Title Page

1. Title:
Efficacy of perineural dexamethasone in prolonging duration of analgesia with peripheral nerve blocks compared to intravenous dexamethasone: A systematic review and meta-analysis

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3. Running Title: Review of perineural vs IV dexamethasone

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Efficacy of perineural dexamethasone in prolonging duration of analgesia with peripheral nerve blocks compared to intravenous dexamethasone: A systematic review and meta-analysis

Abstract

Background: Perineural dexamethasone is regarded as a promising adjunct for prolonging nerve block duration. However, it is uncertain if its effects are from a local effect on the nerves or from systemic absorption of the anti-inflammatory drug. This systematic review aims to compare the impact of perineural dexamethasone vis-a-vis intravenous dexamethasone, as an adjunct to peripheral nerve blocks, on the duration of analgesia postoperatively.

Methods: A total of 2,216 relevant academic articles were identified by comprehensively searching the major databases (PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov) in the period of 0000-2020. All randomized controlled trials comparing the use of perineural dexamethasone to intravenous dexamethasone in peripheral nerve limb blocks were included. Studies involving the use of non-limb blocks, the use of other additives or did not directly compare perineural and intravenous dexamethasone. Studies that involved any surgeries that involved truncal blocks, drug preparations that used other additives in combination with dexamethasone and studies that used different dexamethasone doses for both perineural and intravenous routes were excluded. PROSPERO registration number: CRD42020210257.
**Results:** Fifteen randomized controlled trials (1,467 cases; 738 perineural dexamethasone, 729 intravenous dexamethasone) were eligible. The primary outcome, duration of analgesia, was significantly longer in the perineural dexamethasone group compared to the intravenous dexamethasone group (mean difference (MD), 2.72 hours; 95% confidence interval (95% CI), 1.42-4.01; p<0.0001). Perineural dexamethasone also prolonged sensory block (MD, 3.45 hours; 95% CI, 1.36-5.54; p=0.001) and had lower 24-hour postoperative pain scores (MD, -0.74; 95% CI, -1.40 to -0.07; p=0.03). There were no significant differences in motor block duration (p=0.18) and 24-hour opioid requirements (p=0.21).

**Conclusion:** This review further confirms the increased efficacy of perineural dexamethasone over intravenous dexamethasone in prolonging analgesia duration of peripheral nerve blocks. However, the extent of block prolongation is small and may not represent a clinically meaningful difference.

**Keywords:** Perineural dexamethasone; Perineural steroids; Adjuvants; Acute pain; Regional anaesthesia; Nerve block.
Introduction

Moderate to severe pain is common after orthopedic surgery. As such, peripheral nerve blocks are frequently employed in these surgeries to improve perioperative pain control, reduce opioid consumption as well as reduce opioid-related side effects.1

One of the major problems with single shot peripheral nerve blocks is the relatively short duration of action of the currently available local anesthetics. Consequently, patients may experience significant pain after the block has worn out.2 To mitigate this, perineural catheters have been used to extend the duration of analgesia. However, these catheters can be challenging to perform, time- and labour-intensive to manage, and carry the risk of block failure. They are also susceptible to a number of complications such as catheter dislodgement, pump-related issues3 and catheter site infection4. Furthermore, increasingly faced with the pressure of discharging patients early, the use of perineural catheters may become less relevant in the future.

Consequently, an adjuvant that can prolong a peripheral nerve block is highly desirable. Several systematic reviews and meta-analyses have established the superiority of perineural dexamethasone in extending the duration of block effects5–7. In 2017, a meta-analysis by Pehora et al6 estimated that perineural dexamethasone, when compared to placebo, prolonged the duration of peripheral nerve blocks by 6.7 hours. However, the underlying mechanism of action behind this phenomenon is unclear. Postulated reasons include systemic absorption of dexamethasone leading to an anti-inflammatory effect8, as well as local effects such as the modulation of C-fibres and local vasoconstriction9,10. Meta-analyses performed on studies performed up until 2018 have correspondingly showed that perineural dexamethasone results in a longer duration of action when compared to similar doses of intravenous dexamethasone, ranging between 0.48 and 3.96 hours11–13.
Since then, additional randomized controlled trials looking at the effects of perineural vis-à-vis intravenous dexamethasone have emerged. This review aims to provide an update on the current literature pertaining to the efficacy of perineural dexamethasone compared to intravenous dexamethasone in prolonging the analgesic duration of peripheral nerve blocks for upper and lower limb surgeries.
**Materials and Methods**

This systematic review and meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42020210257).

**Search methods**

An electronic search was conducted on the following databases from the earliest records until November 2020: Pubmed, Embase, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The following search terms were used: (“Perineural Dexamethasone” OR “Perineural Steroid” OR “Dexamethasone” OR “Steroid”) AND (“Nerve block” OR “Peripheral nerve block” OR “Regional anaesthesia” OR “Regional anesthesia”).

Two reviewers (ET and YT) independently reviewed each title and abstract from all search entries to exclude irrelevant studies. The full texts of the remaining studies were then further examined against the inclusion and exclusion criteria. Disagreements on any study eligibility were arbitrated by a third reviewer (CL).

**Selection criteria**

The inclusion criteria included all published or unpublished randomized controlled trials involving adult patients undergoing upper and lower limb surgeries which compared the duration of analgesia (as defined by time to first analgesic request or time to first pain sensation) following perineural dexamethasone compared to intravenous dexamethasone. All randomized controlled trials that fulfilled the criteria were included in the analysis without language restrictions.
Studies that involved any ongoing trials, subjects who were children or animals, surgeries that involved truncal blocks, drug preparations that used other additives in combination with dexamethasone and studies that used different dexamethasone doses for both perineural and intravenous routes were excluded.

**Quality assessment**

The validity of each included study was independently assessed by two reviewers (ET and YT) using the revised Cochrane Collaboration risk-of-bias tool15. This tool addresses seven domains of possible bias in each study: appropriate randomization process, adequate allocation concealment, blinding of the participants, personnel involved and outcome assessment process, missing outcome data, selective reporting of results, and any other types of biases15. The quality of evidence for each outcome in our review was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach16. Grading of the studies started from high quality and was downgraded based on the degree of risk of bias, indirectness of the evidence, inconsistency and imprecision of effect estimates across studies, and presence of possible publication or reporting bias. All discrepancies were resolved through a consensus process involving a third author (CL).

**Data extraction**

Two reviewers (ET and YT) independently extracted data into a standardized form on Microsoft Excel. The following data was collected from each study on the form: Author names, publication year, sample size, type of surgery, type of PNB performed, local anesthetic used (type of local anesthetics, concentration and volume), dose of dexamethasone given, time to first analgesic request,
time to first pain sensation, duration of sensory block, duration of motor block, postoperative cumulative opioid requirements, postoperative pain scores at various time points, incidence of adverse events including postoperative nausea and vomiting, hyperglycemia and prolonged paresthesia or motor block. Should additional data be required, attempts were made to contact authors of the relevant studies for provision of more information. Any disagreements were resolved by discussion with a third reviewer (CL).

**Data analysis and statistical methods**

To standardize the data for analysis, outcomes assessing duration of effect were converted to hours. All opioid use was converted to their oral morphine analgesic equivalent doses using the Faculty of Pain Medicine of the Australian and New Zealand College of Anesthetists Opioid Calculator17. Data that was measured as median and interquartile range were translated to approximated mean and standard deviation values using Hozo’s validated formula18.

Statistical analyses were performed using the Review Manager (RevMan) Software Version 5.419 and R Studio version 1.2.133520. Random-effects modelling was used for all pooled data. Continuous data were compared using mean differences and 95% confidence intervals. Dichotomous data were pooled and analyzed using the Mantel-Haenszel odds ratio with 95% confidence intervals. \( I^2 \) test was used to estimate the degree of statistical heterogeneity. Sensitivity analyses were performed to assess the robustness of the results. Subgroup analyses were performed if there was significant heterogeneity detected. A funnel plot and Egger’s test were performed to evaluate risk of publication bias. Trial sequential analysis for the primary outcome was performed with Trial Sequential Viewer version 0.9.5.10 Beta, Copenhagen Trial Unit21.
Results

Study selection and characteristics

A total of 2216 articles were identified during the initial search and 232 duplicates were removed (Figure 1). After screening through the titles and abstracts, 56 studies were identified for full-text review, of which 41 studies were excluded as they did not fulfil the inclusion criteria. Of note, two studies22,23 were excluded as they used different doses of dexamethasone for the perineural route compared to the intravenous route, and one study24 was excluded as no surgery was performed. Finally, fifteen randomized controlled trials were included in this systematic review and meta-analysis. These fifteen studies25,26,35–39,27–34 involved a total of 1467 participants, of which 738 were in the perineural dexamethasone group and 729 in the intravenous dexamethasone group. The risk of bias assessment results is presented in Figure 2. No significant publication bias was detected on the funnel plot and Egger’s test (p=0.386).

Holland et al36 performed a two-by-two factorial design study comparing both 4 mg and 8 mg of perineural dexamethasone against equivalent doses of intravenous dexamethasone. In this study, the data was analyzed separately as two studies: “Holland 2018 (Dexa 4mg)” and “Holland 2018 (Dexa 8mg)”.

Of the studies that were done for upper limb surgeries28,29,38,39,30–37, the brachial plexus block was administered with different approaches. Nine of them performed the interscalene approach28,29,32,34–37,39, two performed the supraclavicular approach30,38, one infraclavicular approach33 and one axillary approach31. In those that underwent lower limb surgeries25–27, one study performed femoral nerve blocks25, and two performed sciatic nerve blocks26,27. Regarding the dose of dexamethasone given, five studies used 1 to 4 mg29,35–37,39, ten studies used 5 to 10
mg25–28,30–34,36, and one study used a weight-calculated dose of 0.05 mg/kg 38. Five studies used Ropivacaine 0.5%28,30,32,34,39, three used Ropivacaine 0.75%26,29,35, four used Bupivacaine 0.5% alone30,36,37, one used Bupivacaine 0.5% with Lignocaine 2% and Adrenaline38, two used Bupivacaine 0.25% with Lignocaine 1% and Adrenaline31,33, and one used Bupivacaine 0.5% with adrenaline27. The volume of the local anesthetics given ranged from 5 to 30 ml. Specific details of the studies and the block characteristics are summarized in Table 1.

Risk of bias assessment

The results of the risk of bias assessment are summarized in Figure 2. As per the inclusion criteria, all the studies included in the meta-analysis are randomized controlled trials.

Primary Outcome

Duration of Analgesia

The primary outcome of duration of analgesia was reported by thirteen studies25,26,38,39,28–31,33,34,36,37, with a total of 641 patients in the perineural dexamethasone group and 634 patients in the intravenous dexamethasone group. The duration of action was assessed either as the time to first pain sensation26,30,31,33,36,37,39 or the time to first analgesic request 25,28,29,34,38,39. There was significant heterogeneity observed between the studies. Overall, patients in the perineural dexamethasone group had a significantly longer duration of analgesia compared to intravenous dexamethasone (mean difference (MD) (95% confidence interval (95% CI)) 2.72 hours (1.42 to 4.01), moderate quality evidence, I² 86%, p < 0.0001). See Figure 3. When analyzed separately, subgroup analyses still demonstrated a statistically significant prolongation of both time to first pain sensation (MD(95%CI) 2.58 hours (1.13-4.03), I² 74%, p=0.0005) and time to first analgesic request

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(MD(95%CI) 2.69 hours (0.26-5.11), I² 92%, p<0.03) in the perineural dexamethasone group. See Figures 4 and 5. Trial sequential analysis indicated that firm evidence was reached and perineural dexamethasone was superior to intravenous dexamethasone.

As seen from Figure 3, the trial conducted by Morales et al25 yielded an effect size that is quite different from the other studies. This study looked at the effect of adding dexamethasone to femoral nerve block for knee arthroplasty. The perineural dexamethasone group had a mean duration of analgesia of 1152 minutes while intravenous dexamethasone group had a mean duration of analgesia of 159 minutes. On the account that this study might artificially skew the results towards favouring perineural dexamethasone, a sensitivity analysis with the exclusion of this study was performed. However, this did not result in a significant decrease in the overall heterogeneity of the studies or outcome (MD (95% CI) 2.32 hours (1.12 to 3.52), I² 84%, p = 0.0001).

To account for the significant heterogeneity of the results, several subgroup analyses were performed. When studies that performed upper limb blocks were analyzed separately, the duration of analgesia with perineural dexamethasone remained significantly longer than with intravenous dexamethasone (MD (95% CI) 2.27 hours (1.03 to 3.51), p = 0.0003). A subgroup analysis was performed including only the interscalene block as it is the most common approach. This yielded no significant differences between both groups (MD (95% CI) 1.56 hours (-0.15 to 3.28), p = 0.07). Trial sequential analysis indicated that insufficient data is available to refute an effect with interscalene block.

To determine if there was a dose-dependent effect of dexamethasone, studies using dexamethasone doses of 4 mg or less were analyzed separately from studies using dexamethasone doses of more than
Both subgroup analyses showed significantly prolonged analgesic duration, with a mean difference of 3.01 hours in the lower dose group (p < 0.0001) and a mean difference of 2.81 hours in the higher dose group (p = 0.02).

**Secondary Outcomes**

**Postoperative Pain Scores**

One study by Kahn(37) reported pain scores in the post-anesthesia care unit and one study by Chun(32) reported 6 hours postoperative pain scores. In the study by Kahn(37), there were no significant differences in pain scores in the post-anesthesia care unit between both groups (MD (95% CI) 0.1 (-0.6 to 0.7), p = 0.999). Similarly, the study by Chun(32) did not find a significant difference in pain scores at 6 postoperatively (perineural dexamethasone: median (IQR) 1 (0 to 2), intravenous dexamethasone: median (IQR) 1 (0 to 2), p = 0.39).

A meta-analysis was performed for both 12 hours and 24 hours postoperative pain scores. Four trials(32,34,35,39) analyzed pain scores at 12 hours postoperatively, showing significantly smaller pain scores in the perineural dexamethasone group (MD (95% CI) -0.68 (-1.05 to -0.37), low quality evidence, I² 19%, p < 0.005). See Figure 6.

Ten trials25,27,29,30,32,34–36,39 compared 24 hour postoperative pain scores, revealing a statistically significant reduction in the perineural dexamethasone group compared to the intravenous dexamethasone group (MD (95% CI) -0.74 (-1.40 to -0.07), low quality evidence, I² 83%, p = 0.03). However, the mean differences at both 12 and 24 hours postoperatively are small and are not considered to be clinically relevant40. See Figure 7.
24-hour Opioid Consumption

Eight trials25–27,30,34,36,39 examined 24 hour oral morphine equivalent requirements which did not show a significant difference between both groups (MD (95% CI) -1.05 mg (-2.71 to 0.61), low quality evidence, I² 76%, p = 0.21). See Figure 8.

Duration of Sensory and Motor block

Six studies26,31,33–35,38 reported on duration of sensory block, demonstrating a prolonged the duration of sensory block with the use of perineural dexamethasone compared to intravenous dexamethasone (MD (95% CI) 3.45 hours (1.36 to 5.54), moderate quality evidence, I² 82%, p = 0.001).

Six trials30,31,33,35,38,39 analyzed duration of motor block, showing no significant difference between both groups (MD (95% CI) 2.01 hours (-0.92 to 4.94), low quality evidence, I² 93%, p = 0.18).

Postoperative Nausea and Vomiting

Six studies25,26,29,30,35,39 compared postoperative nausea and vomiting incidence rates. There was no significant difference observed between both groups, with a pooled incidence of 17.15% in the perineural dexamethasone group and 20.4% in the intravenous dexamethasone group (odds ratio (95% CI) 0.78 (0.46 to 1.34), I² 0%, p = 0.37).

Postoperative Blood Glucose Levels
Postoperative blood glucose levels were reported in three studies. Both Desmet and McHardy reported a statistically but not clinically significantly higher mean postoperative blood glucose level in the intravenous dexamethasone group compared to the perineural dexamethasone group. Desmet showed a mean increase of 0.3 mmol/L in the intravenous group and 0.2 mmol/L in the perineural group, p < 0.05. McHardy demonstrated a mean difference of 0.34 mmol/L (p = 0.02) in the intravenous group compared to the perineural group. Another study, Chun, reported no significant differences in the two groups (mean (95% CI) 0.5 mmol/L (0.2 to 0.8) vs 0.4 mmol/L (0.2 to 0.6), p = 0.55).

Neurological complications

A total of six studies reported the neurological outcomes of their participants. The studies by Desmet, Aliste, Chun and Rahangdale described no significant short term or long term neurological deficits. However, two studies showed longer-lasting neurological outcomes in their participants. Leurcharsme reported paresthesia in one patient in the perineural dexamethasone group that resolved within one week, compared to no neurological complications in the intravenous dexamethasone group. The study by Holland reported higher incidences of neurological issues in the perineural dexamethasone group. In this study, the incidence of paresthesia was 13% in the 4 mg perineural dexamethasone group and 14% in the 8 mg perineural dexamethasone group. In contrast, the incidence of paresthesia was 6% in the 4 mg intravenous dexamethasone group and 11% in the 8 mg in the intravenous dexamethasone group. These differences are not statistically significant, and an in-depth review of the cases led to the authors concluding that the occurrence of paresthesia was unlikely to be related to the use of dexamethasone.
Satisfaction scores

Satisfaction scores were recorded in seven studies\textsuperscript{25,27–30,34,37}. Of these, five studies\textsuperscript{27,28,30,34,37} reported similar mean satisfaction scores between both groups, one\textsuperscript{25} reported improved patient satisfaction scores with perineural dexamethasone and another\textsuperscript{29} showed better satisfaction scores with intravenous dexamethasone.
Discussion

Compared to placebo, perineural dexamethasone, when added to a local anesthetic, was estimated to increase the duration of analgesia by 6.7 hours when compared to a placebo. However, it is unclear if this is due to systemic dexamethasone absorption. This study involving 15 randomized controlled trials and 1467 patients suggests that there might be a local effect considering that the duration of analgesia is longer in the perineural dexamethasone group when compared to IV dexamethasone. The results of this study is similar to a previous meta-analysis performed in 2017. However, in contrast to this study, the impact of perineural dexamethasone on the duration of analgesia is more modest than previously estimated.

In this study, perineural dexamethasone, when compared with the intravenous route, only increased the duration of analgesia by 2.72 hours. The results from Morales et al appear to be an outlier. Although effort was made to determine why their results differ greatly from the rest of the studies, no reasonable explanation was found. Nevertheless, the exclusion of this study resulted in an even more modest difference of 2.32 hours in the duration of analgesia. We believe that 2.32 hours is likely to be closer to the true effect size.

Although a subgroup analysis of patients undergoing interscalene block demonstrated no statistically significant differences between the perineural and IV dexamethasone groups, there is a trend towards a longer duration of analgesia for the perineural group. A trial sequential analysis confirms that this may potentially be due to an inadequate sample size. Importantly, there were no clinically relevant differences in 24-hour postoperative pain scores, 24-hour opioid consumption or satisfaction scores.
A potential concern regarding the use of perineural dexamethasone is that of neurotoxicity. There are animal studies that have raised concerns over the potential neurotoxic effects of dexamethasone. Despite this, we caution against labelling dexamethasone as neurotoxic based on animal cell-culture studies with methodological flaws. Perineural dexamethasone has been used in the past for many acute and chronic pain indications with no suggestion of increased neurotoxicity. Consistent with other meta-analyses looking at perineural steroids, our study did not highlight any concerns linking the use of perineural steroids with poor neurological outcomes.

There are several limitations to this study. The most significant of which is the heterogeneity of the studies. Although the primary outcome measure included in the studies was the duration of analgesia, there was a lack of standardization as to how this was defined or assessed. For example, the duration of analgesia was defined as the time to first pain sensation in some studies and the time to first analgesic request in others. Furthermore, the methods of collecting the data were different in these studies – for example, some utilized retrospective telephone interviews while others utilized patient-filled diaries. Heterogeneity may have also resulted from differences in the exact nature of the surgery, as well as differences in surgical techniques.

Another limitation of this study is that there is clarity on how researchers handled the time to first analgesia when patients did not require rescue analgesia. Apart from the study by Desmet et al which reported no significant differences in the number of patients who did not require rescue analgesia at 48 hours post-surgery (4 out of 49 patients in the perineural dexamethasone group
compared to 5 out of 49 in the intravenous dexamethasone group), the rest of the studies did not report the number of patients who did not require rescue analgesia and how this data was handled.

Taken together, this systematic review and meta-analysis makes a weak recommendation that perineural dexamethasone should not be routinely administered as an adjunct to local anesthetic. In its place, the use of intravenous dexamethasone may be considered. It may be able to extend the duration of analgesia and can also be used to prevent postoperative nausea and vomiting. The basis of this recommendation is that an increase in the duration of analgesia of 2.32 hours is unlikely to be clinically relevant. Furthermore, the use of perineural dexamethasone did not result in the improvement of other pain-related parameters such as pain scores or opioid consumption. The lack of standardization with regards to how the primary outcome was defined and assessed in many of the studies also affects the reliability of the pooled result. Nevertheless, this review does not recommend further studies on this topic, given that they are very unlikely to drastically change the results of this study and lead to a change in our recommendation.

**Conclusion**

This systematic review and meta-analysis shows that perineural dexamethasone, when used as an adjunct to local anesthetic, results in a longer duration of analgesia when compared to intravenous dexamethasone. However, the effect size is small and may not be clinically meaningful. It is also not associated with a clinically significant reduction in 24-hour pain scores or opioid consumption. We make a weak recommendation that perineural dexamethasone should not be routinely administered to patients to prolong the duration of analgesia following a peripheral nerve block. Intravenous dexamethasone may be considered in its stead.
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<th>No. of participants (Intravenous)</th>
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Figure 1. PRISMA flow diagram.
Figure 2. Risk of bias table of included studies.
Figure 3. Forest plot: Perineural vs intravenous dexamethasone, Duration of analgesia in hours.

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<td>15 ± 2.6</td>
<td>20 ± 1.6</td>
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<td>2.50 (0.79, 4.21)</td>
</tr>
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<td>Holland 2018 (5mg)</td>
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</tr>
<tr>
<td>Kahn 2018</td>
<td>21.5 ± 7.14</td>
<td>62 ± 4.6</td>
<td>62 ± 4.6</td>
<td>4.55 (0.37, 8.73)</td>
</tr>
<tr>
<td>Leibovitch 2016</td>
<td>12 ± 2.12</td>
<td>12 ± 0.72</td>
<td>12 ± 0.72</td>
<td>3.43 (2.58, 4.33)</td>
</tr>
<tr>
<td>Malhotra 2020</td>
<td>21.1 ± 9.5</td>
<td>61 ± 16.6</td>
<td>61 ± 16.6</td>
<td>2.72 (0.54, 4.92)</td>
</tr>
<tr>
<td>Moraes 2016</td>
<td>19.2 ± 16.65</td>
<td>77 ± 2.85</td>
<td>77 ± 2.85</td>
<td>21.30 (0.22, 22.39)</td>
</tr>
<tr>
<td>Rosenfeld 2016</td>
<td>8.4 ± 0.5</td>
<td>42 ± 9.2</td>
<td>42 ± 9.2</td>
<td>7.68 (0.80, 14.67)</td>
</tr>
</tbody>
</table>

Total (95% CI): 641

Heterogeneity: τ² = 4.12, Chi² = 85.20, df = 12 (P = 0.0001); I² = 66%
Test for overall effect: Z = 4.12 (P = 0.0001)

Figure 4. Forest plot: Subgroup analysis, Perineural vs intravenous dexamethasone, Time to first pain sensation in hours.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Perineural dexamethasone</th>
<th>Intravenous dexamethasone</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abidiyah 2015</td>
<td>25 ± 10.89</td>
<td>25 ± 7.65</td>
<td>25 ± 5.55</td>
<td>0.00 (0.49, 4.96)</td>
</tr>
<tr>
<td>Aistle 2016</td>
<td>21.1 ± 4.6</td>
<td>75 ± 4.6</td>
<td>75 ± 4.6</td>
<td>4.09 (2.53, 5.47)</td>
</tr>
<tr>
<td>Dawson 2015</td>
<td>24.1 ± 9.75</td>
<td>39 ± 5.6</td>
<td>39 ± 5.6</td>
<td>3.30 (0.62, 5.98)</td>
</tr>
<tr>
<td>Desmoul 2013</td>
<td>23.8 ± 4.6</td>
<td>42 ± 4.6</td>
<td>42 ± 4.6</td>
<td>-0.61 (1.88, 0.06)</td>
</tr>
<tr>
<td>Goldbrot 2013</td>
<td>15 ± 2.6</td>
<td>20 ± 1.6</td>
<td>20 ± 1.6</td>
<td>2.50 (0.79, 4.21)</td>
</tr>
<tr>
<td>Holland 2018 (5mg)</td>
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</tr>
</tbody>
</table>

Total (95% CI): 642

Heterogeneity: τ² = 2.89, Chi² = 26.07, df = 7 (P = 0.0004); I² = 74%
Test for overall effect: Z = 3.49 (P = 0.0005)

Figure 5. Forest plot: Subgroup analysis, Perineural vs intravenous dexamethasone, Time to first analgesic request in hours.
Figure 6. Forest plot: Perineural vs intravenous dexamethasone, 12-hour postoperative pain scores.

Figure 7. Forest plot: Perineural vs intravenous dexamethasone, 24-hour postoperative pain scores.

Figure 8. Forest plot: Perineural vs intravenous dexamethasone, 24-hour oral morphine equivalent consumption in mg.