Obstetrical and Pediatric Anesthesia

Prophylactic ephedrine prevents hypotension during spinal anesthesia for Cesarean delivery but does not improve neonatal outcome: a quantitative systematic review

[L'administration prophylactique d'éphédrine prévient l'hypotension pendant la rachianesthésie pour Césarienne, mais n'améliore pas l'évolution néonatale : une revue méthodique quantitative]

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Purpose: The objective of this systematic review was to assess the effectiveness and safety of ephedrine compared with control when given prophylactically to prevent hypotension during spinal anesthesia for Cesarean delivery.

Source: Randomized, controlled trials obtained through MEDLINE, EMBASE, the Cochrane Controlled Trials Registry, contact with leading experts, and a reference list of published articles were analyzed. The following keywords were utilized: spinal anesthesia, hypotension, Cesarean section, pregnancy complications, pregnancy outcome, fetal outcome, neonatal outcome, umbilical blood cord gases, vasopressor and ephedrine. Clinical trials were considered if they compared prophylactic ephedrine, given by any dose or route, *vs* control.

Principal findings: The 14 clinical trials identified included data from a total of 641 patients. Ephedrine was more effective than control for preventing hypotension (relative risk [RR], 0.73; 95% confidence interval [CI], 0.63 to 0.86). Most importantly, there was no difference in the risk of fetal acidosis, defined as umbilical arterial pH < 7.2 (RR, 1.36; 95% CI, 0.55 to 3.35) or the incidence of low Apgar scores (< 7 or < 8) at one minute (RR, 0.77; 95% CI, 0.29 to 2.06) and five minutes (RR, 0.72; 95% CI, 0.24 to 2.19).

Conclusions: Prophylactic ephedrine is more effective than control for preventing hypotension during spinal anesthesia for elective Cesarean delivery but a clinically relevant positive effect on neonatal outcome was not observed. Therefore, the routine use of prophylactic ephedrine to prevent any adverse effects of maternal hypotension following spinal anesthesia for Cesarean delivery is not supported by the current systematic review.

Objectif : *Évaluer l'efficacité et l'innocuité de l'éphédrine, comparée à un témoin, administrée de manière prophylactique pour prévenir l'hypotension pendant la rachianesthésie lors de l'accouchement par Césarienne.*

Source : *Nous avons analysé des essais randomisés et contrôlés obtenus de MEDLINE, EMBASE, l'Index Cochrane des essais randomisés et contrôlés, personnes-ressources autorisées et une liste de références d'articles publiés. Les mots clés ont été : spinal anesthesia, hypotension, Cesarean section, pregnancy complications, pregnancy outcome, fetal outcome, neonatal outcome, umbilical blood cord gases, vasopressor et ephedrine. Nous n'avons considéré que les essais cliniques qui comparaient l'éphédrine prophylactique à un témoin, sans égard à la dose et à la voie d'administration.*

Constatations principales : *Les 14 essais cliniques retenus comportaient des données sur 641 patientes. L'éphédrine a été plus efficace que le médicament témoin dans la prévention de l'hypotension (risque relatif [RR], 0,73 ; intervalle de confiance [IC] de 95 %, 0,63 à 0,86). Le plus important est l'absence de différence de risque d'acidose fœtale, définie par un pH de l'artère ombilicale < 7,2 (RR, 1,36 ; IC de 95 %, 0,55 à 3,35) ou l'incidence d'indice d'Apgar < 7 ou < 8 à une minute (RR, 0,77 ; IC 95 %, 0,29 à 2,06) et à cinq minutes (RR, 0,72 ; IC 95 %, 0,24 à 2,19).*

Conclusion : *L'administration préventive d'éphédrine agit plus efficacement qu'un médicament témoin contre l'hypotension pendant la rachianesthésie pour Césarienne, mais aucun effet positif de pertinence clinique sur l'évolution néonatale n'est observé. Notre revue systématique ne corrobore donc pas l'usage courant d'éphédrine*

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prophylactique comme prévention de tout effet indésirable sur l'hypotension maternelle suivant la rachianesthésie pendant la césarienne.

SPINAL anesthesia offers a fast, profound, and high quality sensory and motor block in women undergoing Cesarean delivery.[1] The most common complication of spinal anesthesia for Cesarean delivery is hypotension, with a reported incidence greater than 80%.[2] Unfortunately, the actual incidence of postsubarachnoid hypotension in this patient population is difficult to ascertain due primarily to a lack of a standard definition of maternal hypotension. Maternal hypotension may have detrimental effects on uterine blood flow, fetal well-being and ultimately neonatal outcome as measured by umbilical artery pH and Apgar scores.[3]

Lateral uterine displacement and *iv* prehydration are commonly used to prevent hypotension but these have limited efficacy and a vasopressor drug is often required.[2,4] Although vasopressors unquestionably have a role in the treatment of hypotension,[2] their prophylactic use is more controversial. Some studies have shown no significant reduction of maternal hypotension associated with the prophylactic use of ephedrine when compared with control.[5,6] In other studies, women given ephedrine before or during induction of spinal anesthesia had a lower incidence of maternal hypotension compared with those not given a vasopressor.[1,4,7]

To identify evidence-based recommendations for clinical practice and further areas of research, we conducted a systematic review of randomized controlled trials (RCTs) of prophylactic vasopressor use in obstetrics. Because the main drug that has been investigated in this context is ephedrine, other drugs were excluded in this review. The purpose of the current systematic review was to compare the effects and consequences of ephedrine *vs* controls of placebo or no ephedrine for the prevention of hypotension during spinal anesthesia during Cesarean delivery.

Materials and methods

Systematic search

A systematic search of electronic databases (MEDLINE 1966-May 2000, EMBASE 1988-May 2000, Cochrane Controlled Trials Register) was performed. Full reports of RCTs that examined the effect of ephedrine compared with a control of either placebo or no ephedrine for women at risk of maternal hypotension during spinal anesthesia or combined spinal-epidural anesthesia for Cesarean delivery were included. The electronic search strategy included the 'optimal sensitive search strategy'[8] with the following MeSH and textwords: *"spinal anesthesia", "hypotension", "Cesarean section", "pregnancy complications", "pregnancy outcome", "fetal outcome", "neonatal outcome", "umbilical blood cord gases", "vasopressors"* and *"ephedrine"*. The main clinically important and reliable measures of outcomes were maternal hypotension, reactive hypertension, maternal heart rate, maternal uterine circulation, nausea and/or vomiting and neonatal outcomes (Apgar scores at one and five minutes, umbilical arterial and venous pH and standard base excess). Ephedrine administered before, during or immediately after induction of spinal anesthesia, irrespective of dose or mode of administration was considered in this systematic review. Additional reports were identified from reference lists of retrieved reports and review articles of hypotension during spinal anesthesia and review articles of vasopressors. Leading experts were contacted to seek further published and unpublished trials. There was no language restriction.

Data extraction

The selection of trials for inclusion in the systematic review was performed independently by the reviewers (A.L. and W.N.) after using the search strategy described above. Trials were examined for duplicate data. Data were abstracted independently by A.L. and W.N. using a standardized data collection form. There was no attempt to blind the reviewers (A.L. and W.N.) to the authors or results of the relevant trials. Details of anesthetic technique, study population, prehydration, uterine displacement and definition of maternal hypotension were collected. Where appropriate, the primary author of a RCT was contacted for clarification of data. Discrepancies were resolved by discussion, or advice was sought from a third party (T.G.).

The quality of the eligible trials was assessed independently. The level of allocation concealment, defined as the process used to prevent the foreknowledge of group assignment in a RCT, was graded as A (adequate), B (unclear), or C (inadequate), as previously described.[9] Blinding, losses to follow-up and whether the authors did a sample size calculation before trial commencement were recorded. The reasons for trial exclusion from the review were recorded.

Statistical analysis

The main outcome was prevention of maternal hypotension by ephedrine *vs* control. We used the specific definition of hypotension that was used in each

individual trial and made no attempt at standardization. Consequences associated with the use of ephedrine that we assessed were reactive hypertension, maternal heart rate, low Apgar scores (< 7 or < 8 as defined by trial authors) and fetal acidosis which we defined as umbilical arterial pH < 7.20).[10] In RCTs [4,11] with more than one ephedrine treatment arm, we combined the data from each treatment arm for dichotomous outcomes (hypotension, hypertension, nausea and/or vomiting and Apgar scores). For continuous data (umbilical arterial and venous pH and standard base excess), the greatest ephedrine dose treatment arm was used as it was not possible to combine data from all ephedrine arms when only summary group means were reported.

The DerSimonian and Laird random-effects model was used to combine data for both continuous and dichotomous outcomes, because the treatment and conditions in these studies were expected to be heterogeneous. This model incorporates both between-study (different treatment effects) and within-study (sampling error) variability.[12] The pooled relative risk (RR) and 95% confidence interval (95% CI) were calculated for dichotomous data. The weighted mean difference (WMD) method was used to pool continuous data. Heterogeneity was analyzed using the Q-statistic with a threshold for the $P < 0.10$. Where heterogeneity (inter-study variation) was found, the studies that seemed to be the major contributors to the heterogeneity were evaluated in an attempt to discover the reasons. All meta-analyses were done using Arcus Quickstat software (version 1.2; Addison Wesley Longman Ltd, Cambridge, UK).

Sensitivity analyses for hypotension were done to estimate the robustness of results according to allocation concealment (adequate *vs* unclear/inadequate), blinding (double-blinding *vs* single-blinding) and intervention type (ephedrine given before hypotension *vs* ephedrine given when a small decrease in arterial pressure was detected).

A funnel plot (plot of treatment effect against trial precision) was used to detect bias in the meta-analysis of prophylactic ephedrine trials on preventing hypotension. In the presence of bias which will usually lead to an over-estimate of the treatment effect, the funnel plot will be skewed and asymmetrical. The degree of asymmetry was measured by Egger's method[13] using EasyMa software (version 2000, Michel Cucherat, Lyon, France). Sources of asymmetry in funnel plots can be due to selection bias (publication bias, English language bias, citation bias, multiple publication bias), true heterogeneity, data irregularities, choice of effect measure and chance.[13]

To judge whether therapy was worthwhile for an individual, the absolute magnitude of benefit was estimated by calculating the numbers-needed-to-treat (NNT). As a NNT derived from meta-analysis can be sensitive to factors that change the baseline risk, a more useful NNT was estimated by applying the pooled relative risk to a relevant baseline risk.[14] We chose 80%[2] as the baseline risk to calculate a clinically useful NNT.

Results

Included and excluded trials

Nineteen articles were initially considered for inclusion, but after consideration, six were excluded. Reasons for exclusion were observational studies,[15–17] use of general anesthesia,[18] epidural anesthesia[19] and abstract of a conference meeting.[20]

There were 13 articles describing 14 RCTs of ephedrine *vs* placebo or no ephedrine ($n = 641$; Table). Trials were conducted between 1976 and 2001. There was one trial that had two vasopressor arms (ephedrine, angiotensin) and a control arm.[21] One study described two separate ephedrine dose-response trials: *iv* bolus (trial 1) and continuous *iv* infusion (trial 2).[11] Multiple ephedrine groups were used in several trials.[4,5,11(trial 1, trial 2), 22]

Ephedrine was given before hypotension developed in 13 of 14 RCTs.[1,4–7,11,21–26] The authors administered ephedrine before spinal anesthesia in three trials,[7,21,24] during induction of spinal anesthesia in one trial[6] and immediately after induction of spinal anesthesia in other trials.[1,4,5,11,22,23,25–27] In one trial, ephedrine was given immediately after there was any decrease in arterial pressure to less than the baseline.[27] In all trials, "rescue" doses of ephedrine were given if hypotension developed (Table).

In all trials, the women were described as healthy or were graded as ASA physical status I or II. There were no reports of trials recruiting women undergoing emergency Cesarean delivery, and therefore, we have assumed that all trials included in this systematic review involved women undergoing elective Cesarean delivery. Drugs used for spinal anesthesia included tetracaine,[7,21,22] bupivacaine,[5,6,27] and hyperbaric bupivacaine.[1,4,11,23–26] The combined spinal-epidural anesthesia technique was used in two trials.[1,26] All trials specified the use of uterine displacement. *Iv* fluid prehydration was given in all trials except one in which the ephedrine group was not given prehydration.[25]

There was adequate allocation concealment (A) in four trials.[1,4,5,26] Despite attempts to contact the primary author, we were uncertain whether randomization occurred in the earliest trial[7] but the groups appeared comparable. All other trials were classified as

TABLE Characteristics of included trials

Study	*Methods*	*Participants*	*Anesthesia*	*Intervention*	*Outcome*
Gutsche (1976)[7] USA	Double-blinded, ? randomized trial. No details about withdrawals. No sample size calculation.	17 ASA I-II women. Exclusion: no details given.	Prehydration crystalloid (mean 844 mL) *iv* 8 to 25 min before induction. Left lateral tilt 5 to 10 degrees. Tetracaine 9 to 10 mg.	Ephedrine 50 mg *im* before spinal induction. Comparison: no intervention Rescue: 10 to 20 mg *iv* ephedrine when necessary to maintain SBP > 100 mmHg.	Hypotension (SBP < 100 mmHg), hypertension (no exact definition), nausea and/or vomiting, Apgar scores.
Kang (1982)[22] USA	Single-blinded, randomized controlled trial. No details about randomization method. Unclear allocation concealment (B). No details about withdrawals. No power calculation.	44 healthy repeat Cesarean delivery, mean age 30 yr. Exclusion: no details given.	Prehydration 15 $mL \cdot kg^{-1}$ lactated Ringer's solution within 20 min of induction. Left lateral tilt. Tetracaine 0.5%.	Ephedrine given immediately after spinal 5 $mg \cdot min^{-1}$ *iv* infusion for 2 min, then adjusted to keep 90% to 100% baseline SBP. Another group had ephedrine 20 mg *iv* bolus when SBP < 20% baseline. Rescue: ephedrine 10 mg *iv* bolus when necessary.	Hypotension (decrease SBP > 10% of baseline infusion group, decrease SBP > 20% of baseline bolus control group), reactive hypertension (SBP > 1 baseline), nausea and vomiting, Apgar scores, umbilical Apgar scores, umbilical standard base excess.
Kangas-Saarela (1990)[27] Finland	Single-blinded, randomized controlled trial. No details about randomization method. Unclear allocation concealment (B). No details about withdrawals. No sample size calculation.	16 healthy women, mean age 28 to 30 yr. Exclusions: no details given.	Left lateral 15 degree tilt. Bupivacaine 12.5 mg.	15 $mL \cdot kg^{-1}$ Ringer's solution for 20 min before spinal and ephedrine 10 mg *iv* increments as soon as any fall from baseline pressure. SBP kept within 90 to 100% of baseline SBP Comparison: Ringer's solution 20 $mL \cdot kg^{-1}$ No details about rescue ephedrine.	Hypotensoin (decrease SBP > 30% of baseline or < 100 mmHg), nausea and vomiting, Apgar scores.
Olsen (1994)[23] Denmark	Single-blinded, randomized controlled trial. No details about randomization method.	26 healthy women, mean age 30 to 31 yr. Exclusions: no details given.	Predydration 750 mL saline. Right wedge 15 degree tilt. Hyperbaric bupivacaine 13 mg.	Normal saline 750 mL + 500 mL for 15 min (actual 1.6 L), then ephedrine 0.15	Hypotension (not exactly defined), nausea, vomiting Apgar scores, umbilical arterial pH and standard

TABLE - *continued*

Study	*Methods*	*Participants*	*Anesthesia*	*Intervention*	*Outcome*
	Unclear allocation Concealment (B). Two withdrawals due to technical difficulties with ephedrine infusion No sample size calculation done.			mg·kg^{-1} *iv* bolus, followed by ephedrine 0.4 mg·kg^{-1}·hr^{-1} infusion. Comparison: normal saline 750 mL + 20 mL·kg^{-1} for 15 min (actual 2.5 L). Rescue: ephedrine 10 mg *iv* boluses every min if MAP > 10 mmHg below baseline.	base excess.
Ramin (1994)[21] USA	Randomized controlled trial. No blinding. No details about randomization method. Unclear allocation concealment (B). No sample size calculation done.	20 healthy repeat Cesarean delivery. Exclusions: labour, hypertension, diabetes, platelet counts < 100,000/mm^3, prolonged prothrombin or partial thromboplastin time, fetal distress, cardiac or pulmonary disease, any medical illness, or a known history of drug abuse.	Prehydration 2.0 L lactated Ringer's solution 15 to 20 min before induction. Left lateral tilt 15 degree. Tetracaine 8 to 9 mg.	Ephedrine 10 mg·hr^{-1} *iv* infusion to maintain diastolic BP 0 to 10 mmHg above baseline before induction of spinal anesthesia. Control: no intervention Rescue: ephedrine *iv* boluses when necessary.	Hypotension (decrease MAP > 30% of baseline), nausea and vomiting, Apgar scores, umbilical arterial and venous pH and standard base excess.
Chan (1997)[25] Hong Kong	Single-blinded, randomized controlled trial. No details about randomization medhod. Unclear allocation concealment (B). No details about withdrawal of patients. No sample size calculation done.	46 healthy women, mean age 31 to 32 yr. Exclusions: no details given.	Left lateral 15 degree tilted position. Hyperbaric bupivacaine 11.5 mg and morphine 0.25 mg.	Ephedrine 0.25 mg·kg^{-1} *iv* infusion over 3 min immediately after spinal induction. Comparison: Hartmann's solution 20 mL·kg^{-1} over 10 to 15 min immediately before spinal anesthesia. Rescue: ephedrine 6 mg *iv* bolus every min and increase *iv* fluid infusion rate.	Hypotension (decrease SBP > 20% of baseline), maternal uterine circulation, nausea and vomiting, Apgar scores umbilical arterial and venous pH and standard base excess.
Webb (1998)[24] South Africa	Randomized, double-blinded, placebo-controlled trial. No details of randomization	40 women. Exclusions: obesity resulting in impalpable lumbar spines, hypertension	Prehydratoin 500 mL Ringers' lactate over 15 to 20 min. Uterine displacement	Ephedrine 37.5 mg *im* 5 to 14 min before spinal anesthesia. Comparison: normal	Hypotension (SBP < 100 mmHg or decrease > 30% of baseline), reactive hypertension

TABLE - *continued*

Study	*Methods*	*Participants*	*Anesthesia*	*Intervention*	*Outcome*
	method. Unclear allocation concealment (B). No details about withdrawal of patients. No sample size calculation done.	(BP > 150/90), conventional contraindications to spinal anesthesia (coagulopathy, sepsis hypovolemia).	(details not given). Hyperbaric bupivacaine 11 to 25 mg.	saline *im* injection. Rescue: ephedrine 5 mg *iv* bolus every min. and increase fluid infusion rate.	(increase > 30% of baseline), tachycardia, Apgar scores, umbilical venous pH.
King (1998)[5] USA	Randomized, double-blinded, placebo-controlled trial. Adequate allocation concealment (A). No details about withdrawal of patients. No sample size calculation done.	30 healthy women, mean age 27 to 32 yr. Exclusions: history of hypertension, preeclampsia, preterm labour, juvenile onset diabetes, cocaine or methamphetamine use, cardiac disease, or those in whom regional anesthesia was inappropriate.	Prehydration 15 $mL \cdot kg^{-1}$ normal saline over 10 min before spinal anesthesia. Bupivacaine 12 mg and fentanyl 10 µg. Left uterine displacement.	Ephedrine 10 mg bolus within 1 min after induction of spinal anesthesia. Another group had ephedrine 20 mg infusion over 12 min within 1 min after induction of spinal anesthesia. Comparison: normal saline. Rescue: ephedrine 10 mg *iv* when necessary.	Hypotension (decrease SBP > 20% of baseline), Apgar scores.
Carvalho (2000)[11] Study 1 Brazil	Randomized controlled trial. No details about randomization method. Unclear allocation concealment (B). No blinding. No details about withdrawal of patients. No sample sizes calculation done.	80 healthy women, mean age 27 to 29 yr. Exclusions: no details given.	Prehydration 10 $mL \cdot kg^{-1}$ lactated Ringer's solution. Wedge uterine displacement. Hyperbaric bupivacaine 12.5 mg and morphine 25 µg.	Three ephedrine *iv* bolus groups (5 mg, 10 mg, 15 mg) after induction of spinal anesthesia. Comparison: no ephedrine *iv* bolus. Rescue: ephedrine 5 mg *iv* bolus when necessary.	Hypotension (decrease SBP > 20% of baseline), reactive hypertension (increase SBP > 20% of baseline), nausea, vomiting, Apgar scores, umbilical arterial pH.
Carvalho (2000)[11] Study 2 Brazil	Randomized controlled trial. No details about randomization method. Unclear allocation concealment (B). No blinding. No details about withdrawal of patients. No sample size calculation done.	100 healthy women, mean age 27 to 30 yr. Exclusions: no details given.	Prehydration 10 $mL \cdot kg^{-1}$ lactated Ringer's solution. Wedge uterine displacement. Hyperbaric bupivacaine 12.5 mg and morphine 25 µg.	Four ephedrine infusion groups (0.5 $mg \cdot min^{-1}$, 1 $mg \cdot min^{-1}$, 2 $mg \cdot min^{-1}$ infusion, 4 $mg \cdot min^{-1}$. Comparison: no ephedrine infusion. Rescue: ephedrine 5 mg *iv* bolus when necessary.	Hypotension (decrease SBP > 20% of baseline), reactive hypertension (increase SBP > 20% of baseline), nausea, vomiting, Apgar scores, umbilical arterial pH.
Ngan Kee (2000)[4] Hong Kong	Double-blinded, randomized, placebo controlled trial. Randomization by	80 women, ASA I/II mean age 31 to 33 yr. Exclusions: preexisting or pregnancy induced	Prehydration 20 $mL \cdot kg^{-1}$ lactated Ringer's solution given for 10 to 15	Three ephedrine *iv* bolus groups (10 mg, 20 mg, 30 mg) given 1 min after induction of spinal	Hypotension (decrease SAP > 20% of baseline and < 100 mmHg), reactive hypertension

TABLE - *continued*

Study	*Methods*	*Participants*	*Anesthesia*	*Intervention*	*Outcome*
	coded, opaque, shuffled envelopes. Allocation concealment adequate (A). No patients withdrew from study. Sample size calculation done.	hypertension, known cardiovascular or cerebrovascular disease, contraindications to spinal anesthesia.	min. Left lateral tilt. Hyperbaric bupivacaine 10 mg and fentanyl 15 µg.	anesthesia. Comparison: normal saline *iv* bolus. Rescue: ephedrine 10 mg *iv* bolus every min when necessary.	(increase SAP > 20% of baseline), nausea or vomiting, Apgar scores, umbilical arterial and venous pH.
Vercauteren (2000)[1] Belgium	Double-blinded, placebo controlled trial. Allocation concealment adequate (A). One withdrew due to combined spinal-epidural technical difficulty and one withdrew due to inadequate combined spinal-epidural anesthesia. No sample size calculation done.	48 women, mean age 29 to 30 yr undergoing combined spinal-epidural anesthesia. Exclusions: semi-urgent Cesarean delivery Cesarean delivery, active labour, gestational age < 37 weeks, initial SBP > 150 mmHg.	Prehydration 1.0 L lactated Ringer's solution and 0.5 L hydroxyethylstarch 6%. Left lateral tilt 15 degree. Hyperbaric bupivacaine 6.6 mg with sulfentanil 3.3 µg.	Ephedrine 5 mg *iv* bolus. Comparison: normal saline *iv* bolus. Rescue: ephedrine 5 mg *iv* bolus when necessary.	Hypotension (SBP < 100 mmHg or decrease > 30% baseline), bradycardia (decrease HR > 30% of baseline), nausea or vomiting, Apgar scores, umbilical arterial and venous pH.
Tsen (2000)[6] USA	Double-blinded, placebo controlled trial. Unclear allocation concealment (B). No details about withdrawals. Sample size calculation done.	40 women, mean age 32 to 35 yr undergoing spinal anesthesia. Exclusions: cardiac, pulmonary, renal or other systematic diseases, history of medications that would alter hemodynamic response.	Prehydration 10 mL·kg lactated Ringer's soluction over 15 min. Left lateral tilt by wedge. Bupivacaine 12 mg with fentanyl 10 µg.	Ephedrine 10 mg *iv* bolus given with spinal anesthesia. Comparison: normal saline *iv* bolus. Rescue: ephedrine 10 mg *iv* bolus when necessary.	Hypotension (20% decrease in MAP), hypertension (not defined), tachycardia (not defined), Apgar scores.
Ayorinde (2001)[26] UK	Double-blinded, placebo controlled trial. Adequate allocation concealment (A). No withdrawals. Sample size calculation done.	54 women, mean age 30 to 31 yr undergoing combined spinal-epidural anesthesia for elective Cesarean delivery. Exclusion: known hypertensive patients, resting arterial pressure > 160/90 mmHg.	Prehydration 500 mL lactated Ringer's solution. Left lateral 15 degree tilted position. Hyperbaric 11 mg bupivacaine with fentanyl 20 µg.	Ephedrine 45 mg *im* given immediately after spinal anesthesia. Comparison: normal saline *im* injection. Rescue: ephedrine 6 mg *iv* bolus when necessary if patient became hypotensive or reported nausea, vomiting or dizziness.	Hypotension (> 25% decrease in MAP), hypertention (> 25% increase in MAP), bradycarida (HR < 60), Apgar scores, umbilical venous pH.

ASA = American Society of Anesthesiologists physical status; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure; SBP = systolic blood pressure.

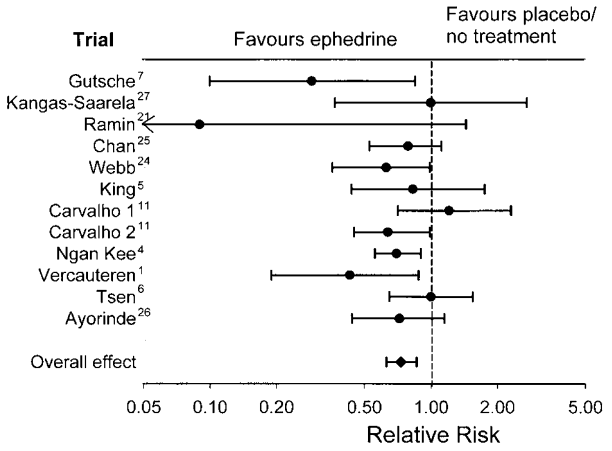

FIGURE 1 Meta-analysis of trials. The effect of prophylactic ephedrine *vs* control on hypotension. Data are relative risk with 95% confidence intervals.

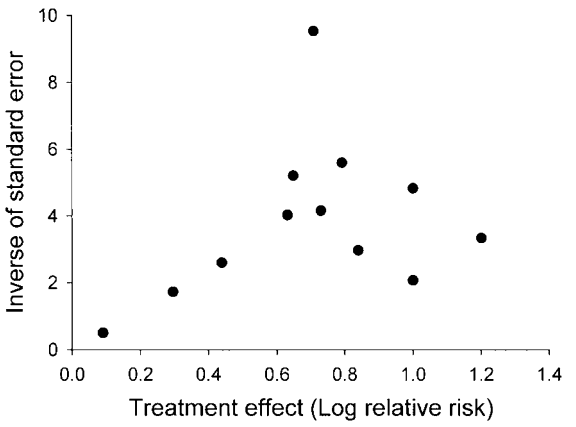

FIGURE 2 Funnel plot for 12 randomized controlled trials of prophylactic ephedrine *vs* control on hypotension.

having unclear allocation concealment (B) because the randomization procedure was not described. There was double-blinding in seven trials.[1,4–7,24,26] There was no blinding in three trials.[21,11 (trial 1, trial 2)] All other trials were single-blinded. Details about withdrawals from the trial were given in three trials.[1,4,23] Sample size calculations were done in three recent trials.[4,6,26]

Maternal outcomes

Hypotension

Of the 14 trials included in this review, 12 had sufficient data for a meta-analysis of ephedrine to prevent hypotension. One trial was excluded because there was no specific definition for hypotension.[23] Another trial was excluded because different definitions of hypotension were used in the ephedrine and control groups.[22] There were several definitions of hypotension used within two trials.[1,25] In these trials we accepted the definition as a decrease of systolic blood pressure (SBP) > 20% from baseline[25] and a SBP < 100 mmHg.[1]

The mean baseline risk of hypotension in the control group was 69% (95% CI, 63% to 75%) in the 11 trials. Disregarding the dose of ephedrine used, data pooled from 12 trials (n = 571) were homogeneous (Q statistic = 13.94, df = 11, P = 0.24) and showed that ephedrine was more effective for preventing hypotension than control (RR, 0.73; 95% CI, 0.63 to 0.86; Figure 1). There was no evidence of bias in this meta-analysis as shown by the symmetry in the funnel plot (intercept = 0.53, 90% CI, -0.48 to 1.54, P = 0.41; Figure 2).

Sensitivity analysis performed after excluding Gutsche's trial[7] because of uncertainty about randomization showed that the overall summary effect size was robust (RR, 0.74; 95% CI, 0.65 to 0.85). Another sensitivity analysis performed after exclusion of the trial by Kangas-Saarela *et al.*[27] in which ephedrine was not given unless there was any decrease in arterial pressure to less than the baseline, showed that the overall RR was 0.73 (95% CI, 0.61 to 0.86). Kangas-Saarela *et al.*[27]showed that there was no difference between giving ephedrine or fluid intervention for the prevention of hypotension (RR,1.00; 95% CI, 0.37 to 2.73).

The level of allocation concealment did not affect the overall summary effect size. In restricting the meta-analysis to only trials that had adequate allocation concealment [1,4,5,26] the overall RR was 0.69 (95% CI, 0.58 to 0.83) with no evidence of heterogeneity (Q statistic = 2.04, df = 3, P = 0.56). In trials where allocation concealment was unclear,[6,7,11,21,24,25,27] the overall RR was 0.76 (95% CI, 0.59 to 0.99) with no evidence of heterogeneity (Q statistic = 11.50; df = 7; P = 0.12).

Meta-analysis of double-blinded studies[1,4–7,24,26] showed that ephedrine was significantly associated with a smaller risk of hypotension compared with control (RR, 0.70; 95% CI, 0.57 to 0.87). In contrast, this association was not significant in single-and open-blinded studies (RR, 0.79; 95% CI, 0.58 to 1.08).[11(trial 1, trial 2), 21,25,27]

Hypertension

The authors of eight trials recorded data on reactive hypertension.[4,6,7,11 (trial 1, trial 2), 22,24,26] Although hypertension was defined specifically in many trials, it was not standardized. Gutsche[7] and Tsen[6] reported a nil incidence of hypertension in both ephedrine and control groups without giving a specific definition. When we restricted the analysis to trials in which specific definitions of reactive hypertension were given,[4,11 (trial 1, trial 2), 22,24,26] there was no evidence that ephedrine was associated with reactive hypertension (RR, 1.63; 95% CI, 0.93 to 2.84).

Abnormal maternal heart rate

Maternal tachycardia was defined in one trial[24] as heart rate > 120 and there was no difference in the incidence between ephedrine (14/20) and placebo (13/20) groups. Maternal bradycardia was defined in one trial by Vercauteren *et al.*[1] as heart rate < 30% of baseline; in this trial the incidence of bradycardia was small in both ephedrine (0/24) and placebo (1/24) groups. In another trial,[26] bradycardia (heart rate < 60 beats·min^{-1}) did not occur in either ephedrine or placebo groups. Combining these two trials showed that ephedrine was not associated with bradycardia (RR, 0.52; 95% CI, 0.04 to 5.96).

Nausea and vomiting

There was no difference in the incidence of nausea (RR, 0.82; 95% CI, 0.57 to 1.18),[1,11(trial 1, trial 2),23] vomiting (RR, 0.73; 95% CI, 0.35 to 1.52)[1,11 (trial 1, trial 2),23] or nausea and vomiting (RR, 0.71; 95% CI, 0.37 to 1.37)[4,7,21,22,25,27] between the ephedrine and control groups.

Uterine vasculature

The uterine vasculature was assessed in a subgroup of patients (n = 11) in one trial using Doppler ultrasound.[25] There was no difference in the uterine artery pulsatility index between ephedrine and fluid control groups.[25]

Neonatal outcomes

APGAR SCORES

The Apgar scores were recorded at one minute and five minutes in all trials. A low Apgar score at one minute was defined as < 7 in all trials except Webb (1998)[24] and Kang (1982)[22] in which it was defined as < 8. With the exception of one trial,[1] all neonates had an Apgar score at one minute above the threshold. There was no difference between ephedrine and control groups in the incidence of low Apgar score at one minute (RR, 0.77; 95% CI, 0.29 to 2.06). A low Apgar score at five minutes was defined as < 8 in three trials,[1,7,24] and in all other trials it was defined as < 7. No neonates had low Apgar score at five minutes. The overall effect size suggested that there was no difference in low Apgar score at five minutes between ephedrine and control groups (RR, 0.72; 95% CI, 0.24 to 2.19).

Umbilical pH and fetal acidosis

The authors reported umbilical arterial pH in eight trials[1,4,11 (trial 1, trial 2), 21–23,25] (n = 301) but these trials were heterogeneous (Q statistic = 15.99, df = 7, P = 0.03). The mean umbilical arterial pH in the control groups ranged from 7.23[25] to 7.29.[1,23] The incidence of fetal acidosis (umbilical arterial pH < 7.2) was available in six trials (n = 350).[1,4,11 (trial 1, trial 2), 21,23] There was no difference in the risk of fetal acidosis between ephedrine and control groups (RR, 1.36; 95% CI, 0.55 to 3.35). Seven trials[1,4,21,22,24–26] (n = 292) reported umbilical venous pH. However, these trials were heterogeneous (Q statistic = 18.60, df = 6, P < 0.01).

Standard base excess

Four trials [21–23,25] (n = 136) showed that there was no significant difference between ephedrine and control for arterial standard base excess (WMD = -0.85, 95% CI = -2.32 to 0.61). The range of arterial standard base excess in the placebo or control groups was -1.8 [21] to -5.9.[25] Three trials[21,22,25] (n = 110) were heterogeneous (Q statistic = 6.91, df = 2, P = 0.03) when venous standard base excess was analyzed.

Discussion

The current systematic review has shown that prophylactic ephedrine was more effective than control for preventing hypotension in healthy parturients undergoing spinal anesthesia for elective Cesarean delivery. However, this effect did not translate into a significant reduction in nausea and/or vomiting or any difference in neonatal outcome.

To apply the results of this meta-analysis to a clinical setting so that anesthesiologists can judge whether prophylactic ephedrine is worthwhile for an individual, we calculated the NNT. If our results were applied to a baseline risk of 80%,[2] the NNT would be 4.6 (95% CI, 3.4 to 8.9) meaning that for every 100 women who receive ephedrine, 22 (95% CI, 11 to 30) will not develop hypotension who would have done so had they not received ephedrine. Therefore, the overall benefit of prophylactic ephedrine for the prevention of maternal hypotension during spinal anesthesia is small; this implies that clinical practice may be better focused on treatment after hypotension has occurred.

There was wide variation in the ephedrine regimens used in the trials included in our review. This most

likely reflects regional differences in practice around the world and between individual anesthesiologists. It is important to note that our meta-analysis did not discriminate between doses, precise timing or routes of administration of ephedrine. Meta-regression,[28] a statistical technique to assess whether specific factors (such as timing and routes of administration of ephedrine) influence the overall treatment effect was not carried out because of the small number of trials available in this systematic review.

As there was no standardized dose of ephedrine used across trials, this systematic review did not answer the question about what dose should be used to prevent maternal hypotension. Intuitively, one would expect that all investigators would have given an adequate and effective prophylactic dose of ephedrine. Although ephedrine has a small benefit, this may be due to an inadequate dose of ephedrine used in some trials or that ephedrine has limited effectiveness.

Therefore, to determine the relative effects of dose, timing and route of ephedrine administration, it is necessary to refer to the results of individual RCTs. For example, in a previous dose-finding RCT, we found that the efficacy of prophylactic ephedrine for the prevention of hypotension, when given as an *iv* bolus one minute after intrathecal injection, was dose-dependent.[4] Furthermore, our meta-analysis was limited to ephedrine as there was insufficient data on other vasopressors given prophylactically at the time we performed the search for RCTs. However, we note that a recent RCT showed that prophylactic *im* phenylephrine 4 mg was associated with a twofold decrease in developing hypotension compared with control (RR = 2.00, 95% CI, 1.10 to 3.57).[26] These findings suggest that further work to determine the optimal technique of prophylactic ephedrine administration and trials of other prophylactic vasopressors are warranted.

The efficacy of crystalloid bolus in the management of hypotension associated with spinal anesthesia for Cesarean delivery has been examined.[29,30] In a non-blinded study that used a sequential analysis design, a preload of 20 $mL \cdot kg^{-1}$ lactated Ringer's solution reduced the incidence of hypotension from 71% to 55% but did not affect neonatal outcome or ephedrine requirement.[29] After this, a randomized blinded trial showed no beneficial effect of 1000 mL crystalloid.[30] In this systematic review, only one trial compared prophylactic ephedrine infusion with fluid preloading.[25] Although the incidence of moderate hypotension (20% reduction in SBP) was similar, there was a lower incidence of severe hypotension (30% reduction in SBP) in the ephedrine group (35%) compared with the fluid group (65%).[25] The reason why crystalloid bolus has only limited efficacy can be attributed to its rapid redistribution out of the intravascular space, which results in a relatively small augmentation of circulating volume.

There was no association between the use of ephedrine and fetal acidosis in our review. This is in contrast with the observational study by Shearer[16] who reported a significant association, with a three-fold greater incidence of fetal acidosis in the ephedrine group compared with control (no ephedrine). The authors postulated that the decreased uteroplacental perfusion that results from hypotension may be further compromised by the α-agonist vasoconstricting properties of ephedrine,[16] but this had not been confirmed by studies that have assessed uterine vascular resistance using Doppler ultrasound.[25,31] Nonetheless, further studies are required to confirm the safety and efficacy of prophylactic ephedrine in cases where there is compromised uteroplacental blood flow.

There are several limitations to the present systematic review. As there was no standard definition of hypotension in this systematic review, we chose to rely upon the definition of hypotension given by the authors of each trial. Therefore, there is some degree of clinical heterogeneity between trials. The quality of trials included in this systematic review was fair, with four trials that had both adequate allocation concealment and double-blinding. Compared with trials that have adequate allocation concealment or are double-blinded, trials with unclear allocation concealment or are not double-blinded are associated with a larger treatment effect (41% and 17% respectively).[9] However, our sensitivity analyses showed that quality of the trials did not appear to influence the overall treatment effect. Finally, some caution is needed in interpreting the results of this meta-analysis which is based on results of many small trials as subsequent large trials have disagreed with meta-analyses 10% to 23% of the time.[32] Nevertheless, in the absence of a large multi-centered trial on this issue, the best strategy for appraising the available evidence is the use of meta-analysis. We believe that the findings from this systematic review are robust, as there was no evidence of bias from the funnel plot.

In summary, there is evidence that prophylactic ephedrine has limited efficacy for the prevention of hypotension during spinal anesthesia for Cesarean delivery. The optimal route, dose and timing are undetermined and we found no evidence that ephedrine was associated with improved neonatal outcome.

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References

1 *Vercauteren MP, Coppejans HC, Hoffmann VH, Mertens E, Adriaensen HA.* Prevention of hypotension by a single 5-mg dose of ephedrine during small-dose spinal anesthesia in prehydrated cesarean delivery patients. Anesth Analg 2000; 90: 324–7.

2 *Rout CC, Rocke DA.* Prevention of hypotension following spinal anesthesia for cesarean section. Int Anesthesiol Clin 1994; 32: 117–35.

3 *Wright RG, Shnider SM.* Hypotension and regional anesthesia. *In:* Shnider SM, Levinson G. (Eds.). Anesthesia for Obstetrics, 3rd ed. Baltimore: Williams & Wilkins, 1993: 397–406.

4 *Ngan Kee WD, Khaw KS, Lee BB, Lau TK, Gin T.* A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2000; 90: 1390–5.

5 *King SW, Rosen MA.* Prophylactic ephedrine and hypotension associated with spinal anesthesia for cesarean delivery. Int J Obstet Anesth 1998; 7: 18–22.

6 *Tsen LC, Boosalis P, Segal S, Datta S, Bader AM.* Hemodynamic effects of simultaneous administration of intravenous ephedrine and spinal anesthesia for cesarean delivery. J Clin Anesth 2000; 12: 378–82.

7 *Gutsche BB.* Prophylactic ephedrine preceding spinal analgesia for cesarean section. Anesthesiology 1976; 45: 462–5.

8 *Egger M, Davey Smith G, Altman DG.* Systematic Reviews in Health Care: Meta-Analysis in Context, 2nd ed. London: British Medical Journal Publishing Group, 2001.

9 *Schulz KF, Chalmers I, Hayes RJ, Altman DG.* Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408–12.

10 *Roberts SW, Leveno KJ, Sidawi JE, Lucas MJ, Kelly MA.* Fetal acidemia associated with regional anesthesia for elective cesarean delivery. Obstet Gynecol 1995; 85: 79–83.

11 *Carvalho JCA, Cardoso MMSC, Capelli EL, Amaro AR, Rosa MCR.* Prophylactic ephedrine during cesarean delivery spinal anesthesia. Dose-response study of bolus and continuous infusion administration (Portugese). Rev Bras Anestesiol 1999; 49: 309–14.

12 *Mosteller F, Colditz GA.* Understanding research synthesis (meta-analysis). Ann Rev Public Health 1996; 17: 1–23.

13 *Egger M, Davey Smith G, Schneider M, Minder C.* Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–34.

14 *Smeeth L, Haines A, Ebrahim S.* Numbers needed to treat derived from meta-analyses-sometimes informative, usually misleading. BMJ 1999; 318: 1548–51.

15 *Datta S, Alper MH, Ostheimer GW, Weiss JB.* Method of ephedrine administration and nausea and hypotension during spinal anesthesia for cesarean section. Anesthesiology 1982; 56: 68–70.

16 *Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap III LC.* Fetal effects of prophylactic ephedrine and maternal hypotension during regional anesthesia for cesarean section. J Matern Fetal Med 1996; 5: 79–84.

17 *Haruta M, Funato T, Saeki N, Naka Y, Shinkai T.* Ephedrine administration for cesarean section under spinal anesthesia (Japanese). Nippon Sanka Fujinka Gakkai Zasshi 1987; 39: 207–14.

18 *Rout CC, Rocke DA, Brijball R, Koovarjee RV.* Prophylactic intramuscular ephedrine prior to caesarean section. Anaesth Intensive Care 1992; 20: 448–52.

19 *Ramanathan S, Grant GJ.* Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 1988; 32: 559–65.

20 *Yokoyama H, Kubota N, Toda K.* Continuous infusion of dopamine to maintain stable arterial pressure during spinal anaesthesia for caesarean section. Eur J Anaesthesiol 1997; 14: 72–3.

21 *Ramin SM, Ramin KD, Cox K, Magness RR, Shearer VE, Gant NF.* Comparison of prophylactic angiotensin II versus ephedrine infusion for prevention of maternal hypotension during spinal anesthesia. Am J Obstet Gynecol 1994; 171: 734–9.

22 *Kang YG, Abouleish E, Caritis S.* Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. Anesth Analg 1982; 61: 839–42.

23 *Olsen KS, Feilberg VL, Hansen CL, Rudkjøbing O, Pedersen T, Kyst A.* Prevention of hypotension during spinal anaesthesia for caesarean section. Int J Obstet Anesth 1994; 3: 20–4.

24 *Webb AA, Shipton EA.* Re-evaluation of im ephedrine as prophylaxis against hypotension associated with spinal anaesthesia for caesarean section. Can J Anaesth 1998; 45: 367–9.

25 *Chan WS, Irwin MG, Tong WN, Lam YH.* Prevention of hypotension during spinal anaesthesia for caesarean section: ephedrine infusion versus fluid preload. Anaesthesia 1997; 52: 896–913.

26 *Ayorinde BT, Buczkowski P, Brown J, Shah J, Buggy DJ.* Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during caesarean section. Br J Anaesth 2001; 86: 372–6.

27 *Kangas-Saarela T, Hollmén AI, Tolonen U, et al.* Does ephedrine influence newborn neurobehavioural

responses and spectral EEG when used to prevent maternal hypotension during caesarean section? Acta Anaesthesiol Scand 1990; 34: 8–16.
28 *Berlin JA, Antman EM.* Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials 1994; Doc No 134.
29 *Rout CC, Rocke DA, Levin J, Gouws E, Reddy D.* A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology 1993; 79: 262–9.
30 *Jackson R, Reid JA, Thorburn J.* Volume preloading is not essential to prevent spinal-induced hypotension at caesarean section. Br J Anaesth 1995; 75: 262–5.
31 *Ngan Kee WD, Lau TK, Khaw KS, Lee BB.* Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section. Anesthesiology 2001; 95: 307–13.
32 *Ioannidis JPA, Cappelleri JC, Lau J.* Issues in comparisons between meta-analyses and large trials. JAMA 1998; 279: 1089–3.