Review Article
Benefits of ropivacaine infiltration for reducing postoperative pain after thyroid surgery: a meta-analysis of randomized controlled trials

Ning Wang, Juyi Zhang, Jia Ming

Department of Breast and Thyroid Surgery, Second Hospital Affiliated to Chongqing Medical University, Chongqing, China

Received February 22, 2019; Accepted May 10, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: Introduction: The effect of ropivacaine infiltration on postoperative pain after thyroid surgery remains controversial. Here, a systematic review and meta-analysis was conducted to explore the influence of ropivacaine infiltration versus placebo on postoperative pain after thyroid surgery. Methods: PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases were searched through November 2018 for randomized controlled trials (RCTs) assessing the effect of ropivacaine infiltration versus placebo on postoperative pain after thyroid surgery. This meta-analysis is performed using the random-effect model. Results: Four RCTs involving 335 patients are included in the meta-analysis. Overall, compared with control group for thyroid surgery, ropivacaine infiltration shows significantly positive effect on (Std. MD=-0.87; 95% CI=-1.69 to -0.04; P=0.04), and postoperative analgesic consumption (Std. MD=-1.71; 95% CI=-2.94 to -0.47; P=0.0007), but has no special influence on surgical duration (Std. MD=0.12; 95% CI=-0.21 to 0.44; P=0.49), hospital stay (Std. MD=0; 95% CI=-0.34 to 0.34; P=1.00), nausea and vomiting (RR=0.58; 95% CI=0.19 to 1.75; P=0.33). Conclusions: Ropivacaine infiltration produces favorable impact on pain management for thyroid surgery.

Keywords: Ropivacaine infiltration, postoperative pain, thyroid surgery, randomized controlled trials, meta-analysis

Introduction
Minimally invasive operation has been widely developed for the surgery [1-3]. In particular, the advantages of minimally invasive thyroidectomy are improved in terms of superior postoperative cosmetic outcomes, lower complication rates, and faster recovery after incorporation of the Robot System compared to conventional open thyroidectomy [4-8]. However, immediate postoperative pain still commonly occurs after minimally invasive thyroidectomy due to the flap dissection that is required to establish an adequate operative field [9-12].

Various methods have been developed to alleviate the pain after minimally invasive thyroid surgery, and they mainly include thyroidectomy with the bilateral axillo-breast approach, and local infiltration of the flap site with the anesthetic agent levobupivacaine and ropivacaine which are were administered by spray or subcutaneous injection [13-17]. Local infiltration with anesthetic agents is found to have important potential in reducing postoperative pain. Ropivacaine has the advantage of long block duration, better safety and lower toxicity than levobupivacaine [18]. Its low lipophilic profile enables to reduce the possibility to induce cardio- and central nervous system toxicity [19, 20].

However, the benefit of ropivacaine infiltration versus placebo for pain control after thyroid surgery has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [14, 21, 22]. With accumulating evidence, a systematic review and meta-analysis of RCTs was performed here to explore the efficacy of ropivacaine infiltration versus placebo for pain control after thyroid surgery.

Materials and methods
Ethics approval and patient consent were not required because this is a systematic review
and 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) [23].

Search strategy and study selection

Two investigators independently searched the following databases (inception to November 2018): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: ropivacaine, and thyroid surgery or thyroidectomy. Reference lists of the screened full-text studies were also checked to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients undergoing thyroid surgery; (ii) intervention: ropivacaine infiltration; (iii) comparison: matched placebo; (iv) study design: RCT.

Data extraction and outcome measures

The following information was extracted: author, number of patients, age, female, body mass index, the number of total thyroid surgery and detail methods in each group etc. Data have been extracted independently by two investigators, and discrepancies are resolved by consensus. The corresponding author was also contacted to obtain the data when necessary.

The primary outcome was pain scores. Secondary outcomes included analgesic consumption, surgical duration, hospital stay, nausea, and vomiting.

Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale [24]. 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 [25].

Statistical analysis

The standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (pain scores, analgesic consumption, surgical duration, hospital stay) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (nausea and vomiting) was used for analysis. A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and I^2 > 50% indicates significant heterogeneity [26]. Whenever significant heterogeneity was present, potential sources of heterogeneity were searched via omitting one study in turn for the meta-analysis or performing subgroup analysis. 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. A total of 309 potentially relevant articles were identified initially. Finally, four RCTs that met the inclusion criteria were included in the meta-analysis [14, 21, 22, 27].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in Table 1. The four studies were published between 2007 and 2017, and sample sizes range from 34 to 148 with a total of 335. The concentrations of ropivacaine infiltration ranged from 0.1% to 2%.

Among the four studies included here, two studies reported pain scores [22, 27], three studies reported analgesic consumption [14, 22, 27], four studies reported surgical duration [14, 21, 22, 27], two studies reported hospital stay [14, 22], three studies reported nausea and vomiting [14, 22, 27]. Jadad scores of the four included studies vary from 4 to 5, and all four studies are considered to be high-quality ones according to quality assessment.

Primary outcome: pain scores

This outcome data is analyzed with the random-effects model, and compared to control group for thyroid surgery and ropivacaine infiltration resulted in significant pain scores (Std. MD=-0.87; 95% CI=-1.69 to -0.04; P=0.04) with significant heterogeneity among the studies (I^2=81%, heterogeneity P=0.02) (Figure 2).
Ropivacaine for thyroid surgery

Sensitivity analysis

Significant heterogeneity was observed among the included studies for pain scores, but there are just two RCTs, and it was not available to perform sensitivity analysis via omitting one study in turn.

Secondary outcomes

In comparison with control group for thyroid surgery, ropivacaine infiltration is able to reduce the postoperative analgesic consumption (Std. MD=-1.71; 95% CI=-2.94 to -0.47; P=0.0007; Figure 3), but exhibits no obvious impact on surgical duration (Std. MD=0.12; 95% CI=-0.21 to 0.44; P=0.49; Figure 4), hospital stay (Std. MD=0; 95% CI=-0.34 to 0.34; P=1.00; Figure 5), nausea and vomiting (RR=0.58; 95% CI=0.19 to 1.75; P=0.33; Figure 6).

Discussion

One meta-analysis aims to investigate five types of analgesic interventions for acute postoperative pain management, and they include epidural analgesia, local anesthetic wound infiltration, systemic N-methyl-d-aspartic acid (NMDA) receptor antagonists, systemic nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic opioids. The results find that preemptive epidural analgesia resulted in consistent improvements in postoperative pain scores, analgesic consumption and time to first rescue analgesic request, while local anesthetic wound infiltration and NSAID administration can significantly reduce analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores [28]. Thyroidectomies are not included in that meta-analysis. Our meta-analysis include four RCTs involving ropivacaine infiltration after thyroid surgery.

A previous study reveals that preoperative surgical site injection with local anesthetics is effective to reduce the pain intensity after conventional open thyroidectomy [29]. In that study, 0.25% levobupivacaine spray on the flap site after thyroid surgery in 58 patients results in the reduction in pain scores and analgesic consumption at 1, 6, 24, and 48 hours after surgery [15]. One RCT involved 34 women, and preoperative ropivacaine injection of the flap site reduced the pain score, analgesic consumption, and additional analgesic requirement at 2, 6, 18, 30, 42, and 66 hours after surgery [14]. Pain scores and analgesic consumption are remarkably reduced after ropivacaine for thyroid surgery in our meta-analysis, but there is no statistical difference of surgical duration, hospital stay, nausea and vomiting between ropivacaine group and control group.

In addition, preoperative local infiltration may be more effective for pain control than postoperative spray, because most of the spray tends to drain out postoperatively [14, 30]. A mixture of ropivacaine and epinephrine is reported to significantly and safely alleviate postoperative pain.
### 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)</th>
<th>Total thyroid surgery</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lee 2017</td>
<td>74</td>
<td>35.5±8.8</td>
<td>66</td>
<td>23.3±4.0</td>
<td>21</td>
<td>225 mg of ropivacaine and epi-nephrine 1 mg/1 mL diluted by 1:100,000 with 100 mL of normal saline injected into the subcutaneous layer of the flap site for hydrodissection</td>
</tr>
<tr>
<td>2</td>
<td>Bae 2016</td>
<td>53</td>
<td>40.5±9.4</td>
<td>49</td>
<td>22.2±3.5</td>
<td>49</td>
<td>40 mL of 0.25% ropivacaine was instilled into the skin flap</td>
</tr>
<tr>
<td>3</td>
<td>Kang 2015</td>
<td>17</td>
<td>38.0±10.1</td>
<td>-</td>
<td>22.1±2.3</td>
<td>14</td>
<td>0.1% ropivacaine with saline (3 mg/kg) injection prior to skin incision</td>
</tr>
<tr>
<td>4</td>
<td>Motamed 2007</td>
<td>25</td>
<td>41±6</td>
<td>18</td>
<td>-</td>
<td>12</td>
<td>Wound infiltration with 15 ml of ropivacaine 2% at end-of-surgery</td>
</tr>
</tbody>
</table>

<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)</th>
<th>Total thyroid surgery</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>74</td>
<td>38.0±9.3</td>
<td>69</td>
<td>22.9±2.5</td>
<td>20</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>50</td>
<td>39.9±11.1</td>
<td>47</td>
<td>22.4±2.7</td>
<td>43</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>17</td>
<td>34.7±7.6</td>
<td>-</td>
<td>21.8±2.7</td>
<td>13</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>25</td>
<td>43±8</td>
<td>20</td>
<td>-</td>
<td>14</td>
<td>Matched placebo</td>
</tr>
</tbody>
</table>
pain in cesarean section patients [31]. Epinephrine is frequently used in hydro-dissection during bilateral axillo-breast approach to reduce bleeding during flap formation due to its ability to induce peripheral vasoconstriction and yield a spotless flap. The use of epinephrine can decrease the estimated blood loss (18.0 vs 30 mL) and operation time (155.3 vs 163.6 minutes) in the ropivacaine-epinephrine group compared to control group [21].

Figure 2. Forest plot for the meta-analysis of pain scores.

Figure 3. Forest plot for the meta-analysis of analgesic consumption.

Figure 4. Forest plot for the meta-analysis of surgical duration (min).

Figure 5. Forest plot for the meta-analysis of hospital stay (day).

Figure 6. Forest plot for the meta-analysis of nausea and vomiting.
Ropivacaine for thyroid surgery

Ropivacaine infiltration can provide improved pain control after thyroid therapy.

Conclusions
Ropivacaine infiltration can provide improved pain control after thyroid therapy.

Disclosure of conflict of interest
None.

Address correspondence to: Jia Ming, Department of Breast and Thyroid Surgery, Second Hospital Affiliated to Chongqing Medical University, Chongqing, China. E-mail: mjia1001@sina.com

References


