Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis

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CRD summary
The authors concluded that limited data suggested that adding midazolam to other intrathecal agents could safely reduce perioperative nausea, vomiting and pain during caesarean delivery, but further safety data is required. While the review was generally well-conducted and the conclusion reflected the evidence, it was unclear why caesarean delivery was highlighted when no analysis was conducted for this specific group.

Authors' objectives
To evaluate the effectiveness and side-effects of intrathecal midazolam used as an adjunct to other spinal anaesthetic agents in perioperative settings.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 2007. Search terms were reported. No language restrictions were applied. In addition, reference lists of related reviews and identified studies were screened and two specified Health Technology Assessment websites were searched.

Study selection
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible if they compared midazolam with placebo containing intrathecal spinal medications in peri-operative settings. Studies evaluating more than one active component within the same treatment arm were included if both the treatment and control groups were exposed to the other active components. Studies in patient with chronic pain were excluded.

The primary review outcomes were the proportion of patients with nausea and vomiting, and the time to request for rescue analgesia. Other outcomes included visual analogue pain scores two to four hours after midazolam administration, change in respiratory status or respiratory depression, duration of motor blockade, and neurological deficit or symptoms postoperatively.

The included trials evaluated 1 to 2.5mg doses of intrathecal midazolam. Some trials specified use of preservative-free midazolam and other studies did not provide details. All but two trials compared intrathecal midazolam with intrathecal placebo and used the same co-agents in both treatment groups; these agents included bupivacaine, buprenorphine, clonidine, lignocaine, fentanyl and diamorphine. The remaining two trials used different co-agents or different doses of co-agents in treatment and placebo groups. Participants in the included trials were obstetric patients or were undergoing general or orthopaedic surgery. Where reported, the duration of follow-up ranged from one hour to six weeks.

Two reviewers independently selected studies.

Assessment of study quality
Two reviewers independently assessed validity using method of randomisation, allocation concealment, blinding, inclusion and exclusion criteria, and intention-to-treat analysis.

Data extraction
Dichotomous data were extracted as odds ratios (OR) with 95% confidence intervals (CI) with mean differences with 95% confidence intervals used for continuous data. Where studies reported medians, means and standard deviations were estimated.

Two reviewers independently extracted data onto a standardised form; there were no disagreements.

Methods of synthesis
Pooled odds ratios and weighted mean differences (WMDs) with 95% confidence intervals were calculated using random-effects models. Heterogeneity was assessed using the $I^2$ statistic. Sensitivity analysis was undertaken by excluding two trials that used different concurrent treatments in midazolam and control groups. Publication bias was assessed using a funnel plot.

**Results of the review**

Thirteen RCTs were included (n=672 patients). All trials reported use of intention-to-treat analysis, eight trials reported adequate double-blinding and four reported adequate allocation concealment.

Intrathecal midazolam was associated with a statistically significant reduction in the incidence of nausea and vomiting (OR 0.50, 95% CI 0.27 to 0.90; no significant heterogeneity, $I^2=4\%$), a significant increase in the time to request for rescue analgesia (WMD 98.7 minutes, 95% CI 76.1 to 121.4) and significantly reduced Visual Analogue Scale pain scores between two and four hours (WMD -0.98, 95% CI -1.6 to -0.4). Significant heterogeneity was found for time to request rescue analgesia ($I^2=98.5\%$) and Visual Analogue Scale pain scores ($I^2=92.4\%$).

Neurological symptoms after intrathecal midazolam were uncommon (1.8%). There was no significant difference between intrathecal midazolam and control in the duration of motor blockade or incidence of neurological symptoms. No cases of respiratory depression were reported in 192 patients (eight trials). The results for nausea and vomiting were unchanged after excluding the two trials that used different concurrent treatment in midazolam and control groups.

The funnel plot showed no significant evidence of publication bias.

**Authors’ conclusions**

Based on limited data, adding midazolam to other intrathecal agents appeared to reduce perioperative nausea, vomiting and pain during caesarean delivery, but further research is required to verify the clinical safety.

**CRD commentary**

The review question was clearly stated. Inclusion criteria were defined for participants and study design, and primary review outcomes were specified. The drug of interest was defined, but allowable differences between experimental and control treatments were not entirely clear. Several relevant sources were searched and no language restrictions were applied to the search. It was not clear if attempts were made to minimise publication bias, but a funnel plot showed no evidence of this. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs were included, validity was assessed using specified criteria and results were reported. Trials were combined using meta-analysis, but the significant heterogeneity for some outcomes suggested that pooled estimates may not be reliable. Potential reasons for differences between trials were discussed. The authors acknowledged that they made no adjustment for statistical dependency where multiple comparison groups shared a control group. The review was generally well-conducted and the authors’ cautious conclusions appeared to reflect the limited evidence. However, it was not clear why the authors specified patients undergoing caesarean section in their conclusions, since there were no sub-group analyses of the four trials for this group of patients.

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

**Practice:** The authors stated that the clinical compatibility of intrathecal midazolam with other agents must be carefully considered and should have been formally tested before using such treatments in clinical practice.

**Research:** The authors stated that a multicentre register or a large RCT with long-term follow-up (at least six weeks) is required to verify the safety of intrathecal midazolam. Cost-effectiveness analyses and pharmacoeconomic analyses are also required.

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