Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials

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CRD summary
The authors concluded that adding clonidine to intrathecal local anaesthetic had beneficial effects on some, but not all measures of motor and sensory block. Adding clonidine reduced intra-operative pain but increased the risk of arterial hypotension. Given the low quality of the included studies and the possibility of publication bias, the reliability of the results is questionable.

Authors' objectives
To assess the efficacy and harm associated with adding clonidine to intrathecal local anaesthetics for surgery.

Searching
MEDLINE, EMBASE, CINAHL, BIOSIS Previews, INDMED and Cochrane Central Register of Controlled Trials were searched (1966 to October 2006). The search strategy was reported in the review. Bibliographies of relevant papers were searched by hand. Authors were contacted for translations or relevant information.

Study selection
Randomised controlled trials of more than 10 patients per group that compared an intrathecal anaesthetic plus clonidine with the same intrathecal anaesthetic plus placebo or no other treatment in adults undergoing surgery were eligible for inclusion. Trials of healthy volunteers or those testing intrathecal clonidine for labour were not eligible.

Included studies used a clonidine dose ranged from 15 to 150 μg. Local anaesthetics used were hyperbaric or isobaric bupivacaine, hyperbaric mepivacaine, isobaric prilocaine or hyperbaric tetracaine. Patients underwent one of the following types of surgery: orthopaedic, urologic, gynaecologic, abdominal, orthopaedic and lower abdominal, or Caesarean delivery.

No outcome inclusion criteria were stated. In the included studies, one or more of the following outcomes were reported: time to 2 segment regression; time to regression to L2; time to complete sensory block; extent of cephalic spread; time to complete motor block; duration of complete motor block; time to first request for analgesia; and intra-operative pain. The adverse effects reported were intra-operative arterial hypotension and intra-operative bradycardia. Definitions of the adverse effects varied between trials and were reported in the review.

One reviewer assessed all the abstracts for inclusion.

Assessment of study quality
Three reviewers assessed validity using a modified Oxford scale (ranging from 1 to 7) based on the following criteria: randomisation, allocation concealment, blinding and description of withdrawals.

Data extraction
One author performed the data extraction, which was then independently checked by two other authors. Discrepancies were resolved by discussion with a fourth reviewer.

Methods of synthesis
Results were combined using a fixed-effect meta-analysis if data on any particular outcome were from more than five trials, or more than 100 patients treated with clonidine, and if the meta-analysis showed no significant heterogeneity (P>0.1). Weighted mean differences (WMD) for continuous outcomes and pooled relative risks (RR) for binary outcomes were estimated. Numbers needed to treat (NNT) or harm (NNH) were estimated using the RR and control event rate. Heterogeneous studies were combined in a narrative synthesis in which the numbers of studies reporting statistically significant positive or negative results were reported together with treatment effects (the range of the mean
difference between treatment groups).

Where there was statistical heterogeneity, the authors used linear regression to investigate if the clonidine dose response was responsible.

Other specified sensitivity analyses were also conducted.

**Results of the review**
The review included 22 trials (1,445 participants). The median quality score was 2.5 (range 1 to 7). Fourteen studies were double blinded, randomisation was adequately described in 10 studies and allocation concealment was described in four studies.

Time to 2 segment regression (nine studies, 12 comparisons, 374 participants): 10 comparisons showed a significant increase with clonidine compared to control, with treatment effects ranging from 14 to 75 minutes. There was a statistically significant dose response effect, \( P=0.006 \).

Time to regression to L2 (seven studies, nine comparisons, 275 participants): seven comparisons showed a significant increase with clonidine compared to control, with treatment effects ranging from 11 to 128 minutes. There was a statistically significant dose response effect, \( P<0.001 \).

Time to complete sensory block (10 studies, 13 comparisons, 481 participants): one comparison showed a significant increase with clonidine compared to control, with treatment effects ranging from -6 to 28 minutes. There was weak evidence of a dose response effect.

Extent of cephalic spread (nine studies, 14 comparisons, 365 participants): five comparisons showed a significant increase in the number of blocked dermatomes, two showed a significant decrease. There was no evidence of a dose response effect.

Time to complete motor block (seven studies, 11 comparisons, 305 participants): there were no statistically significant differences between clonidine and control, WMD 0.72, 95% CI -0.04, 1.49.

Duration of complete motor block (10 studies, 13 comparisons, 402 participants): 11 comparisons showed a significant increase with clonidine compared to control, with treatment effects ranging from 6 to 131 minutes. There was no evidence of a dose response effect.

Time to first request for analgesia (nine studies, 13 comparisons, 472 participants): 12 comparisons showed a significant increase with clonidine compared to control, with treatment effects ranging from 35 to 310 minutes. There was no evidence of a dose response effect.

Intra-operative pain (seven studies, eight comparisons, number of participants not reported): clonidine was associated with a significantly reduced risk of intra-operative pain compared to control, RR 0.24, 95% CI 0.09, 0.64, NNT 13.

Intra-operative hypotension (17 studies, 23 comparisons, 858 participants): clonidine was associated with a significantly increased risk of intra-operative hypotension compared to control, RR 1.81, 95% CI 1.44, 2.28, NNH 8.

Intra-operative bradycardia (13 studies, 19 comparisons, 561 participants): clonidine was not significantly associated with risk of intra-operative hypotension.

None of the results were substantially altered in the sensitivity or subgroups analysis.

**Authors' conclusions**
Adding clonidine to intrathecal anaesthetic prolongs the regression of sensory block, time to first request of analgesic and duration of complete motor block. Clonidine decreases the risk of intra-operative pain, increases the risk of arterial hypotension and has no effect on time to achieve complete motor or sensory block, or on the risk of bradycardia.
The authors addressed a clear research question and intervention criteria were clearly stated. Participant and outcome inclusion criteria were not specified, and few data were given regarding the patients included in the review, making it hard to assess the generalisability of the results. The authors searched several computerised databases. Having no language restriction excluded the possibility of language bias. However, the search and study selection was performed by only one reviewer, meaning that there could have been bias and/or error during this phase of the review. No attempt was made to assess publication bias in the review, and the authors acknowledge that such bias is a possibility. Three authors independently assessed validity, which minimised the risk of error. The authors reported that the included studies were generally of poor quality and acknowledged that this was likely to have led to an overestimation of effect. No subgroup analysis of high quality trials was reported. Assessing multiple outcomes may have led to some results being reported as statistically significant by chance.

The a priori decisions regarding when to synthesise the results using meta-analysis were appropriate. Most of the results were reported using a narrative synthesis, grouped according to outcome. In these cases, when the authors decided not to conduct a meta-analysis because of statistical heterogeneity, they reported the median treatment effect between groups. This value was misleading, as it was not a weighted summary measure; it has not been reported in this abstract.

Given the low quality of the included diverse studies and the possibility of publication bias, the reliability of the results is questionable.

Implications of the review for practice and research

Practice: the authors did not state any implications for practice.

Research: the authors stated that further research should address whether adding clonidine to intrathecal anaesthetic is more advantageous than using a higher dose of anaesthetic without clonidine, and the optimal dose of clonidine.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.