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ORIGINAL ARTICLE

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Ephedrine versus phenylephrine as a vasopressor for spinal anaesthesia-induced hypotension in parturients undergoing high-risk caesarean section: meta-analysis, meta-regression and trial sequential analysis

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ABSTRACT

Background: Phenylephrine is the preferred vasopressor for the prevention and treatment of spinal anaesthesia-induced hypotension during caesarean section, because studies on low-risk elective patients found it to have a less detrimental effect on umbilical artery pH compared with ephedrine. However, limited data exist from high-risk parturients and parturients with uteroplacental insufficiency.

Methods: We systematically searched for randomised, controlled, double-blinded trials of these two vasopressors in high-risk caesarean sections. We applied conventional meta-analysis, trial sequential analysis, computing the required information size that would exclude type I and II errors, contour-enhanced funnel plot testing for publication bias, meta-regression to assess the dose–response relationship, and the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE). The incidence of fetal acidosis (umbilical arterial pH <7.2) was the primary outcome.

Results: Eight trials (712 patients) with low risk of bias were identified. Pooling six studies of patients with preeclampsia and other reasons for fetal compromise, as well as subgroup analysis of the preeclampsia studies, revealed no significant differences in the incidence of fetal acidosis. Trial sequential analysis showed that the required information size was not reached. The funnel plot was not suggestive of publication bias. Meta-regression showed no dose-response relationship. The GRADE score was moderate quality.

Conclusions: Despite several studies and a large number of patients there was insufficient evidence to make a recommendation for choice of vasopressor in high-risk caesarean section. Trials with adequate power to detect differences in the incidence of fetal acidosis between ephedrine and phenylephrine are required to provide evidence-based guidance.

Keywords: Vasopressor; Spinal-anaesthesia; Caesarean section; Fetal compromise; Meta-analysis

Introduction

Hypotension remains a frequent side-effect in women having spinal anaesthesia for caesarean section, affecting up to 50% of cases.[1] The alpha-adrenergic receptor agonist phenylephrine has become the preferred vasopressor in this setting because it is associated with a lower incidence of fetal acidosis compared with ephedrine.[2,3] Prophylactic infusion of phenylephrine significantly reduces the incidence of maternal hypotension.[4] Of note, the studies on which these conclusions were based were at elective caesarean sections in healthy parturients at term.[3]

In the healthy uterus at term there is an excess blood flow that easily meets the fetal oxygen demand.[5] In cases where uterine blood flow is compromised it is possible that vasoconstriction by an alpha-adrenergic agonist might critically reduce the oxygen supply and impair the fetal acid-base status. It may therefore be

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inappropriate to extrapolate the results obtained from healthy pregnancies to high-risk pregnancies.

In studies of high-risk caesarean section, no difference in umbilical artery pH was observed between ephedrine and phenylephrine.[6,7] However, these studies were of a retrospective design that is prone to bias. We therefore set out to retrieve prospective, randomised, controlled trials comparing ephedrine with phenylephrine in high-risk caesarean sections, and to submit them to a meta-analysis.

Methods

Our meta-analysis was conducted in accordance with the PRISMA statement.[8]

Literature search

A systematic electronic literature search was performed in the databases Medline Epub, Embase.com (Embase plus Medline), CINAHL, Cochrane Central, Scopus, Web of Science, and LILACS/IBECS. The search terms included high-risk pregnancy or preterm or premature or fetal compromise or compromised fetus or compromised placental function or emergency or non-elective or preeclampsia or pre-eclamp* or preeclamp* or uteroplacental insufficiency. Details of the search strategy are given in the Appendix. In addition, we hand-searched the bibliographies of retrieved articles. We excluded abstracts. We also searched in the databases of the World Health Organization (WHO)-acknowledged trial registries (ICTRP) for studies with the keywords "Caesarean" and "vasopressor". The hits of the literature search were entered in the program Endnote and duplicates removed. Relevant articles were identified by two authors independently (MH, MK).

Inclusion and exclusion criteria

The criteria for inclusion of studies were defined according to the PICO acronym:

Patients: women undergoing spinal anaesthesia for high-risk caesarean section

Intervention: use of ephedrine for the prevention or treatment of spinal anaesthesia-induced hypotension

Comparator: use of phenylephrine for the prevention or treatment of spinal anaesthesia-induced hypotension

Outcomes: primary outcome: incidence of fetal acidosis, defined as umbilical artery pH <7.20; secondary outcomes: umbilical arterial pH, nausea, vomiting, bradycardia, hypertension.

Exclusion criteria: patients <18 years-of-age, retrospective studies, case reports, non-randomised studies.

Data extraction and data collection

Two authors (MH, MK) extracted the data from eligible trials independently. The primary outcome of each trial was identified as the outcome that was explicitly defined as the primary outcome or that which was used for the sample size calculation. We requested original data and methodological details from the corresponding author, if necessary. We estimated standard deviation (SD) from interquartile range (IQR) by dividing by 1.35.[9] Mean and SD were derived from median and range by the method described by Hozo et al.[10]

Assessment of risks of bias

The methodological study quality was assessed using the Cochrane Risk of Bias tool (MH, NH). The risks of selection bias (random sequence generation, allocation concealment), performance bias (blinding of participant and personnel), detection bias (blinding of assessor), and attrition bias of each included study were evaluated.

Conventional meta-analysis

Risk ratio (RR) for dichotomous variables or weighted mean difference in case of continuous variables, as well as 95% confidence intervals (CI), were calculated. The I^2 was computed as a measure of heterogeneity.[11] Data were only pooled when there was a minimum of three studies and a minimum of 100 patients per treatment group. The same conditions were applied to subgroup analyses that we planned for studies of similar obstetric pathology (e.g. preeclampsia). For meta-analysis, we used Review Manager (RevMan, version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), applying the random effects model, since we expected clinical and methodological heterogeneity across the studies. P-values <0.05 were considered statistically significant.

Assessment of publication bias: contour-enhanced funnel plots

Publication bias was studied by means of contour-enhanced funnel plots, since asymmetry of a traditional funnel plot does not prove publication bias.[12] We planned to perform the Egger's test to consider the risk of publication bias for our primary outcome when there were ≥10 trials. Egger's test with a P-value of <0.05 indicates publication bias.[13]

Meta-regression

Random effects meta-regression was performed with the ephedrine and phenylephrine dose as moderator in order to assess a dose-response effect. Meta-regression, bubble plots and contour enhanced funnel plots were performed with R Studio version 1.0.136 with the "meta" package (version 4.9-1) and "metaphor" package (version 2.0–0).

Trial sequential analysis

Trial sequential analysis (TSA) is a tool for quantifying the statistical reliability of data in the cumulative meta-analysis, adjusting significance levels for sparse data and

repetitive testing on accumulating data. The method has been described previously.[14] We performed TSA on the primary outcome including trials we assessed as low risk of bias. Briefly, meta-analyses are sensitive to the risks of type I and type II random errors because of sparse data and repeated testing. Trial sequential analysis calculates the required information size (RIS), defined as the number of participants needed in a meta-analysis to detect or reject a certain intervention effect. Our calculations allowed for a type I error and a type II error of 0.05 and of 0.20, respectively, applying the random effects model and estimating heterogeneity by the diversity (D^2) in the included trials.[15,16] The TSA software was used (version 0.9 Copenhagen Trial Unit, Copenhagen, Denmark).

Grading of Recommendations Assessment, Development, and Evaluation system (GRADE)

The GRADE scale was used to rate the quality of evidence and strength of recommendation of our primary outcome.[17] The GRADE criteria were:

1. *Risk of bias:* as assessed by the Cochrane tool
2. *Inconsistency:* as a measure of heterogeneity, as reflected by the I^2 statistic. If I^2 was $\geq$50% without satisfactory explanation by subgroup analysis/meta-regression, inconsistency was assumed to be given.
3. *Indirectness:* if outcome data were only based on indirect comparisons/outcomes of interest (surrogate markers), or on indirect comparisons of the population of interest.
4. *Imprecision:* as reflected by the TSA. If TSA showed that the number of patients/cases did not exceed the required information size and did not cross an appropriate threshold for significance or futility, then imprecision was assumed.
5. *Publication bias:* as reflected by the contour-enhanced funnel plot or the Egger test.

The evidence was down-graded by one level for a serious risk and for two levels for a very serious risk for each of the above criteria. The quality of evidence was qualified as high or moderate quality if further research is very unlikely or unlikely, respectively, to alter the confidence in the effect estimate. The interpretation as low quality was given if further research is deemed very likely to alter the confidence in the estimate of the effect or as very low quality in case the confidence is very little.

Results

Study selection, study characteristics, and risk of bias

Our search retrieved 189 hits (Fig. 1) of which finally eight studies, including 712 parturients, were analysed.[18–25] Five studies reported on caesarean section for preeclamptic women and three studies on other high-risk cases. Details of the studies are shown in Table 1.

In the trial registries we found no completed trials addressing the topic of this review, that were not included in our analysis. The risk of bias assessment (Fig. 2) was low for all domains of all studies.

Synthesis of results

The number of cases of fetal acidosis, as well as the mean and SD of umbilical artery pH values per treatment arm, were obtained from the authors of the study by Ngan Kee et al. and the incidence of fetal acidosis was obtained from the authors of the study by Dyer et al.[18,22] The study by Abdalla et al. presented median and IQR for umbilical pH; we derived SD from the IQR and used median and SD in the meta-analysis.[19]

Five studies focused on pre-eclampsia[19,22–25] as an indication for caesarean section, two studies focused on pregnancies with fetal compromise,[20,21] and one study by Ngan Kee et al.[18] focused on emergency caesarean section and included women who had emergency caesarean section and labouring women who progressed to caesarean section without fetal compromise. Because the important concern in these studies on fetal compromise and in the pre-eclampsia studies was uteroplacental insufficiency, we pooled the data of the two types of studies and therefore excluded the study by Ngan Kee et al.[18]

For the primary outcome, the incidence of fetal acidosis, no significant difference between ephedrine and phenylephrine was found; the Forest plot is shown in Fig. 3.

Meta-analysis of the subgroup of preeclampsia studies that found similar incidences of fetal acidosis in the ephedrine (41/145) and the phenylephrine group (35/141) showed the risk ratio was 1.15 (95% CI 0.78 to 1.69).[23–25]

The umbilical arterial pH values, reported in the seven studies on uteroplacental insufficiency[19–25] were similar between the ephedrine group (n=345) and the phenylephrine group (n=338) (weighted mean difference −0.01, 95% CI −0.02 to 0.00, I^2=0%). In the subgroup analysis of the preeclampsia studies[19,22–25] there was no significant difference between the treatment arms (data not shown). The number of 1- and 5-min Apgar scores <7 were reported by Dyer et al., with no difference between the treatment arms. [23]

Table 2 shows the meta-analyses of the secondary maternal outcomes. No differences were observed for nausea, vomiting, hypotension, hypertension, and bradycardia. Nausea or vomiting as a composite outcome was reported in one study, with a significantly higher incidence in the ephedrine group (13/102) compared with the phenylephrine group (4/102) (P=0.03).[18]

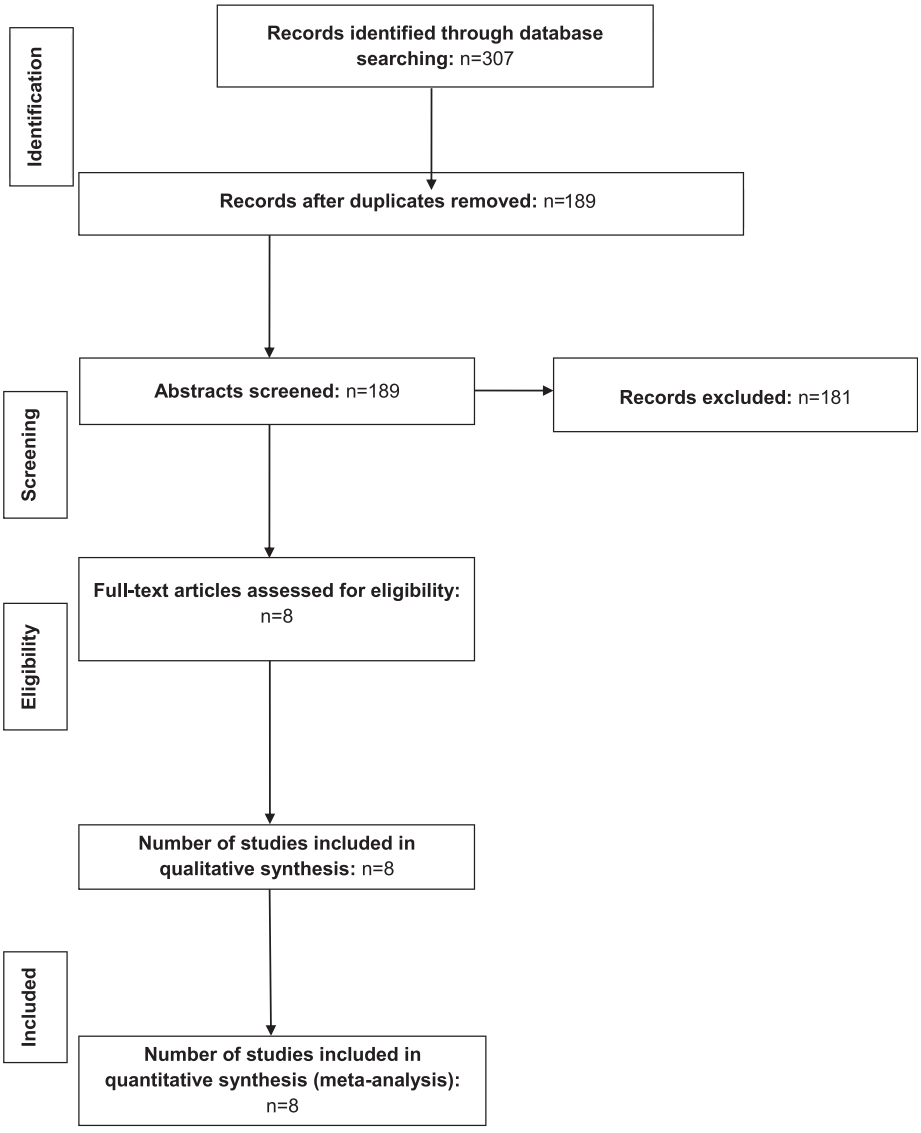

Fig. 1 Selection of studies

Contour-enhanced funnel plots

The Egger test could not be performed because there were fewer than 10 trials. The contour-enhanced funnel plots of the analysis of all studies of uteroplacental insufficiency[19–25] (Fig. 4) and in the preeclampsia studies alone[19,22–25] (Fig. 5) were symmetric, suggesting that there was no publication bias.

Meta-regression

We analysed the proportion of events of fetal acidosis for a dose–response effect of ephedrine and phenylephrine in all studies of uteroplacental insufficiency[19–25] (Fig. 6) and in the preeclampsia studies alone[19,22–25] (Fig. 7). Meta-regression showed no statistically significant association between dosage and the proportion of events in both groups. The beta for the analysis of ephedrine was −0.015 (95% CI −0.099 to 0.069) and for the analysis of phenylephrine the beta was 0.002 (95% CI −0.008 to 0.011).

Trial sequential analysis

The TSAs were performed for the studies of uteroplacental insufficiency[19–25] (Fig. 8) and for the preeclampsia studies alone[19,22–25] (Fig. 9). The TSA monitoring boundaries were not crossed, so a meaningful conclusion cannot be drawn.

Grading of Recommendations Assessment, Development, and Evaluation system

The risk of bias was low, as were the risks for inconsistency and indirectness, and there was no indication of publication bias. Owing to imprecision as reflected by our TSAs, we finally assigned the GRADE level as moderate quality.

Table 1

Author/Year	No. of patients analysed in group		Inclusion Criteria	Exclusion Criteria	Definition of hypotension	Vasopressor regimen	Fluid regimen	Primary outcome
	E	Phe						
Abdallah 2013	20 W 20 I	20 W 20 I	Preeclamptic full-term parturients undergoing elective CS	Classic contra-indications to spinal block, pre-existing systemic disease, known fetal abnormalities, patients taking any medications that could influence the hemodynamic response	25% or more decrease in the maternal BP from baseline or SBP of less than 90 mmHg	Prophylactic use: no E: 6 mg as bolus in case of hypotension P: 75 μg as bolus in case of hypotension Other drugs: Atropine, if heart rate <60 beats/min TDU: n.d.	Preload: 10 ml/kg RL	Impact on fetal outcome (Apgar/fetal blood gasses)
Dyer 2018 IJOA	32 W	32 W	Severe preeclampsia requiring CS for a non-reassuring fetal heart tracing	Patient refusal, any contraindication to spinal anaesthesia, BMI >40, clinical signs of hypovolaemia, Abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopaenia, pulmonary oedema, local or generalized sepsis, spinal deformity, umbilical cord prolapse, prior non-obstetric abdominal surgery, >2 previous CS, human immunodeficiency virus positive with AIDS defining disease Fetal exclusion criteria: persistent bradycardia or any other condition contraindicating spinal anaesthesia, gestational age <28 weeks, estimated weight <900 g, and twin pregnancy.	MAP >20% decrease from baseline and <110 mmHg	E: 7.5 mg P: 50 μg Doses repeated or doubled if no effect of previous dose within 60–90 seconds If MAP <70% from baseline immediately double dose After in total 300 μg P or 45 mg E and lack of effect the prepared alternative vasopressor could be used TDU [median (range)]: E: 15 (7.5–45) mg P: 100 (50–650) μg	Onward: balanced crystalloid, less than 100 ml/h Preload: 300 ml HES	Umbilical artery base excess

Dyer 2018 ANAE	10 W	10 W	Severe early onset preeclampsia (SBP >160 mmHg and/or DBP >110 mmHg, on ≥2 separate occasions; or symptoms of imminent eclampsia with ≥3 + proteinuria and gestation ≤34 weeks) and maternal indication for CS	contraindication to spinal anaesthesia; active labour; BMI >40; pulmonary oedema; umbilical cord prolapse; previous non-obstetric abdominal surgery; >2 previous CS;HIV positive with AIDS-defining disease; non-reassuring fetal heart tracing; <28 weeks gestation; multiple pregnancy	MAP >20% decrease from baseline and <110 mmHg	E: 7.5 mg P: 50 µg Doses repeated or doubled if no effect of previous dose within 60–90 seconds If MAP <70% from baseline immediately double dose After in total 300 µg P or 45 mg E and lack of effect the prepared alternative vasopressor could be used TDU [median (range)]: E: 15 (7.5–37.5) mg P: 50 (50–150) µg	Preload: 300 ml HES	Change in cardiac index of the women following vasopressor administration
Higgins 2017	54 W 74 I	54 W 72 I	Non-labouring women with pre-eclampsia scheduled for CS, ASA II or III, singleton or twin pregnancies	Chronic hypertension, labour or failed trial of labor, body mass index ≥40 kg/m^2, resting heart rate <60 bpm, eclampsia, known fetal anomalies, contraindications to spinal anaesthesia, and emergency procedures	Prophylactic use to keep SBP above 80% from baseline but <160 mmHg. If baseline SBP was >160 mmHg, infusion was not yet started	Prophylactic use: yes, if baseline SBP was <160 mmHg E: 8 mg/ml P: 100 µg/ml 2 ml/2 min, then BP-measurement Stop, if SBP >baseline or >160 mmHg. 1 ml bolus if SBP <80% of baseline Other drugs: Atropine 0.4 mg in case of bradycardia associated with SBP <80% of baseline TDU [median (quartiles)]: E: 4.5 (2.5–11.25) mg P: 445 (200–950) µg	Preload: RL on a minimal rate Co-load: 500 ml bolus RL concurrently with the start of the spinal anaesthesia procedure, thereafter n.d.	Umbilical artery blood pH

(*continued on next page*)

Table 1 (*continued*)

Author/Year	No. of patients analysed in group		Inclusion Criteria	Exclusion Criteria	Definition of hypotension	Vasopressor regimen	Fluid regimen	Primary outcome
	E	Phe						
Jain 2016	45 W	45 W	ASA I-II term pregnant women with spontaneous onset of labor for normal vaginal delivery and later on taken up for emergency CS due to acute fetal compromise	Contraindications for spinal anaesthesia, cardiovascular or cerebrovascular diseases, fetal malformations, hypertensive disorders of pregnancy, diabetes, multiple gestation, growth restricted fetuses having chronic asphyxia, ruptured membranes with meconium stained liquor, or evidence of intrauterine infection. Women undergoing induction as a result of fetal or maternal complications	SBP <90% of baseline	Prophylactic infusion immediately after spinal injection: E: 2.5 mg/min P: 30 μg/min Bolus of E: 4 mg P: 50 μg given for each hypotensive value measured Infusion stopped if SBP >120% of baseline. Infusion reduced to half if SBP >110% but <120% of baseline Other drugs: Atropine 0.6 mg in case of bradycardia TDU [median (IQR)]: E: 29 (25–37.2) mg P: n.d.	On labour room: balanced crystalloid Further fluid regimen: n.d.	Incidence of fetal acidosis in newborns*
Mohta 2016	53 W	53 W	ASA I–II women, singleton pregnancy undergoing emergency CS for potential fetal compromise under spinal anaesthesia; post- and prematurity were included in the study non-reassuring fetal heart rate (FHR) status i.e. FHR >170 or <100 beats/min; FHR deceleration failing to recover after completion of uterine contraction (type-2 dips); meconium-stained liquor with FHR abnormality or thick meconium; cord prolapse; intrauterine growth restriction; oligohydramnios; dystocia; placental abruption, placenta praevia; post- and prematurity	Maternal complications such as preeclampsia; cardiovascular disease; cerebrovascular disease; multiple gestation; known fetal abnormality; patients with contraindications for spinal anaesthesia; maternal baseline SBP <100 mmHg Cases with a severely compromised fetus, where immediate administration of general anaesthesia was considered appropriate	SBP <100 mmHg	E: 8 mg/ml P: 100 μg/ml BP measured every minute, bolus given for each value SBP <100 mmHg measured Other drugs: Glycopyrronium 0.2 mg in case of bradycardia TDU [median (IQR)]: E: 16 (8–16) mg P: 200 (100–200) μg	Co-load: 15 ml/kg RL at the time of spina injection, afterwards minimal flow	Umbilical artery blood pH

Mohta 2018	40 W	40 W	Women with preeclampsia who had a singleton pregnancy and were going to have a caesarean section under spinal anaesthesia	Chronic hypertension or other cardiovascular disease, cerebrovascular disease, known fetal abnormality or severe fetal distress	Decrease in SBP <80% of baseline or SBP <100 mmHg	E: 4 mg/ml P: 50 μg/ml BP measured every minute, bolus given for each moment of hypotension Other drugs: Glycopyrronium 0.2 mg in case of bradycardia TDU [median (IQR)]: E: 8 (4–56) mg P: 100 (50–400) μg	Co-load with 10 ml/kg RL after injection of spinal anaesthesia	Umbilical artery blood pH
Ngan Kee 2008	74 W	74 W	Patients booked on the day of surgery for CS as emergencies, patients in whom labour subsequently proceeded to CS	Pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, multiple gestation, known fetal abnormality or any medical contra-indication to spinal anaesthesia such as thrombocytopenia or coagulopathy	SBP <100 mmHg	Prophylactic use: no E: 10 mg as bolus in case of hypotension P: 100 μg as bolus in case of hypotension Other drugs: Atropine 0.6 mg in case of bradycardia TDU: n.d.	Co-load with up to 2 l RL after injection of spinal anesthesia	Umbilical artery blood pH

ASA: American Society of Anesthesiologists; CS: caesarean section; n.d.: no details provided; W: women; I: infants; (S)BP: (systolic) blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; MAP: mean arterial pressure; E: ephedrine; P: phenylephrine; RL: Ringer's Lactate solution, HES: hydroxyethylstarch. TDU: total dose used; BMI: body mass index. HIV: human immunodeficiency virus. AIDS: acquired immunodeficiency syndrome.

*The primary outcome was mentioned in the introduction as the incidence of fetal acidosis. However, the sample size calculation was performed based on umbilical arterial blood pH <7.2.

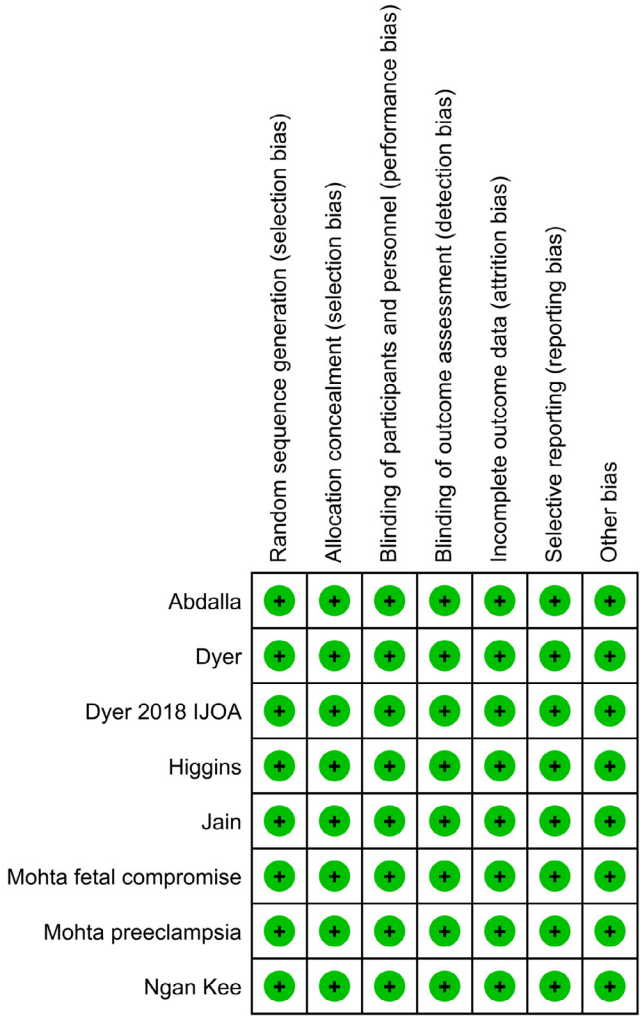

Fig. 2 Risk of bias assessment

Discussion

The results of this meta-analysis did not show a difference in the primary outcome, the incidence of fetal acidosis (umbilical arterial pH <7.20), between ephedrine and phenylephrine when used for high-risk caesarean sections. However, TSA showed that the number of included patients was too small to allow a definitive conclusion. Meta-regression did not reveal evidence of a dose-response relationship with either vasopressor. Our statistical analysis was not suggestive of publication bias, and the overall evidence level according to GRADE was moderate. Thus, there is insufficient evidence to conclude both drugs are similarly suitable for the potentially compromised fetus, so while this meta-analysis did not find differences in fetal outcomes between the two drugs, larger patient numbers and more outcome events are required to clarify the situation in this 'high-risk' caesarean birth population.

Table 2 Secondary maternal outcomes

Outcome	Studies	Number of subjects		RR	95%CI
		E	PhE		
Nausea	21,22,24	139	139	1.23	0.77 to 1.95
Vomiting	21,23,24	139	139	2.00	0.73 to 5.44
Bradycardia	20,21,24,25	192	192	0.23	0.01 to 3.50
Hypertension	20,24,25	139	139	0.70	0.28 to 1.78

E: ephedrine; PhE: phenylephrine; RR: relative risk; CI: confidence interval.

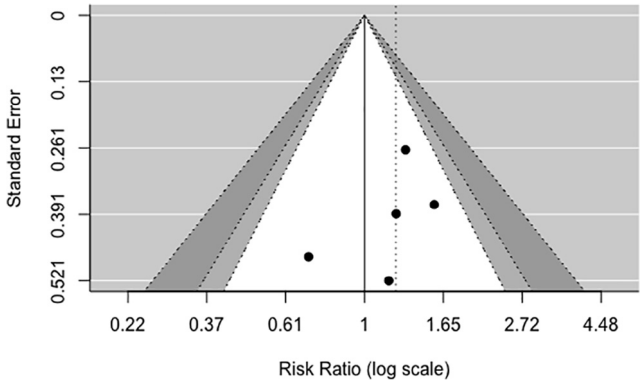

Fig. 4 Contour-enhanced funnel plot all studies of uteroplacental insufficiency: incidence of fetal acidosis with ephedrine versus phenylephrine

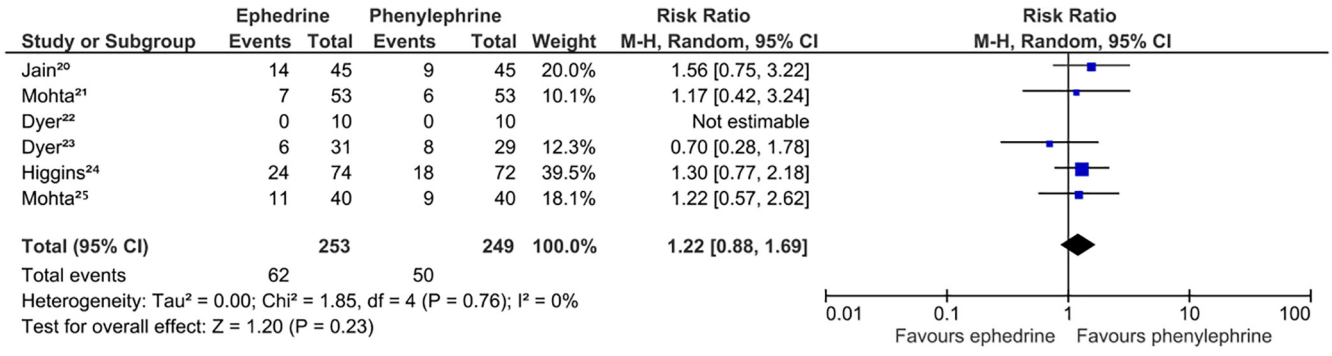

Fig. 3 Meta-analysis of fetal acidosis (umbilical artery pH <7.20)

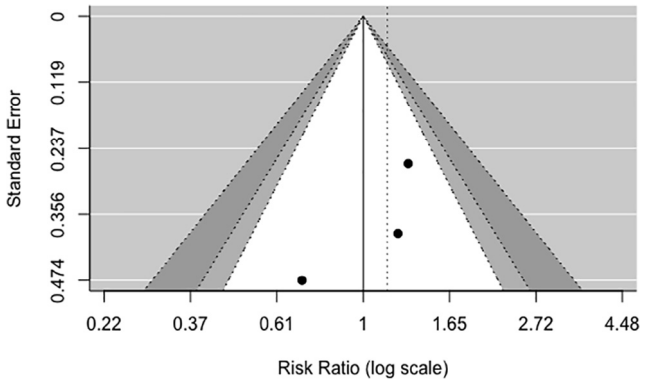

Fig. 5 Contour-enhanced funnel plot of the pre-eclampsia studies: incidence of fetal acidosis with ephedrine versus phenylephrine

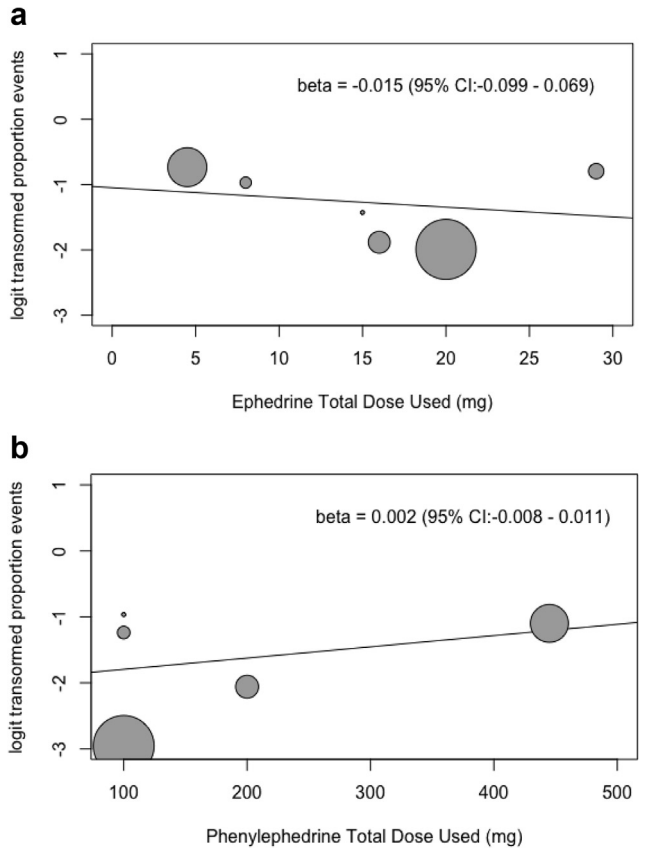

Fig. 6 Meta-regressions of vasopressor doses and incidence of fetal acidosis for all studies of uteroplacental insufficiency. (a) Meta-regression: ephedrine. (b) Meta-regression: phenylephrine

Previous meta-analyses have demonstrated a clearly favourable effect of phenylephrine on the fetal acid-base status after elective caesarean section,[3,26] and phenylephrine is now considered the first choice for these cases.[2] Our current analysis was unable to determine whether this same advantage is also applicable to

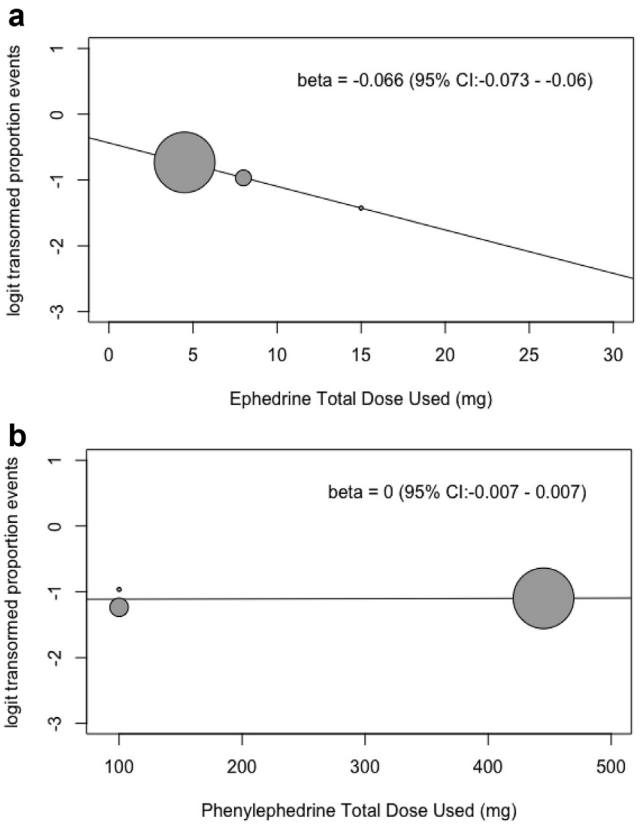

Fig. 7 Meta-regressions of vasopressor doses and incidence of fetal acidosis in the pre-eclampsia studies. (a) Meta-regression: ephedrine. (b) Meta-regression: phenylephrine

high-risk patients. The absence of a measureable difference in effect on fetal pH between the two vasopressors in high-risk cases may relate partly to a lower requirement for vasopressors in these patients, which would reduce maternal and fetal exposure to the drugs. It is well known that the incidence and severity of hypotension is lower, and less ephedrine is required during spinal anaesthesia for caesarean section in patients with preeclampsia, compared with healthy patients.[27–29] The same has been observed in other high-risk patients, such as women in labour.[30] The mechanism underlying fetal acidosis associated with ephedrine has been postulated to be associated with placental transfer and stimulation of fetal metabolism.[31] Use of smaller doses of vasopressors in high-risk patients would reduce any adverse effects of placental drug transfer.

When considering the best vasopressor to use in high-risk caesarean sections, factors other than the effect on fetal acid-base status may also be important. The faster onset and shorter duration of phenylephrine confers greater titratability compared with ephedrine, which may be a clinical advantage in patients who are haemodynamically unstable. Thus, evidence showing that phenylephrine is non-inferior to ephedrine for an adverse outcome such as fetal acidosis would be potentially useful. However, previous studies have used

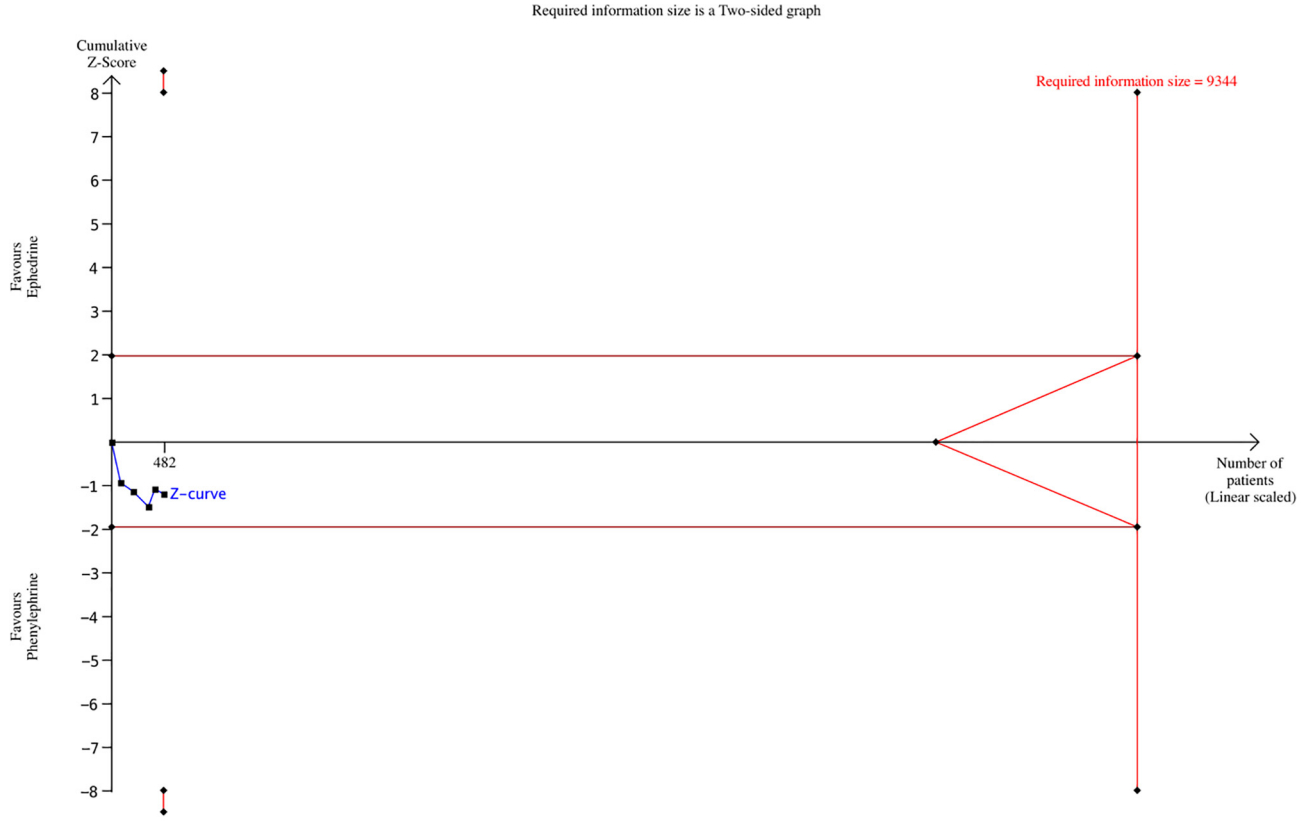

Fig. 8 Trial sequential analysis of the primary outcome, the incidence of fetal acidosis in studies comparing ephedrine with phenylephrine in all studies of uteroplacental insufficiency

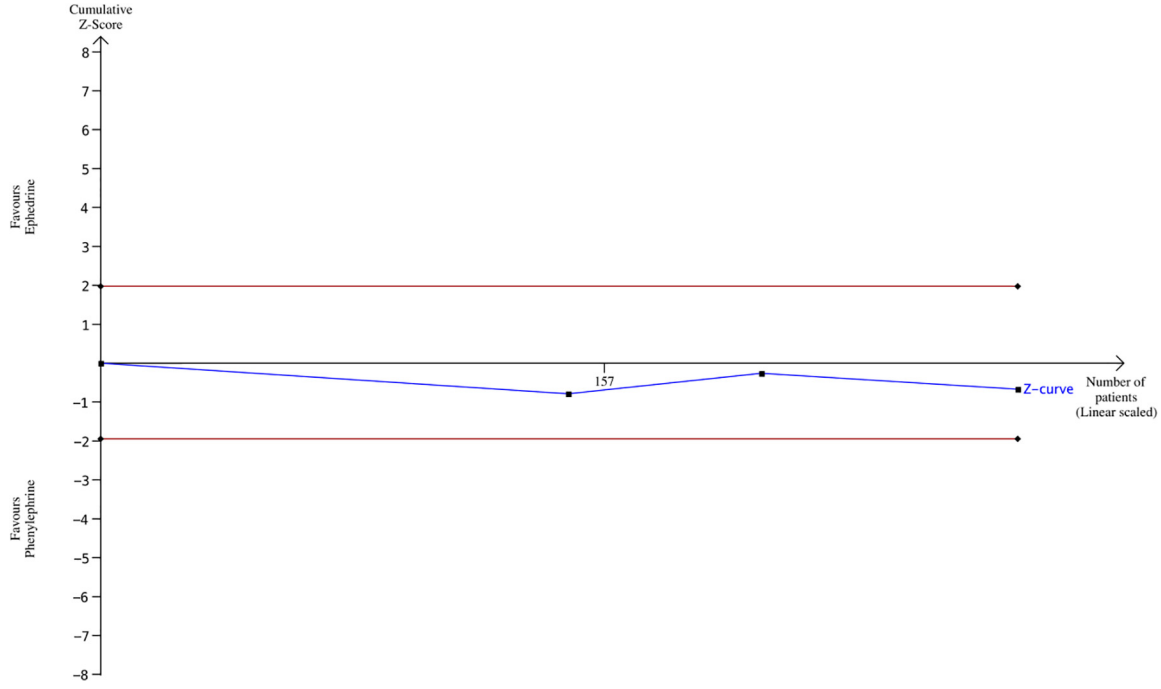

Fig. 9 Trial sequential analysis of the primary outcome, the incidence of fetal acidosis in studies comparing ephedrine with phenylephrine, in pre-eclampsia studies only

study designs aimed to detect superiority. Future studies, using a non-inferiority design, and comparing the effect of ephedrine versus phenylephrine on fetal acidosis in high-risk patients, would be of interest.

We chose fetal acidosis as the primary outcome for analysis because of the established association between low umbilical arterial pH and increased neonatal morbidity. Malin et al. reported in a systematic review and meta-analysis that low umbilical arterial cord pH was significantly associated with neonatal mortality (OR 16.9, 95% CI 9.7 to 29.5), and that there was also an increased risk for hypoxic ischaemic encephalopathy, intraventricular haemorrhage, and cerebral palsy.[32] In our analysis, we chose a pH value of <7.2 to define fetal acidosis. However, there is no clear threshold for the value of uterine arterial pH associated with risk and a range of different definitions of both umbilical arterial pH and base excess has been used in previous studies. That notwithstanding, umbilical arterial pH <7.2 has been used widely in previous anaesthesia trials. Regardless of the definition used, our meta-regression analysis did not show evidence of a significant dose–response relationship.

In the studies we included there were clinically heterogenous patient cohorts, with a variety of underlying pathologies. However, since our review was systematic, we included all studies retrieved by our search (i.e., we considered studies eligible when they used either the search term "high-risk" or "emergency"). In addition, in the studies on preeclampsia there were cases of different severity that may have had an impact on the effect of vasopressors. There was heterogeneity amongst studies in the peri-operative use of intravenous fluids and methods of administration of vasopressors. There is controversy surrounding the optimal intravenous fluid regimen during spinal anaesthesia for caesarean section, but the evidence does not suggest an important effect of the fluid regimen on neonatal outcome. Ngan Kee et al.[33] found, in patients who received vasopressor infusions, that there was no difference in neonatal outcome between patients who received crystalloid pre-hydration versus no pre-hydration or colloid pre-hydration versus no pre-hydration.[34] Similarly, there is controversy surrounding the merits of infusion versus intermittent boluses of vasopressor and comparative studies have not shown any differences in neonatal outcome.[35,36] Therefore, it is unlikely that differences in these factors had a significant influence on the results of our meta-analysis.

In summary, despite several studies including more than 700 patients, our meta-analysis showed that there are insufficient data currently available to make an evidence-based recommendation regarding the choice of ephedrine versus phenylephrine in high-risk caesarean sections. The application of the TSA technique revealed that the required information size has not been reached. This precludes meaningful conclusions. None of the studies entered into our analysis was powered to detect differences in the incidence of fetal acidosis, so we suggest that further research is still needed.

Declaration of interests

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