Peritubal bupivacaine infiltration for postoperative pain reduction after percutaneous nephrolithotomy

REVIEWED BY

Chaowat Pimratana, M.D.; Udomsak Wijitsettakul, M.D.

Buri Ram Hospital, Thailand.

Correspondence to: Chaowat Pimratana;
pchaowat@gmail.com

ABSTRACT

OBJECTIVE

To compare the effect of peritubal bupivacaine infiltration to conventional pain management for postoperative pain reduction after percutaneous nephrolithotomy.

METHODS

Two independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "percutaneous nephrolithotomy" or "PCNL" or "PNL" together with "bupivacaine". We also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCTs). We used the Cochrane Collaboration Tool for assessing the risk of bias. Criteria for inclusion in our meta-analysis included participants with percutaneous nephrolithotomy who were assigned randomly to peritubal bupivacaine infiltration or no local anesthetic infiltration and the outcomes were postoperative pain and time to first demand analgesia.

RESULTS

Eight RCTs were included in the meta-analysis with 652 patients undergoing percutaneous nephrolithotomy; peritubal bupivacaine infiltration (N=327) and no local anesthetic infiltration (N=325). The mean visual analog scale (VAS) at 6 hours postoperative care in peritubal bupivacaine infiltration was significantly lower than that of no local anesthetic infiltration (mean difference (MD), -1.36; 95% confidence interval (CI), -1.54 to -1.19). Five RCTs were included in the meta-analysis for time to first demand analgesia evaluation with 415 patients; peritubal bupivacaine infiltration (N=209) and no anesthetic infiltration (N=206). The mean time to first demand analgesia was longer than no local anesthetic infiltration group (MD, 170.4 minutes; 95% confidence interval, 161.3 to 179.5 minutes).

CONCLUSION

This meta-analysis found that the peritubal bupivacaine infiltration was significant in alleviating immediate postoperative pain and delaying the time to first demand for analgesia after percutaneous nephrolithotomy.

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is considered the standard treatment of large renal calculi, that has been described since the late 1970s.[1] However, the placement of a nephrostomy tube results in distressing peritubal pain requiring the administration of analgesia. Inadequate analgesia can result in delayed mobilization, impaired ventilation, and prolong hospitalization.[2] All structures, including renal capsule, muscle, subcutaneous tissue, and skin contribute to the pain during puncture and dilatation at the time of PCNL.[3,4] Infiltration local bupivacaine at peritubal, including skin, subcutaneous tissue, nephrostomy tract, and renal capsule can reduce postoperative pain, prolong the time to first demand analgesia and reduce consumption of rescue analgesia after PCNL.[2,5] Bupivacaine is a long-acting amide local anesthetic, its mechanism is based on their ability to increase the threshold of electrical excitation of nerve fibers.[6] Peritubal infiltration with bupivacaine is increasing interest in recent years as it is simple, safe, inexpensive and provide postoperative analgesia after PCNL.[2,3,5,7,8] However, prior to this study, there has not yet been a systematic review of the effect of postoperative pain reduction in patients undergoing PCNL. This study, thus, aims to compare the efficacy between peritubal bupivacaine infiltration and no local anesthetic infiltration for pain reduction after PCNL.

METHODS

SEARCHING STRATEGIES

Two independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "percutaneous nephrolithotomy" or "PCNL" or "PNL" together with "bupivacaine". We also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCTs). We used the Cochrane Collaboration Tool for assessing the risk of bias. Criteria for inclusion in our meta-analysis included participants with percutaneous nephrolithotomy who were assigned randomly to peritubal bupivacaine infiltration or no local anesthetic infiltration and the outcomes were postoperative pain and time to first demand analgesia.

INCLUSION CRITERIA
STUDY DESIGN
We included only RCTs

PARTICIPANTS
We included RCTs with patients undergoing percutaneous nephrolithotomy under general anesthesia assigning randomly to peritubal bupivacaine infiltration or no local anesthetia.

INTERVENTIONS AND COMPARISONS
Local analgesic pain control with peritubal bupivacaine infiltration after percutaneous nephrolithotomy compared to no local anesthetic infiltration either saline or no infiltration.

OUTCOMES
Outcomes of studies included postoperative pain in visual analog scale at 6 hours and the time to first demand for analgesia.

EXCLUSION CRITERIA
We removed studies that were duplicated and studies that did not perform general anesthesia

during the operation. The studies with any spinal or epidural anesthesia in adjunct postoperative care were excluded. We excluded intervention groups including usage of other local anesthetic drugs than bupivacaine for peritubular infiltration.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess the quality of the included RCTs comprising the evaluation of randomization, blinding methods and adequate description of withdrawals or dropouts.[9] In addition, we used the Cochrane Collaboration's Tool for demonstration the risk of bias in relation to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying them to be three degrees which are low risk, high risk, and unclear risk of bias.[10]

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication, numbers of participants, outcomes of visual analog scale (VAS) of pain score at 6 hours and time to first demand analgesia after PCNL in each study.

DATA ANALYSES

The outcomes VAS pain score at 6 hours from the eight trials were meta-analyzed and interpreted using the mean difference (MD) and 95% confidence interval (CI). The outcomes time for first demand analgesia after PCNL from the five trials were meta-analyzed and interpreted using MD and 95% CI, too. Both outcomes were shown as the Forest plot. Later we calculate I^2 to evaluate the

heterogeneity among the studies, if I^2 was higher than 50%, the heterogeneity was considered significant. We used a fixed effect and random effect model for meta-analysis. The publication bias was evaluated as Funnel plots. All statistical analyses were using Review Manager 5.3 statistical software.

RESULTS

STUDY CHARACTERISTICS

Initially, there were 97 citations identified by two independent reviewers. Of these, after duplication removed 26 citations were identified. All studies were RCTs. After screened the titles and abstracts, 59 citations were excluded and then twelve full-text articles assessed for eligibility according to inclusion and exclusion criteria. Finally, eighth studies were included in the meta-analysis by the consensus of two reviewers (Figure 1). Eight studies compared between peritubal bupivacaine infiltration and no anesthetic infiltration for VAS at 6 hours and five studies compared between peritubal bupivacaine infiltration and no local anesthetic infiltration for time to first demand analgesia. The characteristics of the included studies are shown in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the eight studies was assessed using the Jadad score to assess the risk of bias (Table 2). The risk of bias was assessed using The Cochrane Collaboration's tool for risk of bias assessment and summarized in Figure 2A and Figure 2B. All studies were randomized and used the double-blind method. Six studies did not describe the randomization method and concealment. The
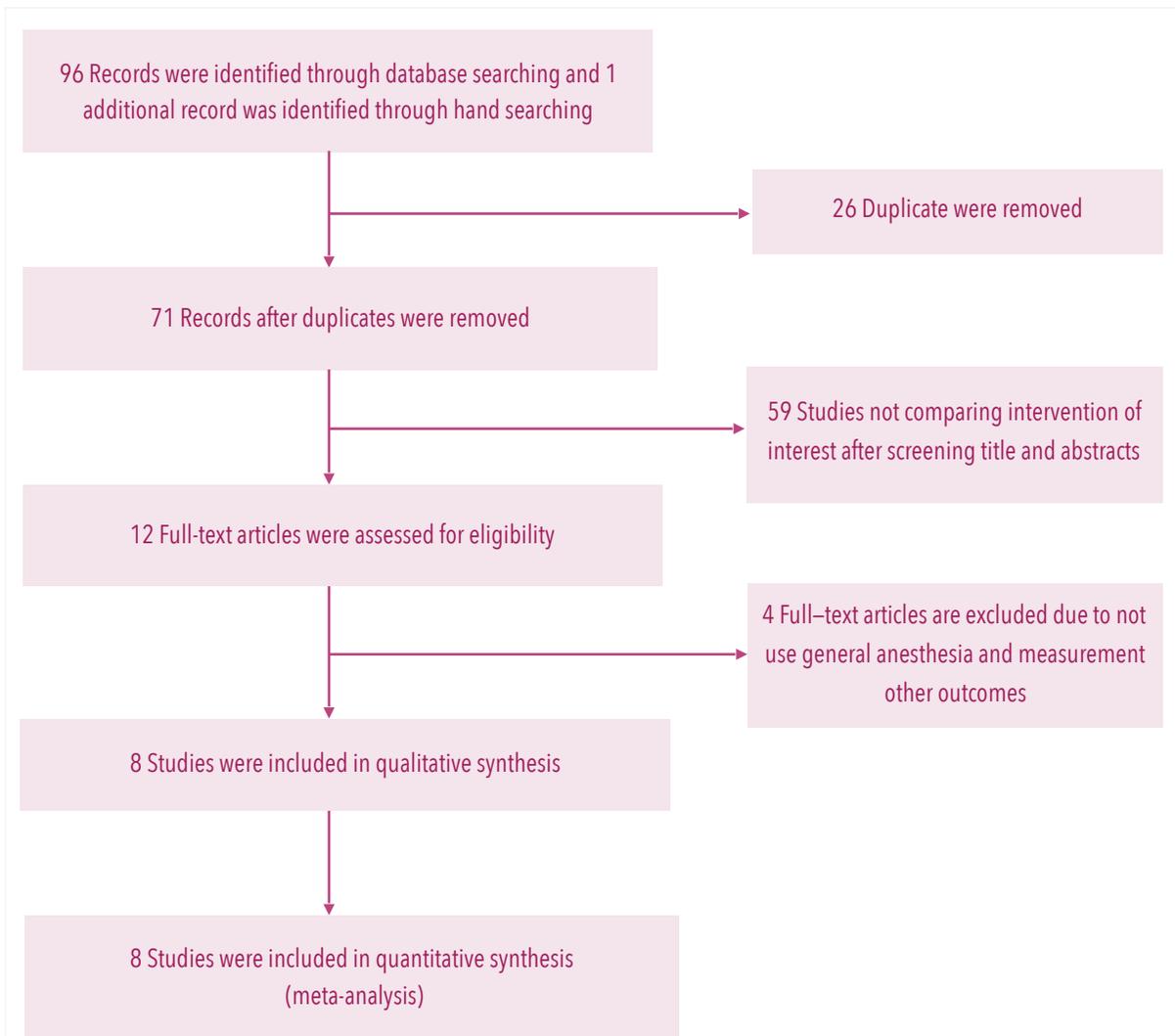
96 Records were identified through database searching and 1 additional record was identified through hand searching

26 Duplicate were removed

71 Records after duplicates were removed

59 Studies not comparing intervention of interest after screening title and abstracts

12 Full-text articles were assessed for eligibility

4 Full–text articles are excluded due to not use general anesthesia and measurement other outcomes

8 Studies were included in qualitative synthesis

8 Studies were included in quantitative synthesis (meta-analysis)

Figure 1. Process of study selection

method of double-blinding did not describe in four studies. One study reported incomplete outcome data.

OUTCOMES

Eight RCTs were included in the meta-analysis with 652 patients undergoing percutaneous nephrolithotomy; peritubal bupivacaine infiltration (N=327) and no local anesthetic infiltration (N=325). The mean VAS at 6 hours postoperative care in peritubal bupivacaine infiltration were significantly lower than no local anesthetic infiltration group (MD, -1.36; 95% CI, -1.54 to -1.19; I^2= 97%) (Figure 3).

Five RCTs were included in the meta-analysis for time to first demand analgesia evaluation with 415 patients; peritubal bupivacaine infiltration (N=209) and no local anesthetic infiltration (N=206). The mean time to first demand analgesia was longer than no local

Table 1. Characteristics of the eight included studies

Study	Year	No. of patients (intervention/control)	Intervention	Control	Outcomes
George E. Haleblian	2007	10/12	0.25% bupivacaine infiltration	Saline infiltration	No significant differences in pain score.
Nirmala Jonnavithula	2008	20/20	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Geeta P Parikh	2011	30/30	0.25% bupivacaine infiltration	Saline infiltration	Intervention significantly reduced pain score, prolonged time to first demand analgesia and reduced total analgesic requirement.
Mustafa Kirac	2013	61/60	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score.
Bannakij Lojanapiwat	2015	53/52	0.25% bupivacaine infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Shariq Anis Khan	2017	47/47	0.25% bupivacaine infiltration	Normal saline infiltration	Intervention significantly reduced pain score.
Isra Karaduman	2017	66/64	0.25% bupivacaine 20 mL + 5mg morphine 0.5 mL infiltration	No infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.
Gokce Dundar	2017	20/20	0.25% bupivacaine infiltration	Saline infiltration	Intervention significantly reduced pain score and prolonged time to first demand analgesia.

anesthetic infiltration (MD, 170.4 minutes; 95% CI, 161.3 to 179.5 minutes; I^2=99%) (Figure 4).

In the studies subgroup of each comparison, the mean VAS in peritubal bupivacaine infiltration were significantly lower than saline infiltration (MD, -2.82; 95% CI, -3.15 to -2.48; I^2=97%) (Figure 5) and the mean time to first demand analgesia in the intervention group were longer than saline infiltration group (MD, 340.1 minutes; 95% CI, 322.8 to 357.5 minutes; I^2=100%) (Figure 6). There was a significantly lower VAS in the intervention group than no infiltration group (MD, -0.83; 95% CI, -1.05 to -0.60; I^2=90%) (Figure 7). The time to first

Table 2. Jadad score

Questions	George E. Haleblian 2007	Nirmala Jonnavithula 2008	Geeta P Parikh 2011	Mustafa Kirac 2013	Bannakij Lojanapiwat 2015	Shariq Anis Khan 2017	Isra Karaduman 2017	Gokce Dundar 2017
1. Was the study described as randomized?	1	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomization describe and appropriate?	0	1	0	1	0	0	0	0
3. Was the study described as double blind?	1	0	1	0	0	1	0	1
4. Was the method of double blinding described and appropriate?	1	0	1	0	0	1	0	1
5. Was there a description of withdrawals and dropouts?	0	1	1	1	1	1	1	1
Total	3	3	4	3	2	4	2	4

analgesic demand in the intervention group longer than no infiltration group (MD, 60.2 minutes; 95% CI, 34.5 to 85.9 minutes; I^2=89%) (Figure 8).

PUBLICATION BIAS

According to our funnel plot which constructed from the eight trials included in the analysis appeared to be asymmetrical and suggested potential publication bias in this review (Figure 9).
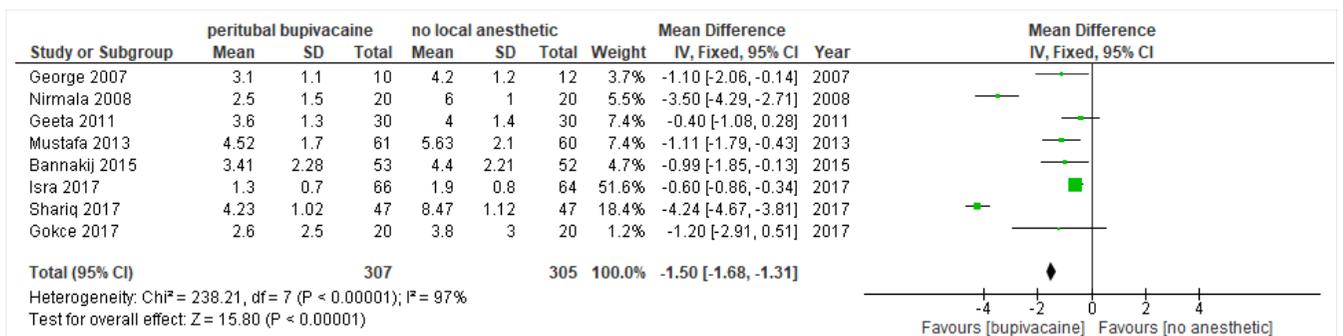
DISCUSSION

SUMMARY OF EVIDENCE

The meta-analysis results indicated that peritubal bupivacaine infiltration reduced the immediate postoperative pain in patients undergoing PCNL and prolonged the time to first demand analgesia when compared to conventional pain management. The data showed high heterogeneity suggesting that there were variations among studies. One of the possible causes of variations among studies was the use of subjective evaluation and measurements to assess the VAS and the time to first demand analgesia. Because pain is both subjective and multidimensional, but postoperative pain measurement most are based on self-reporting of a unidimensional scale aiming to represent subjective pain intensity.[11] The multidimensional evaluation of postoperative status such as a postoperative quality of recovery score would be a useful end-point in perioperative clinical studies.[12]

STRENGTH AND LIMITATIONS OF THE REVIEW

The strength in this systematic review is two independent authors searched for eligible RCTs by screening all titles and abstracts and reading the full-text articles to assess relevant studies, so we
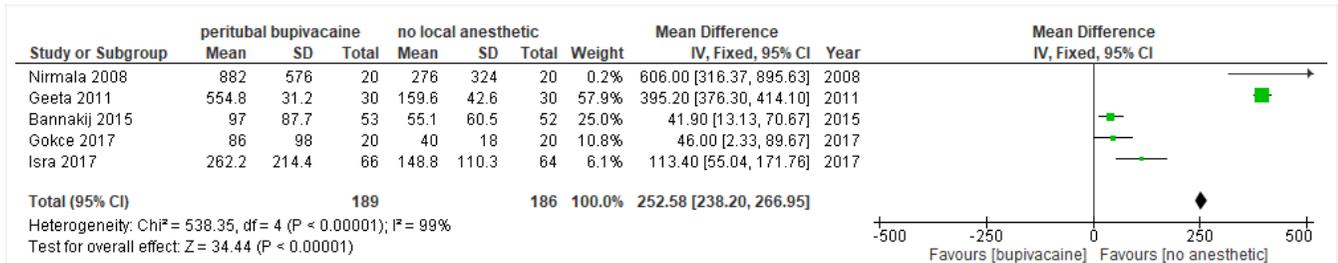
A

B

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

Figure 3. Forest plot: peritubal bupivacaine infiltration versus no local anesthetic infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy

Figure 4. Forest plot: peritubal bupivacaine infiltration versus no local anesthetic infiltration, outcome: time to first demand of analgesia
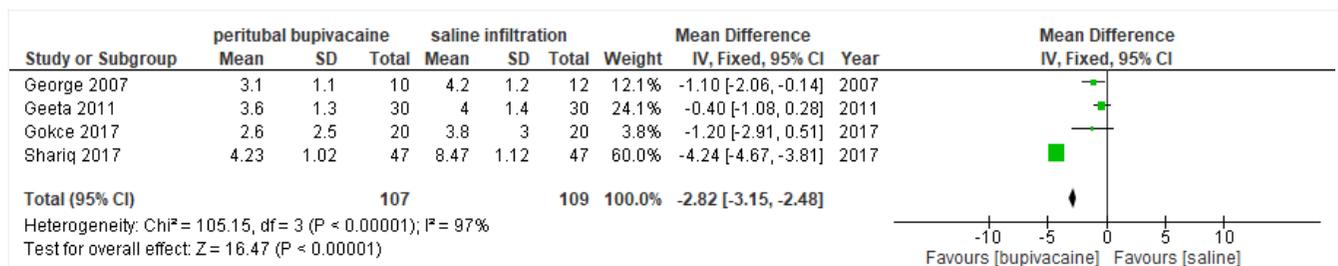

Figure 5. Forest plot: peritubal bupivacaine versus saline infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy
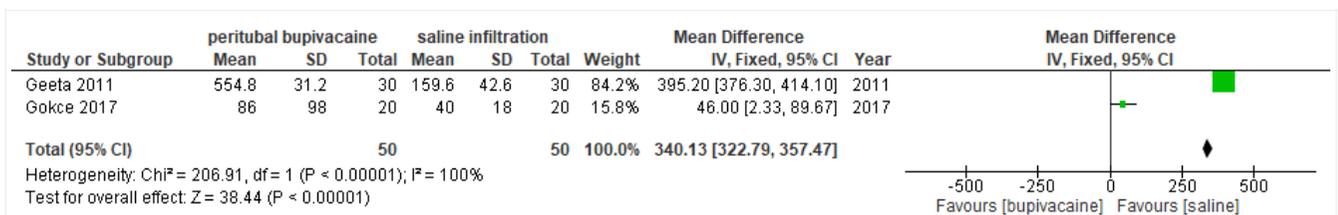

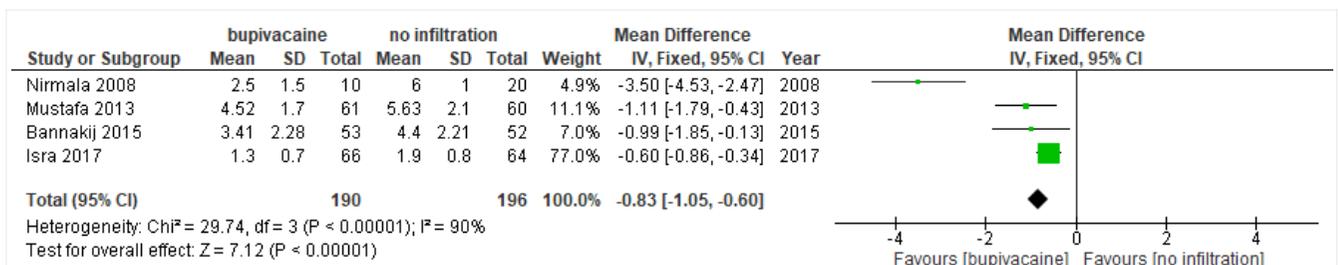**Figure 6. Forest plot: peritubal bupivacaine versus saline infiltration, outcome: time to first demand of analgesia**

Figure 7. Forest plot: peritubal bupivacaine versus no infiltration, outcome: VAS in 6 hours postoperative percutaneous nephrolithotomy

Study or Subgroup	bupivacaine Mean	SD	Total	no infiltration Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Nirmala 2008	882	576	20	276	324	20	0.8%	606.00 [316.37, 895.63]	2008
Bannakij 2015	97	87.7	53	55.1	60.5	52	79.8%	41.90 [13.13, 70.67]	2015
Isra 2017	262.2	214.4	66	148.8	110.3	64	19.4%	113.40 [55.04, 171.76]	2017
Total (95% CI)			139			136	100.0%	60.21 [34.51, 85.92]	

Heterogeneity: Chi² = 18.39, df = 2 (P = 0.0001); I² = 89%
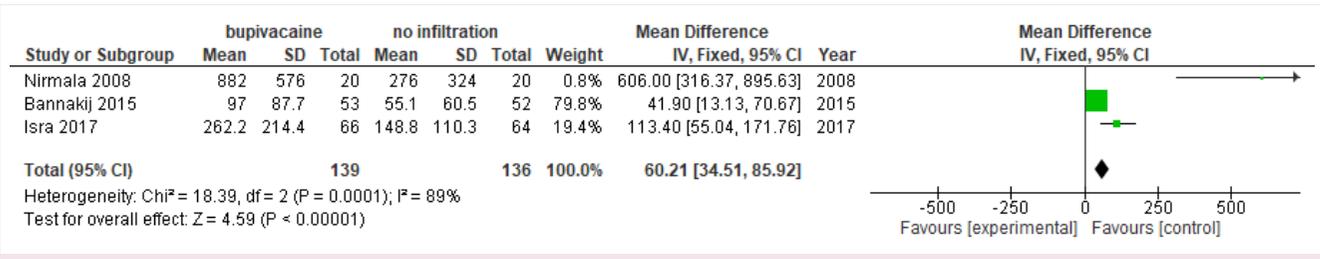Test for overall effect: Z = 4.59 (P < 0.00001)

Figure 8. Forest plot: peritubal bupivacaine versus no infiltration, outcome: time to first demand analgesia
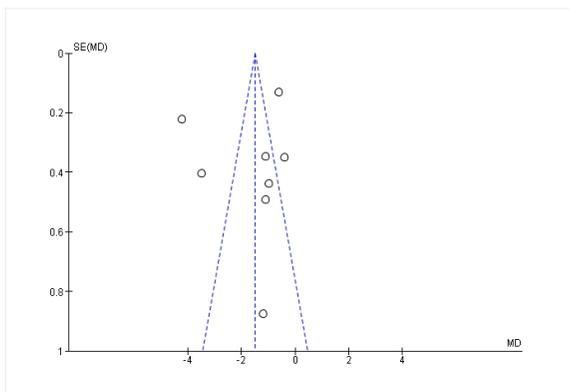

Figure 9. Funnel plot of overall postoperative pain reduction outcomes.

got eligible studies and assured not to miss the important data.

The limitation of this systematic review is the risk of bias. The selection bias, random sequence generation, and allocation concealment were not identified in many studies. The performance bias was presented in half of the included studies due to a lack of blinding of participants and personnel in comparison groups. Baseline preoperative data of VAS did not reveal in all of the included studies. This is a limitation because pain is both subjective and multidimensional and so the VAS cannot capture the complete pain experience. But clinical decisions are made based on existing pain scales, and so it is important to know how much reduction in a VAS score is likely to be clinically meaningful from the patient's perspective.[11]

COMPARISON WITH OTHER STUDIES

PCNL is accepted to be the minimally invasive procedure for large renal stones with less morbidity and mortality, but PCNL still causes significant postoperative pain especially nephrostomy tube placement for tamponade of bleeding along the tract and adequate drainage.[5] Jonnavithola et al. studied the effectiveness of peritubal bupivacaine infiltration of the renal capsule. This technique consisted of the use of a 23 gauge spinal needle along nephrostomy tube at 6 and 12 o'clock and each infiltrated 10 mL of 0.25% bupivacaine into peritubal nephrostomy tract, including skin, subcutaneous tissue, muscle, and renal capsule. That was developed under the rational to relief the pain that might be originated in the renal capsule after PCNL surgery.[3] Munkongsrisuk et al. demonstrated that no significant difference postoperative pain reduction and time to first analgesic demand between only subcutaneous bupivacaine infiltration after PCNL and control group.[13] Recent studies were evaluated the efficacy of peritubal bupivacaine infiltration but there were shown the various results and some studies had few numbers of the participants.[2–5,7,8,14,15] Nonetheless, their outcome

measures might not be reliable as they did not have baseline pain. It is important to know how much reduction in a VAS score is likely to be clinically meaningful from the patient's perspective.[11]

CONCLUSION AND IMPLICATION

This meta-analysis found that the peritubal bupivacaine infiltration was significant in alleviating immediate postoperative pain and delaying the time to first demand for analgesia after PCNL when compared with the no anesthetic infiltration group. However, this study has three key limitations that may limit the implementation of clinical practice. First, the included studies in the meta-analysis lacked a procedure to blind the participants. Second, there was an incomplete baseline VAS pain score. Third, the data showed high heterogeneity. For further study, we suggest having the new RCT that clear study design in allocation concealment, blinding procedure, and well-defined pain score reduction assessment.

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