Original Article
Efficacy of bupivacaine infiltration on pain control in standard percutaneous nephrolithotomy: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The efficacy of bupivacaine infiltration to control pain for standard percutaneous nephrolithotomy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of bupivacaine infiltration on pain control for standard percutaneous nephrolithotomy. Methods: We search PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases through January 2018 for randomized controlled trials (RCTs) assessing the effect of bupivacaine infiltration on pain control in standard percutaneous nephrolithotomy. Meta-analysis is performed using the random-effect model. Results: Six RCTs involving 337 patients are included in the meta-analysis. Overall, compared with control group for standard percutaneous nephrolithotomy, bupivacaine infiltration can significantly reduce VAS at postoperative 12 h (Std. MD=-0.87; 95% CI=-1.27 to -0.48; P < 0.0001) and 24 h (Std. MD=-0.78; 95% CI=-1.24 to -0.32; P=0.0008), as well as prolong the time of first analgesic demand (Std. MD=1.02; 95% CI=0.43 to 1.62; P=0.0008), but has no remarkable influence on VAS at postoperative 6 h (Std. MD=-0.33; 95% CI=-0.81 to 0.15; P=0.18), doses of analgesic usage (Std. MD=-0.50; 95% CI=-1.24 to 0.24; P=0.18), operative time (Std. MD=0.13; 95% CI=-0.14 to 0.40; P=0.33), hospital stay (Std. MD=0.07; 95% CI=-0.30 to 0.45; P=0.70), nausea/vomiting (RR=0.52; 95% CI=0.27 to 1.00; P=0.05). Conclusions: Bupivacaine infiltration has important ability to alleviate the pain and prolong the time of first analgesic demand for standard percutaneous nephrolithotomy.

Keywords: Bupivacaine infiltration, pain control, standard percutaneous nephrolithotomy, randomized controlled trials, meta-analysis

Introduction

Percutaneous nephrolithotomy is a safe and effective approach to treat large and complex renal stones [1-3]. Percutaneous nephrolithotomy has widely accepted in clinical work because of the lower complication and morbidity rates compared to open stone surgery. However, many patients suffer from obvious pain, discomfort related to a nephrostomy tube, and distress [4, 5]. Various technical modifications have been developed for standard percutaneous nephrolithotomy in order to reduce the morbidity and postoperative pain [6-9].

The decrease in size of percutaneous nephrolithotomy tract (miniperc), tubeless percutaneous nephrolithotomy and local anesthetic infiltration are developed to make the surgery more acceptable to patients [10-13]. Especially, peri-tubal or tubal local anesthetic infiltration during percutaneous nephrolithotomy procedures has been reported to significantly alleviate postoperative pain [6, 14].

However, the use of bupivacaine infiltration on pain control for standard percutaneous nephrolithotomy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [15-17]. With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to investigate the efficacy of bupivacaine infiltration on pain control after standard percutaneous nephrolithotomy.

Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and
Bupivacaine on pain control in percutaneous nephrolithotomy

meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [18].

Search strategy and study selection

Two investigators have independently searched the following databases (inception to January 2018): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: bupivacaine, and nephrolithotomy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing standard percutaneous nephrolithotomy; (ii) intervention: peritubal bupivacaine infiltration; (iii) comparison: no infiltration or normal saline infiltration; (iv) study design: RCT. Patients with tubeless percutaneous nephrolithotomy are excluded.

Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, body mass index or weight, female, and detail methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary. No simplifications and assumptions are made. The primary outcomes are visual analogue score (VAS) at postoperative 6 h, 12 h, and 24 h. Secondary outcomes include first analgesic demand, doses of analgesic usage, operative time, hospital stay, and nausea/vomiting.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [19]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [20].

Statistical analysis

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (VAS at postoperative 6 h, 12 h and 24 h, first analgesic demand, doses of analgesic usage, operative time, and hospital stay) and (risk ratio) RR with 95% CIs for dichotomous outcomes (nausea/vomiting). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I² statistic, and I² > 50% indicates significant heterogeneity [21]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (< 10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 455 potentially relevant articles are identified initially. Finally, six RCTs that meet our inclusion criteria are included in the meta-analysis [14-17, 22, 23].

The baseline characteristics of the six eligible RCTs in the meta-analysis are summarized in Table 1. The six studies are published between 2007 and 2015, and sample sizes range from 22 to 105 with a total of 337. Peritubal infiltra-
## Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>NO.</th>
<th>Author</th>
<th>Number</th>
<th>Age (years)</th>
<th>Female (n)</th>
<th>Body mass index (kg/m²) or weight (kg)</th>
<th>Stone size (mm)</th>
<th>Methods</th>
<th>Jada scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lojanapiwat 2015</td>
<td>53</td>
<td>56.64 ± 11.34</td>
<td>18</td>
<td>22.54 ± 3.46 kg/m²</td>
<td>40.0 ± 18.3</td>
<td>Peritubal injection with 10 mL of 0.25% bupivacaine</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Sharifi 2014</td>
<td>20</td>
<td>39.6 ± 12.1</td>
<td>7</td>
<td>76.6 ± 11.12 kg</td>
<td>39.3 ± 8.3</td>
<td>Peritubal infiltration with 5 mL of 0.25% bupivacaine</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Kirac 2013</td>
<td>36</td>
<td>42.5 ± 13.2</td>
<td>14</td>
<td>-</td>
<td>30.5 ± 10.1</td>
<td>Peritubal 20 mL infiltration of 0.25% bupivacaine</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Parikh 2011</td>
<td>30</td>
<td>40</td>
<td>3</td>
<td>60.73 kg</td>
<td>-</td>
<td>Peritubal 10 mL of 0.25% bupivacaine</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Jonnavithula 2009</td>
<td>20</td>
<td>41.8</td>
<td>12</td>
<td>59.4 kg</td>
<td>-</td>
<td>Peritubal 20 mL of 0.25% bupivacaine</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Halebian 2007</td>
<td>10</td>
<td>45.7</td>
<td>-</td>
<td>94.1 kg</td>
<td>-</td>
<td>Peritubal 1.5 mg/kg of 0.25% bupivacaine</td>
<td>3</td>
</tr>
</tbody>
</table>
Bupivacaine on pain control in percutaneous nephrolithotomy

Table 1. Forest plot for the meta-analysis of VAS at postoperative 6 h.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bupivacaine group</th>
<th>Control group</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirac 2013</td>
<td>4.08</td>
<td>1.3</td>
<td>1.5</td>
<td>36</td>
</tr>
<tr>
<td>Sharifi 2014</td>
<td>3.1</td>
<td>1</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>56</td>
<td>54</td>
<td>0.9</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.00; df = 1 (P = 0.98); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.36 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Forest plot for the meta-analysis of VAS at postoperative 6 h.

Figure 3. Forest plot for the meta-analysis of VAS at postoperative 12 h.

Figure 4. Forest plot for the meta-analysis of VAS at postoperative 24 h.

Figure 5. Forest plot for the meta-analysis of first analgesic demand (min).

Figure 6. Forest plot for the meta-analysis of doses of analgesic usage (mg).

Percutaneous nephrolithotomy is performed with 5-20 ml of 0.25% bupivacaine or 1.5 mg/kg of 0.25% bupivacaine.

Among the six studies included here, two studies report VAS at postoperative 6 h, 12 h and 24 h [16, 17], three studies report first analgesic demand [15, 16, 23], four studies report doses of analgesic usage [15-17, 23], three studies report operative time [15-17], two studies report hospital stay [16, 17], and two stud-
Bupivacaine on pain control in percutaneous nephrolithotomy

Primary outcomes: VAS at postoperative 6 h, 12 h and 24 h

These outcome data are analyzed with the random-effects model, and the pooled estimate of the two included RCTs suggested that compared to control group for standard percutaneous nephrolithotomy, bupivacaine infiltration has no remarkable influence on VAS at postoperative 6 h (Std. MD=0.33; 95% CI=-0.81 to 0.15; P=0.18), with low heterogeneity among the studies (I²=36%, heterogeneity P=0.21) (Figure 2), but is associated with significantly reduced VAS at postoperative 12 h (Std. MD=0.87; 95% CI=1.27 to 0.48; P < 0.0001), with no heterogeneity among the studies (I²=0%, heterogeneity P=0.98) (Figure 3). In addition, VAS at postoperative 24 h is found to be substantially decreased after bupivacaine infiltration (Std. MD=0.78; 95% CI=1.24 to 0.32; P=0.0008), with no heterogeneity among the studies (I²=24%, heterogeneity P=0.25) (Figure 4).

Sensitivity analysis

No or low heterogeneity is observed among the included studies for the primary outcomes, and thus we do not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

Secondary outcomes

Compared to control group for standard percutaneous nephrolithotomy, bupivacaine infiltration can substantially increase the time of first analgesic demand (Std. MD=1.02; 95% CI=0.43 to 1.62; P=0.0008; Figure 5), but shows no significant impact on doses of analgesic usage (Std. MD=0.50; 95% CI=0.17 to 1.48; P=0.18; Figure 6), operative time (Std. MD=0.13; 95% CI=0.14 to 0.40; P=0.33; Figure 7), hospital stay (Std. MD=0.07; 95% CI=-0.30 to 0.45; P=0.70; Figure 8), nausea/vomiting (RR=0.52; 95% CI=0.27 to 1.00; P=0.05; Figure 9).
Bupivacaine on pain control in percutaneous nephrolithotomy

Discussion

Postoperative pain has emerged as an important problem for percutaneous nephrolithotomy, and can result in poor life quality, anxiety, delayed mobilization, increased postoperative complications and prolonged hospitalization [24-26]. With better understanding of acute pain physiology, new analgesic agents, better analgesia delivery procedures and better local anesthetic infiltration techniques are used to alleviate postoperative pain [22, 23, 27]. Several techniques have been developed for percutaneous nephrolithotomy, including multimodal analgesic regimens, the use of small nephrostomy tube, tubeless percutaneous nephrolithotomy, mini-percutaneous nephrolithotomy, local analgesic infiltration and renal capsule analgesic infiltration [28-30].

Peritubal local infiltration of bupivacaine demonstrates important ability to relieve the pain after percutaneous nephrolithotomy [14, 22]. Our meta-analysis suggests that peritubal local infiltration of bupivacaine is able to substantially reduce the pain intensity at postoperative 12 h and 24 h, as well as improve the time of first analgesic demand after percutaneous nephrolithotomy, but has no import influence on VAS at postoperative 6 h, doses of analgesic usage, operative time and hospital stay.

Traditional opioid analgesics (e.g. meperidine and morphine) are used in postoperative pain management, and they can cause various side effects including postoperative nausea and vomiting, drowsiness, respiratory depression, ileus, urinary retention and constipation [31-33]. The local anesthesia can effectively reduce the systemic response of drugs, which is revealed in general surgery, gynecology, cesarean sections, hysterectomy, thyroid surgery, mastectomy, total-hip arthroplasty, and cervical spine surgery [34-36]. No increase in nausea/vomiting is observed after percutaneous nephrolithotomy in our meta-analysis. Postoperative pain is caused by the dilatation of renal capsule and parenchyma of access tract with local inflammation reaction, and renal capsule and parenchyma are richly innervated of pain-conductive neurons [22, 23]. These theoretically support the results of our meta-analysis.

This meta-analysis has several potential limitations that should be taken into account. Firstly, our analysis is based on only six RCTs and five of them have a relatively small sample size (n < 100). More RCTs with large samples should be conducted to confirm this issue. Next, although there is no significant heterogeneity when performing sensitivity analysis, different doses of 0.25% bupivacaine may have an influence on the pooling results. Finally, some unpublished and missing data may lead bias to the pooled effect.

Conclusions

Peritubal local infiltration of bupivacaine is effective and safety to control the pain after standard percutaneous nephrolithotomy, and should be recommended to be administrated in clinical work with caution.

Disclosure of conflict of interest

None.

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Bupivacaine on pain control in percutaneous nephrolithotomy


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