Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis

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Editor’s key points

- Dexmedetomidine has been used to prolong the duration of local anaesthetics (LAs).
- In this meta-analysis, nine randomized controlled trials on perineural dexmedetomidine in neuraxial and peripheral nerve blocks were selected.
- Dexmedetomidine prolonged block duration.
- More studies are required to establish the safety of using dexmedetomidine as a perineural adjunct to LAs.

Summary. Nerve blocks improve postoperative analgesia, but their benefits may be short-lived. This quantitative review examines whether perineural dexmedetomidine as a local anaesthetic (LA) adjuvant for neuraxial and peripheral nerve blocks can prolong the duration of analgesia compared with LA alone. All randomized controlled trials (RCTs) comparing the effect of dexmedetomidine as an LA adjuvant to LA alone on neuraxial and peripheral nerve blocks were reviewed. Sensory block duration, motor block duration, block onset times, analgesic consumption, time to first analgesic request, and side-effects were analysed. Results were combined using random-effects modelling. A total of 516 patients were analysed from nine RCTs. Five trials investigated dexmedetomidine as part of spinal anaesthesia and four as part of a brachial plexus (BP) block. Sensory block duration was prolonged by 150 min [95% confidence interval (CI): 96, 205, \( P < 0.00001 \)] with intrathecal dexmedetomidine. Perineural dexmedetomidine used in BP block may prolong the mean duration of sensory block by 284 min (95% CI: 1, 566, \( P = 0.05 \)), but this difference did not reach statistical significance. Motor block duration and time to first analgesic request were prolonged for both intrathecal and BP block. Dexmedetomidine produced reversible bradycardia in 7% of BP block patients, but no effect on the incidence of hypotension. No patients experienced respiratory depression. Dexmedetomidine is a potential LA adjuvant that can exhibit a facilitatory effect when administered intrathecally as part of spinal anaesthesia or peripherally as part of a BP block. However, there are presently insufficient safety data to support perineural dexmedetomidine use in the clinical setting.

Keywords: acute pain; regional techniques; anaesthetic techniques; regional; brachial plexus; analgesic techniques; subarachnoid; analgesics; postoperative; sympathetic nervous system; dexmedetomidine

Regional anaesthesia techniques provide important advantages compared with general anaesthesia and systemic analgesia, including excellent pain control, reduced side-effects, and shortened stay in the post-anaesthesia care unit. However, these early advantages can be short-lived and limited by the relatively brief duration of action of currently available local anaesthetics (LAs), potentially resulting in block resolution before the period of worst postoperative pain. Increasing the volume (dose) of LAs may prolong the duration of analgesia, but may also increase the risk of LA systemic toxicity. Although continuous catheter-based nerve blocks can extend postoperative analgesia, their placement requires additional time, cost, and skill. While a novel sustained-release encapsulated (liposomal) preparation of bupivacaine is presently undergoing investigation in phase III trials, a variety of perineural adjuvants, including buprenorphine, clonidine, dexamethasone, magnesium, and midazolam, have been used to prolong the duration of analgesia of nerve blocks with varying degrees of success. Dexmedetomidine, an \( \alpha_2 \) adrenoreceptor agonist, was first proposed as an adjuvant capable of prolonging duration of sensory and motor block produced by nerve blocks by Memiş and colleagues. However, the series of clinical trials that followed produced contradictory results. Some trials have shown that perineural dexmedetomidine reduces the onset time and prolongs the duration of sensory and motor block. Conversely, other trials have demonstrated either a delay in
sensory and motor block onset time\(^{27}\) or no effect on sensory and motor block duration\(^{24}\) with the use of perineural dexmedetomidine. The primary objective of this quantitative review is to determine whether the administration of perineural dexmedetomidine as an LA adjuvant for neuraxial and peripheral nerve blocks can prolong the duration of analgesia compared with LA alone.

**Methods**

The PRISMA\(^{28}\) recommendations were followed in the preparation of this manuscript.

**Eligibility criteria**

We sought to identify all randomized controlled trials (RCTs) that examined the effects of adding perineural dexmedetomidine to LA (dexmedetomidine group) compared with LA alone (control group) on neuraxial or peripheral nerve block characteristics, postoperative analgesia, and dexmedetomidine-related side-effects in surgical patients undergoing regional anaesthesia. Blocks performed for either anaesthesia or postoperative analgesia were included. RCTs were excluded if dexmedetomidine was used as a stand-alone perineural agent without LA,\(^{29}\) or administered via a non-perineural route,\(^{23}\)\(^{24}\)\(^{30–38}\) if continuous nerve blocks were performed,\(^{39}\)\(^{40}\) and if blocks were performed in paediatric patients where block characteristics could not be assessed.\(^{41–44}\) Only trials that explicitly mentioned obtaining approval from the local ethics committee or institutional review board were considered. The use of dexmedetomidine as part of i.v. regional anaesthesia (Bier block) was not considered for the purposes of this review.

**Literature search**

We retrieved RCTs from the US National Library of Medicine database, MEDLINE; the Excerpta Medica database, Embase; Cochrane Database of Systematic Reviews; and Cochrane Central Register of Controlled Trials databases (January 1985–August 2012). The search terms dexmedetomidine and medetomidine were used in combination with the search terms perineural, adjuvant, adjunct, and admixture. Searches were combined using the Boolean operator AND with medical subject headings analgesia/pain relief/pain control/pain prevention/and pain management and the medical subject headings regional anaesthesia/nerve block/block/neuraxial block/central block/peripheral block. The search was limited to trials published in the English language. We also reviewed the reference lists of selected trials for additional RCTs. Trials that are unpublished or in progress were not included.

**Data collection and presentation**

The two authors (F.W.A. and R.B.) independently evaluated the methodological quality of the included trials using the Jadad score\(^{45}\) and a final score was designated by consensus for each RCT. We selected sensory block duration as the primary endpoint, while motor block duration, sensory and motor block onset time, analgesic consumption, time to first analgesic request, pain scores,\(^{46}\) and dexmedetomidine-related adverse effects (hypotension, bradycardia, respiratory depression, and postoperative sedation)\(^{47}\)\(^{48}\) were defined as secondary endpoints. The authors each used a standardized

![Table 1: Trial characteristics. Dex, dexmedetomidine; n, number of trials.](https://academic.oup.com/bja/article-abstract/110/6/915/246059)
data sheet to extract and record trial results, which were compared and any differences were resolved by reexamination of the source trials.

Meta-analysis

Data entry was performed by one author (F.W.A.) and rechecked by another (R.B.). Meta-analytic techniques (Revman 5.1, Cochrane Library, Oxford, UK) were used to pool data whenever possible. Data from trials with more than two intervention groups receiving different doses of dexmedetomidine via the same route were combined into a single group as recommended by the Cochrane Handbook. Dichotomous and continuous outcomes were analysed using random-effects modelling. The odds ratio (OR) and 95% confidence intervals (CIs) are reported for dichotomous outcomes, while the standardized mean difference and 95% CI are reported for continuous outcomes. Differences were considered statistically significant when the 95% CI did not include 1 for OR and 0 for the standardized mean difference. Heterogeneity of the pooled results was assessed using the $I^2$ statistic.

Results

We retrieved 37 articles, of which nine met our inclusion criteria. Tables 1 and 2 present the trial characteristics and outcomes assessed for each trial, respectively. The methodological quality of all nine trials was good; six trials achieved a Jadad score of 5 out of 5, while the remaining three achieved a score of 4 out of 5. The countries of origin for all eight trials were Middle Eastern; all protocols were approved by the local ethics committee or institutional review board of their respective institutions. Figure 1 summarizes the search results, including the RCTs retrieved, excluded, and presently reviewed. Twenty-eight trials were excluded because of the interventions examined (n=14), populations studied (n=7), active comparators (n=5), study design (n=1), and language of publication (n=1) (Appendix). The trials reviewed included a total of 516 patients for analysis; 274 patients in the dexmedetomidine group and 242 in the control group. Five trials examined the effect of neuraxial dexmedetomidine administered intrathecally as part of spinal anaesthesia and control groups (Table 3).

Dexmedetomidine-related adverse effects

Because of the diversity in the definitions of dexmedetomidine-related adverse effects in the reviewed trials, the results of these outcomes are reported as ‘standardized units’. The incidence of hypotension was similar between the dexmedetomidine and control groups (Table 3). The incidence of bradycardia was higher in patients who received dexmedetomidine as part of a BP block (7% vs 0%, $P<0.03$), but there was no difference with intrathecal administration. The observed bradycardia was transient, successfully reversed by i.v. atropine administration, and did not recur later during the postoperative period.

Respiratory depression was explicitly assessed in four trials. None of the patients in these trials experienced respiratory depression.

The incidence of postoperative sedation was evaluated in four trials that examined the intrathecal administration of dexmedetomidine; a six-point measurement scale was used in two of the trials and a four-point scale was used in the other two trials. The heterogeneity of scales used and the inconsistency in reporting rates of occurrence precluded any quantitative analyses. Qualitatively, one trial reported higher sedation levels in a group of patients receiving high-dose intrathecal dexmedetomidine (15 µg) without specifying the actual rate of occurrence, while
Table 2  Trial outcomes. ACL, anterior cruciate ligament repair; AXB, axillary nerve block; Dex, dexmedetomidine; ICB, infraclavicular block; Intraop, intraoperative; N/D, not defined; NS, normal saline; Postop, postoperative; SCB, supraclavicular block; TURBT, transurethral resection of bladder tumour; TURP, transurethral resection of prostate tumour; TVT, tension-free vaginal tape

<table>
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<tr>
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<th>Jadad score</th>
<th>Surgery</th>
<th>Block/ use</th>
<th>n</th>
<th>Groups (n)</th>
<th>Local anaesthetic</th>
<th>Adjuvant</th>
<th>Primary outcome</th>
<th>Block characteristics</th>
<th>Analgesic outcomes</th>
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<td>Postop pain</td>
<td>Time to</td>
<td>Analgesic</td>
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<td>request</td>
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<td>consumption</td>
</tr>
</tbody>
</table>

### Neuroaxial Intrathecal

Kanazi and colleagues\textsuperscript{26}  
- Study: 5  
- Surgery: TURBT, TURP  
- Block/ use: Spinal/ surgical  
- n: 60  
- Groups (n): (1) Dex + bupivacaine (16), (2) Clonidine + bupivacaine (16), (3) Bupivacaine (19)  
- Sensory block duration: 12 mg of 0.75% hyperbaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 3 µg (2) Clonidine (3) None  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Al-Mustafa and colleagues\textsuperscript{23}  
- Study: 5  
- Surgery: TURBT, TURP, TVT  
- Block/ use: Spinal/ surgical  
- n: 66  
- Groups (n): (1) Dex 5 µg + bupivacaine (21), (2) Dex 10 µg + bupivacaine (21), (3) NS + bupivacaine (22)  
- Sensory block duration: 12.5 mg of 0.5% isobaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 5 µg (2) Dex 10 µg (3) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Eid and colleagues\textsuperscript{22}  
- Study: 5  
- Surgery: ACL  
- Block/ use: Spinal/ surgical  
- n: 48  
- Groups (n): (1) Dex 10 µg + bupivacaine (15), (2) Dex 15 µg + bupivacaine (16), (3) NS + bupivacaine (22)  
- Sensory block duration: 3 ml of 0.5% hyperbaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 10 µg (2) Dex 15 µg (3) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Gupta and colleagues\textsuperscript{23}  
- Study: 4  
- Surgery: Lower extremity  
- Block/ use: Spinal/ surgical  
- n: 60  
- Groups (n): (1) Dex + ropivacaine (30), (2) NS + ropivacaine (30)  
- Sensory block duration: 3 ml of 0.75% ropivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 5 µg (2) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration

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Neuraxial Intrathecal

Kanazi and colleagues\textsuperscript{26}  
- Study: 5  
- Surgery: TURBT, TURP  
- Block/ use: Spinal/ surgical  
- n: 60  
- Groups (n): (1) Dex + bupivacaine (16), (2) Clonidine + bupivacaine (16), (3) Bupivacaine (19)  
- Sensory block duration: 12 mg of 0.75% hyperbaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 3 µg (2) Clonidine (3) None  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Al-Mustafa and colleagues\textsuperscript{23}  
- Study: 5  
- Surgery: TURBT, TURP, TVT  
- Block/ use: Spinal/ surgical  
- n: 66  
- Groups (n): (1) Dex 5 µg + bupivacaine (21), (2) Dex 10 µg + bupivacaine (21), (3) NS + bupivacaine (22)  
- Sensory block duration: 12.5 mg of 0.5% isobaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 5 µg (2) Dex 10 µg (3) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Eid and colleagues\textsuperscript{22}  
- Study: 5  
- Surgery: ACL  
- Block/ use: Spinal/ surgical  
- n: 48  
- Groups (n): (1) Dex 10 µg + bupivacaine (15), (2) Dex 15 µg + bupivacaine (16), (3) NS + bupivacaine (22)  
- Sensory block duration: 3 ml of 0.5% hyperbaric bupivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 10 µg (2) Dex 15 µg (3) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration  

Gupta and colleagues\textsuperscript{23}  
- Study: 4  
- Surgery: Lower extremity  
- Block/ use: Spinal/ surgical  
- n: 60  
- Groups (n): (1) Dex + ropivacaine (30), (2) NS + ropivacaine (30)  
- Sensory block duration: 3 ml of 0.75% ropivacaine  
- Motor block duration: Sensory block duration  
- Sensory block onset: (1) Dex 5 µg (2) NS  
- Motor block onset: Motor block duration  
- Postop pain: Sensory block duration  
- Time to first analgesic request: Sensory block duration  
- Analgesic consumption: Sensory block duration  
- Hypotension: Sensory block duration  
- Bradycardia: Sensory block duration  
- Postop sedation: Sensory block duration  
- Respiratory depression: Sensory block duration
<table>
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<tr>
<th>Study</th>
<th>Region</th>
<th>Anesthesia</th>
<th>Volume</th>
<th>Solution</th>
<th>Motor block duration</th>
<th>Sensory block duration</th>
<th>Time to first analgesic request</th>
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<tbody>
<tr>
<td>Shukla and colleagues(^5^)</td>
<td>Abdominal, lower extremity</td>
<td>Spinal/surgical</td>
<td>90</td>
<td>(1) Dex + bupivacaine (30) (2) Magnesium + bupivacaine (30) (3) NS + bupivacaine (30)</td>
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<td>Peripheral Brachial plexus</td>
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<tr>
<td>Esmaoglu and colleagues(^2^5^)</td>
<td>Forearm, hand</td>
<td>AXB/ surgical</td>
<td>60</td>
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<td>40 ml of 0.5% levobupivacaine</td>
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<tr>
<td>Gandhi and colleagues(^2^7^)</td>
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<td>SCB/ surgical</td>
<td>75</td>
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<td>39 ml 0.5% levobupivacaine</td>
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<tr>
<td>Ammar and Mahmoud(^1^6^)</td>
<td>Forearm, hand</td>
<td>ICB/ surgical</td>
<td>60</td>
<td>(1) Dex + bupivacaine (30) (2) NS + bupivacaine (30)</td>
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<td>30 ml 0.33% bupivacaine</td>
<td>(1) Dex 0.75 µg kg(^{-1}) in 1 ml (2) NS 1 ml</td>
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three trials reported no difference in sedation between the patients who received intrathecal dexmedetomidine as an adjunct to spinal anaesthesia and those who did not.

We could not quantitatively analyse our remaining secondary endpoints (pain scores, analgesic consumption) due to inconsistent reporting and heterogeneous assessment protocols within and between the source trials. Qualitatively, these results favour the dexmedetomidine group and are presented in Table 4.

**Discussion**

Our review of the literature suggests that the use of dexmedetomidine as a perineural adjuvant can prolong the durations of both sensory and motor block produced by long-acting LAs in spinal blocks. For BP blocks, perineural dexmedetomidine can prolong the duration of motor block; however, the trend towards prolonged sensory block did not reach statistical significance. Dexmedetomidine also hastens the onset of sensory block in spinal anaesthesia and prolongs the time to first analgesic request in the setting of both spinal anaesthesia and BP block. The advantages of dexmedetomidine may be offset by an increased likelihood of transient, reversible bradycardia, and the prolongation of motor block when it is undesirable.

In the context of perineural adjuvants, the efficacy of dexmedetomidine appears to be comparable with buprenorphine and dexamethasone when administered peripherally, and exceeds that of clonidine, magnesium, and midazolam for both intrathecal and peripheral applications. However, unlike clonidine, another α2 adrenoreceptor agonist shown capable of prolonging the

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**Fig 2** Forest plot showing sensory block duration. The sample size, mean, standard deviations, and the pooled estimates of the mean difference are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates.
### Table 3: Quantitative results. N/A, not applicable

<table>
<thead>
<tr>
<th>Block type/outcome</th>
<th>Studies included</th>
<th>Dex mean or n/N</th>
<th>Control mean or n/N</th>
<th>Odds ratio or weighed mean (95% confidence interval)</th>
<th>P-value for statistical significance</th>
<th>P-value for heterogeneity</th>
<th>I² test for heterogeneity</th>
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<tr>
<td>Sensory block onset (min)</td>
<td>26 51–54</td>
<td>5.53</td>
<td>6.82</td>
<td>−1.54 (−2.96, −0.11)</td>
<td>0.04</td>
<td>0.000001</td>
<td>90%</td>
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<td>Motor block onset (min)</td>
<td>26 51 54</td>
<td>9.33</td>
<td>13.15</td>
<td>−4.52 (−9.17, 0.13)</td>
<td>0.06</td>
<td>0.000001</td>
<td>95%</td>
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<td>Motor block duration (min)</td>
<td>26 51 52 54</td>
<td>294.46</td>
<td>156.45</td>
<td>132.22 (87.69, 176.74)</td>
<td>0.00001</td>
<td>0.000001</td>
<td>93%</td>
</tr>
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<td>Time to first analgesic request (min)</td>
<td>52 53</td>
<td>525.68</td>
<td>231.37</td>
<td>292.87 (174.32, 411.41)</td>
<td>0.00001</td>
<td>0.0003</td>
<td>92%</td>
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<td>Incidence of hypotension (n/N)</td>
<td>26 51–54</td>
<td>9/156</td>
<td>8/118</td>
<td>0.73 (0.20, 2.71)</td>
<td>0.64</td>
<td>0.26</td>
<td>25%</td>
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<td>Incidence of bradycardia (n/N)</td>
<td>26 51–54</td>
<td>3/156</td>
<td>2/118</td>
<td>0.97 (0.04, 21.49)</td>
<td>0.98</td>
<td>0.11</td>
<td>60%</td>
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<td>Brachial plexus</td>
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</tr>
<tr>
<td>Sensory block onset (min)</td>
<td>25 27 55 56</td>
<td>13.19</td>
<td>14.89</td>
<td>−1.9 (−5.08, 1.28)</td>
<td>0.24</td>
<td>0.000001</td>
<td>97%</td>
</tr>
<tr>
<td>Motor block onset (min)</td>
<td>25 27 55 56</td>
<td>12.58</td>
<td>14.15</td>
<td>−1.67 (−4.93, 1.58)</td>
<td>0.31</td>
<td>0.000001</td>
<td>97%</td>
</tr>
<tr>
<td>Motor block duration (min)</td>
<td>25 27 55 56</td>
<td>600.72</td>
<td>321.20</td>
<td>267.76 (154.7, 520.06)</td>
<td>0.04</td>
<td>0.000001</td>
<td>100%</td>
</tr>
<tr>
<td>Time to first analgesic request (min)</td>
<td>25 27 55 56</td>
<td>850.97</td>
<td>500.21</td>
<td>344.95 (102.68, 587.23)</td>
<td>0.005</td>
<td>0.000001</td>
<td>99%</td>
</tr>
<tr>
<td>Incidence of hypotension (n/N)</td>
<td>25 27 55 56</td>
<td>2/127</td>
<td>0/127</td>
<td>5.30 (0.25, 114.47)</td>
<td>0.29</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Incidence of bradycardia (n/N)</td>
<td>25 27 55 56</td>
<td>9/127</td>
<td>0/127</td>
<td>10.52 (1.27, 87.08)</td>
<td>0.03</td>
<td>0.54</td>
<td>0%</td>
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</tbody>
</table>

### Table 4: Qualitative results. +, favours Dex; ←→, no difference; Dex, dexmedetomidine; VAS, visual analogue scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Postoperative pain</th>
<th>Analgesic consumption</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuraxial</strong></td>
<td></td>
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<tr>
<td>Intrathecal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanazi and colleagues¹⁶</td>
<td>←→</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Mustafa and colleagues¹¹</td>
<td>←→</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eid and colleagues¹²</td>
<td>+</td>
<td>+</td>
<td>Dex reduces rest VAS pain scores at 8, 12, 24 h (P&lt;0.05). Dex reduces dynamic VAS pain scores at 4, 8, 12, 24 h (P&lt;0.05). Dex reduces i.v. diclofenac consumption by 45% at 24 h; Dex 77.4 mg, control 140.6 mg (P&lt;0.05)</td>
</tr>
<tr>
<td>Gupta and colleagues¹³</td>
<td>+</td>
<td>+</td>
<td>Dex reduces maximum VAS pain scores during first 24 h by 35%; Dex 4.4, control 6.8 (P&lt;0.001). Dex reduces i.m. diclofenac consumption by 64% at 24 h; Dex 72.8 mg, control 202.5 mg (P&lt;0.001)</td>
</tr>
<tr>
<td><strong>Peripheral</strong></td>
<td></td>
<td></td>
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<tr>
<td>Brachial plexus</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ammar and Mahmoud¹⁶</td>
<td>+</td>
<td>+</td>
<td>Dex reduces rest VAS pain scores at 1, 2, 12, 24, 36, 48 h (P&lt;0.05). Dex reduces i.v. morphine consumption by 64% at 48 h; Dex 4.9 mg, control 13.6 mg (P=0.005)</td>
</tr>
</tbody>
</table>
duration of shorter acting\textsuperscript{62–64} but not long-acting\textsuperscript{65 66} LAs, this review demonstrated that dexmedetomidine clearly prolonged the block duration of long-acting LAs. Also, while clonidine produces preferential extension of sensory block,\textsuperscript{67} our review suggests that dexmedetomidine prolongs both sensory and motor block, a difference that may be disadvantageous by delaying rehabilitation and/or discharge, or worse, precipitating falls.

The results of our review are subject to several limitations. The trials included herein were small and characterized by high levels of heterogeneity, factors that limit the clinical combinability of the source trials, and the generalizability of our results. Similarly, the present safety data, however limited, may not apply to other block types as local neurotoxicity and systemic uptake are both influenced by site-specific perfusion levels.\textsuperscript{15} The generalizability of this review is further limited by publication bias as all source studies originated from Middle Eastern countries, which may or may not reflect less stringent Institutional Review Board and/or editorial board policies.\textsuperscript{68} The lack of United States (US) Food and Drug Administration (FDA) approval for the perineural application of dexmedetomidine\textsuperscript{69} almost certainly explains the scant appearance of trials on this topic in US-based indexed journals.\textsuperscript{70–73} The lack of available data from trials already in progress, including at least one phase III trial,\textsuperscript{74} may further contribute to publication bias. Finally, considerable differences existed in the doses of perineural dexmedetomidine; doses varied between 3,\textsuperscript{26} 5,\textsuperscript{51 53} 10,\textsuperscript{51 52 54} or 15 \(\mu\)g\textsuperscript{52} for the intrathecal route, and 30,\textsuperscript{27} 100 \(\mu\)g,\textsuperscript{25 56} or 1 \(\mu\)g kg\textsuperscript{−1}\textsuperscript{55} for the peripheral route. While these dosing inconsistencies most likely reflect the absence of human dose–response studies and/or extrapolation from animal studies,\textsuperscript{75–82} the variable doses of dexmedetomidine, the different types of LAs used, and the variation between trials in selecting endpoints that defined hypotension,\textsuperscript{51 53} bradycardia,\textsuperscript{27 55} and onsets of sensory\textsuperscript{25 27} and motor\textsuperscript{25 27} block may have contributed to the statistically significant heterogeneity of the pooled results. Despite the variability in dexmedetomidine doses used, it is nonetheless noteworthy that significantly prolonged durations of sensory and motor blocks and also time to first analgesic request were achieved even with the lowest doses of dexmedetomidine, namely, 3 \(\mu\)g for intrathecal and 30 \(\mu\)g of peripheral administration.

While we could not demonstrate any association between perineural dexmedetomidine and the frequency of hypotension or respiratory depression, the trials examined herein were not specifically designed to assess safety. While dexmedetomidine may appear safe in the short term,\textsuperscript{83 84} systematic preclinical and subsequent human neurotoxicity data, including the investigation of potential delayed adverse neurological effects and effects related to prolonged perineural exposure, are lacking.\textsuperscript{85} Indeed, relevant neurotoxicity data seem contradictory; while a number of reports suggest that dexmedetomidine is protective against hypoxic–ischemic neuronal injury in rat and human neonatal asphyxia models,\textsuperscript{86–92} dexmedetomidine has also been shown to cause moderate to severe demyelination in white matter when doses as high as 6.1 \(\mu\)g kg\textsuperscript{−1} were administered via an epidural route in rabbits.\textsuperscript{93} While the doses used in the trials reviewed herein did not exceed 0.2 \(\mu\)g kg\textsuperscript{−1} for intrathecal and 1 \(\mu\)g kg\textsuperscript{−1} for peripheral administration, the hazards of drawing conclusions of safety based on isolated small animal data are self-evident.\textsuperscript{15} Finally, none of the reviewed trials justified the safety and compatibility of their dexmedetomidine–LA mixture for peripheral and neuraxial use.

In summary, dexmedetomidine is a potential LA adjuvant that can exhibit a facilitatory effect when administered intrathecally as part of spinal anaesthesia or peripherally as part of a BP block. However, there are presently insufficient safety data to support the use of perineural dexmedetomidine in the clinical setting.

**Declaration of interest**

None declared.

**Funding**

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**References**


Appendix: Excluded trials

<table>
<thead>
<tr>
<th>First author</th>
<th>Reference</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abosedira</td>
<td>J Med Sci 2008; 8: 660–4</td>
<td>Comparator</td>
</tr>
<tr>
<td>Al-Metwalli</td>
<td>Br J Anaesth 2008; 101: 395–9</td>
<td>Intervention</td>
</tr>
<tr>
<td>Bajwa</td>
<td>Indian J Anaesth 2011; 55: 116–21</td>
<td>Comparator</td>
</tr>
<tr>
<td>Bajwa</td>
<td>Saudi J Anaesth 2011; 5: 365–70</td>
<td>Comparator</td>
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<tr>
<td>El-Hakim</td>
<td>Acta Anaesthesiol Scand 2010; 54: 703–9</td>
<td>Intervention</td>
</tr>
<tr>
<td>Jain</td>
<td>South Afr J Anaesth 2012; 18: 105–9</td>
<td>Intervention</td>
</tr>
<tr>
<td>Kol</td>
<td>Clin Durg Investig 2009; 29: 121–9</td>
<td>Intervention</td>
</tr>
<tr>
<td>Mizrak</td>
<td>J Surg Res 2010; 164: 242–7</td>
<td>Intervention</td>
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<tr>
<td>Mirzak</td>
<td>Middle East J Anesthesiol 2011; 21: 53–60</td>
<td>Intervention</td>
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<td>Nasr</td>
<td>Eg J Anaesth 2012; 28: 37–42</td>
<td>Intervention</td>
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<tr>
<td>Paswan</td>
<td>Indian J Res 2011; 5: 6–10</td>
<td>Intervention</td>
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<tr>
<td>Sinha</td>
<td>Anaesth Pain Intensive Care 2012; 16: 38–42</td>
<td>Intervention</td>
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