Urolithiasis (2017) 45:449–455
DOI 10.1007/s00240-016-0950-1

ORIGINAL PAPER

Effect of potassium citrate supplement on stone recurrence before or after lithotripsy: systematic review and meta-analysis

Maurício Carvalho[1,2] · Bruna Olandoski Erbano[2] · Eduardo Yukio Kuwaki[1] · Halyson Pinheiro Pontes[1] · Jonathan Wei Ting Wen Liu[1] · Luis Henrique Boros[1] · Marcelo Oliveira Asinelli[1] · Cristina Pellegrino Baena[1,3]

Received: 9 August 2016 / Accepted: 22 November 2016 / Published online: 3 December 2016

Abstract This meta-analysis summarizes the available evidence on the effectiveness of citrate supplement for preventing the recurrence of nephrolithiasis in patients undergoing extracorporeal shock wave lithotripsy (SWL). Electronic searches were conducted using Medline-PubMed, Web of Science, Embase, BVS (Scielo, Lilacs), and Google Scholar literature databases. The authors worked in pairs to select studies that met the following criteria: randomized controlled trials that were conducted in adults and assessed the effect of potassium citrate supplement before or after SWL therapy for urolithiasis. Our primary aim was to asses the stone-free rate among the groups included in the studies. Fixed effect was used in the meta-analysis with 95% confidence interval (95% CI). Heterogeneity was analyzed by the I^2 value. A total of 2505 references were initially selected. Of those, four were subjected to meta-analysis contributing five samples. These four studies included 374 participants who were followed for a period of 12 months after SWL. Mean potassium citrate dosage was approximately 55 mEq/day (18 mmol). The results showed that citrate supplement significantly protected against the recurrence of nephrolithiasis during 1 year after SWL [RR; 95% CI 0.21 (0.13, 0.31)]. The heterogeneity was not significant across the analyzed studies ($p = 0.224$). The quality of the analyzed studies was generally low. The available evidence shows that citrate supplement effectively reduces the recurrence of nephrolithiasis in patients undergoing SWL. However, statistical analysis of a larger trial conducted with methodological rigor is warranted.

Keywords Lithotripsy · Potassium citrate · Urolithiasis · Stone recurrence

Introduction

Current guidelines recommend SWL as the method of choice for stones up to 2 cm diameter within the renal pelvis and the upper or middle calices, and for stones up to 1.5 cm diameter within the lower pole calices [1]. However, high rates of recurrence are reported, even in patients with a stone-free status after SWL [2–4]. Retained stone fragments following SWL may provide nuclei for the formation of new stones. This could be one of the explanations for the high recurrence rate [5–7].

SWL and surgical procedures for kidney stone removal do not change the underlying metabolic abnormalities that cause recurrent stone formation [8]. Hypocitraturia occurs in 20–60% of patients who form kidney stones [9]. Citrate is an important inhibitor of lithogenesis [10, 11]; it reduces urinary saturation as it forms complexes with calcium, inhibits spontaneous stone nucleation, and delays oxalate crystal aggregation [12]. Recent guidelines recommended potassium citrate therapy for patients with relatively low urinary citrate and recurrent calcium stones [13, 14].

It has been suggested that potassium citrate might lower the risk of kidney stone recurrence in patients treated with SWL [8, 15–18]. However, the existing evidence does not rigorously support this hypothesis regarding the effect of

✉ Bruna Olandoski Erbano
bruoe@hotmail.com

[1] Escola de Medicina, PUCPR-Pontifícia Universidade Católica do Paraná, Rua Imaculada Conceição, 1155-Prado Velho, Curitiba, Paraná, Brazil

[2] Hospital de Clínicas, UFPR-Universidade Federal do Paraná, Rua General Carneiro, 181-Alto da Glória, Curitiba, Paraná, Brazil

[3] Hospital Marcelino Champagnat, Av. Pres. Affonso Camargo, 1399-Cristo Rei, Curitiba, Paraná, Brazil

citrate supplement on nephrolithiasis recurrence rates for 1 year after SWL. Therefore, this systematic review and meta-analysis critically analyzes the available research studies and presents the best available evidence related to the effectiveness of citrate supplement before and after extracorporeal SWL.

Methods

Search strategy

This review was performed with a predefined protocol, in accordance with PRISMA guidelines [19]. We conducted electronic searches using Medline-PubMed, Web of Science, Embase, BVS (Scielo, Lilacs), and Google Scholar databases, and selected suitable references published from the database inception until May 2, 2016. We generated search terms with combinations of Medical Subject Headings (MeSH) and free text words that included terms related to the study population (humans, adults), the interventions (SWL), and the outcomes (e.g., time to stone-free and stone-free period). The investigated terms included "lithotripsy", "citrate", "potassium citrate", "citric acid", and "urolithiasis". There were no language restrictions in our searches.

The reference lists of the selected articles were searched manually to ensure the capture of all relevant studies. Experts in the relevant subject matter and the authors of the obtained studies were contacted for further information when specific data were not available in the published manuscripts.

Inclusion and exclusion criteria

The inclusion criteria were as follows: randomized controlled trials with parallel design; study population restricted to adults (>17 years); and assessment of the effect of potassium citrate supplement before or after SWL therapy for urolithiasis.

The exclusion criteria were as follows: study population including pregnant women, children, patients with congenital anomalies, or comorbidities; studies reporting lithiasis of etiologies other than calcium oxalate; studies on animals; and in vitro, observational, or retrospective studies.

Study identification and selection

The research group was separated into two sub-groups that independently pre-selected all titles and abstracts of the initially identified studies according to the selection criteria. Full texts of the selected studies were retrieved and evaluated by at least two authors to assure that all systematic review criteria were met. Any disagreements regarding article selection were solved through discussion and, if necessary, by a third independent reviewer.

Data extraction

Three authors extracted data using a predefined collection form, and a fourth author reviewed. The extracted data included the following: author; title; journal; year of publication; geographic origin; setting of the study; study design; study funding source; study subject gender, ethnicity, age, and residence; comorbidities; study inclusion and exclusion criteria; intention to treat analysis; participants in the control and intervention group; type and delivery of the intervention; dose and duration of intervention; and citraturia before and after intervention in both groups.

Our primary objective was the stone-free rate among groups. We recorded the number of patients who were stone free at the end of follow-up in each group. We utilized two definitions for stone-free status: (1) in cases where participants were stone-free at baseline, they had to maintain their stone-free status until the end of follow-up; (2) in cases where participants presented residual stone fragments at baseline, they were considered stone-free at the end of follow-up if they became stone-free, or if they maintained the baseline residual fragments, or if they reduced their baseline residual fragments.

Quality of studies

The quality of individual studies and risk of bias were evaluated by two reviewers according to Cochrane's Tool for Bias Assessment [20], which analyzed the following criteria: proper randomization, allocation of participants, blinding of the outcome assessor, results presentation, incomplete data, selective reporting of results, and other sources of bias.

Statistical analysis

The stone-free rate in each study was calculated as the proportion of participants with stone-free status in the intervention group (SWL plus potassium citrate) divided by the proportion of participants with stone-free status in the control group (SWL) [21]. We standardized the time to follow-up described in the included studies as 12 months. Therefore, our estimates are expressed in nephrolithiasis recurrence rates during 1 year. The meta-analysis results are presented as fixed effects with 95% confidence interval (95% CI). Heterogeneity among the studies was assessed using I^2 [22]. Publication bias was assessed by funnel plot. The effect of small studies was tested with the Egger test [22]. The significance level adopted was 5%. All analyses

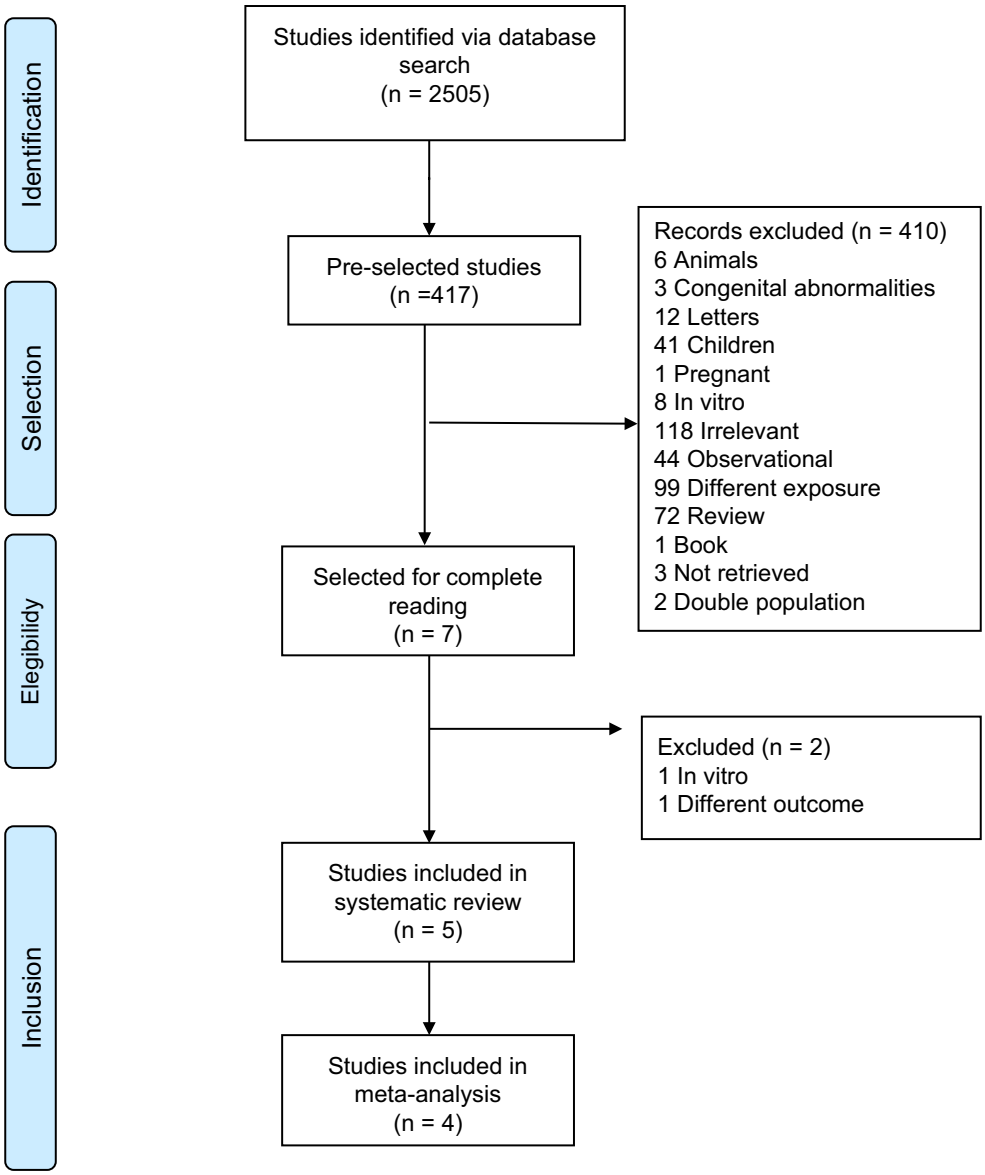

Fig. 1 Flowchart of included studies

were performed with Stata software version 12.0 (StataCorp LP, CollegeStation, Tex, USA).

Results

Identification and selection of the studies

Initially, 2505 references were identified. Among these, 417 references were evaluated as potentially eligible and were retrieved. The reasons for exclusion of the references are presented in Fig. 1. Subsequently, 411 studies were excluded on the basis of information contained in the abstract. Finally, five studies were selected for inclusion in the systematic review after reading the full-text articles [8, 15–18]. Four of the five studies met the inclusion criteria of our meta-analysis [8, 15, 17, 18], totalizing 374 participants. The fifth study [16] was excluded because it was the only one that reported citrate supplement before and during the SWL treatment, and the duration of follow-up differed greatly among the study participants.

General characteristics of the studies selected

Table 1 presents the main characteristics of the studies included in the systematic review, which involved 413 adult participants (age ranged from 17 to 75 years, median age 44 years). No age- or gender-related differences were

Table 1 Main parameters of the studies included in the systematic review

Authors	Year	% Women	Mean age (years)	Follow-up (months)	Citrate supplement	*n*	Drug	Dose
Lojanapiwat et al. [8]	2011	31.57	50.3	12	After	76	Potassium citrate	81 mEq/day (27 mmol)
Soygur et al. [15]	2002	32.14	41.7	12	After	90	Potassium citrate	60 mEq/day (20 mmol)
Verdejo et al. [17]	2001		41.5	12–48	After	100	Potassium citrate	40 mEq/day (13 mmol)
Cicerello et al. [18]	1994	27.5	42	12	After	68	Potassium citrate	55.5–74.1 mEq/day (18.5–24.7 mmol)
Goktas et al. [16]	2012	48	46.1	1 week	Before and during	40	Potassium citrate	30 mEq/day (10 mmol)

reported between intervention and control groups; however, male subjects were the majority in most of the studies.

Citrate supplement after SWL for the intervention group was reported in four studies, with a duration ranging from 1 week to 48 months as presented in Table 1. The mean dose was approximately 55 mEq/day (30–81 mEq/day) (18; 10–27 mmol), generally administered in three daily doses. Most studies encouraged participants in both the intervention and control groups to make lifestyle changes, including substantially increasing daily fluid intake and avoiding oxalate-rich and salty foods.

All studies evaluated citrate levels using the 24-h urine study; however, only two studies described urinary citrate levels at baseline and after follow-up for both the intervention and control groups [8, 18]. Lack of standardization of citraturia levels prevented us from analyzing the impact of hypocitraturia on our outcomes of interest.

One of the studies [18] presented two analyses. The first one included patients with sterile calcium oxalate nephrolithiasis and infection-related stones. The second included only the subgroup of patients with sterile stones. For both analyses, the authors compared stone-free status during follow-up of the intervention group with that of the control group. As the control groups were different, we decided to analyze the two results separately in our meta-analysis, as if they were different studies.

Effects of potassium citrate supplement on stone-free status

Three of the four studies included in the meta-analysis [8, 15, 17] separated their baseline samples into the following two groups: (1) patients with stone-free status after SWL, and (2) patients with residual stone fragments after SWL. We compared only two groups for each study in our meta-analysis, the intervention and control group, independently of stone-free status or residual stone fragments at baseline.

Figure 2 shows the pre- and post-intervention stone-free status of the groups included in the meta-analysis. We did not detect any significant effect of small studies, as indicated by the funnel plot ("Appendix"). The combined effect of the studies showed that potassium citrate supplement after SWL significantly protected patients from recurrence (0.21; 95% CI 0.13–0.31) during 1 year of follow-up. The effect was homogeneous across all studies ($I^2 = 29.7\%$; $p = 0.224$).

Quality of studies

Details of the risk of bias assessment are presented in Fig. 3. Most of the articles lack relevant information that is required for proper assessment of study bias. Random sequence generation and allocation concealment were unclear in all studies. Study participants were not blinded since the intervention groups received citrate supplement orally but the control groups did not receive a placebo. However, two of the five studies had low risk of bias from the blinding assessment. Although some studies analyzed by intention to treat [16, 17], they had relatively low enrollment, and other sources of bias can be expected.

Discussion

Our systematic review and meta-analysis analyzed 2505 references and selected five unique articles that fully met the selection criteria. The results indicate that potassium citrate supplement significantly reduced stone recurrence after SWL treatment during 1 year of follow-up.

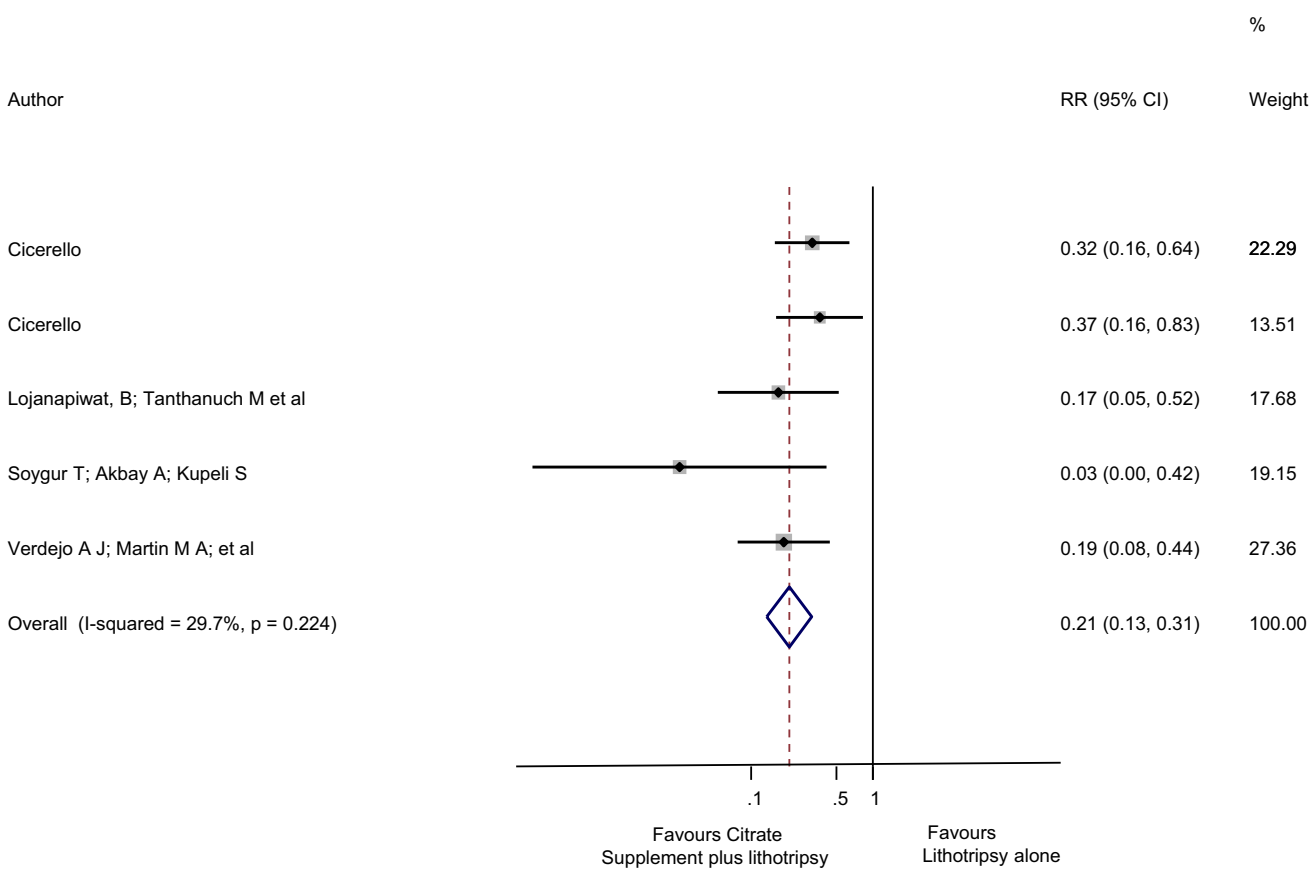

Fig. 2 Meta-analysis of the relative risk of nephrolithiasis recurrence in patients receiving SWL and potassium citrate supplement versus SWL only

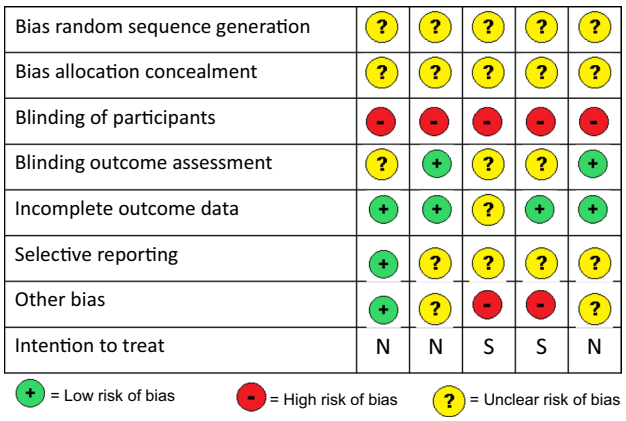

Fig. 3 Assessment of risk of publication bias in included studies

Since its introduction in 1980, SWL has effectively become the treatment of choice for the majority of patients with urinary stones. SWL therapy is noninvasive, is associated with low morbidity, and has high acceptance among patients and physicians [23]. In appropriately selected patients, the overall SWL success rate is greater than 90% for stone clearance. However, several factors affect the outcome of SWL therapy, including stone burden (size and number), stone composition, and location [24]. For example, stones composed of calcium oxalate monohydrate, brushite, or cystine are usually resistant to SWL, whereas struvite calculus responds to SWL treatment [18]. However, the majority of studies included in the meta-analysis had excluded patients with urinary tract infection [8, 15, 17]. Only Cicerello et al. [18]. performed an analysis of 30 struvite stone patients who also received antibiotics for urinary tract infection. It could be anticipated that the effect of potassium citrate in this study would differ from other studies not reporting infected stones. However, citrate potassium supplement also appeared to prevent stone recurrence in this group.

Some authors recommend surgical treatment for kidney stones, such as PCNL, because residual stone fragments after SWL treatment frequently do not pass spontaneously and often lead to stone recurrence [3]. One of the studies

included in our meta-analysis [8] evaluated post-PCNL patients and concluded that potassium citrate supplement also reduces the risk of stone recurrence in this subgroup.

The choice of treatment also considers the stone location. SWL therapy is not generally selected for treatment of lower calyceal calcium stones, which have a lower stone-free rate compared with those of middle and upper calyceal stones [25]. The lower location favor stone fragment retention, which renders the therapy less beneficial. Soygur et al. [15] reported that potassium citrate inhibits calcium oxalate nucleation and growth of the remaining stone fragments in lower calyceal calculi after SWL.

The studies included in this meta-analysis evaluated a considerable percentage of patients with hypocitraturia [8, 15, 18]. However, lack of standardization for measuring citraturia prevented us from performing a consistent comparative analysis. Nevertheless, it is clear that clinical management of stones should include therapies to correct these underlying alterations [8].

In this meta-analysis, our primary outcome was stone-free status. We compared intervention and control groups with respect to stone-free status outcome, independently of patient baseline status (stone-free or presenting residual fragments). However, three of the included studies [8, 15, 17] performed a separate analysis of these baseline groups, and the incidence of stone-free status after potassium citrate intervention was higher in groups with stone-free status at baseline than in those with residual stone fragments. This result can be anticipated because retained stone fragments can aggregate or nucleate new stone formation, causing a higher rate of stone growth [5–7]. For infected stones, the residual fragments may serve as a nidus for persistent infection, thereby maintaining the conditions for further stone formation and growth [18].

Some limitations of this review are acknowledged. We identified few eligible studies that met our selection criteria because we focused on healthy adult subjects without comorbidities. The clinical trials did not utilize a standard protocol and, overall, had low methodological quality, which introduced bias into the quality assessment. Basic trial parameters such as participant age, gender, and follow-up were not adequately described. None of the studies met all of the quality requirements because they did not report rigorous methods of randomization. The study participants were not blinded because the trials did not report the use of placebo in control groups.

However, our meta-analysis does contribute evidence that supports the use of SWL therapy combined with potassium citrate supplement. To the best of our knowledge, this is the most comprehensive systematic review to date on this topic that fulfills all aspects of PRISMA [26]. Although this study supports a positive association between SWL therapy and citrate supplement, additional studies with improved methodological rigor and larger patient cohorts are required to better determine the benefits of routine prescription of potassium citrate after SWL.

In conclusion, the results of this study suggest that potassium citrate supplement significantly protects against recurrence of nephrolithiasis after SWL treatment and that citrate supplement can have an important role in preventing kidney stone formation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This manuscript was not submitted to another journal for simultaneous consideration and has not been published previously (partly or full). No data have been fabricated or manipulated. No data, text or theories by others are presented. Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities at the institutions where the work has been carried out. The authors whose names appear on the submission have contributed sufficiently to scientific work and, therefore, share collective responsibility and accountability for the results. Since this is a systematic review and meta-analysis article, this article does not contain any studies with human participants or animals performed by any of the authors. For this type of study formal consent is not required.

Appendix

See Fig. 4.

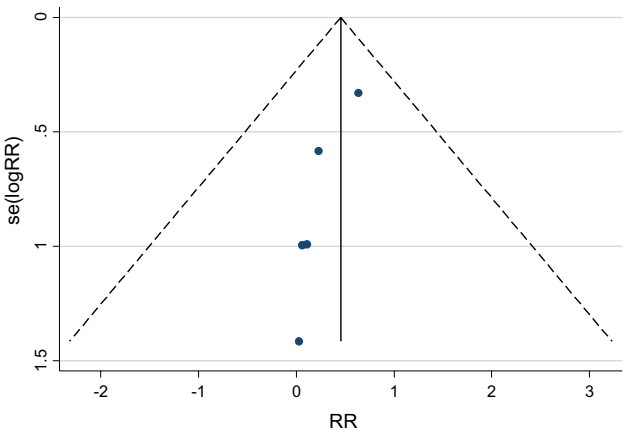

Fig. 4 *Funnel plot* with pseudo 90% confidence limits

References

1 Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T (2016) EAU guidelines on interventional treatment for urolithiasis. Eur Urol 69(3):475–482. doi:10.1016/j.eururo.2015.07.041

2 Chongruksut W, Lojanapiwat B, Tawichasri C, Paichitvichean S, Euathrongchit J, Ayudhya VC, Patumanond J (2011) Kidney stones recurrence and regrowth after extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy. J Med Assoc Thail (Chotmaihet thangphaet) 94(9):1077–1083

3 Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G (1999) A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. J Urol 162(1):27–30. doi:10.1097/00005392-199907000-00007

4 Lingeman JE, Siegel YI, Steele B, Nyhuis AW, Woods JR (1994) Management of lower pole nephrolithiasis: a critical analysis. J Urol 151(3):663–667

5 El-Nahas AR, El-Assmy AM, Madbouly K, Sheir KZ (2006) Predictors of clinical significance of residual fragments after extracorporeal shockwave lithotripsy for renal stones. Journal Endourol Endourol Soc 20(11):870–874. doi:10.1089/end.2006.20.870

6 Pettersson B (1989) Extracorporeal shock wave lithotripsy of renal and ureteral stones–studies on indications, methods and results. Scand J Urol Nephrol Suppl 120:1–80

7 Cicerello E, Merlo F, Maccatrozzo L (2008) Management of residual fragments after SWL. Archivio Italiano di Urologia e Andrologia 80(1):34–38

8 Lojanapiwat B, Tanthanuch M, Pripathanont C, Ratchanon S, Srinualnad S, Taweemonkongsap T, Kanyok S, Lammongkolkul S (2011) Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. Int Braz J Urol 37(5):611–616

9 Zuckerman JM, Assimos DG (2009) Hypocitraturia: pathophysiology and medical management. Rev Urol 11(3):134–144

10 Pak CY (1994) Citrate and renal calculi: an update. Miner Electrolyte Metab 20(6):371–377

11 Pak CY (2004) Medical management of urinary stone disease. Nephron Clin Pract 98(2):c49–c53. doi:10.1159/000080252

12 Pak CY, Fuller C, Sakhaee K, Preminger GM, Britton F (1985) Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol 134(1):11–19

13 Ziemba JB, Matlaga BR (2015) Guideline of guidelines: kidney stones. BJU Int 116(2):184–189. doi:10.1111/bju.13080

14 Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR (2014) Medical management of kidney stones: AUA guideline. J Urol 192(2):316–324. doi:10.1016/j.juro.2014.05.006

15 Soygur T, Akbay A, Kupeli S (2002) Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. J Endourol Endourol Soc 16(3):149–152. doi:10.1089/089277902753716098

16 Goktas C, Horuz R, Akca O, Cetinel CA, Canguven O, Kafkasli A, Albayrak S, Sarica K (2012) The effect of citrate replacement in hypocitraturic cases on the results of SWL: a preliminary prospective randomized study. Int Urol Nephrol 44(5):1357–1362. doi:10.1007/s11255-012-0190-4

17 Verdejo AJ, Martin MA, Ortiz JLM, Rosino EH, Yago FP, Gomez AZ (2001) Effect of potassium citrate in the prevention of urinary lithiasis. Arch Esp Urol 54(9):1036–1046

18 Cicerello E, Merlo F, Gambaro G, Maccatrozzo L, Fandella A, Baggio B, Anselmo G (1994) Effect of alkaline citrate therapy on clearance of residual renal stone fragments after extracorporeal shock wave lithotripsy in sterile calcium and infection nephrolithiasis patients. J Urol 151(1):5–9

19 Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097. doi:10.1371/journal.pmed.1000097

20 Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. doi:10.1136/bmj.d5928

21 Follmann D, Elliott P, Suh I, Cutler J (1992) Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 45(7):769–773

22 Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634

23 Resorlu B, Sancak EB, Akbas A, Gulpinar MT (2014) Time to say good bye to shockwave lithotripsy? World J Urol 32(1):297–298. doi:10.1007/s00345-013-1109-0

24 Rassweiler JJ, Renner C, Chaussy C, Thuroff S (2001) Treatment of renal stones by extracorporeal shockwave lithotripsy: an update. Eur Urol 39(2):187–199. doi:10.1159/000052435

25 Oguz U, Unsal A (2013) The efficacy of medical prophylaxis in children with calcium oxalate urolithiasis after percutaneous nephrolithotomy. J Endourol Endourol Soc 27(1):92–95. doi:10.1089/end.2012.0243

26 Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012. doi:10.1016/j.jclinepi.2009.06.005