REVIEW

Efficacy and Safety of Doxazosin in Medical Expulsive Therapy for Distal Ureteral Stones: A Systematic Review and Meta-analysis

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Purpose: Alpha-blockers have been proven as an effective method for increasing the stone expulsion rate of distal ureteral stones. Limited studies have focused on doxazosin; its efficacy remained unclear. We performed this meta-analysis to investigate the efficacy and safety of doxazosin for patients diagnosed with distal ureteral stones less than 10mm.

Materials and Methods: We systematically searched Ovid MEDLINE®, Cochrane Library, EMBASE, and PubMed for articles comparing doxazosin and conventional care or tamsulosin for distal ureteral stones through October 2019. The outcome measures were stone expulsive rate (SER), stone expulsive time (SET), pain episodes, analgesics consumption, and adverse events.

Results: We included 12 studies involving 836 participants with distal ureteral stones less than 10mm in our review. The present meta-analysis showed doxazosin could significantly increase SER [RR=1.64,95%CI (1.32, 2.04), $P < 0.00001$], shorten SET [WMD=-3.97,95% CI (-5.68, -2.27), $P < 0.00001$] compared with conventional care. In the subgroup analyses, doxazosin showed no benefit in the children subgroup (<16 years old) [RR=1.63,95% CI (0.73,3.64), $P = 0.23$]. No statistically significant difference was observed regarding the effectiveness of doxazosin and tamsulosin in SER, SET, and safety. Nine out of 286 participants reported doxazosin-related adverse events; most were mild to moderate.

Conclusion: This meta-analysis may suggest that doxazosin is a safe and effective MET for distal ureteral stones less than 10mm. It is not demonstrated to have any significant difference with tamsulosin in SER, SET, and safety. However, it showed no benefits for patients < 16 years old.

Keywords: doxazosin; ureteral stones; efficacy; meta-analysis

INTRODUCTION

Urolithiasis is a common presenting medical condition that influences nearly 12% of the world population. Medical expulsive therapy has proven to be an effective method of accelerating the spontaneous passage of a ureteral stone(<10 mm) and potentially minimizing pain and additional complication rates[1]. It has been proved to have cost advantages over observation and ureteroscopy[2].

Alpha-blockers(α-blockers), corticosteroids, and calcium channel blockers are extensively used in the treatment of MET, in which α-blocks seems to be superior to others[3]. Tamsulosin and doxazosin are two representative α-blockers of MET. Tamsulosin is the most commonly used safe and effective α-blocker in the MET distal ureteral stones less than 10 mm. Doxazosin is also one of the commonly used α-blockers representative α-blockers of MET. However, limited studies have focused on doxazosin. Its efficacy remains unclear. Additionally, data are limited concerning the efficacy and safety of doxazosin for urolithiasis compared with tamsulosin[4,5]. For these reasons, a systematic review and meta-analysis were conducted to elucidate the efficacy and safety of doxazosin for distal urolithiasis (stone size <10 mm) compared with conventional care and tamsulosin. We also performed subgroup analyses to determine whether stone size, age, different doses, and follow-up periods modify the effects of doxazosin.

MATERIALS AND METHODS

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses for this systematic literature[6].

Search strategy and selection of studies

Two reviewers (L.Ma and L.Yang) independently searched Ovid MEDLINE®, Cochrane Library, EMBASE, and PubMed database to identify the relevant articles on 1st October 2019. We did not put any limits to publication year or publication language. Additionally, hand searches were also conducted through reference lists to retrieve potential studies. The literature search was carried out with the combinations of the following terms, 'ureter$ stone$ or ureter$ calcul$ or ureter$ lithiasis or nephrolithiasis' and 'doxazosin or alpha-blocke$ or α-blocke$'. If the data was not complete, we sent an email to the corresponding author to obtain the required

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Table 1. Characteristics of included studies.

Study Year	Country	Population; Follow up period	stone size(mm)	Intervention;n; Mean ± SD(age in years)	Control;n;Mean±SD(age in years)	Outcome Measurements
Yilmaz 2005(20)	Turkey	Adults with lower ureteral stones; one month	≤10	doxazosin (4 mg daily); 29;42.13 ±10.46	Diclofenac;28;41.60 ±12.01	1 2 3 4 5
Yilmaz 2005(20)	Turkey	Adults with lower ureteral stones; one month	≤10	doxazosin (4 mg daily) ;29;42.13 ±10.46	Tamsulosin (0.4 mg daily); 29;42.13±10.46	1 2 3 4 5
Liatsikos 2007(15)	Greece	Participants with a distal-ureteral stone;4 weeks	≤5	doxazosin (4 mg daily); 20;47.50±10.33	Diclofenac;15;46.33 ± 10.74	1 2 3 4
Liatsikos 2007(15)	Greece	Participants with a distal-ureteral stone;4 weeks	5-10	doxazosin (4 mg daily); 22;42.13 ±10.46	Diclofenac;16;43.75 ±11.16	1 2 3 4
Ayubov 2007(11)	Uzbekistan	Symptomatic distal ureteral calculi;4 weeks	--	doxazosin (4 mg daily); 30; not mentioned	Diclofenac;31; not mentioned	1 2 3
Mukhtarov 2007(17)	Uzbekistan	Participants with symptomatic distal ureteral calculi;4 weeks	4-6	doxazosin (4 mg daily); 27; not mentioned	Diclofenac;25; not mentioned	1 2 3
Mukhtarov 2007(17)	Uzbekistan	Adults with symptomatic distal ureteral calculi underwent SWL;4 weeks	≥6	doxazosin (4 mg daily); 24; not mentioned	Diclofenac;21; not mentioned	1 2 3
Ayodogdu 2009(10)	Turkey	Children with radiopaque lower ureteral stones;19 days	2-9	doxazosin (0.03 mg/kg daily);19;6.2±2.4	Ibuprofen;20;5.1±2.2	1 2 3 4
Ben 2009(18)	Tunisia	18-76 years old adults with lower ureteral stones;one month	--	doxazosin (4 mg daily); Not mentioned	Tamsulosin 0.4 mg/daily; Not mentioned	1 2 3 4
Zehri 2010(21)	Pakistan	patients with asymptomatic 4-7 mm distal ureteral stone;4 weeks	4-7	doxazosin (2 mg daily at the night); 33;32.63	Diclofenac;32;33.62	1 2 3 4
Gurbuz 2011(14)	Turkey	Adults with distal ureteral stones; two weeks	5-10	doxazosin (4mg daily); 35;34.17 ± 1.1	Diclofenac on demand+ Hyoscine N-Butylbromide;35;40.3 ± 15.9	1 2 3 4 5
Mshemish 2012(16)	Iraq	Patients with lower ureteral stones ;45 days	≤10	doxazosin (4 mg daily) ; 33;44.3±12.5	Meloxicam;34;43.8±13.2	1 2 3 4
Mshemish 2012(16)	Iraq	Patients with lower ureteral stones ;45 days	≤10	doxazosin (4 mg daily) ; 33;44.3±12.5	tamsulosin (0.4mg daily); 34;44.3±12.5	1 2 3 4
Erturhan 2013(13)	Turkey Children with a single radiopaque lower ureteral stone,3 weeks		≤10	doxazosin (0.03 mg/kg/d); 25;6.0 ± 3.5	Ibuprofen ;21;7.2 ± 3.5	1 2 3 4
Sen 2016(19)	Turkey	Adults with distal ureteral radio-opaque stones	≤10 mm	doxazosin (4 mg daily); 25;30 ± 7.6	Diclofenac;19;33 ± 11.3	1 2 3 4
Sen 2016(19)	Turkey	Adults with distal ureteral radio-opaque stones	≤10 mm	doxazosin (8mg daily); 22;37.9 ± 11.5	Diclofenac;19;33 ± 11.3	1 2 3 4
Çelik 2018(12)	Turkey Male adults with non-complicated < 10 mm mid-proximal ureteral stone,6weeks		<10mm	doxazosin (8mg daily); 37;38.2 ± 12.8	Tamsulosin 0.4 mg/daily; 34;43.9 ± 11.5	1 2 3

information. In addition, if different articles were published using the same study, only those with the complete data or the most citations were selected. All searched papers were imported into EndNote| Clarivate Analytics X9 to identify duplicate studies.

Randomized controlled trials (RCTs) comparing doxazosin with placebo or conventional care (hydration and analgesics) or tamsulosin were included. Studies that enrolled participants diagnosed with urolithiasis <10mm in the distal urinary tract were included. Studies were excluded if the enrolled participants presented the following conditions: urinary tract infection, hydronephrosis, ureteric abnormalities, pregnant or lactating women. We excluded studies or arms that received complementary other alpha-blockers (e.g., Silodosin, Alfuzosin), calcium channel blockers (e.g., nifedipine), or other adjuvant medications except for analgesics or surgical interventions (e.g., ureterorenoscopic removal of stones). Studies that compared different doses of doxazosin were also included.

The primary outcomes of included studies needed to be SER and SET. Pain episodes, analgesic consumption, and adverse effects were considered secondary outcomes. L.Ma and L.Yang screened all titles and abstracts to find eligible studies. Any disagreement regarding the decision to include or exclude a study was addressed by consensus of a third reviewer's (S.Y. Zou) independent assessment. Reasons for exclusion were recorded.

Assessment of risk of bias

The risk assessment of bias of RCTs was conducted using the Cochrane risk of bias tool[7]. Participants' allocation, allocation concealment, blinding, and loss to follow-up and intent-to-treat analysis were assessed for

Table 2. Subgroup analyses for SER of doxazosin versus conventional care.

Subgroup	No of studies	No of Participants D/C	Heterogeneity *P*-value	I^2	F/R	RR (95% CI)	*P*-value
Age							
Participants≥16 Yrs	8[11,12,14-21]	275/254	0.007	64%	R	1.64[1.29,2.07]	$P < 0.0001$
Participants<16 Yrs	2[10,13]	43/41	0.04	76%	R	1.63[0.73,3.64]	$P = 0.23$
Stone Size							
5-10mm	4[13-15,17]	68/28	$P < 0.0001$	88%	R	2.03 [1.52, 2.71]	$P < 0.00001$
≤ 5mm	4[13,15,17,21]	106/84	$P = 0.23$	32%	R	1.43 [1.06, 1.92]	$P = 0.02$
Doxazosin dose							
4mg daily	7[11,14-17,19,20]	242/222	$P = 0.006$	67%	R	1.62 [1.25, 2.10]	$P = 0.0003$
≠4mg daily	2[19,21]	55/51	$P = 0.49$	0%	F	2.08 [1.36, 3.1]	$P = 0.0008$
Follow-up periods							
≥4 weeks	6[11,15-17,20,21]	218/202	$P = 0.44$	0%	F	1.47 [1.28, 1.68]	$P < 0.00001$
<4 weeks	4[10,13,14,19]	100/93	$P = 0.0004$	84%	R	2.52 [1.08, 5.92]	$P = 0.03$

the quality of each RCT. Two reviewers (L.Yang and L.Ma) assessed the risk of bias of each domain as 'low risk,' 'unclear risk,' 'or high risk.'

Data extraction

The forms of Cochrane Handbook for Systematic Review[8] were used to extract the basic data of the studies, including, author and year, country, population, follow-up periods, characteristics (sample size and age), intervention (doxazosin), comparator (conventional care or tamsulosin), and the aforesaid outcomes. The first author (L. Ma) completed data extraction. L.Yang double-checked the accuracy of the extracted data.

Statistical Analysis

All statistical analyses were performed by Review Manager software, version 5.3. We adopted the risk ratio (R.R.) for dichotomous outcomes (SER, adverse effects, hospitalization rate), and weighted mean difference (WMD) for continuous outcomes (SET, analgesic consumption), both with 95% confidence intervals(CI). Heterogeneity between studies was evaluated by χ^2 test, P-value and I2 statistics. I2 values of 25%, 50%, and 75% generally represented low, moderate, and high levels of heterogeneity. When I2 value was >50%, a random-effects model was adopted; when I2 value was<50%, a fixed-effects model was applied. *P* -values ≤ 0.05 were considered statistically significant.

Subgroup Analysis

We performed four subgroup analyses to investigate the effect of doxazosin in different populations: age (≥16 vs. <16 years old), stone size (5-10 vs. ≤ 5mm), doxazosin doses (4mg daily vs. ≠ 4mg daily), and follow-up periods (≥ 4 weeks vs. < 4 weeks).

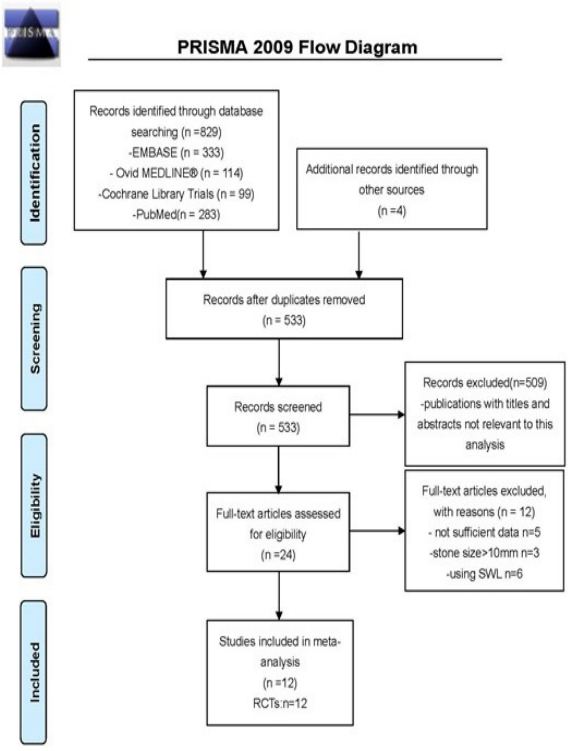

Figure 1. PRISMA flow diagram of study selection and inclusion

RESULTS

Search results

A total of 533 records were identified initially. After screening studies with the inclusion and exclusion criteria, 12 studies (comprising 836 participants) were included in the final analysis[9-20]. All included studies reported SER and SET as primary outcomes. SER was also presented as 'stone clearance' or 'stone expulsion' or 'stone-free rate.' SET was expressed as the date and time of the stone passage. Five studies were conducted in Turkey, and others were held in Greece, Uzbekistan, Tunisia, Pakistan, Iraq. Details of study selection are demonstrated in supplemental **Figure 1**. The characteristics of the included studies are shown in **Table 1**.

All studies enrolled patients with distal-ureteral stones or lower ureteral stones detected by C.T. scan or abdominal radiographs. Ten studies included a total of 654 participants compared doxazosin(n=340) with conventional care(n=314) for the primary outcomes. Four studies compared doxazosin with tamsulosin (112 participants in each group, respectively). All participants aged 5.1±2.2 to 46.33 ± 10.74 years old. All included studies except Mukhtarov[16] and Ben[18] reported adverse events. Pain episodes were reported seven studies, and pain requiring analgesia was included in eight studies.

Assessment of risk of bias

Figure 2 summarized the risk of bias. All of the 12 studies were found to be at moderate to high risk of bias. The funnel plot was used to assess the potential publication bias of all data in the included study. Based on the funnel plot, we found that the shape of the fun-

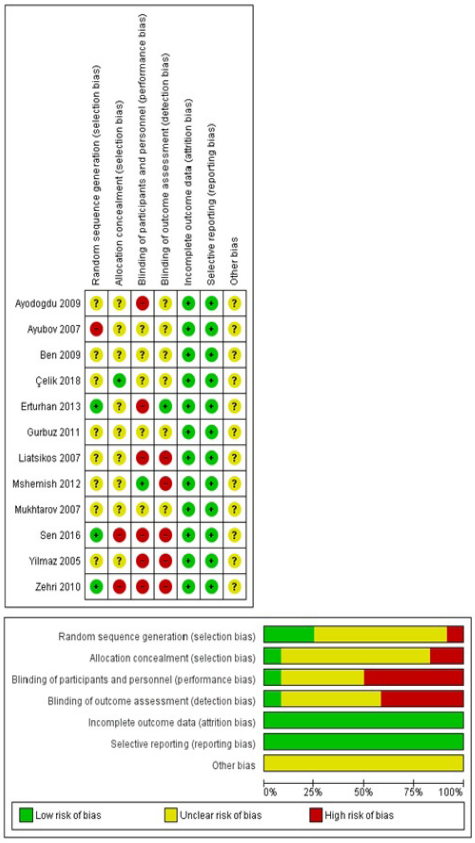

Figure 2. Summary of risk of bias of the included studies. This graph shows all included studies were at high, intermediate, and low risk of bias in various domains

nel plot was asymmetric (**Figure 3**), indicating risks of publication bias.

Primary outcomes

Doxazosin vs. conventional care

Ten studies compared doxazosin with conventional care for SER, including 340 and 314 participants in the doxazosin and conventional care groups, respectively. A random-effects model was adopted based on heterogeneity (P = 0.002, I^2=66%). The pooled analysis revealed that doxazosin could significantly increase SER

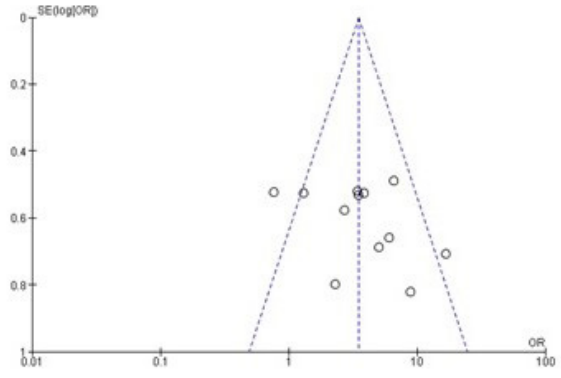

Figure 3. Funnel plot of publication bias.

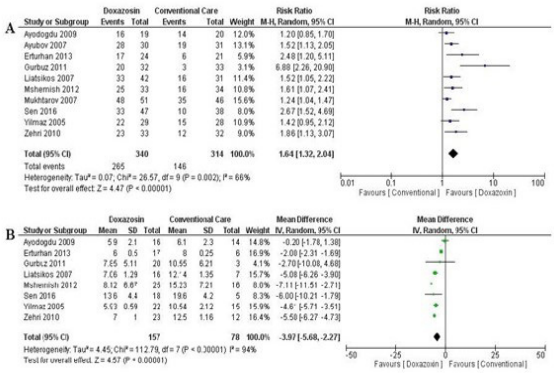

Figure 4. Comparison of doxazosin vs. Conventional care(A for SER; B for SET).

compared with conservative care [RR=1.64,95% CI (1.32, 2.04), P < 0.00001] (**Figure 4A**).

We conducted pre-planned subgroup analyses based on stone size (stone size <5 vs. 5-10 mm), age (≥16 Yrs vs.< 16 Yrs), doxazosin dose (4mg daily vs. <4mg daily), and follow-up period (≥ 4 weeks vs. < 4 weeks), which might be influencing factors of stone passage. All subgroup analyses found consistent results (Table 2), except for the children subgroup [RR=1.63,95% CI (0.73,3.64), P = 0.23].

Ten studies measured SET in days, and two[11,17] were excluded because of insufficient data. In the pooled analysis, there was increased heterogeneity noted between studies (P < 0.00001, I2 = 94%). Thus, the random-effects model was used. Doxazosin was found to significantly shorten the stone expulsion time in comparison with conventional care by direct comparison pooled estimates [WMD=-3.97,95% CI (-5.68, -2.27), P < 0.00001] (**Figure 4B**).

Doxazosin vs. tamsulosin

Four studies compared SER and SET of doxazosin with tamsulosin directly (with 112 participants in each group). According to our pooled analysis, there was no significant difference of SER [RR=0.94, 95% CI (0.80, 1.10), P = 0.45] (Figure 5A) and SET [MD=-0.34, 95% CI (-0.78, 0.09) P = 0.12] (Figure 5B) between the doxazosin and tamsulosin groups. Due to the inadequacy of data, the study of Ben[18] was not included in the analysis of SET but illustrated the consistent result.

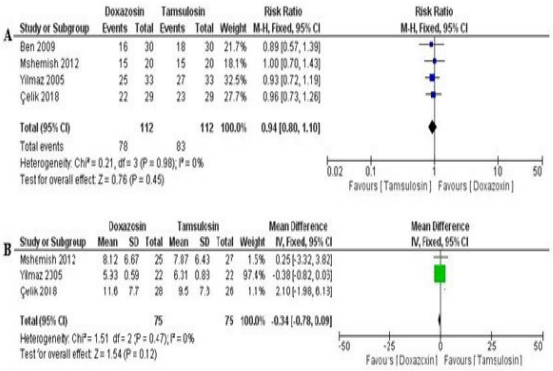

Figure 5. Comparison of Doxazosin vs. Tamsulosin (A for SER; B for SET).

Secondary outcomes

Adverse events observed in the studies referred to doxazosin-related side effects, including symptomatic episodes, syncope, orthostatic hypotension, retrograde ejaculation, nausea, and vomiting. Sen et al. reported that 12% of participants in the 4mg doxazosin group and 18% of participants in the 8mg doxazosin group both experienced adverse events[18]. Mshemish et al. reported that 3% in the tamsulosin group and 6% in doxazosin experienced an episode of hypotension[15], but not statistically significant. In Erturhan et al. 's study, one patient was excluded due to nausea and vomiting [12]. The remaining studies did not report any adverse events.

All included studies, except Celik et al. 's study[11], reported pain episodes or analgesic consumption in the articles. Diclofenac, ibuprofen, meloxicam were used as analgesics in combination with hydration to treat distal ureteral stones. However, we could not perform an overall quantitative analysis of analgesic consumption due to different doses, types of analgesics used in each study. As to pain episodes, four studies reported pain episodes observed during the follow-up period[10,13,16,19]. Heterogeneity was indicated in the pooled analysis ($P < 0.00001$; $I^2 = 100\%$); using the random-effects model, the pooled data showed that there was a statistical difference of pain episodes between doxazosin and conventional care [RR=-131.58,95% CI (-247.50, -15.67), $P < 0.00001$]. Liatsikos et al.[15], Gurbuz et al.[14], and Erturhan et al.[12] reported participants in the doxazosin group experienced fewer pain episodes and used fewer analgesics than the conventional care group, but the results were not statistically significant.

Concerning the comparison of doxazosin and tamsulosin in pain episodes, we could not extract suitable data to implement the quantitative analysis. However, two studies[15,19] reported the total amount of analgesics (diclofenac, mg); The pooled analysis showed that there was no statistical difference between two groups [RR=0.13, 95% CI (-0.03, 0.28), $P = 0.12$].

DISCUSSION

Strong evidence has proven that MET facilitates spontaneous passage of urolithiasis and reduces pain[21]. It is a simple and attractive method because it avoids invasive procedures and cost less than ureteroscopy or open surgeries[22]. α-blockers have been established as superior to calcium-channel inhibitors or corticosteroids, being more likely to pass stones and associated with fewer colic episodes[21]. Abundant studies focused on the most commonly used α-blockers(tamsulosin); limited studies evaluate the efficacy and safety of other α-blockers. We conducted a comprehensive meta-analysis to validate the efficacy and safety of doxazosin. We verified that doxazosin could effectively accelerate the SER, shorten SET, and decrease the associated pain, compared with conventional care. When compared with tamsulosin, we were not able to demonstrate any significant difference for SER, SET, and safety in our meta-analysis.

Stone size is the main factor influencing the spontaneous passage of urolithiasis. In the review of three trials [12,14,16] studying SER with mean stone sizes ≤5 mm, only one study revealed a significantly higher expulsion rate in the doxazosin group[14]. In contrast, regarding doxazosin with stone sizes 5-10mm, all included studies demonstrated a significant benefit in SER. Consistent results were presented in the subgroup analysis of Sridharan et al.[23], α-blockers were not found to enhance SER in patients with ureteral stones <5 mm while increasing SER for ureteral stones ≥5 mm. Campschroer et al.[24] also found a-blockers had a comparable effect on SER in participants with stones of ≤5 mm with conventional care and a significant positive impact in participants with stones of >5 mm SER ($P = 0.16$ vs. $P < 0.001$). However, the results of Liatsikos et al. showed that doxazosin could significantly increase SER and shorten SET in patients with distal ureteral stones<5 mm[14]. Owning to the high likelihood of spontaneous passage of stones ≤5 mm with hydration and analgesics[3,25], we still recommend the application of a-blockers only for stones 5-10mm. Furthermore, MET using α-blockers has also proven to be a cost-effective treatment for ureteral stones[26].

Doxazosin pills were used as the intervention in all included studies. Six trials provided doxazosin for 28 days, three trials provided the drug for about 21 days, one trial provided the drug for about 19 days, and the remaining study provided doxazosin for 42 days. Pooled data in this meta-analysis supported that doxazosin for 28 days facilitated a higher SER than any other administration periods (21days or 19days) ($P < 0.00001$ vs. $P = 0.03$). Our results are consistent with the guidelines that patients should be treated for 4 weeks[27]. However, the included studies in the subgroup (follow-up period < 4 weeks) had large heterogeneity ($P = 0.0004$; $I^2 = 84\%$). Thus the results should be treated with caution. Regarding the optimal dose of doxazosin for participants, most studies [except studies of Zehri[21] and Sen's one arm (8 mg doxazosin)[18]], adopted 4mg daily for adult participants. For children, two studies[9,12] used 0.03 mg/kg/day. Given the data of the present review, doxazosin showed significant effects in increasing SER with 4mg and ≠4mg ($P = 0.0003$ vs. $P = 0.0008$). Only one study compared 4mg and 8mg doses of doxazosin in which there was no statistical difference ($P = 0.207$) [18], indicating equal efficacy with 4 or 8 mg doses. However, Yuceturk, Cem Nedim, et al. conducted a retrospective study to compare another a-blocker(silodosin) 4 mg/day and 8 mg/day for MET of lower ureteral stones, the result showed the SER in 8-mg/day group was statistically higher than the 4-mg/day group ($P = .002$)[1]. Considering higher risks of adverse events corresponded to a higher dose of doxazosin[28], we still recommended a 4 mg dose of doxazosin for 28 days was safe and effective in ureteral stones <10 mm for MET.

In the children subgroup analysis, pooled data of the present review indicated no statistical difference of SER between doxazosin and conventional therapy. A similar result was also reported in the systematic review by Sridharan[23]. However, this was not consistent with the meta-analysis and systematic reviews of Tian et al.[29] and Velazquez et al.[30]. They reported that α-blockers could significantly increase SER in children with distal ureteral stones accompanying fewer adverse effects compared with no therapy. We believe that the inclusion of limited trials in this study and the heterogeneity within trials might cause inconsistent results of doxazosin for children. Nevertheless, more large-scale, high-quality trials are needed to validate the efficacy and safety of α-blockers in the treatment of distal uro-

lithiasis in pediatric patients.

We did not conduct an overall quantitative analysis of the pain episodes and the amount of analgesic consumption due to the massive heterogeneity between studies. However, according to the included articles, the participants in the doxazosin group experienced fewer pain episodes and consumed fewer analgesics compared with participants treated with conventional care. Although the efficacy of doxazosin in reducing pain episodes still requires validation, the benefits of doxazosin for the overall quality of life is for sure.

Doxazosin did not appear to increase the risks of adverse events in all included studies. Only 3 out of 12 studies (9 in 340 participants) reported doxazosin-related adverse events, most of which were mild to moderate. There were no serious adverse events noted in all studies. These results differ from the meta-analysis of Campschroer[24] in which participants receiving an a-blocker were more likely to experience adverse events by 2.7 times. Although the incidence of doxazosin-related adverse events is low, the European Association of Urology[31] guidelines recommend that patients should be counseled about the attendant risks and informed that it is administered for an 'off label' use before using doxazosin for urolithiasis.

This meta-analysis has several limitations. The first limitation is the small number of eligible studies. We included studies of RCTs; other types of studies were not included. Only published papers in English were included, resulting in potential publication bias and language bias. As to the secondary outcomes, we were unable to conduct a meta-analysis for pain episodes, consumption of analgesics, and adverse events due to different outcome indicators.

Moreover, substantial heterogeneity was detected in our main analysis. The heterogeneity possibly originated from variations in study populations, follow-up periods, inclusion and exclusion criteria, and outcome measurements. We used the random-effects model and conducted subgroup analyses to minimise the heterogeneity among studies. Apart from the above limitations, the findings of this meta-analysis remain crucial for accessing the efficacy and safety of doxazosin in the treatment of distal urolithiasis. We suggest that better quality and more robust trials are needed to learn more about the efficacy and safety of doxazosin, especially for children.

CONCLUSIONS

In conclusion, the present review suggests that doxazosin can be used as an effective and safe MET for urolithiasis. We recommend doxazosin in the treatment of patients with urolithiasis, especially for stones 5 to 10mm, excepting children. A once-daily dosage of 4mg for 28 days might be the optimal treatment modality. Additionally, doxazosin is not demonstrated to have any significant difference with tamsulosin in SER, SET, and safety. Due to the various quality of included studies, the findings may change with the publication of comparative studies. Additional large-scale and high-quality randomized controlled trials are required to validate these results.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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