Medicine®

OPEN

The efficacy and safety of diuretics on extracorporeal shockwave lithotripsy treatment of urolithiasis

A systematic review and meta-analysis

Liying Dong, MD[a], Fengyao Wang, MD[b], Hongyan Chen, MD[a], Youyi Lu, MD[a], Yong Zhang, MD[c], Linjing Chen, MD[d], Yuanshan Cui, MD[a,e,*]

Abstract

Background: The aim of this systematic review and meta-analysis was to demonstrate the efficacy and safety of diuretics on extracorporeal shockwave lithotripsy (SWL) treatment of urolithiasis.

Methods: The databases MEDLINE, EMBASE, and the Cochrane Controlled Trial Register of Controlled Trials from January 1980 until November 2019 were searched to identify randomized controlled trials that referred to the use of diuretics on extracorporeal SWL treatment of urolithiasis.

Results: Six randomized controlled trials containing 1344 patients were included in this meta-analysis, which compared diuretics with placebo on extracorporeal SWL treatment of urolithiasis. In the analysis, we found that diuretics on extracorporeal SWL treatment were more effective for the management of urinary stones. Compared with placebo, patients who received diuretics during extracorporeal SWL treatment had significantly higher successful stone clearance rate (Odds ratio; 1.73, 95% confidence interval (CI); 1.35 to 2.21, $P < .0001$), higher stone fragmentation rate (odds ratio; 2.83, 95% CI; 1.30 to 6.16, $P = .009$), less average number of sessions per stone (mean difference; –0.13; 95% CI, –0.25 to –0.01, $P = .03$) and similar average number of shocks per stone (mean difference; –126.89; 95% CI, –394.53 to 140.76, $P = .35$).

Conclusion: This systematic review and meta-analysis indicates that diuretics during extracorporeal SWL was effective in the management of urolithiasis with lower risk of complications.

Abbreviations: CI = confidence interval, MD = mean difference, OR = odds ratio, PCNL = percutaneous nephrolithotomy, RCT = randomized controlled trial, RIRS = retrograde intrarenal surgery, SWL = shockwave lithotripsy.

Keywords: diuretics, extracorporeal shockwave lithotripsy, meta-analysis, randomized controlled trials, urinary stones

1. Introduction

Urinary stone is a multifactorial disease which is common in daily urological practice, and is also a substantial public health problem.[1] Following urinary tract infections and pathologic conditions of the prostate, urinary stone is the third most common disease of the urinary tract, with an estimated prevalence of 2% to 3% and a lifetime recurrence rate of approximately 50%.[2] So far, the management of urolithiasis consist of observation, shockwave lithotripsy (SWL), medical expulsive therapy, ureteroscopy, percutaneous nephrolithotomy

Editor: Giuseppe Lucarelli.

LD and FW contributed equally to this work and are the co-first authors.

This study was funded by the Beijing Municipal Administration of Hospitals' Ascent Plan, Code: DFL20190502, Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support, Code: ZYLX201820.

This article does not contain any studies with human participants or animals performed by any of the authors.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

[a] Department of Urology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, [b] Department of Urology, Qingdao Third People's Hospital, Qingdao, [c] Department of Urology, Beijing Tian Tan Hospital, Capital Medical University, Beijing, [d] Operating Room, The Affiliated YantaiYuhuangding Hospital of Qingdao University, Yantai, Shandong, [e] Department of Urology, Beijing Tian Tan Hospital, Capital Medical University, Beijing, China.

[*] Correspondence: Yuanshan Cui, Department of Urology, Beijing Tian Tan Hospital, Capital Medical University, No.119 South 4th Ring West Road, Fengtai District, Beijing 100070, China, Department of Urology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai China (e-mail: doctorcuiys@163.com).

How to cite this article: Dong L, Wang F, Chen H, Lu Y, Zhang Y, Chen L, Cui Y. The efficacy and safety of diuretics on extracorporeal shockwave lithotripsy treatment of urolithiasis: a systematic review and meta-analysis. Medicine 2020;99:25(e20602).

Received: 7 February 2020 / Received in final form: 20 April 2020 / Accepted: 7 May 2020

http://dx.doi.org/10.1097/MD.0000000000020602

or open and laparoscopic stone surgery, depending on the clinical situation.[3]

The introduction of SWL treatment for urolithiasis in 1983 changed the treatment of smaller stones.[4] In general, ESWL is considered best for the management of urinary stone in most patients, particularly when the stone size is <2 cm.[5] Over time the techniques and indications have been constantly redefined in the pursuit of better outcomes. Success rate of urolithiasis with ESWL depends on several factors that include stone location, stone size, impaction, degree of obstruction, renal function, and so on.[6]

Diuretics increase urinary flow around the stone during SWL, which improves the likelihood of the cavitation phenomenon occurring.[7] Limited evidence has suggested that diuresis therapy may be beneficial for patients during SWL. Therapeutic uncertainty warranted a systematic review and meta-analysis to assess the effects of diuretics therapy for urinary stone following SWL.

2. Materials and methods

2.1. Inclusion criteria

Randomized controlled trials (RCTs) were required to meet the following inclusion criteria:

(1) studied the efficacy of diuresis therapy during SWL for the treatment of urolithiasis,
(2) provided sufficient data for analysis, including stone clearance rate, stone fragmentation rate, average number of sessions per stone and average number of shocks per stone.
(3) the full text of the study could be accessed. If the above inclusion criteria were not met, the studies were excluded from the analysis.

2.2. Search strategy

The databases MEDLINE, EMBASE, and the Cochrane Controlled Trial Register of Controlled Trials from January 1980 until November 2019 were searched to identify RCTs that referred to the use of diuretics during SWL treatment of urolithiasis. The reference lists of the retrieved studies were also searched. The following search terms were used: diuretics, furosemide, SWL, urolithiasis, and randomized controlled trials. Abbreviations (SWL, RCT) were also searched.

2.3. Trial selection

All of the authors independently identified potentially relevant trials and studies. Together, we discussed each of the RCTs that were included and excluded. We excluded studies that either failed to meet the inclusion criteria or had discrepancies that could not be resolved. The study selection process is presented by a diagram in Figure 1.

2.4. Quality assessment

All the identified RCTs were included in the systematic review and meta-analysis regardless of the quality score. The quality of the RCTs were evaluated in terms of sequence generation, blinding, the concealment of allocation procedures, selective outcome reporting, incomplete outcome data, and other sources of bias. The articles were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions v.5.1.0.[8] Based on the quality assessment criteria, each article was rated and assigned to 1 of the 3 following quality categories: +, low risk of bias; –, high risk of bias; ?, unclear risk of bias. Differences were settled down by discussion among the authors.

2.5. Data extraction

We independently performed the data extraction for the systematic review and meta-analysis, which included the following:

(1) the name of the first author and the publication year,
(2) the design of the study,
(3) the therapy that the patients received,
(4) the location of urolithiasis,
(5) the number of the patients and
(6) the outcome measurements of the study.

2.6. Statistical analysis

Regarding the dichotomous outcomes, odds ratios (ORs) were used where available. Mean difference (MD) with 95% confidence intervals (CIs) were used to report continuous outcomes. The comparative effects were initially analyzed by the traditional pairwise meta-analysis method using Cochrane Collaboration review manager software (RevMan v.5.1.0). We estimated the odd risk for dichotomous outcomes and the MD for continuous outcomes pooled across studies by using the DerSimonian & Laird random effects model.[9] A "fixed-effects" statistical model was used if there was no conspicuous heterogeneity. Otherwise a "random-effects" model was used. The tests for heterogeneity were performed using Chi-squared tests with the significance level set at $P < .1$.

3. Results

3.1. Characteristics of individual studies

Based on the inclusion and exclusion criteria, 6 RCTs[10–15] involving 1344 patients were included in the analysis. Table 1 shows the characteristics of the individual RCTs.

3.2. Quality of individual studies

Among the studies in the meta-analysis, all the 6 studies are RCTs. The bias of all the identified RCTs that we searched were at low risk in general. The quality level of individual identified trials was shown in Table 2. The plot was symmetrical and 3 squares were contained in the large triangle, and no obvious evidence of bias was found (Fig. 2).

3.3. Stone clearance rate

In all, 6 studies including 1344 patients (670 in the diuretics group and 674 in the placebo group) contributed to the analysis of successful stone clearance rate. No heterogeneity was found among the trials, so a fixed effects model was chosen for the analysis. Compared with placebo group, the diuretics therapy was associated with a significantly higher successful stone clearance rate (OR; 1.73, 95% CI; 1.35 to 2.21, $P < .0001$) (Fig. 3).

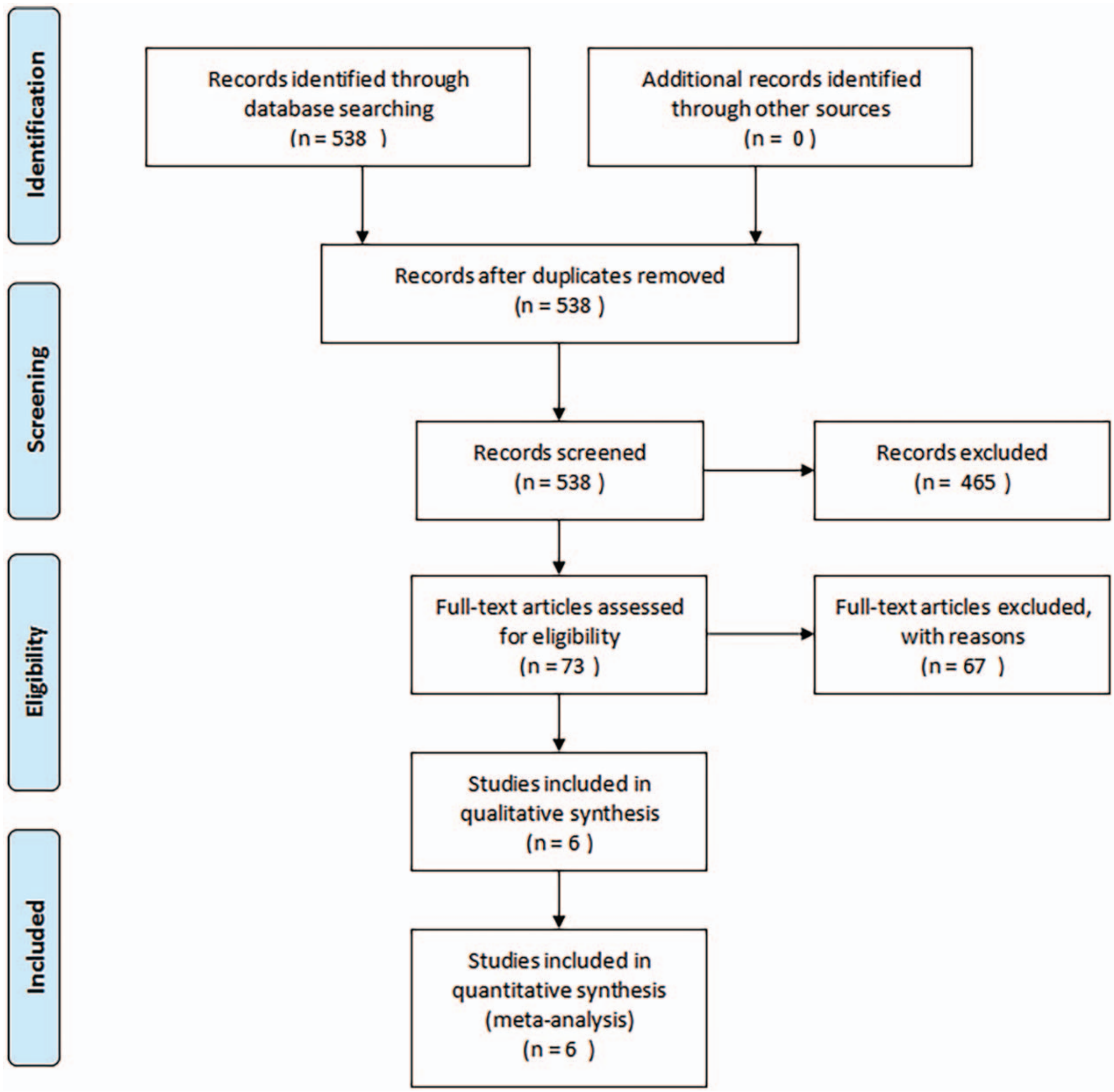

Figure 1. A flow diagram of the study selection process.

3.4. Stone fragmentation rate

Three studies including 289 patients (144 in the diuretics group and 145 in the placebo group) contributed to the analysis of stone fragmentation rate. No heterogeneity was found among the trials, and a fixed effects model was thus chosen for the analysis. Compared with placebo group, the diuretics therapy was associated with a significantly higher successful stone fragmentation rate (OR; 2.83, 95% CI; 1.30 to 6.16, $P=.009$) (Fig. 3).

3.5. Average number of sessions per stone

A total of 5 studies including 1257 patients (626 in the diuretics group and 631 in the placebo group) contributed to the analysis of the average number of sessions per stone. No heterogeneity was found among the trials, the fixed effects model was chosen for the analysis. Compared with placebo group, the diuretics therapy needed less average number of sessions per stone (MD; –0.13, 95% CI, –0.25 to –0.01, $P=.03$) (Fig. 4).

3.6. Average number of shocks per stone

Four studies including 1151 patients (574 in the diuretics group and 577 in the placebo group) were used in the analysis for average number of shocks per stone. From the analysis, we can draw conclusion that there was no significant difference in the average number of shocks per stone between diuretics group and placebo group (MD; –126.89, 95% CI, –394.53 to 140.76, $P=.35$) (Fig. 4).

4. Discussion

SWL has established itself as a first-line treatment method for renal and ureteric calculi since its inception in the early 1980s.

Table 1

Characteristics of randomized controlled trials included in the present meta-analysis.

Study	Design	Therapy		Location of ureteral calculus	Type of lithotripter	Sample size		Follow-up	Exclusion criteria
		Control	Experiment (dose)			Control	Experiment		
Azm TA 2002	RCT	SWL	SWL+ Furosemide (40mg)	ureter	Siemens Lithostar 2 machine	54	52	3 mo	Not mentioned
Zomorrodi A 2008	RCT	SWL	SWL+ Furosemide (40mg)	ureter	Simons Lithostor plus machine	43	44	3 mo	Not mentioned
Ahmed AF 2015	RCT	SWL	SWL+ Furosemide (20mg)	renal	Dornier lithotripter SII, Dornier MedTech, Wessling	100	100	3 mo	Patients with morbid obesity, musclo-skeletal disorder, severe cardio-vascular or neurological diseases, previous failed SWL, UTI, elevated serum creatinine, uncontrolled coagulation disorders, abnormal renal anatomy, severe hydronephrosis, obstructed calyx or urinary tract obstruction at any level in the ipsilateral renal unit.
Kocaaslan R 2015	RCT	SWL	SWL+ Furosemide (40mg)	renal	Modularis Vario Lithostar; Siemens Medical Systems, Elangen	72	69	3 mo	Previous renal and/or ureteral surgery, multiple stones, ureteral or ureteropelvic junction stricture, congenital ureteral and/or renal abnormalities, renal insufficiency, a solitary kidney, or had hydronephrosis of grade II or greater, as found by intravenous urography. Those who were pregnant, allergic to furosemide, or had active coagulopathy, cardiac disease.
Sabharwal S 2017	RCT	SWL	SWL+ Furosemide (40mg)	renal or upper ureteric	Dornier MedTech GmbH, Weßling, Germany	48	48	2 wk	Those with any anatomical abnormality, distal obstruction, coagulopathy, history of any previous intervention on the same side, significant cardiac history or morbidly obese.
Sohu S 2019	RCT	SWL+ 1000 mL 0.9% NaCl	SWL+ 1000 mL 0.9% NaCl+ Furosemide (40mg)	renal	Dornier MedTech, Munich, Germany	357	357	3 mo	Patients with any anatomical abnormality, uncontrolled coagulopathy, untreated UTI, previous renal and/or ureteric surgery, ipsilateral ureteric stone, multiple or bilateral stones, congenital ureteric or renal abnormalities, renal insufficiency, cardiac disease, known hypertensive or morbidly obese. Additionally, patients with history of allergy to furosemide and pregnant women were also excluded.

RCT = randomized controlled trials, SWL = shockwave lithotripsy, UTI = urinary tract infection.

Table 2

Risk of bias for included randomized controlled trials.

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Azm 2002	+	+	+	?	+	+
Zomorrodi 2008	+	+	+	?	+	+
Ahmed 2015	+	+	+	?	+	+
Kocaaslan 2015	+	+	+	?	+	+
Sabharwal 2017	+	+	+	?	+	+
Sohu 2019	+	+	+	?	+	+

ROB = risk of bias; +, low risk of bias; ?, unclear risk of bias.

However, the constant rise in technology and the challenge offered by newer techniques, such as URS, retrograde intrarenal surgery, and percutaneous nephrolithotomy, highlights the need to develop novel strategies to improve its outcomes and thus for SWL to continue to play an important role as a treatment option.[16] So far, significant issues still remain unanswered, including the most appropriate treatment method, choice of patient who will probably end up with residual fragments, as well as unfavourable renal characteristics.[17] As mentioned above, diuretics may improves the likelihood of the cavitation phenomenon occurring during SWL. Several RCTs have reported the promising results of adjunctive diuretics therapy during SWL treatment of urolithiasis. This may be attributed to the benefit of diuretics.

According to the included RCTs, the diuretics may be given before starting treatment to make sure that they should take effect during the ESWL session, so our meta-analysis indicates that diuretics therapy during SWL treatment of urolithiasis significantly improves successful stone clearance rate at the 2 to 12 weeks, stone fragmentation rate and average number of sessions per stone (number of SWL sessions). As for average number of shocks per stone (number of shock waves), there was no significant difference between diuretics group and placebo group. Therefore, this meta-analysis indicates diuretics as an effective therapy for patients undergoing SWL treatment of urolithiasis. Giving diuretic is not difficult as they are freely available. However, use of diuretics in clinical practice remains limited mainly due to the limited evidence. Our article is the first meta-analysis showing superiority of diuretics, and may offer important reference to clinical practice.

It is noteworthy that our meta-analysis suggested that there was no significant difference in average number of shocks per stone between diuretics group and placebo group. Chiong et al investigated percussion, diuresis, and inversion therapy plus SWL therapy versus SWL only. This study found that percussion, diuresis, and inversion therapy plus SWL outcomes were more advantageous than shock wave lithotripsy therapy only in terms of stone-free rates.[18] Tehranchi et al conducted a double-blind, placebo-controlled randomized clinical trial demonstrating that hydrochlorothiazide did not impact on the stone-free rate and using accessory procedure within 3 months; however, it decreased duration of stone-free status and number of ESWL sessions.[19]

The mechanism may be that diuretics will increase urine flow and thus the probability of cavitation.[20] Fragmentation is facilitated by a fluid film interface between the stone and the

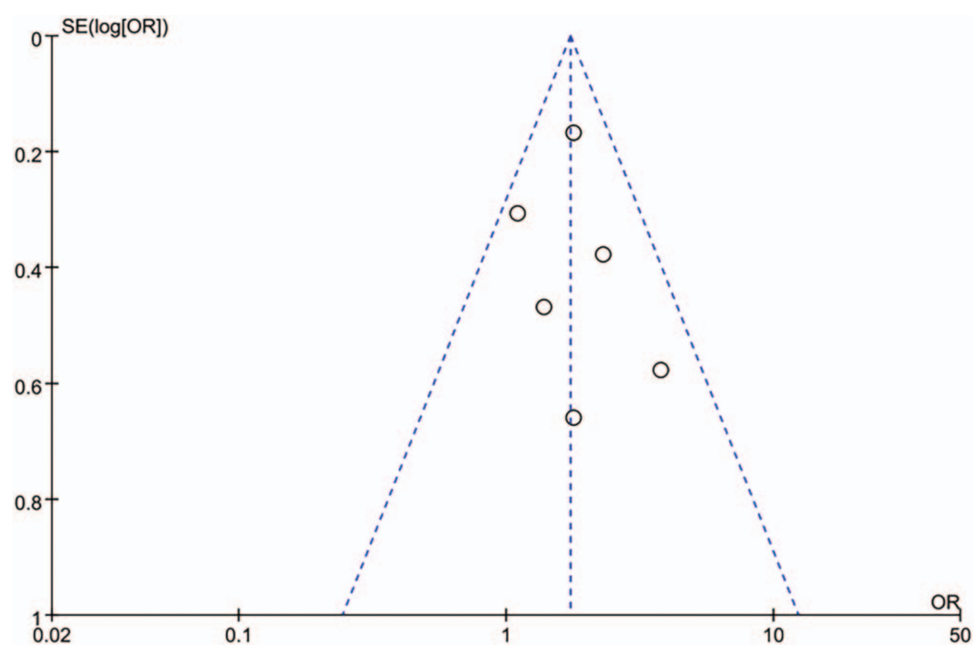

Figure 2. Funnel plot of the studies represented in our analysis. OR = odds ratios, SE = standard error.

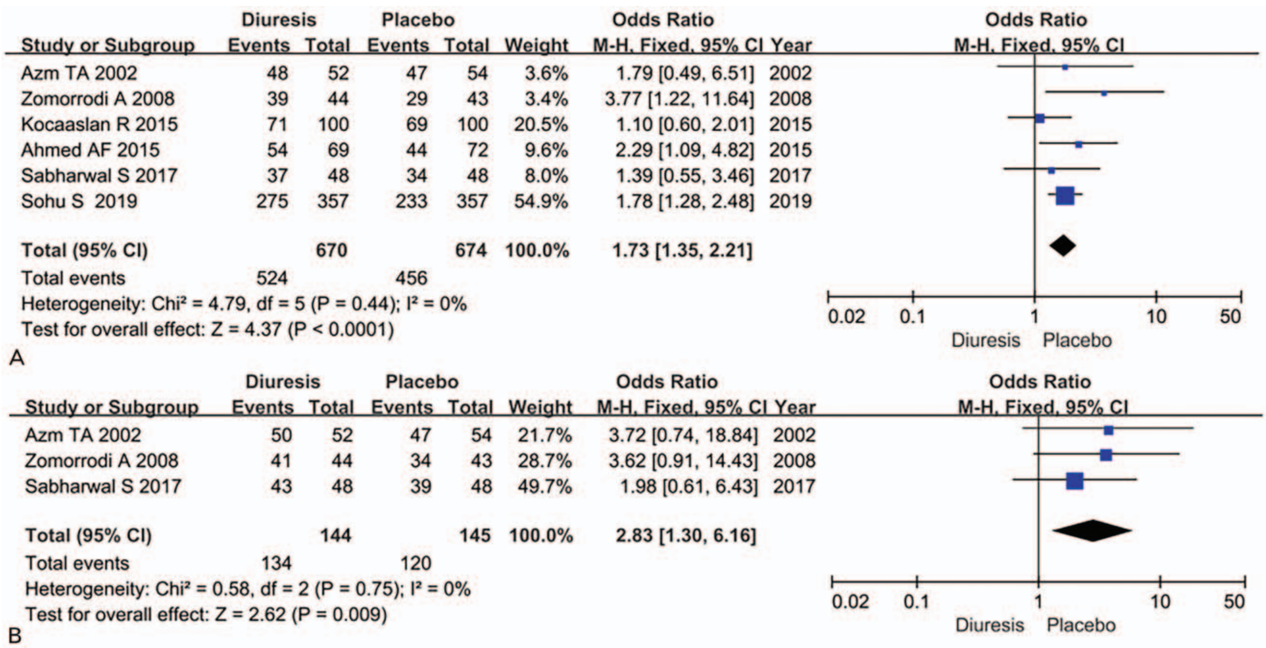

Figure 3. Forest plots showing changes in (a) successful stone clearance rate, and (b) stone fragmentation rate. CI = confidence interval, MH = mantel haenszel.

ureteric wall. Once the initial shockwaves break the outer shell of the calculus, further disintegration of the core may be enhanced by the seepage of fluid below the cracks, creating an interface. Thus, the effect of the collapsing cavitation bubble is accentuated.[14]

Significantly, a delay in the diagnosis and treatment of ureteral obstruction represents the most important prognostic factor for worse results in terms of renal function recovery. In particular, Lucarelli G conducted a study prospectively enrolled a total of 76 patients with obstructive ureteral injury and treated with reconstructive procedures showed that patients who experience delayed relief of ureteral obstruction had decreased long-term renal function as suggested by the lower values of estimated creatinine clearance and mercaptoacetyltriglycine clearance, and were at risk for hypertension or exacerbation of preexisting hypertension.[21] Combined with our article, diuretics therapy during SWL treatment of urolithiasis has an important role in protecting renal function.

All of the diuretics used in the RCTs is Furosemide and the doses ranged from 20 to 40 mg (Table 1). The adverse reaction such as painful, steinstrasse or ureteric stricture were similar between the 2 groups. The diuretics during SWL treatment was

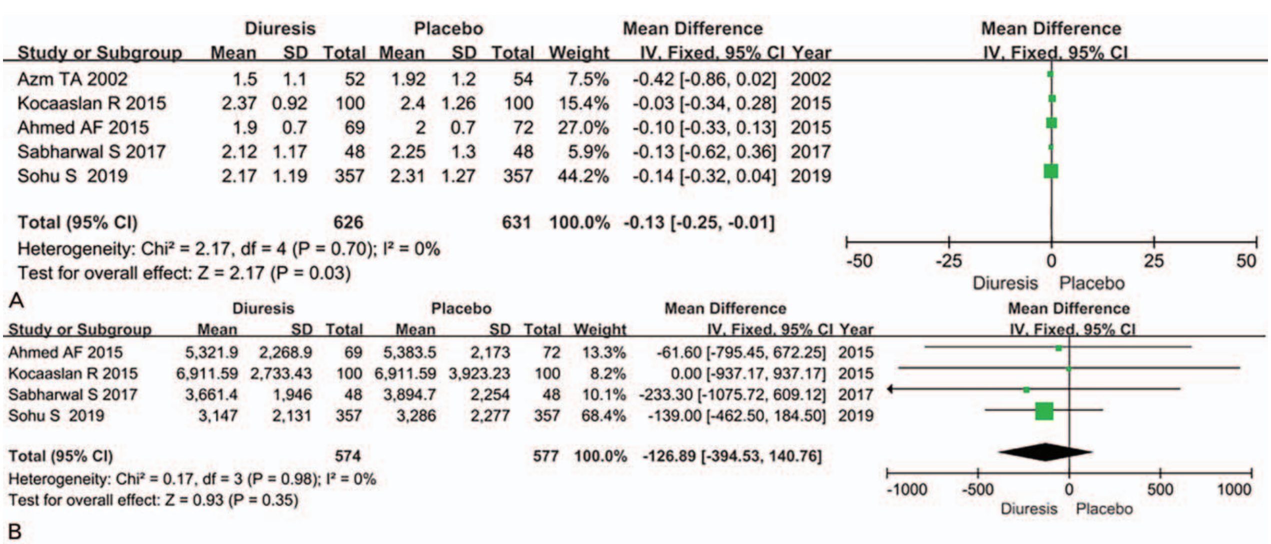

Figure 4. Forest plots showing changes in (a) average number of sessions per stone and (b) average number of shocks per stone. CI = confidence interval, SD = standard deviation, IV = inverse variance.

well tolerated, with no major safety concerns. This demonstrates the safety of diuretics treatment during SWL in treating urolithiasis.

All the RCTs included in our meta-analysis are articles of science citation index with low or moderate risk of bias. Though the quality of all the included studies is high, our study contains several limitations. First, because of limited quantity of relevant original studies, this meta-analysis only included 6 studies with sample sizes that were not large. Second, following times of adjunctive diuretics therapy ranged from 2 to 12 weeks after SWL. Third, the type of lithotripter was not in full accord. In addition, lack of uniform inclusion criteria, different location of the urolithiasis may have resulted in bias. Besides, other end points like the situation of the usage of the alpha blocker treatment after SWL were lack because the data are too scarce to be officially analyzed. After the heterogeneity among individual studies is taken into account, this meta-analysis remains crucial for assessing the efficacy and safety of diuretics therapy versus placebo during SWL for the treatment of urolithiasis. Therefore, further high-quality RCTs are strongly encouraged to confirming this question.

5. Conclusions

This systematic review and meta-analysis indicates that diuretics during extracorporeal SWL was effective in the management of urolithiasis with lower risk of complications.

Author contributions

Yuanshan Cui designed the research, interpreted the data and revised the paper. Liying Dong, Fengyao Wang, Hongyan Chen, Youyi Lu, Linjing Chen and Yong Zhang performed the data extraction, did Meta-analysis and drafted the paper. All of the authors approved the submitted and final versions.

References

[1] Hiller SC, Ghani KR. Frontiers of stone management. Curr Opin Urol 2020;30:17–23.
[2] Yang D, Wu J, Yuan H, et al. The efficacy and safety of silodosin for the treatment of ureteral stones: a systematic review and meta-analysis. BMC Urol 2016;16:23.
[3] Turk C, Petrik A, Sarica K, et al. EAU guidelines on interventional treatment for urolithiasis. Eur Urol 2016;69:475–82.
[4] Bach C, Buchholz N. Shock wave lithotripsy for renal and ureteric stones. Eur Urol 2011;Suppl 10:423–32.
[5] McAdams S, Shukla AR. Pediatric extracorporeal shock wave lithotripsy: predicting successful outcomes. Indian J Urol 2010;26:544–8.
[6] Lee SM, Collin N, Wiseman H, et al. Optimisation of shock wave lithotripsy: a systematic review of technical aspects to improve outcomes. Transl Androl Urol 2019;8:S389–97.
[7] Liu LR, Li QJ, Wei Q, et al. Percussion, diuresis, and inversion therapy for the passage of lower pole kidney stones following shock wave lithotripsy. Cochrane Database Syst Rev 2013;CD008569.
[8] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, v.5.1 (updated March 2011). Cochrane Collaboration Website 2011. http://www.cochrane-handbook.org.
[9] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[10] Azm TA, Higazy H. Effect of diuresis on extracorporeal shockwave lithotripsy treatment of ureteric calculi. Scand J Urol Nephrol 2002;36:209–12.
[11] Zomorrodi A, Golivandan J, Samady J. Effect of diuretics on ureteral stone therapy with extracorporeal shock wave lithotripsy. Saudi J Kidney Dis Transpl 2018;19:397–400.
[12] Ahmed AF, Shalaby E, Maarouf A, et al. Diuresis and inversion therapy to improve clearance of lower caliceal stones after shock wave lithotripsy: a prospective, randomized, controlled, clinical study. Indian J Urol 2015;31:125–31.
[13] Kocaaslan R, Kucukpolat S, Karadag MA, et al. The combination of furosemide and intravenous hydration does not affect the success of shock wave lithotripsy in renal stone treatment: a prospective randomised single blinded trial. Eur J Hosp Pharm 2015;22:353–7.
[14] Sabharwal S, Jeyaseelan L, Panda A, et al. A prospective randomised double-blind placebo-controlled trial to assess the effect of diuretics on shockwave lithotripsy of calculi. Arab J Urol 2017;15:289–93.
[15] Sohu S, Soomro MH, Mangrio RH, et al. Efficacy of extracorporeal shockwave lithotripsy with furosemide and hydration in renal stone management: a randomised controlled trial. Arab J Urol 2019;17:279–84.
[16] Corbo J, Wang J. Kidney and ureteral stones. Emerg Med Clin North Am 2019;37:637–48.
[17] Lee SW, Chaiyakunapruk N, Chong HY, et al. Comparative effectiveness and safety of various treatment procedures for lower pole renal calculi: a systematic review and network meta-analysis. BJU Int 2015;116:252–64.
[18] Chiong E, Hwee ST, Kay LM, et al. Randomized controlled study of mechanical percussion, diuresis, and inversion therapy to assist passage of lower pole renal calculi after shock wave lithotripsy. Urology 2005;65:1070–4.
[19] Tehranchi A, Rezaei Y, Mohammadi-Fallah M, et al. Effects of hydrochlorothiazide on kidney stone therapy with extracorporeal shock wave lithotripsy. Urol Ann 2014;6:208–11.
[20] Albanis S, Ather HM, Papatsoris AG, et al. Inversion, hydration and diuresis during extracorporeal shock wave lithotripsy: does it improve the stone-free rate for lower pole stone clearance? Urol Int 2009;83:211–6.
[21] Lucarelli G, Ditonno P, Bettocchi C, et al. Delayed relief of ureteral obstruction is implicated in the long-term development of renal damage and arterial hypertension in patients with unilateral ureteral injury. J Urol 2013;189:960–5.