Perineural versus intravenous dexamethasone as an adjuvant in regional anesthesia: a systematic review and meta-analysis

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Background: Dexamethasone is a common adjuvant for local anesthetics in regional anesthesia, but the optimal route of administration is controversial. Therefore, we did a systematic review and meta-analysis of randomized controlled trials to assess the effect of perineural versus intravenous dexamethasone on local anesthetic regional nerve-blockade outcomes.

Materials and methods: Medline (through PubMed), Embase, Cochrane, Web of Science, and Biosis Previews databases were systematically searched (published from inception of each database to January 1, 2017) to identify randomized controlled trials. The data of the selected trials were statistically analyzed to find any significant differences between the two modalities. The primary outcome was the duration of analgesia. Secondary outcomes included duration of motor block, postoperative nausea and vomiting, and postoperative analgesic dose at 24 hours. We conducted a planned subgroup analysis to compare the effects between adding epinephrine or not.

Results: Ten randomized controlled trials met the inclusion criteria of our analysis, with a total of 749 patients. Without the addition of epinephrine, the effects of perineural and intravenous dexamethasone were equivalent concerning the duration of analgesia (mean difference 0.03 hours, 95% CI –0.17 to 0.24). However, with the addition of epinephrine, the analgesic duration of perineural dexamethasone versus intravenous dexamethasone was prolonged (mean difference 3.96 hours, 95% CI 2.66–5.27). Likewise, the impact of epinephrine was the same on the duration of motor block. The two routes of administration did not show any significant differences in the incidence of postoperative nausea and vomiting, nor on postoperative analgesic consumption at 24 hours.

Conclusion: Our results show that perineural dexamethasone can prolong the effects of analgesic duration when compared to the intravenous route, only when epinephrine is coadministered. Without epinephrine, the two modalities show equivalent effect as adjuvants on regional anesthesia.

Keywords: anesthesia adjuvants, dexamethasone, regional anesthesia

Introduction

Uncontrolled pain after surgery may produce a range of detrimental acute and chronic effects.¹ In some surgical procedures under regional anesthesia, commonly used local anesthetics cannot provide analgesia for a sufficiently prolonged time. Therefore, local anesthetic–opioid combinations or continuous catheterization are chosen to prolong analgesic duration. However, unintentional opioid-associated side effects and several problems associated with carrying a catheter, especially for day-care patients, make these treatment options unsatisfactory. Since 1982, anesthesiologists have been using a variety of adjuvants added to local anesthetics to enhance regional anesthesia.² Dexamethasone is one of these additives.³
Dexamethasone has been proved to be an effective adjuvant for extending the duration of sensory and motor block for peripheral nerve block when given perineurally. Intravenous injection can also be used for alleviating postoperative pain. However, there are conflicting reports about which of the two routes of administration is the best or if both exert an equivalent effect.

To solve this query, a series of randomized controlled trials (RCTs) were conducted to compare the effect of prolongation of analgesia between perineural and intravenously administered dexamethasone. We carried out a systematic review and meta-analysis to assemble all the associated individual clinical trials to assess the two modalities on the main outcomes: prolonging sensory-block duration, decreasing postoperative nausea and vomiting, and sparing analgesic consumption at 24 hours after surgery.

Materials and methods
This systematic review and the meta-analysis results were reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy
Two authors (WLZ and XFO) independently searched the following databases: Medline (through PubMed), Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Biosis Previews, from inception of each database to January 1, 2017. There were no language restrictions. The full literature-search strategies for PubMed and Embase are presented in Table S1. In brief, we used MeSH terminology for dexamethasone, regional anesthesia, and their synonyms to search the five databases to obtain relevant literature.

Then, all the titles and abstracts were screened and full texts of eligible RCTs retrieved. The references of key English reviews and eligible studies were also manually searched.

Selection criteria
When the titles and abstracts were screened, four selection criteria were applied: 1) population – adult patients (aged ≤19 years) under surgery who received regional anesthesia; 2) intervention – dexamethasone given perineurally as an adjuvant to local anesthetics; 3) control – same-dose dexamethasone given intravenously; and 4) design – RCTs. Studies that satisfied these criteria were retrieved for full texts to be assessed. Meeting abstracts were eliminated due to their incomplete information.

Data extraction
Two authors (WLZ and XFO) independently extracted the following raw data from the selected studies: main authors, year of publication, country, number of patients, type of nerve block, ultraguided localization technique, type and dose of local anesthetics (including dexamethasone and other adjuvants), and main outcomes. Then, concrete data of the following outcomes were extracted: duration of analgesia or sensory block, duration of motor block, incidence of postoperative nausea and vomiting, and postoperative analgesic use (morphine equivalents) at 24 hours. For the continuous type of data, we emailed the corresponding author to obtain the raw data when the variables in full text were not reported as means and SD. If authors did not respond, we used a method of data conversion. For calculation of given means, 95% CIs, SD ((vn × [upper – lower]/2r), given medians, and interquartile ranges, the method reported by Hozo et al was used.

Each of the two aforementioned authors checked these data at least three times. Any disagreements on the results were resolved independently by a third experienced author (JL).

Assessment for risk of bias in included studies
Risks of included studies were assessed by the Cochrane risk-of-bias tool. We classified risk of bias as low, unclear, or high for each of random-sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (such as missing participant data). To grade the qualities of evidence and the strength of recommendations, we used GradePro version 3.6.1 for our four outcomes.

Statistical analysis
Continuous variables, analgesic duration, duration of motor block, and postoperative analgesic use at 24 hours were reported as mean differences (MDs) with 95% CIs. We analyzed postoperative nausea and vomiting as the categorical variable and expressed relative risk with 95% CIs. Heterogeneity of the four outcomes was evaluated by using the $\chi^2$ and $F$ tests. A fixed-effect model was used when $\chi^2$ P-value was >0.1 and $F<$50%. When $P<0.1$ and $F>50$%, we chose a random-effect model, and the planned subgroup analysis was performed to compare adding epinephrine or not to the local anesthetic mixture. Potential publication biases were assessed by funnel-plot analysis. All analyses were performed with RevMan (version 5.3; Cochrane Library, Oxford, UK).
Results
Study selection and characteristics
A flowchart of the study-selection procedure is shown in Figure 1. In order to avoid any missing studies, we did not restrict the design of RCTs in searching Web of Science and Biosis Previews or define the route of administration. A total of 2,939 studies were identified during our first search: 638 articles were removed due to duplication, and 2,301 titles and abstracts were eliminated after screening. Finally, ten studies were included in our ultimate analysis.\textsuperscript{14–23} One study was eliminated due to its high standard deviation, which was even larger than the mean value, possibly due to the small-study effect.\textsuperscript{24,25} The basic information of the ten studies is presented in Table 1. Patients of seven studies received brachial nerve block, one study used a nerve simulator to localize the nerve, and the rest were ultrasound-guided. The remaining studies were on perianal block, sciatic nerve block, and ankle block. Two of the studies were multicenter clinical trials, which were conducted in Canada and Thailand. The dose of dexamethasone ranged from 4 to 10 mg. Three trials added epinephrine with local anesthetics and dexamethasone, and hence they constituted the planned subgroup analysis in this study.

The risks of bias for the ten studies included here were discussed by all the authors; the risks discussed are summarized in Figure S1. One study\textsuperscript{19} did not present the process they used to generate random sequences for group allocation. They also unveiled the allocation results to the anesthesiologists who participated in that trial, and did not refer to any blinding of the outcome assessment, as with another one.\textsuperscript{14} For one of the ten studies,\textsuperscript{22} the methods section did not clearly show the approach used for blinding the participants.

Duration of analgesia
The duration of sensory block or analgesia was reported by nine trials. One\textsuperscript{19} was eliminated due to its definition of median analgesia time, namely time to first analgesic request in >50% of patients, which was far different to other studies’ definitions (Table S2). In a random-effect model, a pooled analysis of nine trials showed that the MD between perineural and intravenous dexamethasone was 1.62 hours (95% CI –0.05 to 3.29, $I^2 = 80\%$; $P = 0.06$; Figure 2A), which indicated that dexamethasone given perineurally or intravenously had a similar effect on the duration of sensory block or analgesia. Due to the high heterogeneity, we conducted a subgroup analysis comparing the addition or exclusion of epinephrine. When epinephrine was used, perineural dexamethasone prolonged anaesthetic duration by 3.96 hours (95% CI 2.66–5.27, $P < 0.00001$).

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**Figure 1** Flowchart of the search strategy.
**Abbreviation:** RCTs, randomized controlled trials.
Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Nerve block</th>
<th>Ultrasound-guided</th>
<th>Local anesthetics (n)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmonem and Rizk</td>
<td>Egypt</td>
<td>56</td>
<td>Perianal block</td>
<td>No</td>
<td>Bupivacaine 100 mg + perineural dexamethasone 8 mg (18), bupivacaine 100 mg + intravenous dexamethasone 8 mg (19), bupivacaine 100 mg + intravenous normal saline (19)</td>
<td>Onset of sensory blockade, onset of motor blockade, duration of analgesia, VAS at 6 hours after rescue analgesic, postoperative nausea and vomiting</td>
</tr>
<tr>
<td>Desmet et al</td>
<td>Belgium</td>
<td>144</td>
<td>Interscalene brachial plexus block</td>
<td>No (nerve stimulator)</td>
<td>Ropivacaine 150 mg + perineural dexamethasone 10 mg (49), ropivacaine 150 mg + intravenous dexamethasone 10 mg (49), ropivacaine 150 mg + intravenous normal saline (46)</td>
<td>Duration of analgesia, pain scores, motor-block scores, analgesic need, sleep disturbance, overall satisfaction, postoperative blood glucose concentrations</td>
</tr>
<tr>
<td>Kawanishi et al</td>
<td>Japan</td>
<td>34</td>
<td>Interscalene brachial plexus block</td>
<td>Yes</td>
<td>Ropivacaine 150 mg + perineural dexamethasone 4 mg (12), ropivacaine 150 mg + intravenous dexamethasone 4 mg (10), ropivacaine 150 mg (12)</td>
<td>Duration of anesthesia, NRS the morning after surgery, analgesic need, sleep disturbance, overall-satisfaction score, postoperative nausea and vomiting, incidence of dyspnea Quality of recovery (QoR-40), pain (NRS 0–11), time to first toe movement, analgesia duration, postoperative opioid consumption, patient satisfaction, recommend technique to family or relative, postoperative neurologic symptoms</td>
</tr>
<tr>
<td>Rahangdale et al</td>
<td>USA</td>
<td>76</td>
<td>Sciatic nerve block</td>
<td>Yes</td>
<td>Bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + perineural dexamethasone 8 mg (27); bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + intravenous dexamethasone 8 mg (23); bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + intravenous normal saline (26)</td>
<td>Duration of analgesia, duration of motor function, VAS pain scores, cumulative intraoperative opioid consumption, cumulative postoperative opioid consumption, postoperative nausea and vomiting, patient satisfaction, occurrence of any block-related complications</td>
</tr>
<tr>
<td>Abdallah et al</td>
<td>Canada</td>
<td>75</td>
<td>Supraclavicular brachial plexus block</td>
<td>Yes</td>
<td>Bupivacaine 150 mg + perineural dexamethasone 8 mg (25), bupivacaine 150 mg + intravenous dexamethasone 8 mg (25), bupivacaine 150 mg + intravenous normal saline (25)</td>
<td>Duration of analgesia, duration of motor function, VAS, administration of &quot;rescue&quot; antiemetic medication, adverse events</td>
</tr>
<tr>
<td>Rosenfeld et al</td>
<td>USA</td>
<td>120</td>
<td>Interscalene brachial plexus block</td>
<td>Yes</td>
<td>Ropivacaine 140 mg + perineural dexamethasone 8 mg (42), ropivacaine 140 mg + intravenous dexamethasone 8 mg (37), ropivacaine 140 mg + intravenous normal saline (41)</td>
<td>Median analgesia time, patient-satisfaction scores, side effects, neurological symptoms, incidence of motor block, analgesic administration, blood glucose values</td>
</tr>
<tr>
<td>Chun et al</td>
<td>South Korea</td>
<td>99</td>
<td>Interscalene brachial plexus block</td>
<td>Yes</td>
<td>Ropivacaine 60 mg + perineural dexamethasone 5 mg (50), ropivacaine 60 mg + intravenous dexamethasone 5 mg (49)</td>
<td>Duration of motor block, duration of sensory block, duration of postoperative analgesia</td>
</tr>
<tr>
<td>Aliste et al</td>
<td>Canada, Thailand</td>
<td>131</td>
<td>Axillary brachial plexus block</td>
<td>Yes</td>
<td>Lidocaine 300 mg, bupivacaine 75 mg, epinephrine 150 μg + perineural dexamethasone 8 mg (64), bupivacaine 300 mg, bupivacaine 75 mg, epinephrine 150 μg + intravenous dexamethasone 8 mg (67)</td>
<td>Duration of motor block, duration of sensory block, duration of postoperative analgesia</td>
</tr>
<tr>
<td>Dawson et al</td>
<td>Australia</td>
<td>90</td>
<td>Ankle block</td>
<td>Yes</td>
<td>Bupivacaine 150 mg + perineural dexamethasone 8 mg (30), bupivacaine 150 mg + intravenous dexamethasone 8 mg (30), bupivacaine 150 mg + intravenous normal saline (30)</td>
<td>Time to return of some sensation or movement, time to return of neurology, pain scores, total postoperative analgesic use</td>
</tr>
<tr>
<td>Leurcharusmee et al</td>
<td>Thailand, Canada</td>
<td>123</td>
<td>Infradavicular brachial plexus block</td>
<td>Yes</td>
<td>Lidocaine 350 mg, bupivacaine 87.5 mg, epinephrine 175 μg + perineural dexamethasone 5 mg (61), lidocaine 350 mg, bupivacaine 87.5 mg, epinephrine 175 μg + intravenous dexamethasone 5 mg (62)</td>
<td>Duration of motor block, duration of sensory block, duration of postoperative analgesia</td>
</tr>
</tbody>
</table>

Abbreviations: NRS, numeric rating scale; VAS, visual analog scale.
Postoperative nausea and vomiting
Six studies assessed the incidence of postoperative nausea and vomiting. The pooled analysis demonstrated that there was no difference between the perineural and intravenous dexamethasone groups (risk ratio 0.87, 95% CI 0.35–2.11; $P=0.75$; Figure 4A), without heterogeneity ($I^2=0$) or publication bias (Figure S3).

Postoperative analgesic use at 24 hours
Postoperative opioid consumption (morphine equivalents) at 24 hours was evaluated by three trials. In this analysis, analgesic use was the same between the two groups (MD $–1.30 \pm 3.89$, 95% CI $–4.23$ to 2.23; $P=0.35$; Figure 4B).

Grade quality
GradePro evaluation of the confidence of evidence is shown in Table 2.

in comparison to the intravenous dexamethasone group, with no heterogeneity ($F=0$). In the absence of epinephrine, both groups had equal analgesic duration (MD 0.03 hours, $F=7\%$, 95% CI $–0.17$ to 0.24; $P=0.75$; Figure 2B). There were no observations of publication biases when constructing the funnel plots (Figure S2).

Duration of motor block
Four trials reported on duration of motor block. The effects on prolonging duration of motor block between the two modalities was statistically insignificant (MD 1.67 hours, $F=94\%$, 95% CI $–2.88$ to 6.22; $P=0.47$; Figure 3A) as revealed by the random-effect model. However, subgroup analysis showed that in the presence of epinephrine, the perineural dexamethasone group had duration prolonged by 4 hours (95% CI 2.82–5.20, $P=3\%$; $P<0.00001$; Figure 3B) when compared to the intravenous dexamethasone group.
Figure 3 Forest plots showing the duration of motor block.

Notes: Analysis of four studies (A) and subgroup analysis by differentiating addition or not of epinephrine (B).

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural Mean</th>
<th>SD</th>
<th>Total</th>
<th>Intraocular Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdallah et al18 2015</td>
<td>25.5</td>
<td>4.6</td>
<td>25</td>
<td>30.1</td>
<td>2.66</td>
<td>25</td>
<td>25.7%</td>
</tr>
<tr>
<td>Aliste et al17 2017</td>
<td>15.7</td>
<td>6.2</td>
<td>61</td>
<td>12.9</td>
<td>5.5</td>
<td>62</td>
<td>25.7%</td>
</tr>
<tr>
<td>Leurcharusmee et al21 2016</td>
<td>29.9</td>
<td>7.3</td>
<td>27</td>
<td>25.9</td>
<td>7.2</td>
<td>23</td>
<td>22.4%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td></td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=19.85, df=3 (P<0.00001); I^2=94%$

Test for overall effect: $Z=0.72 (P=0.47)$

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural Mean</th>
<th>SD</th>
<th>Total</th>
<th>Intravenous Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliste et al23 2017</td>
<td>17.5</td>
<td>4.6</td>
<td>64</td>
<td>12.8</td>
<td>4.5</td>
<td>67</td>
<td>26.3%</td>
</tr>
<tr>
<td>Leurcharusmee et al21 2016</td>
<td>15.7</td>
<td>6.2</td>
<td>61</td>
<td>12.9</td>
<td>5.5</td>
<td>62</td>
<td>25.7%</td>
</tr>
<tr>
<td>Rahangdale et al17 2014</td>
<td>29.9</td>
<td>7.3</td>
<td>27</td>
<td>25.9</td>
<td>7.2</td>
<td>23</td>
<td>22.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>152</td>
<td></td>
<td>75.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=2.06, df=2 (P=0.36); I^2=3%$

Test for overall effect: $Z=6.61 (P<0.00001)$

Not epinephrine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural Mean</th>
<th>SD</th>
<th>Total</th>
<th>Intravenous Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdallah et al18 2015</td>
<td>25</td>
<td>4.6</td>
<td>25</td>
<td>30.1</td>
<td>2.66</td>
<td>25</td>
<td>25.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>25</td>
<td></td>
<td>25.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for subgroup differences: $\chi^2=49.50, df=1 (P<0.00001); I^2=98.0%$

Figure 4 Forest plots comparing perineural and intravenous groups at 24 hours.

Notes: Incidence of postoperative nausea and vomiting (A); postoperative analgesic consumption (B).

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural Events</th>
<th>Total</th>
<th>Intravenous Events</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson et al25 2016</td>
<td>0</td>
<td>30</td>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Kawanishi16 2014</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td>10</td>
<td>16.7%</td>
</tr>
<tr>
<td>Chun et al13 2016</td>
<td>3</td>
<td>50</td>
<td>6</td>
<td>49</td>
<td>62.5%</td>
</tr>
<tr>
<td>Abdallah15 2015</td>
<td>1</td>
<td>25</td>
<td>1</td>
<td>25</td>
<td>10.3%</td>
</tr>
<tr>
<td>Rosenfeld22 2016</td>
<td>1</td>
<td>42</td>
<td>0</td>
<td>37</td>
<td>5.5%</td>
</tr>
<tr>
<td>Abdelmonem and Rizk14 2011</td>
<td>2</td>
<td>18</td>
<td>0</td>
<td>19</td>
<td>5.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>177</td>
<td></td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events 7

Heterogeneity: $\chi^2=3.12, df=4 (P=0.54); I^2=0%$

Test for overall effect: $Z=0.32 (P=0.75)$

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural Mean</th>
<th>SD</th>
<th>Total</th>
<th>Intravenous Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdallah18 2015</td>
<td>13.3</td>
<td>29.55</td>
<td>25</td>
<td>12.5</td>
<td>24.47</td>
<td>25</td>
<td>11.1%</td>
</tr>
<tr>
<td>Rahangdale17 2014</td>
<td>30.3</td>
<td>25.6</td>
<td>27</td>
<td>31.3</td>
<td>20.2</td>
<td>23</td>
<td>15.5%</td>
</tr>
<tr>
<td>Rosenfeld22 2016</td>
<td>12.2</td>
<td>9.3</td>
<td>42</td>
<td>17.1</td>
<td>15.9</td>
<td>37</td>
<td>73.4%</td>
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<tr>
<td>Total (95% CI)</td>
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<td></td>
<td>100.0%</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=3.12, df=4 (P=0.54); I^2=0%$

Test for overall effect: $Z=0.32 (P=0.75)$
Discussion

The results of our review and meta-analysis show that the two modalities of perineural and intravenous dexamethasone as local anesthetic additives can produce a similar effect on the duration of analgesia or sensory block. From the subgroup analysis, we found that the high heterogeneity in the data analysis stemmed from adding epinephrine or not, a well-known adjuvant in local anesthetics to prolong block duration. With epinephrine, prolongation of duration of analgesia and motor block were observed in the perineural dexamethasone group when compared to the intravenous dexamethasone method. Without epinephrine, both groups showed an equivalent effect on analgesia duration. In addition, the incidence of postoperative nausea and vomiting and postoperative analgesic consumption at 24 hours exhibited no statistical significant differences when comparing the two routes of administration.

Such adjuvants as midazolam, ketamine, clonidine, dexametomidine, epinephrine, or dexamethasone are coadministered with local anesthetics in order to enhance the effect of single-shot peripheral nerve block. Although several meta-analyses have demonstrated that dexamethasone given perineurally can extend the analgesic duration of common local anesthetics for brachial plexus block, the effectiveness of intravenous dexamethasone has been controversial. Actually, in a meta-analysis of 38 studies, systemic dexamethasone (>0.1 mg·kg⁻¹) reduced postoperative pain and analgesic consumption. As such, the current paramount issue is to demonstrate that perineural dexamethasone has an extra effect on the duration of analgesia through a direct mechanism on nerve blocking. In this meta-analysis, the pooled results from ten RCTs revealed that dexamethasone (4–10 mg) can produce similar duration of sensory or motor block when administered perineurally or intravenously without epinephrine. In other words, the viewpoint that dexamethasone has a direct inhibition of peripheral nerves needs to be considered carefully and examined again. However, limited evidence in our review and meta-analysis elucidates that there may be a synergistic effect between dexamethasone and epinephrine when given locally.

On the one hand, whether or not dexamethasone has a direct effect on nerve conduction has been disputed. In isolated rat sciatic nerves, neither dexamethasone nor buprenorphine can inhibit the compound action potentials from A and C fibers. In vivo, an animal study demonstrated that bupivacaine plus 67 μg dexamethasone did not increase block duration more than bupivacaine alone. In contrast, a mouse sciatic nerve-blockade model, high-dose (0.5

Table 2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of evidence (grade)</th>
<th>Number of participants</th>
<th>Quality assessment</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Publication bias</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of analgesia: epinephrine</td>
<td>Moderater</td>
<td>172</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Duration of analgesia: not epinephrine</td>
<td>Moderate</td>
<td>170</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
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</tr>
<tr>
<td>Duration of motor block: epinephrine</td>
<td>Moderate</td>
<td>152</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Duration of motor block: not epinephrine</td>
<td>Moderate</td>
<td>176</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
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<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>Moderate</td>
<td>172</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Postoperative opioid use at 24 hours</td>
<td>Moderate</td>
<td>177</td>
<td>Not serious</td>
<td>RCT</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
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<tr>
<td>Note: Number of RCTs not sufficient to reach high-quality evidence. High-quality evidence needs to be relected on the confidence in the estimate of effect.</td>
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Abbreviation: RCT, randomized controlled trial.
mg·kg⁻¹) perineural dexamethasone added to bupivacaine prolonged the duration of sensory and motor block, while low-dose (0.14 mg·kg⁻¹) dexamethasone did not. However, these results should be considered with skepticism, because of the unblinded procedure in that study. Despite the fact that sciatic nerves are commonly used to evaluate the effect of local anesthetic, we cannot directly extrapolate the results from rodents to humans. In addition, the period of block conduction can differ due to the neurobiology of acute postoperative pain in clinical patients. Acute postoperative pain includes not the conduction of nociception, but direct nerve damage and inflammatory mediator release, which activate peripheral nociceptors to deliver information to the central nervous system. Dexamethasone, a long-effective glucocorticoid, has the appropriate anti-inflammatory property by increasing the production of anti-inflammatory substances and decreasing the release of inflammatory mediators. This characteristic may be responsible for its systematic mechanism in prolonging block duration. Overall, further studies are needed to find and prove the precise indirect mechanism of dexamethasone and also its interaction with epinephrine perineurally.

On the other hand, dexamethasone is prescribed “off-label” for perineural administration. Neurotoxicity is a serious problem for local anesthetics and additives that we have to consider. Dexamethasone 133 μg·mL⁻¹ combined with ropivacaine increased neurotoxicity for isolated sensory neurons. As such, the author advised that much attention be paid to the time- and concentration-dependent toxicity when dexamethasone is combined with ropivacaine. In agreement with previous results, in a preliminary animal experiment, we found that solutions of commonly used local anesthetics (bupivacaine, ropivacaine) in combination with nonparticulate dexamethasone sodium phosphate could crystallize, even in physiological pH (unpublished data). Therefore, the patient’s safety might be compromised when crystalliferous solution is unintentionally injected into the subarachnoid space or into the blood vessels.

Considering potential neurotoxicity or hazards from crystallization, the unknown mechanism of action, and the fact that both methods have a similar effect on block duration, controlling nausea and vomiting, and sparing opioid consumption, we conclude that intravenous dexamethasone is preferable to perineural dexamethasone, as it carries fewer risks to the patient. Moreover, a recent published meta-analysis proved that a combination of intravenous dexamethasone with other antiemetics showed more efficacy than a single antiemetic in preventing nausea and vomiting after laparoscopic cholecystectomy.

There are some limitations of this analysis. Firstly, postoperative blood glucose levels and long-term neurological sequelae were not analyzed. Only two of the ten trials chosen here reported blood glucose concentrations after surgery. In these two studies, data demonstrated that there were no significant differences in blood glucose levels between the two routes of administration. Also, no serious relevant neurologic symptoms were found in these clinical trials. Secondly, although heterogeneity was low or inexistent among the four outcomes, there was a risk of bias in some of the studies. Thirdly, this review did not evaluate the interaction between the dosage of dexamethasone and block duration. However, Albrecht et al elucidated that no inconclusive evidence was found between different concentrations of dexamethasone (4–10 mg) and analgesic duration by subgroup analysis.

Knowledge on many aspects of the two modalities is not clear, and further clinical studies are required to explore and determine their mechanism of action. A large-scale, multicenter, prospective, double-blinded RCT is needed to be performed to prove which is the most effective adjuvant, the best method of delivery (local anesthetic, perineural, or intravenous dexamethasone), and whether dexamethasone has a synergistic or additive effect with epinephrine when administered locally. If the most efficient route of administration proves to be additive, then the optimal dose of dexamethasone has to be determined. Finally, prospective studies should investigate the safety of dexamethasone at higher doses (>133 μg·mL⁻¹), when administered perineurally with local anesthetics.

**Conclusion**

Our systematic review and meta-analysis suggests that local epinephrine and dexamethasone have a synergistic effect. However, without epinephrine, intravenous dexamethasone and perineural dexamethasone share similar effects on block duration, postoperative nausea and vomiting, and postoperative analgesic consumption at 24 hours. At present, and considering the potential risk of the off-label use of dexamethasone perineurally and its as yet unknown mechanism of action, the route of intravenous administration is thus preferable. Further animal and human studies are needed to explore the definite relationship and the potential synergistic mechanism between local dexamethasone and epinephrine and to select the most effective route of administration required to guide clinical practice.
Perineural versus IV dexamethasone

Acknowledgment
The authors show much gratitude to Robert McCarthy for supplying the raw data presented in their studies.

Disclosure
The authors report no conflicts of interest in this work.

References
2. Candido KD, Knezevic NN. All adjuvants to local anesthetics were not created equal: animal data evaluating neurotoxicity, thermal hyperalgesia, and relevance to human application. Reg Anesth Pain Med. 2011;36(3):211–212.
Supplementary materials

Table S1 Search strategy

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<td>2</td>
<td>Search (((((((Anesthesia, Conduction[MeSH Terms]) OR Anesthesia, Conduction[Text Word]) OR Conduction Anesthesia[Text Word]) OR Anesthesia, Regional[Text Word]) OR Regional Anesthesia[Text Word]) OR Anesthesia, Spinal[Text Word]) OR Anesthesia, Sacral[Text Word]) OR Regional Anesthesia[Text Word])</td>
</tr>
<tr>
<td>5</td>
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</tr>
</tbody>
</table>
Zhao et al

# Embase

1. exp dexamethasone
   - (dexamethasone or Methylfluorprednisolone or Hexadecadrol or Decameth or Foy Brand of Dexamethasone or Decaspray or Merck Brand of Dexamethasone or Dexasone or ICN Brand of Dexamethasone or Dexpak or ECR Brand of Dexamethasone or Maxidex or Alcon Brand of Dexamethasone or Millicorten or Oradexon or Decaject or Merz Brand 1 of Dexamethasone or Decaject-L A or Decaject L A or Merz Brand 2 of Dexamethasone or Hexadrol).tw.

2. exp regional anesthesia
   - (Anesthesia, Conduction or Conduction Anesthesia or Anesthesia, Regional or Regional Anesthesia).tw.

3. exp epidural anesthesia
   - (Anesthesia, Epidural or Anesthesia, Peridural or Anesthesias, Peridural or Peridural Anesthesia or Peridural Anesthesias or Anesthesia, Extradural or Extradural Anesthesia or Extradural Anesthesias or Epidural Anesthesia or Anesthesias, Epidural or Epidural Anesthesias).tw.

4. exp caudal anesthesia
   - (Anesthesia, Caudal or Caudal Anesthesia or Anesthesia, Sacral Epidural or Epidural Anesthesia, Sacral or Sacral Epidural Anesthesia).tw.

5. exp local anesthesia
   - (Anesthesia, Local or Local Anesthesia or Anesthesia, Infiltration or Infiltration Anesthesia or Neural Therapy of Huneke or Huneke Neural Therapy).tw.

6. exp nerve block
   - (Nerve Block or Block, Nerve or Blocks, Nerve or Nerve Blocks or Nerve Blockade or Blockade, Nerve or Blockades, Nerve or Nerve Blockades or Chemical Neurolysis or Chemical Neurolyses or Neurolyses, Chemical or Neurolysis, Chemical or Chemodenervation or Chemodenervations).tw.

7. exp local anesthetic agent
   - (Anesthetics, Local or Local Anesthetics or Conduction-Blocking Anesthetics or Conduction Blocking Anesthetics or Anesthetics, Conduction-Blocking or Anesthetics, Conduction Blocking or Anesthetics, Topical).tw.

8. exp amydricaine or amylocaine or articaine or aslavital or benzocaine or ben佐furcaine or bucracaine or bumecaine or bupivacaine or butacaine or butanilicaine or butethamine or butoxycaine or butylcaine or carbisocaine or carsticae or centbucridine or cetacaine or chloroprocaine or cinchocaine or cocaine or cyclomethycaine or dibucaine or dimethocaine or diperon or diphenhydramine or dyclalone or emLu or ethyl chloride or etidocaine or eugenol or euprocin or fluros or fomocaine or guafecainol or heptacaine or hexathrinic or hexylcaine or instillagel or ipravacaine or isobutambe or ketocaine or levobupivacaine or lidamidine or lidocaine ornepivacaine orormepylcaine orormutabuthamine ormyrtecaene or oxetacaine or oxybuprocaine or pentacaine or phenacaine or phenol or piperocaine or polidocanol or pramocaine or procaine or propanocaine or propoxycaine or propylcaine or proxymetacaine or pseudococaine or pyrrocaine or quinisocaine or ropivacaine or tanax or tetracaine or tetrodotoxin or tolycaine or tricaine or trimecaine or xyloproct or zolamine).tw.

9. 1 or 2
10. 3 or 4
11. 5 or 6
12. 7 or 8
13. 9 or 10
14. 11 or 12
15. 13 or 14
16. 15 or 16 or 17
17. 19 or 20 or 21 or 22 or 23 or 24 or 25
18. 18 and 26
19. 27 and 28

20. ('clinical':ti,ab and 'trial':ti,ab) or 'clinical trial' exp or random* or 'drug therapy':lnk.af.
21. 27 and 28
Table S2 Definitions

<table>
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<tr>
<th>Study</th>
<th>Duration of analgesia</th>
<th>Duration of motor block</th>
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<tr>
<td>Abdelmonem and Rizk1</td>
<td>Duration of analgesia was measured after the onset of sensory blockade till the patient's first request of analgesia (VAS &gt;3).</td>
<td>None</td>
</tr>
<tr>
<td>Desmet et al2</td>
<td>Duration of analgesia was defined as the time between the performance of the block and the first administration of analgesia.</td>
<td>None</td>
</tr>
<tr>
<td>Kawanishi et al3</td>
<td>Duration of analgesia was defined as the time between the performance of the sensory block and the first administration of analgesia</td>
<td>None</td>
</tr>
<tr>
<td>Rahangdale et al4</td>
<td>Duration of analgesia was defined as the time to first reported pain</td>
<td>Duration of motor block was defined as the time to first toe movement</td>
</tr>
<tr>
<td>Abdallah et al5</td>
<td>Duration of analgesia was defined as the time in hours to the first report of postoperative pain at the surgical site.</td>
<td>Duration of motor block, defined as the time (in hours) to return to normal</td>
</tr>
<tr>
<td>Rosenfeld et al6</td>
<td>Duration of analgesia was defined as the time from injection until the patient detected complete resolution of sensory blockade</td>
<td>None</td>
</tr>
<tr>
<td>Chun et al7</td>
<td>The definition of “median analgesia time” was the time to first analgesic request in &gt;50% of patients.</td>
<td>None</td>
</tr>
<tr>
<td>Aliste et al8</td>
<td>For duration of postoperative analgesia, patients were instructed to record the exact time they first experienced pain at the surgical site.</td>
<td>Duration of motor block, defined as the exact time they first regained movement of their fingers</td>
</tr>
<tr>
<td>Dawson et al9</td>
<td>Durations of blockade was defined as the time until ankle and foot sensation or movement started to return.</td>
<td>None</td>
</tr>
<tr>
<td>Leurcharusmee et al10</td>
<td>For duration of postoperative analgesia, patients were instructed to record the exact time they first experienced pain at the surgical site.</td>
<td>Duration of motor block, defined as the exact time they first regained movement of the fingers</td>
</tr>
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</table>

Abbreviation: VAS, visual analog scale.
Figure S1 Risks of bias for the ten included studies by all authors’ judgment.

Notes: Red, high risk of bias; yellow, unclear risk of bias; green, low risk of bias.

Figure S2 Funnel plots of duration of analgesia: adding epinephrine (left) and not adding epinephrine (right).
Figure S3 Funnel plot of postoperative nausea and vomiting.

References


