Review Article

Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis

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Background: Phenylephrine use has been recommended over ephedrine for the management of hypotension after spinal anesthesia for elective caesarean section. The evidence for this is rather limited because in previous trials, pH was significantly lower after ephedrine, but absolute values were still within normal range. We pooled the available data to define maternal and neonatal effects of the two vasopressors.

Methods: Literature was identified by a systematic search. Hypotension, hypertension, and bradycardia of the mothers, fetal acidosis defined as a pH < 7.20, and the continuous variables base excess (BE) and arterial pCO2 of the neonates were recorded. Meta-analysis using the random effects model was performed, and the weighted mean difference (WMD) or risk ratio (RR), and 95% confidence interval (95% CI) were calculated.

Results: The criteria for eligibility were fulfilled by 20 trials including 1069 patients. The RR of true fetal acidosis was 5.29 (95%CI 1.62–17.25) for ephedrine vs. phenylephrine (P = 0.006). BE values after ephedrine use were significantly lower than after phenylephrine (WMD −1.17; 95% CI −2.01 – −0.33). Umbilical artery pCO2 did not differ. Mothers treated with ephedrine had a lower risk for bradycardia (RR 0.17; 95%CI 0.07–0.43; P = 0.004). No differences between vasopressors were observed for hypotension and hypertension.

Conclusions: Our analysis could clearly demonstrate a decreased risk of fetal acidosis associated with phenylephrine use. In addition with our findings for BE, this suggests a favorable effect of phenylephrine on fetal outcome parameters. The mechanism of pH depression is not related to pCO2.

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The choice of vasopressor for the treatment of hypotension because of spinal anesthesia in parturients undergoing cesarean section has been a subject of a long-lasting debate.1 Because the alpha-agonist phenylephrine was thought to decrease uterine blood flow by increasing peripheral vascular resistance, with potentially deleterious effects for the unborn, ephedrine was favored for many years.2 In recent years, low invasive techniques have been applied to pregnant women that allowed the researchers to define the hemodynamic profile of vasoactive agents in detail.3,4 Hypotension may be the result of a decrease in peripheral vascular resistance counterbalanced by increases of stroke volume and heart rate, and finally leading to an increased cardiac output.4 The authors concluded that hemodynamic stability may be best restored by a low-dose phenylephrine infusion.3 A randomized trial by Dyer et al. confirmed that phenylephrine administration is the fastest and most effective way of restoring mean arterial pressure.4

In addition to these findings, the metabolic consequences of vasopressor administration were recently evaluated. Ephedrine was associated with increased fetal plasma concentrations of lactate, glucose, and catecholamines compared with phenylephrine.5 Finally, phenylephrine was declared the vasopressor of first choice in a 2010 review6 because of these observations of a favorable effect on fetal metabolism. This recommendation has been adopted by the German society of anesthesia.7

The evidence, so far, to support this notion was rather poor. pH and base excess (BE) are considered important outcome parameters of the baby.
A systematic review on this topic was published 9 years ago, reporting a significantly increased risk for lower pH and BE in the ephedrine group. The clinical significance of this finding, however, remained unclear because the pH and BE values were still within the normal range. With the data published until then, these authors, however, failed to demonstrate any difference in the incidence of true fetal acidosis between the ephedrine and phenylephrine treatment arm. Moreover, in the meantime, several other studies appeared providing relevant data. The results of these studies were conflicting. Saravanan et al. showed a significant difference of pH and BE between the ephedrine- and phenylephrine-treated groups. This result was challenged by another study suggesting similar effects of the two agents.

We therefore set out to gather the available evidence and performed a meta-analysis comparing fetal and maternal effects of ephedrine and phenylephrine.

### Methods

#### Literature search


Because Bender et al. reported that a high percentage of relevant literature will be missed by a PubMed search alone, we also performed a hand search of major anesthesia journals and some obstetric journals, and reviewed the reference lists from retrieved articles.

In addition, we hand-searched the abstract bands of the major annual congresses of anesthesiology and regional anesthesia. The hand-searches were done for the issues starting with the January issue from 2000 until the January issue of 2011. We chose this period because the first systematic review on this topic was published in 2002, and its literature search covered the time before. The obtained references were then checked for duplicates.

#### Quality assessment

Each trial was scored for a five-point scale, giving one point for each of the following items: description of the trial as randomized, double-blind, or containing a description of withdrawal and dropouts. Additional points were credited when the methods of randomization and double blinding were described and were adequate. Scoring was performed by two authors independently, and a final score was assigned in consensus.

#### Data extraction and meta-analysis

The number of events and total number of subjects per group (ephedrine, phenylephrine) were extracted from the dichotomous variables maternal hypotension, maternal hypertension, maternal bradycardia, and fetal acidosis defined as a pH < 7.2. The definitions of hypotension, hypertension, and bradycardia used in the included trials were different. The most common definition of maternal hypotension was a decrease of systolic arterial pressure below 80% of the baseline value.

We combined the dichotomous outcome data of the two ephedrine groups of the paper by Hall et al., as well as the data of the two phenylephrine groups of the report by Ayorinde and colleagues.

For the continuous parameters BE and arterial pCO₂, the mean and standard deviation were recorded. In the study by Moran et al., the standard error of the mean was reported in the paper, and we calculated the standard deviation. Data of the lowest ephedrine dose of the study by Hall and colleagues and data of the highest phenylephrine dose group of the study by Ayorinde et al. were chosen. Prof Anna Lee, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, China kindly provided us with the standard deviations of the continuous variables for the reports by the groups of Hall, Thomas, and Alahuhta. In all analyses, the ephedrine group was chosen as the control group.

The random effects model was applied for the meta-analysis of both, dichotomous and continuous variables. The pooled risk ratio (RR) and 95% confidence interval (95% CI) was calculated for binary variables, and the weighted mean difference (WMD) of the pooled continuous data. The software program Review Manager (RevMan) (Computer program), Version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008] was used.
Results

Our literature search retrieved 133 articles of which 20 studies were considered eligible for further analysis (Fig. 1). These reports included a total of 1069 subjects. The quality score of all reports was ≥3 (median 4; range 3–5) so that these reports were used for further analysis.

Neonatal outcome

The RR of fetal acidosis was 5.29 (95%CI 1.62–17.25) for ephedrine compared with phenylephrine that was statistically significant ($P = 0.006$, Fig. 2). The difference of the pooled BE data was also statistically significantly lower in the ephedrine group [WMD of $-1.17$ (95% CI $-2.01$–$-0.33$; $P = 0.006$; Fig. 3)]. Umbilical artery pCO$_2$ data from six studies were used for meta-analysis. No significant difference between the ephedrine or phenylephrine group was found (WMD 1.60; 95%CI $-0.41$–$3.62$; $P = 0.12$).

In 11 trials the number of neonates with Apgar values below 7 measured at 1 and 5 min after delivery were given. Table 1 shows Apgar data at 1 and 5 min after delivery. Only one neonate in the ephedrine group of one study had an Apgar value below 7 after 5 min. One study provided Apgar values 10 min after birth, which were not statistically different (median 9; range 8–10) in the ephedrine group vs. median 10 (range 8–10) in the phenylephrine group. No Apgar data were reported in four articles.

Maternal outcome

The risk of bradycardia was significantly lower in the mothers receiving ephedrine in comparison with the phenylephrine treatment arm (RR 0.17; 95%CI 0.07–0.43; $P = 0.0001$; Fig. 4). Comparing ephedrine- and phenylephrine-treated mothers, there was no significant difference in the risk of hypotension when a vasopressor was given prophylactically (RR 1.13; 95%CI 0.68–1.86; $P = 0.64$). When pooling the studies, applying vasopressors for either treatment or prevention, there was no significant difference in the risk of hypotension (RR 1.03; 95%CI 0.72–1.48; $P = 0.87$). The meta-analysis found no significant difference in
Fig. 3. Neonatal base excess after ephedrine or phenylephrine. CI, confidence interval; SD, standard deviation.

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<th>Author</th>
<th>APGAR 1 min</th>
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<td>Hennebry et al., 2009</td>
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<td>Cooper et al., 2002</td>
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Data are given as median and range.
*Standard deviation.

n.s., not significant.

Fig. 4. Maternal bradycardia after ephedrine or phenylephrine. CI, confidence interval.
the risk of hypertension (RR 1.18; 95% CI 0.86–1.63; \( P = 0.30 \)) between the two vasopressors.

**Discussion**

As a major result, we found that ephedrine use is associated with an increased risk for true fetal aci-
dosis compared with phenylephrine. Ephedrine increased the risk for a lower BE. Apgar values did not differ between the ephedrine and phenyle-
phrine arms. Maternal outcome was characterized by a lower incidence of bradycardia because of ephedrine administration, whereas no significant differences between ephedrine and phenylephrine were found for hypotension or hypertension.

Meta-analyses are considered the pinnacle of evidence-based medicine pooling the data of all existing studies. Meta-analyses can help to resolve the conclusions of contradictory reports. Conflicting results existed on the association of vasopressor use and fetal outcome, as assessed by pH and BE in two trials.9,10 Our meta-analysis suggests that ephedrine causes lower BE values of the neonate than phenylephrine. Our result is in agreement with a previous meta-analysis by Lee et al.8 from 2002. These authors included 264 patients in seven trials. We identified additional 11 studies with 805 patients.

In contrast with Lee et al.,8 we were able to demonstrate a significantly increased risk of true fetal aci-
dosis, as defined by a pH < 7.20. Our analysis included five trials with 263 participants compared with only three studies in the report by Lee et al.8 including less than half of the patients of our anal-
ysis, i.e. 116 parturients. The relevance of fetal aci-
dosis was clearly established by a recent meta-
analysis,29 evaluating the association of various pH thresholds with neonatal outcome. Acidosis defined as a pH < 7.20 resulted into a fourfold increase in mortality and more than twofold increase in mor-
bidity. This study unambiguously showed that umbral artery pH < 7.20 is a marker of unfavora-
ble outcome of the unborn. Because this study by Malin et al.29 established the importance of umbi-
cal artery pH and BE, we did not perform an analy-
sis of venous blood data.

To further elucidate the mechanisms by which ephedrine may cause a higher incidence of fetal aci-
dosis, we performed a meta-analysis of umbilical artery pCO₂ values, revealing no difference between the two vasopressors under study. An increase of umbilical artery pCO₂ can occur due to hypoventi-
lation immediately after birth that is very brief and of no clinical relevance. The group of Ngan Kee published three reports5,10,30 providing umbilical artery lactate data. All studies found significantly higher lactate concentrations after ephedrine. Taken together, these observations suggest that the depress-
ion of neonatal pH is not caused by an increase in pCO₂ but by a metabolic mechanism involving higher lactate production.

The hemodynamic profile of ephedrine is charac-
terized by a delayed onset of action. In a recent investigation by Dyer et al.,4 the maximum effect on arterial blood pressure was observed 89.8 s after ephedrine administration compared with 61.8 s after phenylephrine. This observation was explained with a delayed sympathetic effect of ephedrine, i.e. the release of norepinephrine. This and a long half time make ephedrine more difficult to titrate than phenylephrine.

Phenylephrine caused a significant increase of peripheral resistance, leading to a sharp rise of arte-
rial blood pressure, and a decrease in cardiac output that was paralleled by bradycardia.4

The choice of phenylephrine was questioned by Beilin31 because of a high percentage of hypertensive episodes. Our combined data from various studies suggest that there is no significantly increased risk with phenylephrine use, neither when given for prevention nor for treatment.

Also, both agents seem to be equally effective in their potential to treat hypotension because no sig-
nificant differences in the incidence of low blood pressure between groups were observed. However, the authors of the included trials used different defi-
nitions of maternal hypotension so that the inci-
dence of hypotension in different studies is difficult to compare. Recently, we could demonstrate that even minor changes in the definition of hypotension can cause significant differences in the incidence of hypotension.32

The more favorable effects clearly recommend the use of phenylephrine. A survey carried out in 2007 revealed that more anesthesiologists still prefer ephedrine.33 According to a survey published in 2001, ephedrine was still the vasopressor of first choice for 95.2% of the respondents.34 This percent-
age had dramatically changed, and in a more recent survey, 32% of the clinicians used ephedrine for prophylaxis or treatment compared with 26% and 23% using phenylephrine for prevention and treat-
ment, respectively.33 Despite the decrease over time, the percentage remains still high. It could be specu-
lated that practitioners may feel more comfortable with ephedrine that has a long history of use in
obstetrics. Our analysis can probably provide convincing arguments that may help to translate evidence into clinical practice.

It should be emphasized that most of the studies only included healthy women undergoing scheduled cesarean section. It is tempting to extrapolate these findings to emergency cesarean deliveries. Cooper and colleagues35 analyzed emergency cesarean deliveries and did not find a significant difference in the fetal pH data between ephedrine and phenylephrine administration. In this study, non-reassuring fetal heart trace was the only factor associated with low umbilical artery pH.35 This study was a retrospective analysis, and a prospective randomized controlled trial is warranted to define the effects of these vasopressors in emergency cesarean deliveries.

In summary, ephedrine use is associated with lower pH and BE of the neonate. We also found a significantly higher risk for fetal acidosis with ephedrine than with phenylephrine. Comparing the maternal effects, phenylephrine caused an increased risk for maternal bradycardia, with no differences for hypotension or hypertension. These findings provide compelling evidence of favorable effects of phenylephrine in the management of hypotension in elective cesarean deliveries under spinal anesthesia.

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Conflicts of interest: Authors declare no conflicts of interest.

References


Vasopressors in spinal anaesthesia


