Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials

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CRD summary
The authors concluded that adding clonidine to intermediate or long-acting local anaesthetics for single-shot peripheral nerve or plexus blocks prolonged duration of analgesia and motor block, but increased hypotension, fainting and sedation. There were some limitations in the review, but overall evidence appeared to support the authors’ conclusions.

Authors’ objectives
To evaluate the effects of adding clonidine to local anaesthetics for peripheral single-injection nerve or plexus block in adults undergoing surgery without general anaesthetic.

Searching
MEDLINE, EMBASE, CINAHL, BIOSIS Previews and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to June 2008 without language restrictions. Search terms were reported. Reference lists in retrieved articles were screened.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared clonidine plus local anaesthetic to local anaesthetic alone for peripheral single-injection nerve or plexus block in adults (aged >18 years) undergoing any type of surgery (except peribulbar block for eye surgery) without general anaesthetic. Studies had to have more than 10 patients per treatment group and had to assess intraoperative and/or postoperative pain outcomes and/or drug-related adverse effects. Studies that used other additional agents were included so long as the same agents were used in all treatment arms.

The included studies evaluated plexus blocks (all but one were brachial; one was cervical) and a variety of different nerve blocks (sciatic/femoral, midhumeral, ilioinguinal/iliohypogastric and ankle). Clonidine doses ranged from 30mg to 300mg (most patients received 150mg). Clonidine was used in combination with intermediate (mostly mepivacaine or lidocaine) and long-acting (mainly ropivacaine) local anaesthetics. Patients underwent a variety of surgical procedures (details were reported).

The review assessed duration of analgesia and motor and sensory block, time to onset of block, incomplete block/block failure and adverse effects.

One reviewer selected studies. Queries were discussed with another two authors.

Assessment of study quality
One reviewer assessed validity using a modified seven-point Oxford scale that assessed method of randomisation, level of blinding and reporting of drop-outs. This assessment was checked by two other reviewers. Discrepancies were resolved by discussion with a further two reviewers.

Data extraction
Means and standard deviations of continuous data were extracted or calculated; odds ratios (OR) were used for dichotomous data. Authors were contacted for additional information if required.

One reviewer extracted data. Extracted data were checked by two other reviewers. Discrepancies resolved by discussion with a further two reviewers.

Methods of synthesis
Pooled Peto odds ratios and weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated using either a random-effects model (in the presence of significant statistical heterogeneity, <0.1) or a fixed-effect model (where heterogeneity was absent). The number needed to harm (NNH) was calculated. Sensitivity analysis was used to examine the effects of type of local anaesthetic in axillary plexus block studies (intermediate or long-lasting). Linear dose-responsiveness of clonidine dose was examined.

**Results of the review**

Twenty RCTs were included (n=1,054 patients). Median quality score was 4 out of 7 (range 1 to 6). Twelve studies were double blind, seven adequately described the randomisation method and four described allocation concealment.

Addition of clonidine was associated with a statistically significant increase in the duration of postoperative analgesia (WMD 123 minutes, 95% CI 74 to 169; 13 RCTs, 17 comparisons), sensory block (WMD 74 min, 95% CI 37 to 111; 10 RCTs, 13 comparisons) and motor block (WMD 141 min, 95% CI 82 to 199; seven RCTs, 11 comparisons). Significant heterogeneity was found in all three analyses (p<0.001).

Clonidine was associated with a significant decrease in time to onset of sensory block (WMD -2.2 minutes, 95% CI -4.1 to -0.4; eight studies; significant heterogeneity was found, p<0.001), but not in time to onset of motor block (four studies). There was no significant effect on incomplete anaesthetic block (16 studies).

Addition of clonidine was associated with a statistically significant increase in risk of arterial hypotension (OR 3.61, 95% CI 1.52 to 8.55; seven RCTs; NNH 11), orthostatic hypotension/faintness (OR 5.07, 95% CI 1.20 to 21.4; two RCTs; NNH 10), bradycardia (OR 3.09, 95% CI 1.10 to 8.64; seven RCTs; NNH 13) and sedation (OR 2.28, 95% CI 1.15 to 4.51; four RCTs; NNH 5). Data were homogeneous apart from sedation (p<0.04).

No evidence of dose responsiveness was found for any outcome.

Results of sensitivity analyses were reported.

**Authors’ conclusions**

Addition of clonidine to intermediate or long-acting local anaesthetics for single-shot peripheral nerve or plexus blocks prolonged duration of analgesia and motor block by about two hours. Increased risk of hypotension, fainting and sedation may limit its usefulness. Dose-responsiveness remained unclear.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched. Attempts were made to minimise language bias, but not publication bias. Methods were used to minimise reviewer errors and bias in data extraction and validity assessment. Methods for study selection may have led to error and bias. Study validity was assessed and results were reported. Appropriate methods were used for meta-analyses. Heterogeneity was assessed. Influence of clonidine dose was examined. Sensitivity analyses were conducted. Although heterogeneity was found for several analyses, forest plots showed studies had a consistent direction of treatment effect. There were some limitations in the review, but overall evidence appeared to support the authors’ conclusions.

One reviewer’s salary was provided by the Evidence-based Critical Care Anesthesia and Pain Treatment Foundation, Geneva, Switzerland.

**Implications of the review for practice and research**

**Practice**: The authors stated that the optimal clonidine dose is unknown.

**Research**: The authors stated that it may be useful to evaluate the effects of very small doses of perineural clonidine and other alpha agonists in addition to local anaesthetics in peripheral and plexus blocks and to study the effects of using ultrasound guidance.

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