed that compared with patients treated with alpha-blocker alone, those treated with combination therapy had less pain at 3 days (MD = −3.14, 95% CI −3.44 to −2.84, P <0.00001); 7 days (MD = −3.77, 95% CI −4.02 to −3.52, P <0.00001) and 4 weeks (MD = −1.00, 95% CI −1.40 to −0.60, P <0.00001) (Figure 6).

Urinary Sensation Scale

Two studies reported the USS[13,14], which patients used to assess the degree of urination urgency on a five-point scale (1 = no urination, 2 = mild urination, 3 = moderate urination, 4 = severe urination and 5 = urinary incontinence)[26]. The pooled results showed that the USS score was significantly lower with combination therapy than with alpha-blocker monotherapy at 3 days (MD = −0.93, 95% CI −1.10 to −0.77, P < 0.00001) and 7 days (MD = −0.53, 95% CI −0.68 to −0.38, P < 0.00001). Moreover, the bladder irritation symptoms of patients with urinary urgency significantly improved after the addition of muscarinic antagonists (Figure 7).

Adverse Effects

Three studies reported the occurrence of adverse effects, including headache, dizziness, fatigue, orthostatic hypotension, retrograde ejaculation, constipation, dry mouth and rhinitis. There was no significant heterogeneity (I^2 = 0%); therefore, a fixed effects model was used to compare the adverse effects between combination therapy and alpha-blocker alone. The meta-analysis (Figure 8) showed that combination therapy and alpha-blocker alone had no significant differences in the adverse effects of headache and dizziness (RR = 1.35, 95% CI 0.76 to 2.42, P = 0.31); fatigue (RR = 1.66, 95% CI 0.56 to 4.89, P = 0.36); orthostatic hypotension (RR = 0.97, 95% CI 0.14 to 6.66, P = 0.97); retrograde ejaculation (RR = 0.71, 95% CI 0.23 to 2.17, P = 0.55) and rhinitis (RR = 0.66, 95% CI 0.09 to 4.88, P = 0.68) but significantly differed in terms of the adverse effects of constipation and dry mouth (RR = 3.86, 95% CI 1.77 to 8.44, P = 0.0007).

Sensitivity Analysis

Among the eight studies included in this meta-analysis, heterogeneity existed among certain outcome indicators. Therefore, a sensitivity analysis was conducted to determine the sources of heterogeneity for each outcome. Sequential exclusion of each study had a significant impact on the SER but not on the SET, indicating instability of results.

Publication Bias

The funnel plots showed outliers among the eight studies, indicating potential publication bias for SER or SET (Supplementary Figure 1 and Figure 2).

Discussion

Currently, the European Association of Urology (EAU)/American Urological Association (AUA) guidelines recommend the use of alpha blockers for distal ureteral stones[27, 28]. Several systematic reviews and meta-analyses have evaluated the efficacy of alpha blockers for ureteral stones in the past few years[29-32]. However, no systematic review or meta-analysis has evaluated the efficacy and safety of muscarinic antagonists combined with alpha-blockers in medical expulsion therapy for distal ureteral stones. This meta-analysis and the pooled results demonstrated significantly higher SER with combination therapy than with alpha-blocker or muscarinic antagonist monotherapy (combination therapy: 79.5% vs. alpha-blocker monotherapy: 68%, P = 0.04; combination therapy: 76.7% vs. muscarinic antagonist monotherapy: 50%, P < 0.00001). Moreover, combination therapy reduced the number of PEs and urinary symptoms. However, there were no significant differences in SET and adverse effects, except for constipation and dry mouth.

Factors affecting ureteral calculi expulsion include stone location, size, number and structure; ureteral smooth muscle spasm; mucosal oedema or inflammation and ureteral anatomy[33]. The most important obstruction site for passing calculi is the distal end of the ureter, especially the intramural ureter, which is the narrowest part[10]. Considering that the distal ureter is adjacent to the bladder, stones are easily embedded in the stenosed inner wall segment, predisposing patients to renal ureteral colic or accompanying urinary urgency and frequency, similar to overactive bladder (OAB)[33]. Based on these, we investigated whether the combined use of standard drugs for OAB (muscarinic antagonists) and lower ureteral calculi (alpha-blockers) can exert synergistic effects to improve stone removal efficiency, alleviate LUTS caused by lower ureteral calculi and relieve pain. Alpha-adrenergic antagonists block adrenergic receptors in the bladder to enhance the effects of muscarinic antagonists, which reduce muscarine release

from the prostate or urethra and enhance the effects of alpha-blockers[34, 35]. Dual treatment enhances bladder storage and relieves LUTS and pain.

Alpha-blockers are generally used for MET of distal ureteral calculi[36]. In humans, alpha 1A- and 1D-adrenergic receptors are mainly expressed in the smooth muscle cells of the ureter. Alpha-adrenergic blockers act on the distal ureter and relieve lower urinary tract obstruction and irritation by reducing ureteral smooth muscle tension, thereby, causing relaxation and relieving smooth muscle spasm[37]. In addition to accelerating the expulsion of small distal ureteral stones and relaxing spastic smooth muscles, alpha-blockers can provide analgesic effects and reduce LUTS to some extent[38]. Treatment with alpha-adrenergic antagonists is recommended for distal ureteral calculi ≥5 mm, according to the AUA, EAU, and Urological Association of Asia guidelines, and for distal ureteral calculi <10 mm, according to the Canadian Urological Association and the National Institute for Health and Care Excellence[39, 40]. In this meta-analysis, the mean stone size of all patients was 7.1 mm, which is consistent with the recommended guidelines on the use of alpha-adrenergic antagonists for stone expulsion. However, in a study by Hermans et al., the average number of analgesics taken before distal ureteral stone passage was three in the group treated with tamsulosin (n = 50) and seven in the placebo group (n = 50), underscoring the fact that although tamsulosin can alleviate pain to a certain extent, the demand for analgesics remained high[41]. According to the EAU guidelines, the standard treatment for relieving renal and ureteral colic is intake of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac sodium[42]. Maldonado found that although NSAIDs, such as diclofenac and indomethacin suppositories, can alleviate acute pain from distal ureteral stones, the effect was slow in many patients, the root cause of pain was not resolved and gastrointestinal adverse effects were common[43].

Muscarinic antagonists selectively block M2 and M3 receptors on the detrusor muscle cells of the bladder, reduce involuntary bladder contractions or alter contraction thresholds, decrease afferent bladder nerve activity and increase bladder volume. To reduce urinary urgency and frequency, address urinary incontinence and improve the health-related quality of life [12, 44, 45], muscarinic antagonists are commonly used to treat patients with OAB. Renal ureteral colic, urinary urgency and frequency and pain on the glans penis associated with the distal ureter may be controlled by muscarinic antagonists[25, 46]. Kaplan found that compared with placebo, the combination of tolterodine and tamsulosin significantly improved urge incontinence (−0.88 vs. −0.31, P = 0.005); episodes of urinary urgency without urinary incontinence (−3.33 vs. −2.54, P = 0.03) and urinary frequency for 24 h (−2.54 vs.−1.41, P < 0.001) and per night (−0.59 vs.−0.39, P = 0.02) in men with moderate to severe LUTS[47]. Meanwhile, inhibition of glandular secretion is the main adverse effect of muscarinic antagonists. The feeling of dry mouth prompts patients to drink a lot of water, which increases urine volume and flow and may be beneficial to stone excretion.

Three systematic reviews have evaluated the effectiveness of mirabegron for treating ureteral stones[48–50], and the pooled results demonstrated that mirabegron significantly increased SER in patients with distal ureteral stones. This meta-analysis showed that constipation and dry mouth were the main adverse effects of combination therapy, compared with alpha-blocker alone. Dry mouth and constipation are common antimuscarinic drug-related adverse events. In the future, reducing these toxic adverse effects will enable patients to have better tolerance of combination therapy. Existing evidence suggests that β3-adrenergic receptor agonists, such as mirabegron and vibegron, have a lower incidence of dry mouth than antimuscarinics, such as tolterodine)[51, 52]. Based on these reasons, the combination of new β3-adrenergic receptor agonists and alpha blockers is a promising treatment option for distal ureteral stones.

Combination therapy with alpha-blocker and muscarinic antagonist not only improved bladder irritation but also significantly alleviated renal and ureteral colic caused by stones. Among the clinical trials on tamsulosin alone to assist in the expulsion of 5–10-mm distal ureteral calculi, the reported frequencies of renal ureteral colic were 1.60 ± 1.0[47], 1.70 ± 1.2[44], 1.60 ± 1.0[47] and 2.90 ± 0.90[53] times. In the articles included in this meta-analysis[13,14, 20], the PEs among patients treated with tamsulosin alone and combination therapy were 3.2 ± 2.1 and 2.8 ± 1.8 times, 2.27 ± 0.91 and 1.39 ± 1.34 times and 2.25 ± 0.90 and 1.38 ± 1.37 times, respectively. These data indicated that pain was less with combination therapy than with tamsulosin alone. The VAS was significantly lower in the combination therapy group than in the alpha-blocker monotherapy group. Moreover, the lower mean number of PEs and VAS with combination therapy than with monotherapy make it reasonable to speculate that the combination of alpha-blockers and muscarinic antagonists can relieve the onset pain from renal ureteral colic. In Erturhan 2007 [19], although the SD data on PE and VAS were missing, the data showed a trend of less degree of colic with combination

therapy than with alpha-blocker alone (VAS: 4.1 vs. 4.7). Chu et al. only recorded the number of patients requiring meperidine (Demerol) analgesia for severe renal colic in the combination therapy and alpha-adrenergic antagonist alone (0 vs. 5) , respectively[24]. Based on these available data from the two articles, pain control and alleviation of patient discomfort were more effective with combination therapy than with alpha-blocker alone.

Limitations

This meta-analysis had some inevitable limitations. First, due to the small number of included studies and large heterogeneity of the partial results, the I^2 statistic was not effective enough. Second, majority of the randomised studies in this systematic review were small single-centre studies that reported insufficient raw data, which precluded subgroup analyses by stone size and drug type and limited the strength of our conclusions. Therefore, multicentre, randomised, placebo-controlled trials are needed for further validation. Third, like any systematic review, our analysis was limited by the data included in the studies, and we had to rely as much as possible on imperfect datasets. Nevertheless, to the best of our knowledge, these were the best available data that showed the effectiveness of combining alpha-blockers and muscarinic antagonists to improve the symptoms of patients with lower ureteral stones. To support our findings, future clinical trials may further investigate the use of serum biomarkers, such as C-reactive protein, which was reported to be associated with MET failure at relatively high levels[54].

Conclusion

For patients with solitary lower ureteral stones measuring less than 10 mm, the combination of adrenergic alpha-blockers and muscarinic antagonists appears to be more effective than alpha-blocker monotherapy in enhancing stone expulsion, mitigating renal colic, and alleviating lower urinary tract symptoms. Although stone expulsion time is not significantly impacted, the increased risk of dry mouth and constipation must be weighed against the potential clinical benefits. Future high-quality, multicenter trials are warranted to confirm these findings and to explore better-tolerated combinations, such as beta-3 agonists paired with alpha-blockers.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author contributions

HD contributed to the study conception and design. Material preparation was performed by CC, CM, SZ, and NF. Data collection and analysis were performed by ZN, ZH, CC, SZ, CM and NF. The first draft of the manuscript was written by NF, CC, SZ, CM and HD. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data that support the findings of this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author Hui Ding (dingh08@126.com).

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Figure legends
Figure 1. PRISMA flow diagram

Figure 2. Quality assessment using the risk of bias (ROB) tool

Figure 3. Comparison of stone excretion rate (SER) for distal ureteral stones
Comparisons of SER between (A) combination therapy and alpha-adrenergic blockers, (B) combination therapy and muscarinic antagonists, and (C) alpha-adrenergic blocker monotherapy and muscarinic antagonist monotherapy

Figure 4. Lower ureteric stone excretion time
Comparison between combination therapy and alpha-blocker monotherapy

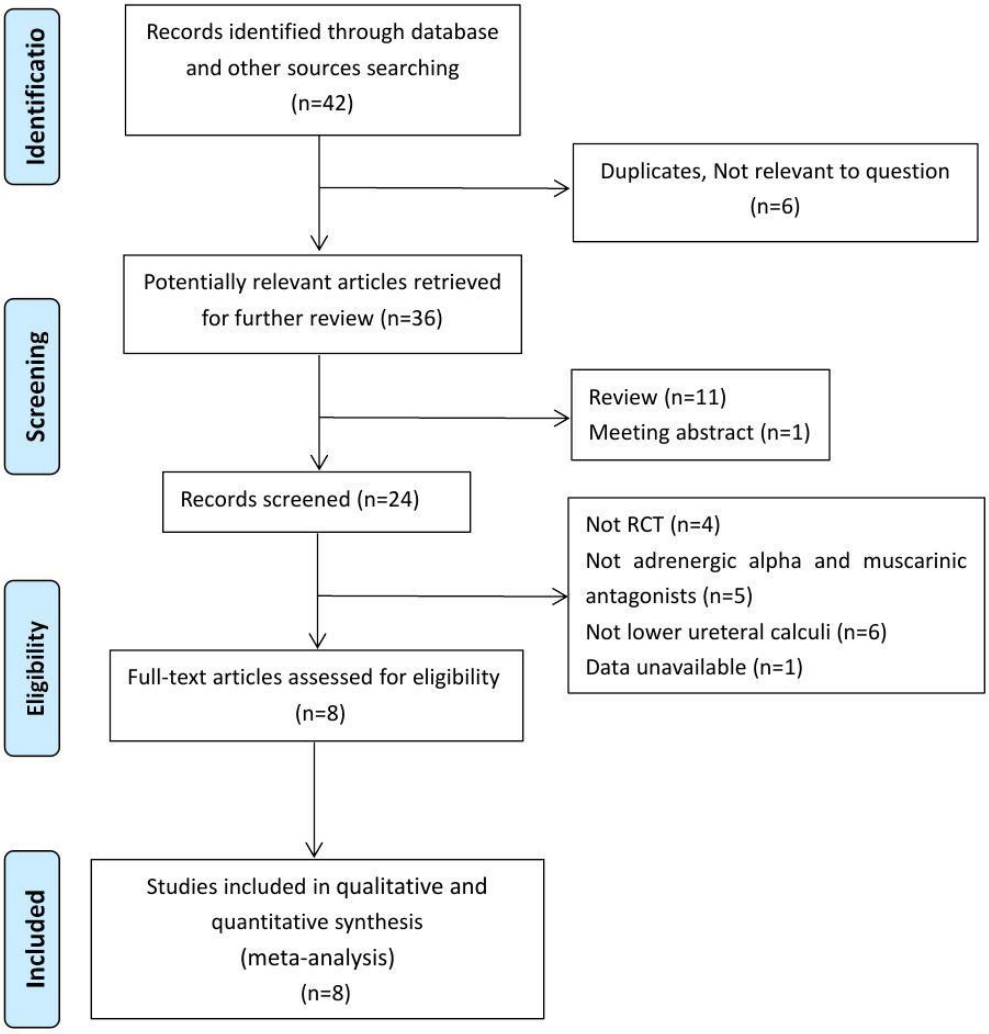
Figure 5. Frequency of renal colic
Comparison between combination therapy and alpha-blockers monotherapy for lower ureteric stone treatment

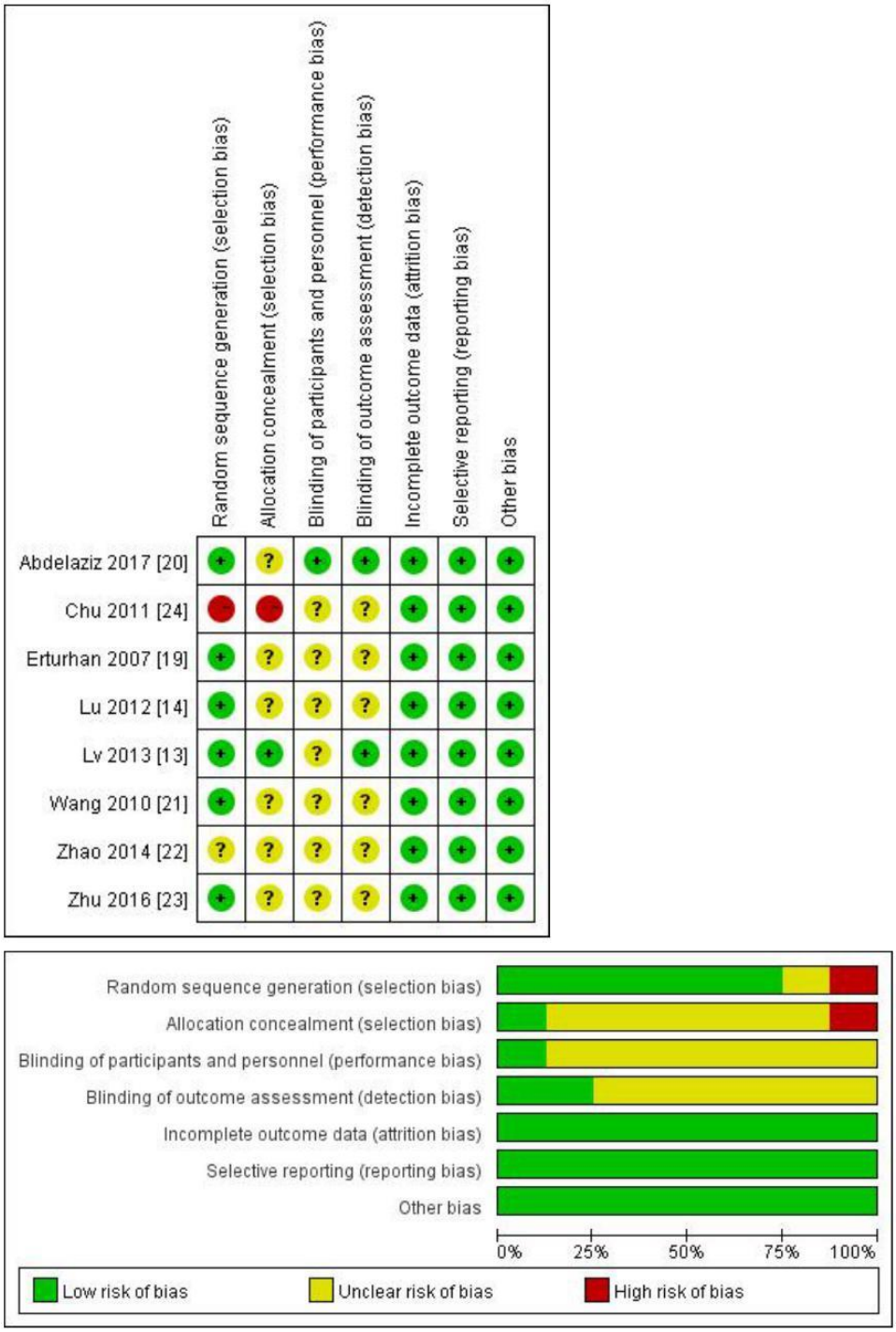
Figure 6. VAS after lower ureteric stone treatment
Comparisons between combination therapy and alpha-blocker monotherapy after 3 days, 7 days and 4 weeks

Figure 7. USS after lower ureteric stone treatment
Comparisons between combination therapy and alpha-blocker monotherapy after 3 days and 7 days

Figure 8. Adverse effects of lower ureteric stone treatment

Comparison between combination therapy and alpha-blocker monotherapy





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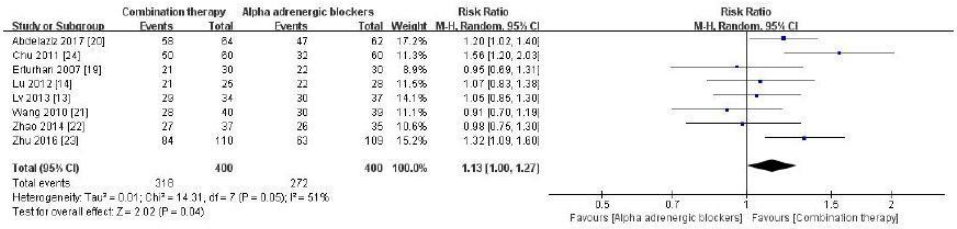

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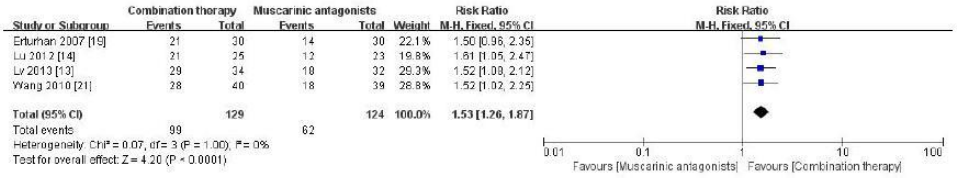

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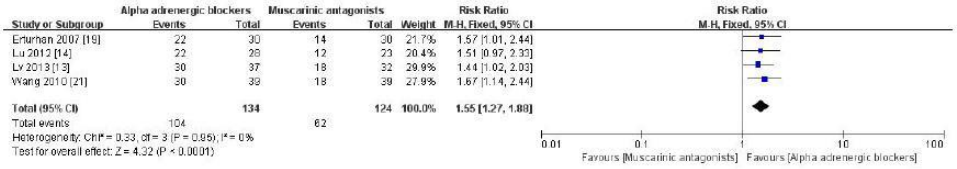
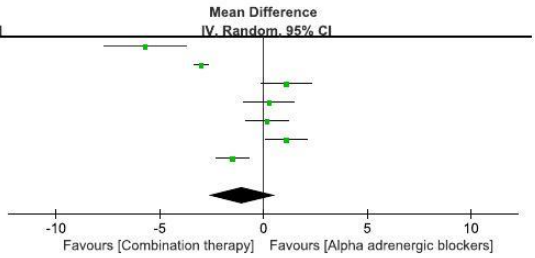


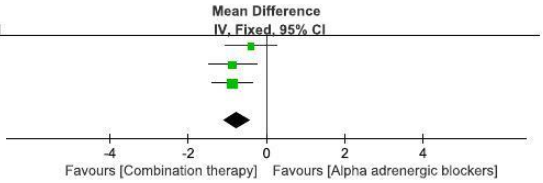
Study or Subgroup	Combination therapy Mean	SD	Total	Alpha adrenergic blockers Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdelaziz 2017 [20]	11.65	5.32	64	17.35	6.21	62	12.4%	-5.70 [-7.72, -3.68]
Chu 2011 [24]	4	1	60	7	1	60	15.3%	-3.00 [-3.36, -2.64]
Erturhan 2007 [19]	7.5	2.75	30	6.4	2.125	30	14.2%	1.10 [-0.14, 2.34]
Lu 2012 [14]	7.9	2.31	25	7.63	2.28	28	14.2%	0.27 [-0.97, 1.51]
Lv 2013 [13]	7.79	2.11	34	7.62	2.42	37	14.5%	0.17 [-0.88, 1.22]
Wang 2010 [21]	6.4	2.2	40	5.3	2.5	40	14.5%	1.10 [0.07, 2.13]
Zhu 2016 [23]	6.3	2.1	68	7.8	2.5	61	14.9%	-1.50 [-2.30, -0.70]
Total (95% CI)			**321**			**318**	**100.0%**	**-1.01 [-2.62, 0.59]**

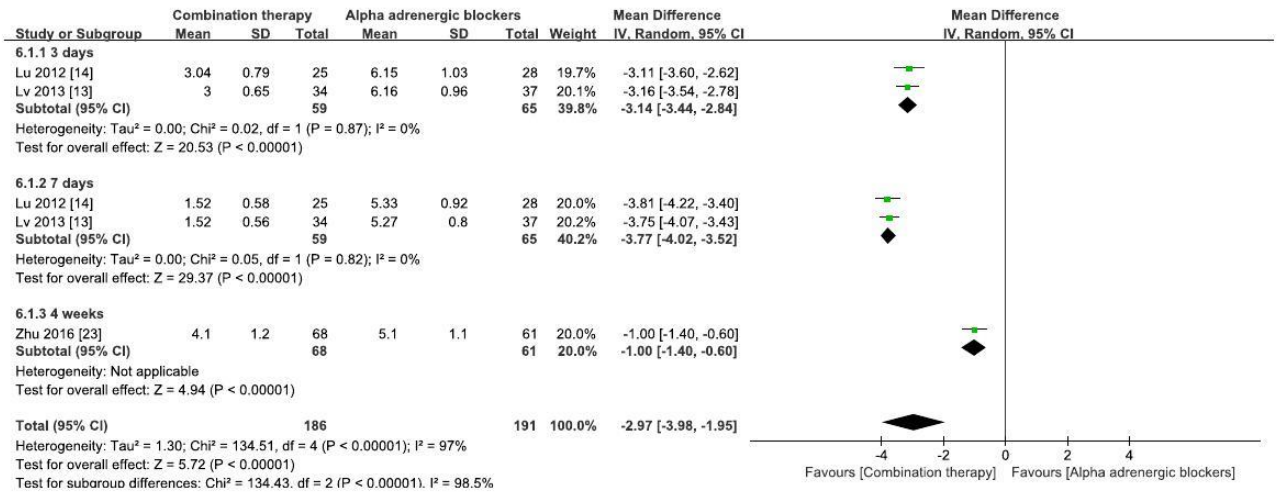
Heterogeneity: Tau² = 4.33; Chi² = 132.03, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.24 (P = 0.22)

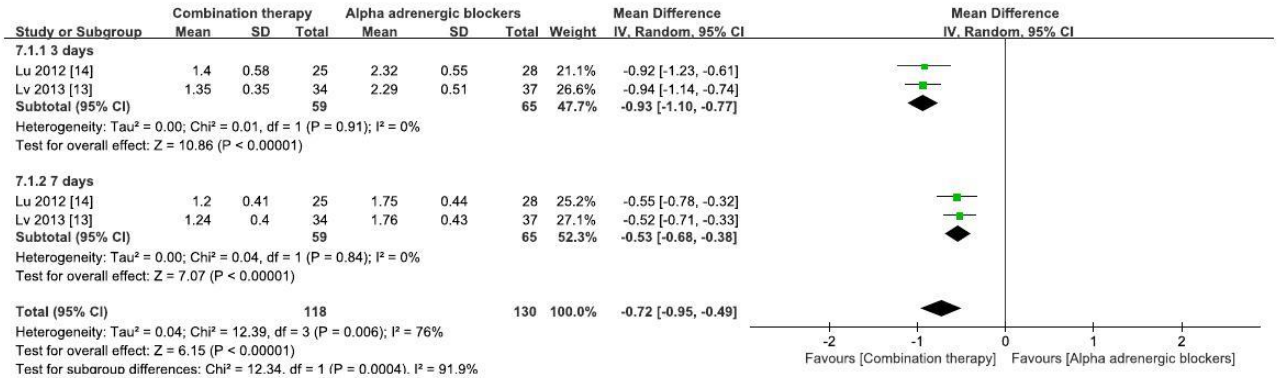


Study or Subgroup	Combination therapy Mean	SD	Total	Alpha adrenergic blockers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abdelaziz 2017 [20]	2.8	1.8	64	3.2	2.1	62	26.4%	-0.40 [-1.08, 0.28]
Lu 2012 [14]	1.38	1.37	25	2.25	0.9	28	30.9%	-0.87 [-1.50, -0.24]
Lv 2013 [13]	1.39	1.34	34	2.27	0.91	37	42.7%	-0.88 [-1.42, -0.34]
Total (95% CI)			**123**			**127**	**100.0%**	**-0.75 [-1.10, -0.40]**

Heterogeneity: Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.19 (P < 0.0001)







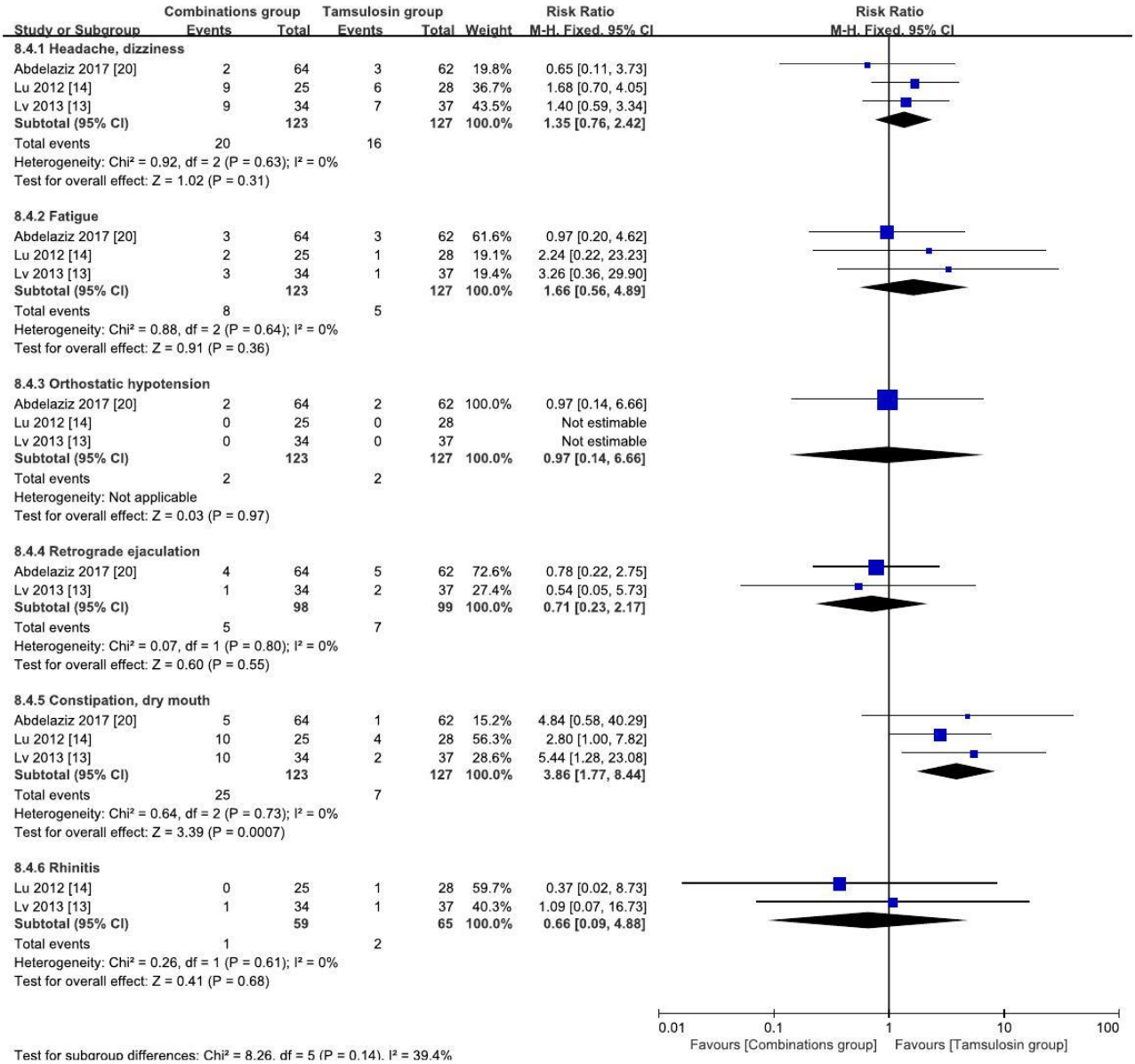


Table 1 Characteristics of the included studies of lower ureteric stones in meta-analysis

Study Authors, year	Stone size	Patients	Intervention	Follow-up	Mean/median age (years)	Number of male/female	Ureteral stone side (Left/Right)
Erturhan 2007 [19]	stones less than 10 mm	120	Tamsulosin (30)	≤3 weeks	32.7	64/56	53/67
			Tamsulosin+tolterodine (30)		35.8		
			Tolterodine (30)		34.7		
			Nothing (30)		31.4		
Wang 2010 [21]	4 mm-10 mm	160	Tamsulosin (40)	2 weeks	35.4	84/76	NA
			Tamsulosin+tolterodine (40)		34.3		
			Tolterodine (40)		33.8		
			Nothing (40)		35.5		
Chu 2011 [24]	4 mm-8 mm	120	Tamsulosin (60)	≤3 weeks	32	81/39	NA
			Tamsulosin+tolterodine (60)		37		
Lu 2012 [14]	stones less than 9 mm	76	Naftopidil (28)	2 weeks	32.19	39/37	39/37
			Naftopidil+tolterodine (25)		33.67		
			Tolterodine (23)		34.32		
Lv 2013 [13]	stones less than 9 mm	103	Tamsulosin (37)	2 weeks	32.14	64/39	59/44
			Tamsulosin+tolterodine (34)		33.36		
			Tolterodine (32)		34.35		
Zhao 2014 [22]	4 mm-10 mm	120	Tamsulosin (40)	≤15 days	36	80/40	NA
			Tamsulosin+tolterodine (40)		35		
			Tamsulosin+frusemide (40)		37		
Zhu 2016 [23]	stones less than 10 mm	129	Tamsulosin+tolterodine (68)	≤4 weeks	35.7	NA	NA
			Tamsulosin (61)		37.5		
Abdelaziz 2017 [20]	stones less than 10 mm	126	Tamsulosin+placebo (62)	≤4 weeks	39.02	61/25	47/39
			Tamsulosin+trospium (64)		36.43		

NA, not available.

Table 2 Summary of the results in the included studies.

Study	Comparators	Stone expulsion rate (%)	Mean days to stone expulsion ±SD (days)	Pain episodes ±SD (times)	Urinary Sensation Scale ±SD	Visual analog scale ±SD
Erturhan 2007 [19]	Tamsulosin (30)	22, 73.3%	6.4±2.083	1.7	NA	4.7
	Tamsulosin+tolterodine (30)	21, 70%	7.5±2.6957	2.1		4.1
	Tolterodine (30)	14, 46.6%	11.4±2.6957	4.5		8.5
	Nothing (30)	12, 40%	12.2±3.676	4.7		8.8
Wang 2010 [21]	Tamsulosin (39)	30, 76.9%	5.3 ± 2.5	NA	NA	NA
	Tamsulosin+tolterodine (40)	28, 70%	6.4 ± 2.2			
	Tolterodine (39)	18, 46.2%	10.7 ± 1.8			
	Nothing (38)	16, 42.1%	12.8 ± 3.4			
Chu 2011 [24]	Tamsulosin (60)	32, 53.3%	7 ± 1	NA	NA	NA
	Tamsulosin+tolterodine (60)	50, 83.3%	4 ± 1			
Lu 2012 [14]	Naftopidil (28)	22, 78.6%	7.63 ± 2.28	2.25 ± 0.90,	3days	3days
	Naftopidil+tolterodine (25)	21, 84.0%	7.90 ± 2.31	1.38 ± 1.37	2.32±0.55	6.15 ± 1.03
	Tolterodine (23)	12, 52.2%	10.71 ± 2.72	1.54 ±1.18	1.4±0.58	3.04 ± 0.79
					1.34±0.49	3.13 ± 1.32
					7days	7days
					1.75 ± 0.44	5.33 ± 0.92
					1.2 ± 0.41	1.52 ± 0.58
					1.22 ±0.42	1.56 ± 0.51
Lv 2013 [13]	Tamsulosin (37)	30, 81.1 %	7.62±2.42,	2.27±0.91	3days	3days
	Tamsulosin+tolterodine (34)	29, 85.29%	7.79±2.11,	1.39±1.34	2.29 ± 0.51	6.16 ± 0.96
	Tolterodine (32)	18, 56.25%	10.57±2.71	1.38±1.20	1.35 ± 0.54	3.00 ± 0.65
					1.31 ± 0.47	3.31 ± 1.49
					7days	7days
					1.76 ± 0.43	5.27 ± 0.80
					1.24 ± 0.40	1.52 ± 0.56
					1.19 ± 0.40	1.53 ± 0.51
Zhao 2014 [22]	Tamsulosin (35)	26, 74.3%	NA	NA	NA	NA
	Tamsulosin+tolterodine (37)	27, 73%				
	Tamsulosin+frusemide (38)	33, 86.8%				
Zhu 2016 [23]	Tamsulosin+tolterodine (68)	58, 85.3%	6.3 ± 2.1	NA	NA	4.1 ± 1.2
	Tamsulosin (61)	43, 70.5%	7.8 ± 2.5			5.1 ± 1.1
Abdelaziz 2017 [20]	Tamsulosin (62)	47, 75.8%	17.35 ± 6.21	3.2 ± 2.1	NA	NA
	Tamsulosin+trospium chloride (64)	58, 90.62%	11.65 ± 5.32	2.8 ± 1.8		

NA, not available.