A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for Cesarean delivery

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Authors' objectives
To compare ephedrine with phenylephrine in the management of hypotension in women undergoing spinal anaesthesia for Caesarean delivery.

Searching
MEDLINE (from 1966 to June 2001), EMBASE (from 1988 to June 2001) and the Cochrane Controlled Trials Register were searched using appropriate search terms (listed in the review). The reference lists of retrieved articles and reviews were also checked, and authors were contacted for any unpublished trials. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCT) that had been reported as full papers were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared ephedrine with phenylephrine were reviewed. Studies where drug administration was before, during or after induction of spinal anaesthesia, regardless of dose or mode of administration, were eligible for inclusion. The dose of both drugs varied in the included studies, but generally the goal was to maintain the systolic blood-pressure above 100 mmHg. The mode of administration was intravenous bolus, intravenous bolus followed by infusion and intramuscular. Both drugs were administered immediately after the induction of spinal anaesthesia.

Participants included in the review
Women undergoing spinal anaesthesia for Caesarean section. The studies included between 17 and 81 healthy women with an overall age range (where reported) of 27 to 33 years.

Outcomes assessed in the review
The outcomes were occurrence of hypotension, hypertension and bradycardia (primary study authors' definitions), uterine and umbilical blood circulation, Apgar scores at one and five minutes, and umbilical arterial and venous pH values and standard base excess.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the trials.

Assessment of study quality
The quality of the studies was assessed in terms of concealment of allocation, blinding, losses to follow-up and a priori sample size calculation. The quality assessment was performed independently.

Data extraction
Two reviewers independently extracted pertinent data on study details and outcome results using a standardised data collection form. The reviewers were not blinded to the author or results.

Methods of synthesis
How were the studies combined?
Both the continuous and dichotomous outcomes were combined using a random-effects model (DerSimonian and Laird). The relative risks (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous data, while the weighted mean differences (WMDs) were calculated for continuous data.

How were differences between studies investigated?
Heterogeneity was investigated using the Q statistic. Where significant heterogeneity existed (p<0.1) the studies were not pooled. No sensitivity analyses were performed due to the small number of trials.

Results of the review
Seven studies (n=292) were included in the review.

The studies were considered to be of a good quality, with all being double-blind. There was no difference between the treatments for the management, prevention and treatment of hypotension (7 trials; RR 1.00, 95% CI: 0.96, 1.06), the treatment of hypotension (4 trials; RR 1.00, 95% CI: 0.95, 1.05), or the risk of hypotension (3 trials; RR 1.09, 95% CI: 0.71, 1.69). There was no difference in the risk of hypertension between the two treatments (3 trials; RR 0.65, 95% CI: 0.08, 5.13).

Patients in the phenylephrine group were more likely to develop bradycardia (3 trials; RR 4.79, 95% CI: 1.47, 15.60).

Women in the phenylephrine group had neonates with higher umbilical arterial pH values (6 trials; WMD 0.03, 95% CI: 0.02, 0.04), but there was no difference between the treatments for incidence of true foetal acidosis (3 trials; RR 0.78, 95% CI: 0.16, 3.92) or Apgar score of more than 7 at one and five minutes (6 trials; RR 0.77, 95% CI: 0.17, 3.51 and RR 1.00, 95% CI: 0.21, 4.83, respectively).

Authors' conclusions
The evidence does not support the traditional view that ephedrine is better than phenylephrine in the management of maternal hypotension during spinal anaesthesia for Caesarean section.

CRD commentary
The review addressed a well-defined and clinically relevant question. The search for RCTs was reasonable thorough, although the possibility that some studies were missed cannot be ruled out, particularly as only studies reported in full were considered. The conduct of the review appears to have been good with the study selection, quality assessment and data extraction all being conducted independently by two reviewers. All of the included studies were of a good quality and details of each primary study were tabulated. The meta-analyses as performed seem appropriate, however, no details of the results of heterogeneity tests are given in the review. Overall, the findings of the review are supported by the data presented, but the different doses of ephedrine and phenylephrine used in the primary studies may not have been considered sufficiently.

Implications of the review for practice and research
Practice: The authors state that the evidence does not support the traditional view that ephedrine is better than phenylephrine in the management of maternal hypotension during spinal anaesthesia for Caesarean section.

Research: The authors suggest that a large RCT with a primary outcome of foetal acidosis should be conducted.

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