Ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean section: an updated meta-analysis
Lin FQ, Qiu MT, Ding XX, Fu SK, Li Q

CRD summary
This review concluded that use of ephedrine and phenylephrine were equally effective for preventing maternal hypotension during caesarean section under spinal anaesthesia. Phenylephrine was superior to ephedrine for treating hypotension in women giving birth, shown by higher umbilical blood pH values. Given the limited number of included women and trials for most outcomes, these conclusions should be treated with caution.

Authors' objectives
To compare the efficacy of ephedrine and phenylephrine for the management of spinal anaesthesia-induced hypotension during caesarean sections.

Searching
The following databases were searched up to September 2011 without language restriction: MEDLINE, EMBASE and The Cochrane Library. Search terms were reported. References lists of relevant publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared ephedrine with phenylephrine for the treatment or prevention of spinal anaesthesia-induced hypotension during elective caesarean sections were eligible for inclusion. Eligible trials had to use spinal or combined spinal-epidural anaesthesia. Trials including patients with pregnancy complications or other severe diseases were excluded. The primary outcome was incidence of maternal hypotension. Secondary outcomes were umbilical arterial and venous pH values in neonates.

The dosing regimens used for ephedrine and phenylephrine varied between included trials. Over half of included trials compared prophylactic use of ephedrine and phenylephrine for the prevention of hypotension. Most trial performed spinal anaesthesia; only one trial performed combined epidural spinal anaesthesia. All trials used bupivacaine as local anaesthetic for spinal anaesthesia. Most included trials adopted intravenous pre-hydration. The definitions of hypotension varied between included trials. Included trials were conducted from 1991 to 2010.

Two reviewers independently assessed studies for inclusion, with any disagreement resolved by discussion.

Assessment of study quality
The quality of included trials was assessed using the risk of bias tool according to Cochrane Handbook. These criteria included sequence generation, allocation concealment, blinding, incomplete data and selective reporting. Each trial was judged as being at high risk of bias, low risk of bias and uncertain of bias.

Two reviewers independently performed quality assessment, with any disagreements resolved by discussion with a third reviewer.

Data extraction
For dichotomous outcomes, data were extracted on event rates to calculate relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcomes, data were extracted on mean and standard deviations to calculate mean differences with 95% confidence intervals.

Two reviewers independently performed data extraction, with any disagreements resolved by discussion.

Methods of synthesis
The trials were combined in a meta-analysis. The pooled relative risks or standardised mean differences (SMDs), with 95% confidence intervals, were calculated using a random-effects model. Statistical heterogeneity was assessed using the Q statistic and I².
Sensitivity analyses were performed to assess the effect of individual trials on the results. Subgroup analyses were conducted by different administration routes (intravenous or intramuscular).

Publication bias was assessed using the funnel plot and Begg’s and Egger's tests.

**Results of the review**

Fifteen trials were included in the review (742 women). The authors reported that most of trials had a low risk of bias. No further results on risk of bias were reported (either in the paper or supplementary materials).

**Prevention of hypotension:** There were no significant differences between patients receiving ephedrine and those receiving phenylephrine for the incidence of hypotension (seven RCTs), umbilical arterial pH values (two RCTs) and venous pH values (four RCTs). Substantial heterogeneity was observed for the outcomes of hypotension ($I^2=67\%$) and umbilical arterial pH values ($I^2=92\%$).

**Treatment of hypotension:** Pregnant women who received phenylephrine had neonates with higher umbilical arterial pH values (SMD -1.32, 95% CI -2.35 to -0.30; five trials) and venous pH values (SMD -0.79, 95% CI -1.09 to -0.49; four trials) compared with women who received ephedrine. There was no significant difference in the incidence of intraoperative hypotension between the two groups. Substantial heterogeneity was observed for the outcome of umbilical arterial pH values ($I^2=91\%$).

Results of sensitivity and subgroup analyses were also reported.

The funnel plot suggested the presence of publication bias, but Egger's and Begg's tests did not show the evidence of publication bias.

**Authors’ conclusions**

Prophylactic use of ephedrine and phenylephrine were equally effective for the prevention of maternal hypotension during caesarean section under spinal anaesthesia. Phenylephrine was superior to ephedrine for the treatment of maternal hypotension, evidenced by higher umbilical blood pH values in neonates.

**CRD commentary**

The review addressed a clear research question, supported by appropriate inclusion criteria. Relevant databases were searched. Efforts were made to find published studies but not unpublished studies, so the potential for publication bias was increased. Publication bias was formally assessed and suggested that there was some evidence of publication bias; however, a small number of studies may have limited the power of the tests of publication bias. No language restriction was applied to the search, which reduced the risk of language bias. Sufficient attempts were made to minimise errors and biases during the review process.

Appropriate criteria were used to assess trial quality. The authors reported that most trials had a low risk of bias, but further result details were not reported. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors’ conclusions reflected the evidence presented, but the authors did not discuss the clinical significance of their results. Caution is required in interpreting these results given the small number of included trials for most pooled outcomes and the limited number of parturients.

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

The authors did not state any implications for practice or further research.

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