Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review
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Authors' objectives
To evaluate the adverse effects of intrathecal opioids for labour analgesia.

Searching
MEDLINE, EMBASE and the Cochrane Library (Issue 1, 2001) were searched using the following terms, either alone or in combination: 'combined spinal epidural', 'intrathecal', 'spinal', 'subarachnoid', 'labor', 'opioid', 'randomised', 'randomized', 'controlled' and 'control'. The last search was conducted in January 2001. Locally available anaesthetic journals were also searched, including the International Journal of Obstetric Anaesthesia up to January 2001. The bibliographies of retrieved reports were also examined. Articles in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Abstracts, letters, comments, editorials and review articles were excluded.

Specific interventions included in the review
Studies that compared any intrathecal opioid with or without a local anaesthetic with any analgesic regimes that excluded intrathecal opioids were eligible for inclusion in the review. The included studies used three intrathecal steroids (sufentanil, fentanyl and morphine) with and without various doses of intrathecal or epidural bupivacaine. The controls used different doses of epidural or intrathecal bupivacaine, epidural lidocaine, combinations of epidural bupivacaine, and different doses of epidural sufentanil or fentanyl and intravenous sufentanil.

Participants included in the review
Women receiving labour analgesia were eligible. Most of the participants were nulliparous.

Outcomes assessed in the review
Studies that reported dichotomous data on the adverse effects were eligible for inclusion. The primary outcome in the review was the incidence of one or more episodes of foetal bradycardia, as defined by the authors, occurring within one hour after the injection of the study drugs and not related to maternal hypotension. The included studies defined foetal heart rate abnormalities as tachycardia, decelerations or bradycardia occurring at any time during labour. The other outcomes assessed in the review were the rates of Caesarean section due to any foetal heart rate abnormalities and due to foetal bradycardia, spontaneous and instrumental delivery, use of oxytocin, Apgar scores, and maternal pruritus.

How were decisions on the relevance of primary studies made?
One author screened all the retrieved reports for relevance.

Assessment of study quality
Validity was assessed using the 5-point scale described by Jadad et al. (see Other Publications of Related Interest), which assesses adequacy of randomisation, degree of blinding and the treatment of withdrawals and drop-outs. The relevant validity data were extracted by one author and checked by at least two others.

Data extraction
Relevant data were extracted by one author and checked by three others. The tables presented in the review included details of the analgesia protocols, quality items, and exclusions. The authors were contacted for clarification of ambiguous data, missing data and unpublished data.
Methods of synthesis
How were the studies combined?
The pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a fixed-effect model where there was no evidence of heterogeneity (p>0.1), and using a random-effects model when heterogeneity was detected. For studies with no event rates, 0.5 was added to all cells for that study. The Peto odds ratio (OR) was used in view of the rarity of bradycardia. The number-needed-to-harm (NNH) and 95% CI was calculated using the RR (or the OR) and the average control event rate when there were many groups with zero event rates.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test.

Results of the review
Twenty-four RCTs (3,513 women) were included in the review.

The median quality score was 3.5 (range: 1 to 5). The median trial size was 73 women (range: 24 to 1008). In most trials it was unclear whether the women were allowed to ambulate or not.

Foetal heart rate abnormalities (17 RCTs, 2,081 women): there was no significant difference between intrathecal opioids and controls. The RR was 1.17 (95% CI: 0.87, 1.57). Heterogeneity was not detected (p=0.99).

Foetal bradycardia (9 RCTs, 927 women): intrathecal opioids significantly increased foetal bradycardia compared with the control. The OR was 1.81 (95% CI: 1.04, 3.14) and the NNH was 28 (95% CI: 11, 594). Heterogeneity was not detected (p=0.96).

Caesarean section due to any indication (17 RCTs, 2,954 women): there was no significant difference between intrathecal opioids and controls. The RR was 1.03 (95% CI: 0.87, 1.21). Heterogeneity was not detected (p=0.98).

Caesarean section due to foetal heart rate abnormalities (8 RCTs, 1,560 women): there was no significant difference between intrathecal opioids and controls. The RR was 0.86 (95% CI: 0.60, 1.23). Heterogeneity was not detected (p=0.99). The studies described foetal heart rate abnormalities as non-reassuring heart rate, heart rate abnormalities, bradycardia or foetal distress.

Pruritus (20 RCTs, 2,163 women): intrathecal and epidural opioids significantly increased pruritus compared with the control; 58 and 30% for intrathecal and epidural opioids, respectively, versus 0.6% with the control. The RR with opioid controls was 1.71 (95% CI: 0.97, 3.02). Significant heterogeneity was detected (p<0.01). The RR with non-opioid controls was 29.6 (95% CI: 13.6, 64.6) and the NNH was 1.7 (95% CI: 1.0, 3.9). Significant heterogeneity was not detected (p=0.99).

There was no statistically significant difference between intrathecal opioids and control for instrumental delivery (15 RCTs), the use of oxytocin during labour (7 RCTs), or the incidence of an Apgar score of less than 7 (11 RCTs, 1,623 infants). These results were presented in the review. Significant heterogeneity was not detected in any of these analyses, except for pruritus with opioid controls.

Authors’ conclusions
Intrathecal opioids for labour increase the risk of foetal bradycardia and maternal pruritus. The risk of subsequent Caesarean section is not increased.

CRD commentary
This was a well-conducted and clearly presented review. The aims of the review were stated and the inclusion criteria were defined in terms of the intervention, study design, participants and outcomes. Several relevant sources were searched and no language restrictions were applied. Only one reviewer selected the studies. The exclusion of unpublished material may have resulted in publication bias. Validity was assessed using validated criteria and the methods used to assess validity were described. Relevant data were extracted and presented in tabular format, and the
methods used to extract the data were described. Statistical heterogeneity was assessed and the data were, generally, appropriately combined in a meta-analysis. However, for the one analysis where significant heterogeneity was found, potential reasons were not explored. The evidence presented supports the authors' conclusions.

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

Practice: The authors state that further research is needed before intrathecal opioids may be recommended for routine analgesia in labour.

Research: The authors state that a large RCT evaluating the effect of intrathecal opioids on foetal well-being is needed.

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