Review Article

Silodosin as a medical expulsive therapy for distal ureteral stones: A systematic review and meta-analysis

Muhammad Zaniar Ramadhani[1,2], Yudhistira Pradnyan Kloping[1,2], Ilham Akbar Rahman[1,2], Niwanda Yogiswara[1,2], Mohammad Ayodhia Soebadi[1,3], Johan Renaldo[1,2]*

[1]Department of Urology, Faculty of Medicine, Universitas Airlangga, [2]Dr. Soetomo General-Academic Hospital, Surabaya, East Java, [3]Universitas Airlangga/Rumah Sakit Universitas Airlangga Teaching Hospital, Surabaya, Indonesia
*E-mail: joeurologi@gmail.com

ABSTRACT

Introduction: Tamsulosin is the most commonly used medical expulsive therapy (MET). However, it does not alleviate ureteral colic. It is important to develop MET that can reduce ureteral colic while maintaining a high stone clearance rate. Silodosin is an α1A adrenoceptor with high affinity and selectivity for the distal ureter, which may reduce ureteral colic and enable stone expulsion for distal ureteral stones. Therefore, we performed this systematic review and meta-analysis to evaluate the efficacy of silodosin as MET and its role in reducing ureteral colic among patients with distal ureteral stones.
Materials and Methods: This research was conducted in accordance with the Cochrane Handbook for Systematic Review and Intervention, in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42021249003). A comprehensive literature search was performed in several databases including Medline, EMBASE, and Scopus up to July 2021 for randomized trials comparing silodosin with placebo for MET. RevMan 5.4 was used for data analysis.
Results: A total of six randomized controlled trials were included in this analysis with a total of 907 patients. Our analysis revealed that the patients who received silodosin had significantly higher stone expulsion rate (SER) (odds ratio [OR] 3.33, 95% confidence interval [CI] 2.34, 4.76, $P < 0.01$), significantly shorter stone expulsion time (SET) (mean difference –3.79, 95% CI –4.51, –3.06, $P < 0.01$), and lower analgesic use (OR 0.4, 95% CI 0.23, 0.69, $P < 0.01$) compared to the group receiving placebo.
Conclusion: Silodosin showed significantly higher SER, lower SET and lower analgesic use in patients with distal ureteral stones as compared to a placebo.

INTRODUCTION

Urolithiasis is one of the three most common urological diseases, following urinary tract infection and benign prostatic hyperplasia. Approximately 2%–3% of the global population suffers from urolithiasis, with a recurrence rate of 20%.[1-3] Currently available treatment options for patients with urinary stones are watchful waiting for spontaneous expulsion, extracorporeal shockwave lithotripsy, surgery, and medical expulsive therapy (MET.[4,5] Previous studies have proven the role of alpha-blockers, calcium channel antagonists, furosemide, and corticosteroids for assisting in the spontaneous expulsion of stones. Of these, alpha-blockers are the most commonly used option.[6,7] Alpha-blockers increase the chances of stone passage by approximately 48%. Several trials have also reported a pooled risk ratio of 1.54 for MET.[6] A previous study has reported the rate of stone

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expulsion with silodosin as 82% and tamsulosin as 58%.[8] Among all the alpha-blockers, tamsulosin is most commonly used for MET, with a 19% improvement in the rate of stone clearance for ureteral stones, especially in the distal ureter.[2] In 2015, Ding *et al*. suggested that tamsulosin does not alleviate ureteral colic. An effective MET is expected to alleviate ureteral colic in addition to improving the chances of stone clearance. Several studies have evaluated silodosin, an α1A adrenoceptor antagonist, with a higher affinity and selectivity to the distal ureter, because it offers a higher stone expulsion rate (SER) compared to the other alpha-blockers.[2] In this systematic review and meta-analysis, we aimed to evaluate the efficacy of silodosin as a MET and its role in improving the SER, reducing the stone expulsion time (SET), and reducing the ureteral colic among patients with distal ureteral stones.

MATERIALS AND METHODS

Study design and protocol registration

This research was a systematic review and meta-analysis of intervention and was performed in accordance to the Cochrane Handbook for Systematic Review and Intervention, in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42021249003).

Search strategy and eligibility criteria

We systematically searched for relevant articles through Medline, Embase, and Scopus database from their inception up to July 2021 using keywords related to "silodosin" and "medical expulsive therapy (MET)." The titles and abstracts were screened by two independent reviewers using a pre-specified eligibility criteria. All randomized controlled trials (RCTs) which evaluated patients with distal ureteral stones and prescribed silodosin as the intervention as compared to a placebo or no intervention and reported the outcome of SER, SET, and analgesic use were eligible for inclusion in this meta-analysis. Non-randomized studies (cohort, case–control, case series, and cross-sectional) and those which evaluated patients with multiple stones were excluded.

Data collection and quality assessment

Data extraction was performed by two independent reviewers using a standardized data collection form. Any dispute between the reviewers was solved by reviewing the full text with the senior authors. The data collection form comprised of the first author's name, study design, description of the stone characteristics, participant's age, intervention protocol, and the outcomes included in the meta-analysis. SER was defined as the rate of stone expulsion in the subject after receiving the intervention. The monitoring of the expulsed stone could be performed by any of the available methods. For example, patients could be advised to strain the urine to search for the stone or an imaging modality such as ultrasonography kidney, ureter, and bladder or an X-ray could be utilised if the stone could not be visualized in the urine. SET was defined as the time (days) required for the expulsion of the stone after the administration of the drug. The quality of the eligible trials was evaluated using the Cochrane's risk of bias (RoB) V2, which comprises of the assessment of the bias from the randomization process, the bias caused by deviation from the intended intervention, the bias due to incomplete or different measurement of outcome, and the bias caused by selective reporting.

Data synthesis

The effect size estimates of the dichotomous outcomes were expressed as odds ratio (OR) and those of the continuous outcomes were pooled as mean difference (MD) with 95% confidence interval (95% CI). We assessed the heterogeneity among the included trials using the heterogeneity *P* value and I^2 index. If the heterogeneity *P* value was < 0.5 and the I^2 was <50%, the fixed-effects method (Mantel–Haenszel) was used; otherwise, the random-effects method was used to conduct the analysis. If the *P* value of the meta-analysis was <0.5, the results were considered statistically significant. The statistical software Review Manager 5.4 (Cochrane Collaboration, UK) was used to perform the meta-analyses.

RESULTS

Search results and study characteristics

The initial search from PubMed, EMBASE, and Scopus yielded a total of 1057 records. Of them, 374 records were excluded during the duplication removal process, and 683 articles were screened by the title and abstracts, as shown in Figure 1.[5,9-14]

Full texts of 23 articles were accessed for eligibility. Finally, six trials were considered to be eligible for inclusion in this study. The included trials were single-center trials and were conducted in five different countries (Turkey, India, Japan, United States, and Taiwan). All trials used a similar intervention protocol, 8 mg of silodosin per day for a period of 2–8 weeks. A total of 907 participants enrolled in the RCTs were analyzed. The average age of the patients ranged from 39 to 57 years. The quality assessment using the Cochrane's RoB 2 [Figure 2] revealed that there were some concerns in the domain of the bias due to deviation from the intended intervention and in the domain of the bias due to missing outcome data as the description of the methods and the result section of the included trials were incomplete. Nevertheless, the overall results demonstrated that almost all the included trials had a low RoB. The baseline characteristics of the included studies are listed in Table 1.

Efficacy of silodosin on stone expulsion rate

A total of six trials were included in the analysis of SER [Figure 3], in which 278 patients were allocated to

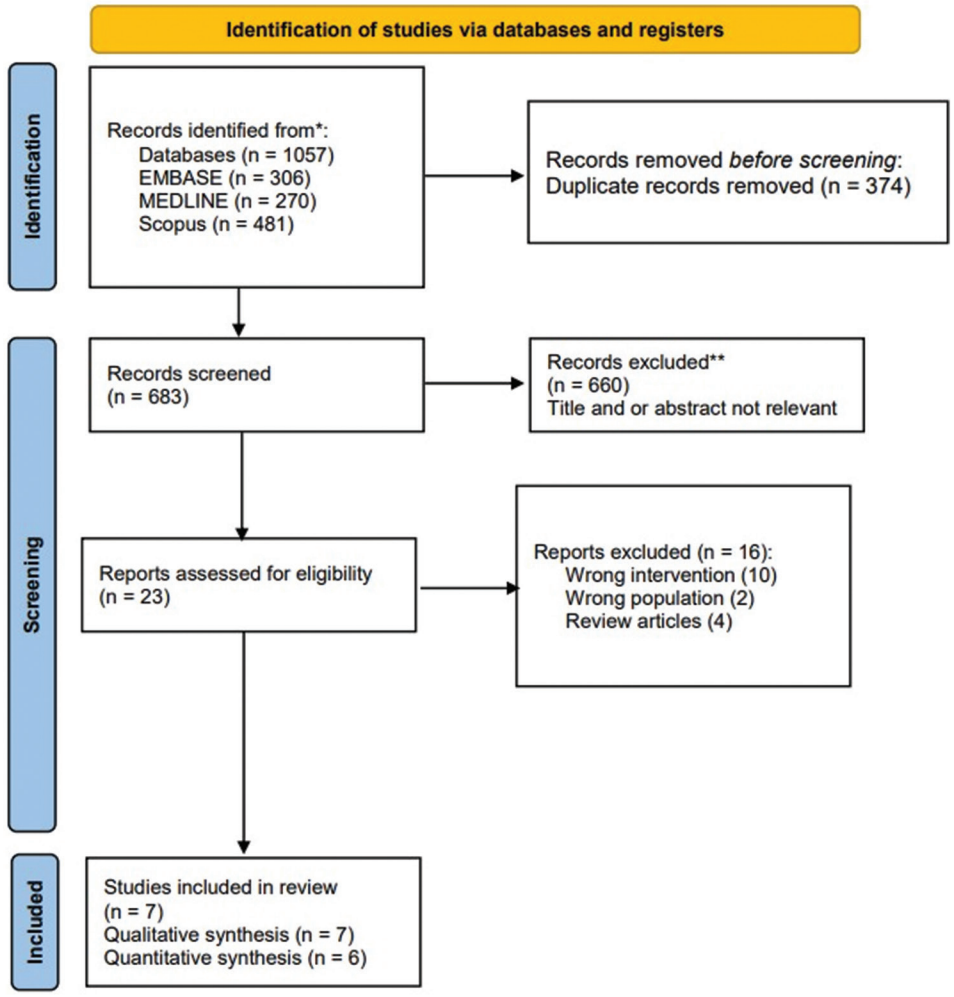

Figure 1: PRISMA flowchart showing search strategy and screening, PRISMA: Preferred reporting Items for Systematic Reviews and Meta-Analyses

Table 1: Baseline characteristics of included studies

Author's name	Study type (RCT/non-RCT)	Population	Mean age (years)		Total samples	Intervention protocol
			Silodosin	Placebo		
Wang, 2016[15]	RCT	Radiopaque distal ureteral stone <10 mm	51.42±8.68	51.51±10.03	123 (62-61)	Silodosin 8 mg PO/24 h/2 weeks
Bayar, 2020[16]	RCT	4-10 mm unilateral ureteral stone	40±15	39.1±14.6	113 (54-59)	Silodosin 8 mg PO/24 h/4 weeks
Cholaraju, 2020[22]	RCT	4-7 mm unilateral distal ureteral stone, age >20 years old	20-70	20-70	90 (45-45)	Silodosin 8 mg PO/24 h/1 month
Itoh, 2011[17]	RCT	<10 mm proximal (29.8%), mid (8.8%), and distal (61.3%) ureteral stone	57.2±12.7	56.5±10.1	181 (89-92)	Silodosin 8 mg PO/24 h/8 weeks
Itoh, 2013[20]	RCT	5-10 mm unilateral distal ureteral stone	56.3±11.7	55.8±10.4	111 (55-56)	Silodosin 8 mg PO/24 h/4 weeks
Sur, 2014[18]	RCT	4-10 mm unilateral proximal (34.5%), mid (17.6%), and distal (47.8%) ureteral stone, age >18 years old	47±13	47±15	232 (115-117)	Silodosin 8 mg PO/24 h/4 weeks
Rathi, 2014[5]	RCT	≤10 mm distal ureteral stone	Not reported	Not reported	57 (29-28)	Silodosin 8 mg PO/24 h/4 weeks

RCT=Randomized controlled trial, PO=Per os

the silodosin group and 285 patients were allocated to the control group. The forest plot using the fixed-effects model demonstrated that the patients who received 8 mg of silodosin per day had a significantly higher SER as compared to the group receiving the placebo (OR 3.33, 95% CI 2.34, 4.76, $P < 0.01$).

Efficacy of silodosin on stone expulsion time

Meta-analysis of four RCTs ($n = 474$) revealed that the patients who received silodosin intervention had a significantly shorter SET as compared to the control group (MD –3.79, 95% CI –4.51, –3.06, $P < 0.01$). The forest plot in Figure 4 shows that the trials had low heterogeneity (heterogeneity $P = 0.32$, $I^2 = 14\%$), and thus, the fixed-effects model was chosen for the analysis.

Efficacy of silodosin on analgesic use

Figure 5 shows the pooled estimated effect size of the silodosin on the analgesic use. The forest plot from the combined analysis of the two trials indicated that the heterogeneity was low (heterogeneity $P = 0.59$, $I^2 = 0\%$), and therefore, the fixed-effects model was selected for the analysis. The meta-analysis revealed that the patients who received silodosin treatment had a significantly lower analgesic use (OR 0.4, 95% CI 0.23, 0.69, $P < 0.01$).

DISCUSSION

Alpha-blockers have been shown to improve the rates of spontaneous expulsion of ureteral stones.[15] The use of alpha-blockers as a MET has been recommended by both the European Association of Urology and the American Urological Association.[5] The alpha-adrenergic receptor has three subtypes, α1A, α1B, and α1D. Out of these 3, the

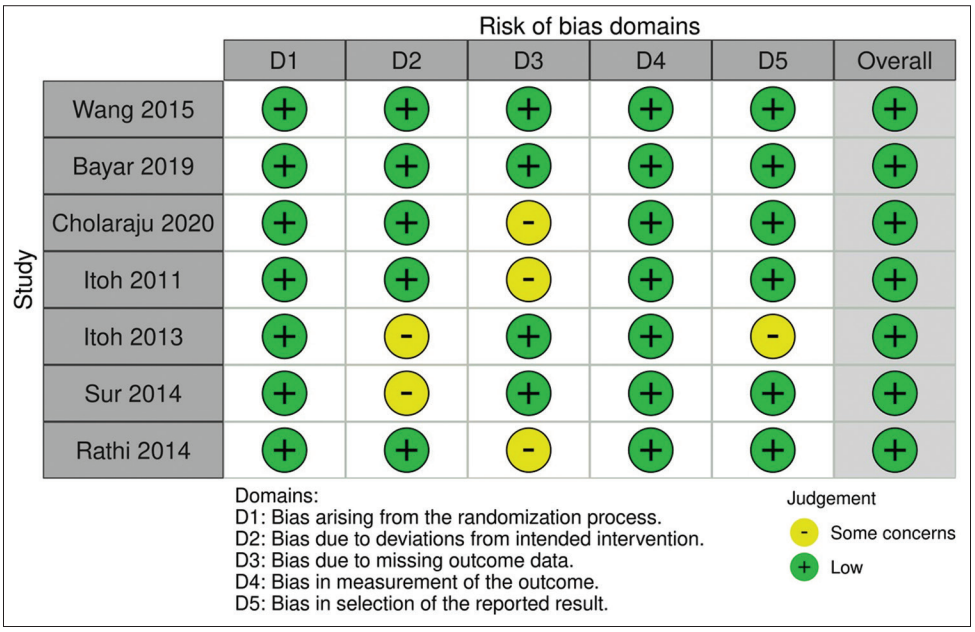

Figure 2: Risk of bias assessment of included studies

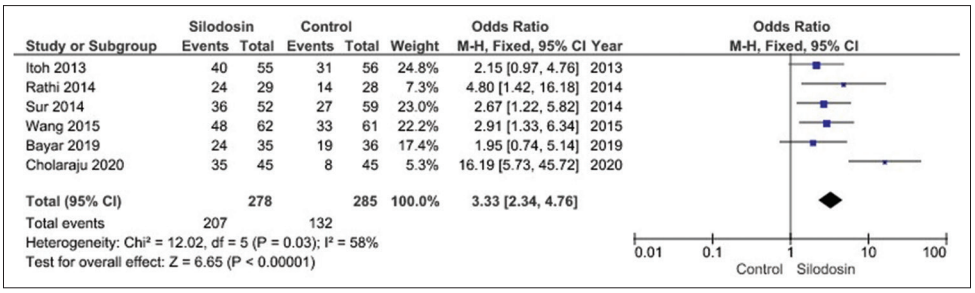

Figure 3: Forest plot analysis of stone expulsion rate between silodosin group and control group. M-H = Mantel–Haenszel, CI = Confidence interval

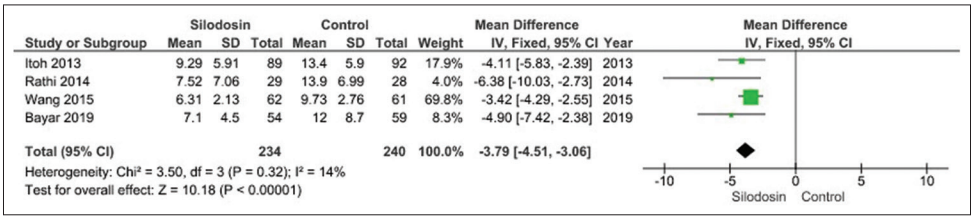

Figure 4: Forest plot analysis of stone expulsion time between silodosin group and control group. M-H = Mantel–Haenszel, CI = Confidence interval

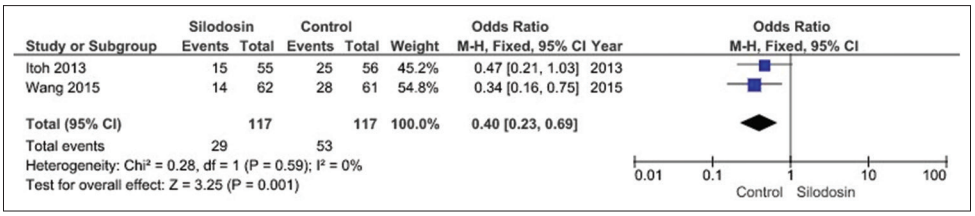

Figure 5: Forest plot analysis of analgesic use between silodosin group and control group. M-H = Mantel–Haenszel, CI = Confidence interval

α1A receptor has been shown to play an important role in the contraction of the ureter.[16,17] Tamsulosin, which is specific for α1A and α1D receptors, is proven to be effective in patients with distal ureteral stones. Newer studies have suggested that silodosin can be an effective alternative.[18] Itoh *et al*. were one of the first authors to evaluate the role of silodosin as a MET. They reported a shorter SET in patients who received silodosin as compared to the control group (10.27 vs. 15.19 days; $P < 0.001$).[19] In 2013, Itoh *et al*. performed a RCT to evaluate the efficacy of silodosin in patients with distal ureteric stones and found that the patients who received silodosin had a significantly shorter SET as compared to the control group (9.29 vs. 13.4 days; $P = 0.012$).[20] Another RCT by Wang *et al*. also found a shorter SET in patients receiving silodosin (3.4 days, $P < 0.01$).[9] Based on the pooled results of the four RCTs, a significant difference was found in the SET between the silodosin and the control groups (MD – 3.79; 95% CI – 4.51, –3.06; $P < 0.00001$).[9,10,20] Even though a positive impact seemed apparent, in the first study conducted by Itoh *et al*. evaluating the efficacy of 8 mg of silodosin for 8 weeks an improvement in the SER was not seen (66.3% vs. 50%; $P = 0.056$).[11] The second study by Itoh *et al*. also failed to show a significant improvement in the SER (72.7% vs. 55.3%; $P = 0.106$). However, a significant improvement in the SER was found for stones <5 mm in size (75.9% vs. 17.9%; $P < 0.01$).[20] In contrast with the findings of the two previous studies, Wang *et al*. reported that patients receiving silodosin had a significantly higher SER as compared to the control group (77% vs. 54.1%; $P = 0.006$). Sur *et al*. also reported an insignificant difference in the SER between the silodosin and the control group (52% vs. 44%; $P = 0.2$) but the difference was significant if only the patients with distal ureteral stones were analyzed (OR 2.7; 95% CI 1.2–5.8; $P = 0.01$).[12] Rathi *et al*. compared silodosin, tamsulosin, and placebo as a MET and showed that silodosin had the highest SER compared to the other two (86.2%, 76.6%, and 50%, respectively). However, they concluded that the difference between the silodosin and tamsulosin was not statistically significant. Another RCT by Bayar *et al*. divided patients with ureteral stones into three groups, and compared silodosin with mirabegron and placebo and reported an insignificant difference (64.8%, 52.5%, and 55.4%; $P = 0.391$, respectively). Based on the pooled results of six studies, this review shows that the patients who were prescribed 8 mg of silodosin had a significantly higher SER as compared to the control group (OR 3.3; 95% CI 2.34, 4.76; $P < 0.001$).

In a study by Cholaraju *et al*.,[14] patients were randomly chosen to take plenty of oral fluids and given NSAIDs (diclofenac sodium). Another 45 patients were treated with Silodosin 8 mg HS for one month, along with oral fluids and NSAIDs (diclofenac sodium). The effect of silodosin in the passage of calculi in the distal ureter compared to NSAIDs and oral fluids was studied. In the group given silodosin, the stone expulsion rate was 77.7%. While on the other 45 patients who were not given α-blocker, the stone expulsion rate was only 17.8%. The difference between this study group is significant (OR 16.2; 95% CI 5.7-45.7; $P < 0.05$).[22]

Studies have reported that alpha-blockers can reduce the analgesic requirement by reducing the frequency of ureteral colic in an obstructed ureter.[15] Therefore, this review also evaluated the frequency of analgesic use. We discovered that silodosin can significantly reduce the analgesic requirement (OR 0.4; 95% CI 0.23–0.69; $P = 0.001$). It is also considered to be safe, based on its mild adverse effects, the most common side effects being retrograde ejaculation (9.2%), nausea (7.6%), and dizziness (6.7%). The selectivity of silodosin to the α1A receptors and its low affinity to α1B receptors, commonly found in the blood vessels, and to the α1D receptors found in the detrusor and coronary arteries, indicates that silodosin has excellent uroselectivity. Therefore, is has high efficacy in the urogenital tract along with low adverse events pertaining to the cardiovascular system.[21] In theory, silodosin has shown good tolerability in patients with ureteral stones who are on antihypertensive medications. Several studies have shown that the combination of silodosin and antihypertensive drugs does not increase the risk of postural hypotension.[11,13,21,22]

This review has several limitations. The included studies had different intervention protocols with different durations of treatment with silodosin. A subgroup analysis regarding the duration of treatment was not possible due to the limited number of studies. Thus, a recommendation regarding the duration of treatment with silodosin could not be made in this study. However, all the included studies prescribed silodosin for atleast 2 weeks; therefore, this study demonstrated that administration of silodosin, for a minimum period of 2 weeks, can improve the stone expulsion rates in patients with distal ureteral stones. The stone characteristics in the various included studies were also different, which has led to heterogeneity in the

meta-analysis. Also, several studies did not classify the stones based on the location and the size; thus, a subgroup analysis was not possible. Based on these limitations, the findings of this review should be interpreted meticulously and may warrant future studies.

CONCLUSION

A significantly higher SER was found in patients with distal ureteral stones who received silodosin as compared to those who did not. The SET and analgesic requirement was also lower in the silodosin group.

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