Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis
Engelman E, Marsala C

CRD summary
The authors concluded that the addition of intrathecal clonidine to intrathecal morphine provided small clinical benefits, but increased the frequency of hypotension. The results were heavily influenced by one trial, with an additional treatment. There were some limitations in the review, but the cautious conclusions reflect the evidence presented and seem reliable.

Authors' objectives
To evaluate the efficacy of adding intrathecal clonidine to intrathecal morphine for acute postoperative pain.

Searching
Seven databases, including EMBASE and PubMed, were searched in January 2012, for relevant studies. Search terms were reported. The references of the included articles and previous reviews were searched.

Study selection
Randomised controlled trials (RCTs) that compared intrathecal morphine plus clonidine against intrathecal morphine alone, for adults undergoing surgery under general anaesthesia, were eligible. Patients had to have received a single-shot spinal analgesia before the start of surgery. The outcomes of interest were the time to first postoperative analgesia request, and the total morphine use during the first 24 hours after operation. Trials had to report either of these two outcomes. Specific adverse events considered were postoperative nausea and vomiting, postoperative sedation, respiratory depression, pruritus and hypotensive events.

The type of surgery, the doses of intrathecal morphine and clonidine, the amounts of intraoperative opioids, and the postoperative analgesic treatments varied between the included trials.

The authors did not report how many reviewers selected trials for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad scale (details were not reported). The authors did not report how many reviewers assessed quality.

Data extraction
The data were extracted to calculate mean differences and odds ratios with their 95% confidence intervals. The authors did not report how many reviewers extracted the data.

Methods of synthesis
Mean differences or odds ratios, with their 95% confidence intervals, were pooled using a random-effects model. A subgroup analysis was conducted, based on the dose of intrathecal clonidine assessed. Heterogeneity in the meta-analyses was assessed using $I^2$ and $T^2$. Publication bias was assessed in a funnel plot and using Egger's test. Sensitivity analyses were conducted (details in the paper).

Results of the review
Seven trials (10 comparisons) were included (503 patients). Two trials scored 2, one trial scored 4, and four trials scored 5 on the Jadad scale.

The meta-analysis revealed a significant delay in the time to first analgesic request with intrathecal morphine plus clonidine 90 to 150 micrograms (μg), compared with intrathecal morphine alone (MD 1.73 hours, 95% CI 1.29 to 2.18; $I^2=0$; one RCT; two comparisons). It also showed that clonidine 90μg to 150μg reduced the amount of postoperative morphine (MD -4.68mg, 95% CI -6.00 to -3.36; $I^2=8%$; two RCTs).
No significant differences between the two groups were found for clonidine 25μg to 30μg, and 50μg to 75μg, for postoperative morphine.

There were no statistically significant differences in adverse effects (nausea and vomiting, over-sedation, respiratory depression, and pruritis) between patients with or without clonidine, apart from a statistically significant increase in hypotension (OR 1.78, 95% CI 1.02 to 3.12; I²=0; four RCTs).

The results of the sensitivity analyses were reported. There was no evidence of publication bias.

**Authors' conclusions**
The addition of intrathecal clonidine to intrathecal morphine provided small clinical benefits, but increased the frequency of hypotension. The results were heavily influenced by a trial in which intrathecal fentanyl was also given.

**CRD commentary**
The review question and inclusion criteria were clear. Efforts were made to find published trials, but unpublished data were not sought. No evidence of publication bias was found, but funnel plots for less than 10 studies have little meaning, so publication bias cannot be ruled out. It was unclear if language restrictions were applied.

The authors did not report the number of reviewers involved in study selection, quality assessment and data extraction, so reviewer bias and error were possible. The authors reported the score on the Jadad scale for each trial, but not the details (score ranged from 2 to 5). This made it difficult to determine the reliability of the trials. Appropriate methods were used to pool the data and to assess heterogeneity.

There were some limitations in the review, but the authors' cautious conclusions reflect the evidence presented and seem reliable.

**Implications of the review for practice and research**
The authors did not state any implications for practice and research.

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