Efficacy and safety of phosphodiesterase type 5 inhibitors for the treatment of distal ureteral calculi of 5 to 10 mm in size: A systematic review and network meta-analysis

Jia-Kun Li | Shi Qiu | Kun Jin | Xiao-Nan Zheng | Xiang Tu | Si-Wei Bi | Xin-Yang Liao | Yi-Ge Bao | Lu Yang | Qiang Wei

Department of Urology, Institute of Urology, West China Hospital of Sichuan University, Chengdu, Sichuan, P.R. China

Correspondence
Qiang Wei and Lu Yang, Department of Urology, Institute of Urology, West China Hospital of Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan 610041, P.R. China.
Emails: weiqiang163163@163.com; wycleflue@163.com

Funding information
Science and Technology Department of Sichuan Province, Grant/Award Numbers: 2014FY0219, 2013SZ0006; The National Natural Science Foundation of China, Grant/Award Numbers: 81300551, 81270841, 81200551, 81370855, 81270841, 81300627

To evaluate the Efficacy and safety of phosphodiesterase type 5 inhibitors as a medical therapy for distal ureteral calculi by means of a systematic review and network meta-analysis (NMA). We searched the Embase, Medline, and the Cochrane Central Register of Controlled Trials for randomised controlled trials (RCTs) published before May, 2017. Stone passage rate as the primary outcome. We used random effects model for pairwise meta-analyses and Bayesian random effects model for NMA. We evaluated the quality of evidence by the GRADE framework for each network estimate. Five RCTs (861 patients) comparing four different interventions. The results of NMA showed that compared with tamsulosin alone, tamsulosin combined with tadalafil group was associated with significantly higher stone passage rate (odds ratio [OR] 2.55, 95% credible intervals [Crl] 1.11 to 5.89). When considering stone expulsion rate, compared with tamsulosin, silodosin was ranked best (OR 3.58, 95% Crl 1.13 to 11.91), followed by tamsulosin combined with tadalafil (OR 2.55, 95% Crl 1.11 to 5.89) and tadalafil alone (OR 1.86, 95% Crl 0.95 to 4.25). No significant difference was found considering safety profiles between any interventions. This meta-analysis indicates that tamsulosin combined with tadalafil is an effective treatment option for ureteral stones with a low occurrence of side effects. Clinicians should take all known safety and compliance of patients into account when choosing an optimal strategy. Since sample size of included studies, further RCTs are strongly encouraged to address the clinical question.

KEYWORDS
network meta-analysis, phosphodiesterase 5 inhibitors, ureteral calculi

1 | INTRODUCTION

Urolithiasis as a common disease in urology has a rising incidence and approximate 20% population suffering from ureteral stones. The National Health and Nutrition Examination Survey (NHANES) indicates that the prevalence rate of urinary calculus has increased over the last 30 years in the United States. This translates into a remarkable projected economic burden, with an extra $1.24 billion/year approximated by 2030. Many studies have reported spontaneous stone passage rates of all calculi up to 50%, and of calculi <5 mm in size up to 85% between 28 and 40 days. Minimally invasive treatment is possible when...
there is no spontaneous expulsion of stones. This is a very effective
but not harmless way and occupies a large part of the cost of the
health system. Thus, by looking for more accurate and effective drugs
to reduce surgical intervention and delayed treatment, the therapeutic
spectrum has shifted to the improvement of medical expulsive therapy
(MET).7

MET, especially alpha-blockers, has been proposed as support-
ive medication for patients with ureteral stones for facilitating stone
passage and decreasing the need for interventional procedure.1,8
Selective alpha-blockers and calcium antagonists are the traditionally
treatment option and have been proven to be effective in a
variety of clinical trials. However, a large multicenter randomized con-
trolled trial (RCT) found that neither tamsulosin or nifedipine was clin-
ically useful in promoting expulsion because there is no need for
further intervention within 4 weeks of patients with ureteral colic.9
Therefore, the benefits of MET seem unclear with such conflicting
data.10 Over the past 10 years, the possibility in MET to use phospho-
diesterase type 5 inhibitors (PDE5i) has been studied due to their
direct influences on ureteral smooth muscle relaxation in animals and
human models.7 Investigators have focused on how can the effective
implementation with PDE5i in clinical practice, and the results of
these studies displayed that tadalafil prescription owns positive
benefits.11–15

Despite numerous MET interventions evaluated in previous RCTs
to treat ureteral stones, further studies and more data were still
needed for quantitatively analyzing PDE5i in head-to-head compari-
sions. Thus, we employed a network meta-analysis (NMA) of all RCTs,
including PDE5i, alone and in combination with other pharmacological
approaches.

2 | METHODS

The present study was performed on the grounds of the Preferred
Reporting Items for Systematic Review and Meta-analysis (PRISMA)
statement.

2.1 | Selection criteria

1. Studies: Databases were searched from the earliest record to May
2017. Only RCTs with full-text articles were eligible for inclusion.
We limited our systematic review to trials published in English due
to resource constraints, and excluded studies that were identified
as fraudulent or were retracted.16

2. Participants: Women and men over 18 years of age who were
diagnosed with single, unilateral symptomatic distal ureterolithia-
sis with a ureteral calculus of 10 mm or less in its largest dimen-
sion were included.

3. Interventions: Studies had to examine treatment with PDE5i com-
pared with placebo or control for treatment of ureteric stones.

4. Outcomes: The primary outcome was stone passage rate. The sec-
ondary outcomes were stone expulsion time, analgesic use, hospi-
tal visits, colic episodes, and side effects.

2.2 | Information sources and search strategy

A search strategy was designed for studies published in Medline via
the pubmed, Cochrane Central Register Clinical Trials (CENTRAL) and
Embase databases. Electronic searches were supplemented by citation
tracking of the relevant systematic reviews and included trials.
The following search terms were used: “PDE5i” or “phosphodiesterase type 5 inhibitors”; “ureteral stones”; and “randomized controlled trial”.

2.3 Study selection and data collection

Three reviewers screened the titles and abstracts in duplicate to determine potential eligibility and entries identified by any reviewer proceeded to the full-text eligibility review. Pre-tested eligibility forms were used for full text review, which was also performed in duplicate, with a third adjudicator helping to reach consensus in situations of disagreement. The same process was followed for data abstraction and methodological quality/risk of bias appraisal. Data were abstracted in duplicate and authors of primary publications were contacted when required for missing information.

2.4 Statistical analysis and meta-analysis

A pair-wise meta-analysis applying random-effects model was done firstly in RevMan 5.3 (Cochrane Collaboration, Oxford, UK). We estimated relative curative effects through the application of mean difference (MD) for continuous outcomes and odds ratio (OR) for dichotomous outcomes, both with 95% confidence interval (CI). The statistical heterogeneity among studies was assessed by the Cochran’s Q test and the I² statistic. A P value of 0.05 or less for the Q test or an I² greater than 50% indicates substantial study heterogeneity.

For indirect and mixed comparisons, we conducted random-effects Bayesian NMAs employing Markov chain Monte Carlo methods in WinBUGS version 1.4.3 which use informative prior distributions for all treatment effects as well as the between-study variance parameter. The results of NMA with effect sizes (MD or OR) and their credible intervals (CrI) were summarized. The pooled estimates were obtained using the Markov Chains Monte Carlo method. Three Markov chains were run synchronously with various arbitrarily chosen initial values.

To check for inconsistency, the loop-specific approach was performed on behalf of assessing the diversity between direct and indirect estimates for a specific comparison in the loop. We employed the node-splitting method, excluding one direct comparison at a time and estimating the indirect treatment effect for the excluded comparison. To check for the assumption of consistency, the design-by-treatment model was conducted.

2.5 Quality of evidence

The GRADE was carried out to evaluate the evidence quality of estimates derived from NMA. In this approach, direct evidence from RCTs starts at high quality and can be downgraded based on risk of bias, imprecision, indirectness, inconsistency (or heterogeneity), and publication bias to levels of moderate, low, and relatively low quality.
3 | RESULTS

3.1 | Characteristics of included studies

In our initial research, we identified seven studies.11–15,23,24 Two of them were excluded when we went through the full text because they did not measure up to the previously inclusion criteria.23,24 (Figure 1). Five RCTs (861 patients) published in recent 3 years were included ultimately. Three interventions were included: tamsulosin group, tadalafil group, and tamsulosin plus tadalafil group. Tamsulosin group consisted of five studies including 384 patients.11–15 Tadalafil group consisted of three studies including 234 patients.11–13 Tamsulosin plus tadalafil group consisted of two studies including 153 patients (Table 1).14,15 Figure 2 presents the provides the network graphs for stone passage rate and stone expulsion time.

3.2 | Risk of bias assessment results

Five (100.00%) studies were found with low risk of bias on random sequence generation and four (80.00%) studies with low risk of bias on allocation concealment. Only three (60.00%) studies had low risk of bias on both binding of participants and outcome assessment. Supporting Information Table 1 displayed the results from the risk of bias assessment.

3.3 | Stone passage rate

Five studies (Four Treatment) including 771 patients were involved in the analysis. When considering the result of NMA, compared with tamsulosin, silodosin was ranked best (OR 3.58, 95% Crl 1.13 to 11.91; SUCRA = 82.5%), followed by tamsulosin combined with tadalafil (OR 2.55, 95% Crl 1.11 to 5.89; SUCRA = 63.3%) and tadalafil alone (OR 1.86, 95% Crl 0.95 to 4.25; SUCRA = 32.4%). In the pairwise meta-analysis, compared with tamsulosin alone, combination of tamsulosin and tadalafil led to no statistic difference (OR 1.24, 95% CI 0.73 to 2.08, P = 0.216). But there is a trend toward increase in stone passage rate favoring tadalafil was observed compared with tamsulosin (OR 1.15, 95% CI 0.93 to 1.30, P = 0.249) was found. No heterogeneity was found among the studies (I² = 0). No significant difference was found between any other agents (Table 2).

3.4 | Stone expulsion time

Five studies (four treatment) including 771 patients were involved in the analysis. In the pairwise meta-analysis, time to expel stones in tadalafil group was significantly less than tamsulosin group (MD −0.33, 95% CI −0.62 to −0.03, P = 0.028). Medium heterogeneity was found with an I² index of 58.3%. A more remarkable benefit was also found in the combination of tamsulosin and tadalafil group compared with tamsulosin (MD −0.42, 95% CI −0.64 to −0.19) with good consistency (I² = 0). NMA suggested that, compared with tamsulosin, silodosin was ranked best (MD −2.22, 95% CI −4.39 to −0.9; SUCRA = 91.2%), followed by combination of tamsulosin and tadalafil (MD −1.82, 95% CI −3.57 to 0.02; SUCRA = 67.9%) and tadalafil (MD −1.31, 95% CI −2.70 to 0.06; SUCRA = 14.7%). No significant difference was found between any other agents, when assessing the comparative efficacy (Table 2).

3.5 | Hospital visits

Two studies (three treatment) including 306 patients were involved in the analysis. In the pairwise meta-analysis, number of hospital visits in tamsulosin plus tadalafil group was significantly less than tamsulosin group (MD −0.76, 95% CI −1.02 to −0.49, P = 0.000) with an I² index of 12.3%. The result of NMA showed that the number of hospital visits in tamsulosin plus tadalafil group was significantly less than tamsulosin group (MD −0.75, 95% CI −1.57 to −0.01). But no statistic difference between tadalafil and tamsulosin was witnessed (Table 2).

3.6 | Colic episodes

Five studies (four treatment) including 771 patients were involved in the analysis. In the pairwise meta-analysis, tamsulosin plus tadalafil

---

**FIGURE 2** Network of eligible comparisons for outcomes. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). A, Network of stone passage rate; B, Network of stone expulsion time.
### Table 2: Summary effect of pairwise and network meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment</th>
<th>Number of Studies*</th>
<th>Pairwise Meta-analysis (95% CI)</th>
<th>P</th>
<th>Cochran’s Q p-Value</th>
<th>Network Meta-analysis (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stone passage rate</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>1.10 (0.93, 1.30) (OR)</td>
<td>0.00</td>
<td>0.249</td>
<td>1.86 (0.95, 4.25) (OR)</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>1.14 (0.93, 1.37) (OR)</td>
<td>0.00</td>
<td>0.216</td>
<td>2.55 (1.11, 5.89) (OR)</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.58 (1.13, 11.91) (OR)</td>
</tr>
<tr>
<td>Headache</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>1.44 (0.89, 2.27) (OR)</td>
<td>0.00</td>
<td>0.132</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>0.815 (0.46, 1.43) (OR)</td>
<td>0.00</td>
<td>0.476</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.81 (0.30, 2.05) (OR)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>1.34 (0.82, 2.20) (OR)</td>
<td>0.00</td>
<td>0.243</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>0.82 (0.46, 1.43) (OR)</td>
<td>0.00</td>
<td>0.476</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.83 (0.26, 2.38) (OR)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>1.16 (0.65, 2.06) (OR)</td>
<td>0.00</td>
<td>0.617</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>1.16 (0.26[3].5[1]) (OR)</td>
<td>0.0%</td>
<td>0.845</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.40 (0.06, 2.10) (OR)</td>
</tr>
<tr>
<td>Backache</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>1.38 (0.79, 2.42) (OR)</td>
<td>15.3%</td>
<td>0.262</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>0.66 (0.36, 1.21) (OR)</td>
<td>0.00</td>
<td>0.179</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.04 (0.28, 3.55) (OR)</td>
</tr>
<tr>
<td>stone expulsion time</td>
<td>Tamsulosin (reference)</td>
<td>3 (465)</td>
<td>-0.33 (-0.62, -0.03) (MD)</td>
<td>58.3%</td>
<td>0.028</td>
<td>-1.31 (-2.70, 0.06) (MD)</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>-0.42 (-0.64, -0.19) (MD)</td>
<td>0.00</td>
<td>0.000</td>
<td>-1.82 (-3.57, 0.02) (MD)</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-2.22 (-4.39, -0.09) (MD)</td>
</tr>
<tr>
<td>Hospital visits</td>
<td>Tamsulosin (reference)</td>
<td>2 (306)</td>
<td>-0.76 (-1.02, -0.49) (MD)</td>
<td>12.3%</td>
<td>0.000</td>
<td>-0.75 (-1.57, -0.00) (MD)</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2 (306)</td>
<td>-1.35 (-1.59, -1.10) (MD)</td>
<td>0.00</td>
<td>0.000</td>
<td>-1.15 (-1.99, -0.29) (MD)</td>
</tr>
<tr>
<td></td>
<td>Silodosin</td>
<td>1 (90)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-1.06 (-2.09, 0.04) (MD)</td>
</tr>
</tbody>
</table>

CI, 95% confidence intervals; 95% CrI, 95% credible intervals; MD, mean difference; OR, odds ratio, 95%. Using GRADE to rate quality of evidence from a network meta-analysis involved several steps: The pairwise meta-analyses (DerSimonian and Laird random effects model) of these two comparisons were conducted and are reported here in comparison with the estimates from the network analysis. The table shows comparison of estimates from pairwise meta-analysis compared to NMA. Quality of evidence as judged based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. First, we rated quality of evidence for direct comparisons; second, we rated quality of evidence for indirect estimates (starting at the lowest rating of the two pairwise direct estimates that contribute as first-order loops to the indirect estimate, which can be rated down further for imprecision or intransitivity), and then third, rating the quality of evidence for the network combining direct and indirect estimates. In this step, if direct and indirect estimates from second-order comparisons are similar, the higher of the ratings was assigned to the network meta-analysis estimates.

*Number of studies with direct comparison (participants).
was significantly better than tamsulosin respecting colic episodes (MD 1.35, 95%CI 1.10 to 1.59, P = 0.000). No heterogeneity was found among the studies no statistical difference between tadalafil and tamsulosin was observed (MD −0.45, 95%CI −1.11 to 0.22, P = 0.187). However serious heterogeneity among the studies was found (I² = 91.6%). The result of NMA showed that the colic episodes number in tamsulosin plus tadalafil group was significantly less than tamsulosin group (MD −1.15, 95% CrI −1.99 to −0.29) (Table 2).

3.7 | Analgesic use

Pairwise meta-analysis showed that dosage of analgesia used in tadalafil group was significantly more than tamsulosin group (MD = 0.31, 95%CI 0.01 to 0.61, P = 0.040). But medium heterogeneity was found (I² = 29.2%). Times to use analgesia in tamsulosin plus tadalafil group was significantly less than tamsulosin group (MD 1.13, 95%CI 0.85 to 1.40, P = 0.001) with an I² index of 14.7% (Table 2).

3.8 | Side effects

Five studies (four treatment) including 771 patients described the side effects associated with treatment. In the pairwise meta-analysis, there was no statistic difference between tamsulosin group and tamsulosin plus tadalafil group in terms of headache, dizziness, backache, orthostatic hypotension, and abnormal ejaculation. (P > 0.05). The result of NMA showed no statistic difference among each group (Table 2).

4 | DISCUSSION

In recent years, urolithiasis as a common disease in urology has a rising incidence. This study is the most comprehensive and updated NMA comparing effect of PED5i with other METs options. According the result of NMA, this study has demonstrated that combination therapy with tadalafil and tamsulosin improved stone passage rate, hospital visits, and colic episodes. Silodosin was also more effective than tamsulosin alone at improving stone passage rate, but this study has been unable to demonstrate the significant difference between tadalafil and tamsulosin; The evidence on safety profile of discrepant kinds of METs among patients with ureteric stones was limited and showed unclear difference.

PED5is are the first-line medication for erectile dysfunction. Hence, the prescription of tadalafil in cases of lower ureteric stones with erectile dysfunction may provide an additional advantage in the erectile function. Kc et al11 reported that in the last 20 to 30 minutes after ingestion of tadalafil, 75% of the patients felt mild penile erection and no patient presented with priapism. A recent study25 evaluated the effectiveness of intercourse in patients with distal ureteral stones (5-10 mm) and found that the average time of intercourse of 3-4 per week for married men and women with distal ureteral stones resulted in an increase in the rate of expulsion. This effect is assumed associated with nitric oxide released during intercourse which be able to induce ureteric relaxation. In this research, tadalafil tended to have shorter stone expulsion time than tamsulosin in NMA. As for pairwise meta-analysis, tadalafil demonstrated significant superiority to tamsulosin considering stone expulsion time. However, no evidence favoring tadalafil was observed in respect to stone passage rate. Therefore, although tadalafil seems to be an alternative proposal for patients of lower ureteric stones with erectile dysfunction, further research is needed to ascertain which instructions optimally increase patients’ performance.

Additionally, NMA revealed that the concomitant use of tamsulosin and tadalafil was associated with 1.55 times improvement in the stone passage rate than tamsulosin alone. We also found a trend toward higher stone passage rate considering combination strategy with tadalafil and tamsulosin compared with tamsulosin in pairwise meta-analysis. Moreover, in both pairwise meta-analysis and NMA, the combination therapy reported better hospital visits and colic episodes results than tamsulosin alone. In the aspects of headache, dizziness, backache, orthostatic hypotension, and the rate of abnormal ejaculation, we found tamsulosin combined with tadalafil was equal to tamsulosin alone. Last year, a meta-analysis data showed that compared with tamsulosin monotherapy, tadalafil monotherapy, or combined with tamsulosin has a significantly higher stone expulsion rate.30 These combination of findings provides some support for the concomitant use of tamsulosin combined with tadalafil in the patients with the size of ureteral calculus no more than 10 mm.

Silodosin is a new introduction of alpha blocker with higher selectivity for alpha-1A receptor than alpha-1B receptor.26 In this research, compared with tamsulosin alone, silodosin has higher stone passage rate and less stone expulsion time from the NMA and even better than tamsulosin combined with tadalafil (no statistical difference) in these two aspects. The efficacy demonstrated by silodosin in ureteral calculus patients is not surprising, due to its strong biologic basis.26 Considering hospital visits, colic episodes and safety profiles, silodosin is equal to tamsulosin alone, tadalafil alone or tamsulosin combined with tadalafil. Because of this unique property, it has shown that less blood pressure related adverse effects were mediated by the α-1B receptors. In October 2008, silodosin was approved by the the US Food and Drug Administration (FDA) for lower urinary tract symptoms and benign prostatic hyperplasia.27 Elgalaly et al. also reported that silodosin had higher stone expulsion rate and less stone expulsion time compared to tamsulosin in present study.28 In 2017, Rahman et al. analyzed 120 patients study. They found compared with tamsulosin, silodosin had significantly higher expulsion rate, less expulsion time and less pain episodes.29 This finding has resulted in recent studies using silodosin for MET.30 Further more head to head research should be done to investigate the comparative effect of silodosin on MET of ureteral calculi.

This study is the first NMA to investigate the efficacy and tolerability of tadalafil and tamsulosin combined with tadalafil. All the studies referred are RCTs from SCI data base. The quality of the search strategies designed for each database, which were highly sensitive and specific for the detection of records related to the question of the systematic review. The salient features of the study were prominent because they included only between 5 and 10 mm stones, as mentioned earlier, a subgroup of ureteral calculi with real indications of for MET.26,27 Although the present study is the first meta-analysis to examine the effect of tadalafil for distal ureteral stones, several pitfalls should be clarified. Firstly,
limitations of systematic reviews and meta-analyses mainly include the quality of a small number of available studies and the composition of their clinical trial reports. This restriction does not necessarily mean bad or good methodological quality. However, this variable may lead to an underestimation of quality, as the best tool for assessing quality is the Cochrane Collaboration tool, which requires an appropriate report to appropriately balance the project. However, these studies are usually very risky in terms of bias in tool items. Secondly, positive studies are more likely to be published than negative, the present results might have been affected by publication bias. Thirdly, the absence of description of the allocation concealment in all included trials may result in some undetected bias of the present study. Further more, other predisposing factors, such as smoking, family history, body mass index, obesity, and dietary habits were not adjusted due to the natural limitations of the meta-analysis study. In addition, most included study did not assessment of the impact of tadalafil on the frequency of sexual intercourse of the study population which also have a potential role in the distal ureteral stone spontaneous expulsion. We cannot evaluate the analgesic use in NMA because difference between units of measurement. Finally, the samples were heterogenous and some variables were insufficiently described in the original studies such as the numbers of stone episodes, the time to take medicine and the time interval between drugs. They may affect the status of patients and results. Thus further well-designed, double-blinded, multi-centric RCTs are strongly encouraged to address the clinical question.

This research will serve as a base for future studies and suggest conducting trials with larger sample sizes and better methodological quality to improve the recommendations derived from this systematic review and NMA. Moreover, in the RCTs we reffered, most patients are male. Thus, further research can be more specific in terms of gender, especially in women. Finally, different studies of outcomes for analgesic use in different units of measurement, the further study with the same unit of dosage of times will contribute to statistical analysis of the results.

5 | CONCLUSIONS

The study has shown that combination therapy with tadalafil and tamsulosin was safe, efficacious and well tolerated. Clinicians should take all known safety and compliance of patients into account when choosing an optimal strategy. Considering the limited quantity and small sample size of included studies, more further well-designed, double-blinded, multi-centric RCTs are strongly encouraged to address the clinical question.

CONFLICTS OF INTEREST

All authors declare no conflicts of interests.

REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.