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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.[1–3] However, these early advantages can be short-lived[3] and limited by the relatively brief duration of action[4 5] of currently available local anaesthetics (LAs),[6] potentially resulting in block resolution before the period of worst postoperative pain.[7 8] Increasing the volume (dose) of LAs may prolong the duration of analgesia,[9] but may also increase the risk of LA systemic toxicity.[10] Although continuous catheter-based nerve blocks can extend postoperative analgesia,[11 12] their placement requires additional time, cost, and skill.[13] While a novel sustained-release encapsulated (liposomal) preparation of bupivacaine is presently undergoing investigation in phase III trials,[14] a variety of perineural adjuvants,[15] including buprenorphine,[16] clonidine,[17] dexamethasone,[18] magnesium,[19] and midazolam,[20 21] have been used to prolong the duration of analgesia of nerve blocks with varying degrees of success. Dexmedetomidine, an α_2 adrenoreceptor agonist,[22] was first proposed as an adjuvant capable of prolonging duration of sensory and motor block produced by nerve blocks by Memiş and colleagues.[23] However, the series of clinical trials that followed produced contradictory results.[24–27] Some trials have shown that perineural dexmedetomidine reduces the onset time and prolongs the duration of sensory and motor block.[23 25 26] 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.

Table 1 Trial characteristics. Dex, dexmedetomidine; *n*, number of trials

Author/year	Quantity (*n*)	Percentage
Source database		
Medline	4	44.4
Google scholar	2	22.2
Hand search	2	22.2
Grey literature	1	11.1
Trial source journal		
Listed in Index Medicus	4	44.4
Not listed in Index Medicus	5	55.5
Trial source country		
Egypt	2	22.2
India	3	33.3
Jordan	1	11.1
Lebanon	1	11.1
Turkey	2	22.2
Jadad score		
5 (excellent quality)	6	66.6
4	3	33.3
3	0	0
2	0	0
1 (poor quality)	0	0
Number of subjects		
<50	1	11.1
50–100	8	88.8
Age		
Adult (≥18)	9	100
Paediatric (<18)	0	0
Gender		
Female	0	0
Male	1	11.1
Both	8	88.8
Outcomes assessed		
Analgesia	9	100
Block characteristics	9	100
Dex side-effects	9	100
Location of surgery		
Abdominal	2	22.2
Extremity, upper	4	44.4
Extremity, lower	2	22.2
Combination	1	11.1
Disposition		
Inpatient	3	33.3
Outpatient	2	22.2
Both	2	22.2
Unspecified	2	22.2

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