International Journal of Surgery 60 (2018) 48–59

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis

Chao Xu[a], Su Liu[b], YiZhou Huang[a], XiaoWei Guo[a], HanBing Xiao[a], DunYi Qi[b,*]

[a] Department of Anesthesiology, Xuzhou Medical University, Xuzhou, Jangsu, China
[b] Department of Anesthesiology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jangsu, China

ARTICLE INFO

Keywords:
Phenylephrine
Ephedrine
Cesarean delivery
Spinal anesthesia
Meta-analysis

ABSTRACT

Background: In the past 20 years, many studies compared phenylephrine with ephedrine to prevent or treat hypotension in elective or emergency cesarean delivery and parturients with pre-eclampsia. A meta-analysis of the abovementioned trials is needed.

Methods: Several databases (PubMed, Embase, Web of Science and Cochrane Library) were searched from inception to April 2018 for trials comparing phenylephrine with ephedrine in cesarean delivery. The primary outcome is the incidence of maternal hypotension.

Results: Thirty-six trials (2439 patients) with elective cesarean delivery, three trials (400 patients) with emergency cesarean delivery and three trials (192 patients) with parturients with pre-eclampsia were included and analyzed. The incidence of hypotension did not differ in the elective surgery group (relative risk 0.83, 95% CI 0.66 to 1.05), emergency surgery group (relative risk 1.02, 95% CI 0.87 to 1.19) and pre-eclamptic parturients group (relative risk 0.93, 95% CI 0.63 to 1.37). The phenylephrine group had a higher incidence of bradycardia and lower incidences of tachycardia and nausea or vomiting in all three patient groups. The phenylephrine group also had lower fetal acidosis rate, higher umbilical artery and vein pH values and less base excess in the elective surgery. The abovementioned outcomes were similar in the emergency surgery group and the pre-eclampsia group. Publication bias for hypotension was detected. However, the trim and fill method demonstrated that the publication bias had little impact on hypotension. Trial sequential analysis of hypotension in elective surgery showed that this meta-analysis lacked a sufficient cumulative sample size and that further studies should be included.

Conclusion: Phenylephrine and ephedrine were both effective in maintaining hemodynamic balance. Newborns benefited more from phenylephrine in elective cesarean delivery, but not in emergency cesarean delivery or in parturients with pre-eclampsia. More trials should be included to achieve more conclusive results.

1. Introduction

Despite the current promotion of vaginal delivery in parturients, cesarean delivery still accounts for a large proportion of deliveries, including 32.7% of all parturients in the US [1] and 46.2% in China [2]. Spinal anesthesia is the preferred anesthetic method for cesarean delivery to provide satisfactory analgesia and muscle relaxation. However, hypotension caused by spinal anesthesia due to blockade of sympathetic nerves can threaten the safety of parturients and fetuses through maternal decline of cerebral perfusion, nausea and vomiting, and decreased uteroplacental perfusion [3,4]. Several measures are used to prevent or treat hypotension caused by spinal anesthesia, including prehydration, limb compression, left lateral tilt of the operating table or vasopressor administration [5].

Hypotension can be rapidly corrected by vasopressors, and the two most popular drugs are phenylephrine and ephedrine. However, which vasoactive agent is better remains controversial. The historically preferred drug was ephedrine, which mainly activated β-adrenergic receptors, thus increasing cardiac output and maintaining placental blood flow, while phenylephrine activated α-adrenergic receptors, contracting placental vessels and impairing uteroplacental perfusion [6]. Nevertheless, several randomized controlled trials (RCTs) have indicated that a higher cord blood pH and a lower incidence of fetal acidosis were found in parturients receiving phenylephrine compared to those receiving ephedrine [7–9]. A meta-analysis [10] published in 2012 comparing phenylephrine with ephedrine in cesarean delivery

* Corresponding author. Department of Anesthesiology, Affiliated Hospital of Xuzhou Medical University, Xuzhou medical University, Huaihai West Rd #99, Xuzhou, 221000, China.
E-mail address: qdy0828@163.com (D. Qi).

https://doi.org/10.1016/j.ijsu.2018.10.039
Received 16 July 2018; Received in revised form 21 September 2018; Accepted 22 October 2018
Available online 31 October 2018
1743-9191/

revealed that the incidence of hypotension did not differ between the two groups. However, the meta-analysis above only contained a small number of studies of elective cesarean delivery, resulting in inconclusive outcomes. Recently, the two drugs were compared in emergency cesarean delivery [6,11,12] and in parturients with pre-eclampsia [13–15].

Therefore, we conducted this meta-analysis to compare phenylephrine with ephedrine in maintaining hemodynamic stability and fetal acid-base equilibrium, with more RCTs regarding not only elective cesarean delivery but also emergency cesarean delivery and parturients with pre-eclampsia, and carried out a trial sequential analysis (TSA) to identify whether the results were conclusive and robust. The primary outcome was the incidence of maternal hypotension and the secondary outcomes were other maternal outcomes and fetal outcomes.

2. Materials and methods

The meta-analysis was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087466.). The entire study was conducted under Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.1. Literature search

Publications in the following databases were systematically searched until April 2018 without any language limits: PubMed, Embase, Web of Science and Cochrane Library. The Clinical Trials Registry (www.clinicaltrials.com), references of included studies and Google Scholar were checked to identify more trials. Two authors searched the databases according to three aspects: Participants, parturients submitted to cesarean delivery; Intervention group, phenylephrine; and Comparison group, ephedrine. The integrated search history of PubMed is shown in Appendix 1.

2.2. Selection criteria

Two authors independently removed duplicate articles, screened the records by titles and abstracts, and determined the final selection of studies after carefully reading the full texts. Any disagreement was discussed to achieve a consensus. The included articles met the following criteria: (1) parturients undergoing cesarean delivery, including elective surgery, emergency surgery and patients with pre-eclampsia; (2) spinal anesthesia or combined spinal epidural anesthesia (excluding totally epidural anesthesia and general anesthesia); (3) either a phenylephrine group or an ephedrine group without combination of the two drugs; (4) at least one of the required outcomes: Maternal outcomes: the incidences of hypotension, hypertension, bradycardia, tachycardia, and nausea or vomiting; Neonate outcomes: the incidence of fetal acidosis, the number of Apgar scores, umbilical artery (UA) and umbilical vein (UV) blood gas analysis; (5) study design: RCTs. In our meta analysis, the definition of hypotension was the decrease of systolic blood pressure (SBP) exceeding 20% SBP baseline value; the definition of hypertension was the increase of SBP exceeding 20% SBP baseline value; heart rate (HR) less than 60 beat per minute (bpm) was deemed as bradycardia; HR more than 100 bpm was deemed as tachycardia; UA pH less than 7.20 was deemed as fetal acidosis. Emergency surgery included parturients who were initially scheduled for vaginal delivery in the labor room but subsequently received cesarean delivery.

2.3. Data collection

Before data collection, one author designed the data extraction form, which included the title, authors, country, language of publication, number of groups, number of patients in each group, specific anesthesia protocol, data for continuous and binary outcomes, surgery type (elective or emergency surgery, parturients with pre-eclampsia), with or without prehydration, goals of vasopressor use (prevention or treatment of hypotension) and some elements used to assess the risk of bias. If the required data was unavailable, then we would get in touch with the relevant authors for detailed information. The data were collected individually by two researchers. If a controversy arose, a third researcher was consulted to achieve a definitive conclusion.

2.4. Risk of bias assessment

The risk of bias was determined by the Cochrane risk of bias tool specifically evaluating the bias of RCTs [17]. The following aspects of each trial were classified into low, unclear or high risk: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessments; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. Bias assessment was conducted by two researchers individually followed by a discussion to resolve differences.

2.5. Statistical methods

The statistical software programs used in our meta-analysis were Review Manager 5.3 (Cochrane, London, UK), Stata 12.0 (StataCorp, College Station, Texas). Parturients who only received phenylephrine were included in the intervention group, and those who received only ephedrine were included in the comparison group. For binary outcomes, the relative risk (RR) with 95% CI was computed by a inverse variance method. In continuous outcomes, weighted mean difference (WMD) with 95% CI was computed using method of Mantel-Haenzsel. To reduce the impact of potential heterogeneity caused by methodological and clinical differences between trials, random-effects models were selected for this meta-analysis [18]. Heterogeneity was calculated by the $\chi 2$ and I^2 tests [19]. Outcomes with a P value of $\chi 2 < 0.10$ or a quantitative assessment of the I^2 test $> 50\%$ were regarded as obviously heterogeneous, warranting cautious interpretation of the result. If obvious heterogeneity occurred, we conducted sensitivity analysis to judge whether this result was robust via excluding one trial at a time and synthesizing the remaining trials. We respectively analyzed every outcome of all included studies, which were divided into three conditions: elective cesarean delivery, emergency cesarean delivery and patients with pre-eclampsia. A subgroup analysis was conducted only for elective cesarean delivery according to the goals of vasopressors (prevention or treatment of hypotension) and with or without prehydration before anesthesia. Publication bias was evaluated by the observed symmetry of a funnel plot and the quantitative statistical methods of Begg [20] and Egger [21]. If publication bias was obvious, the trim and fill method was applied to explore the impact on the outcomes via comparing the effect sizes before and after 'trimming and filling' [22]. The trim and fill method was conducted in two steps: first, obtaining an effect size after trimming the asymmetric small sample studies in the funnel plot; second, obtaining another effect size after filling an equal number of small sample studies in the funnel plot. If the difference between the two effect sizes is not significant, the publication bias has little impact on the stability of the outcome. The statistically significant threshold was $P < 0.05$.

2.5.1. Trial sequential analysis

To reduce the increased type I error caused by interim analyses in RCTs, monitoring boundaries are applied to determine whether the P value is small enough to terminate this trial prematurely. Adding each trial into a cumulative meta-analysis will also increase type I errors [23]. Similar to monitoring boundaries in RCTs, TSA boundaries are used in meta-analyses to determine whether conclusions are decisive

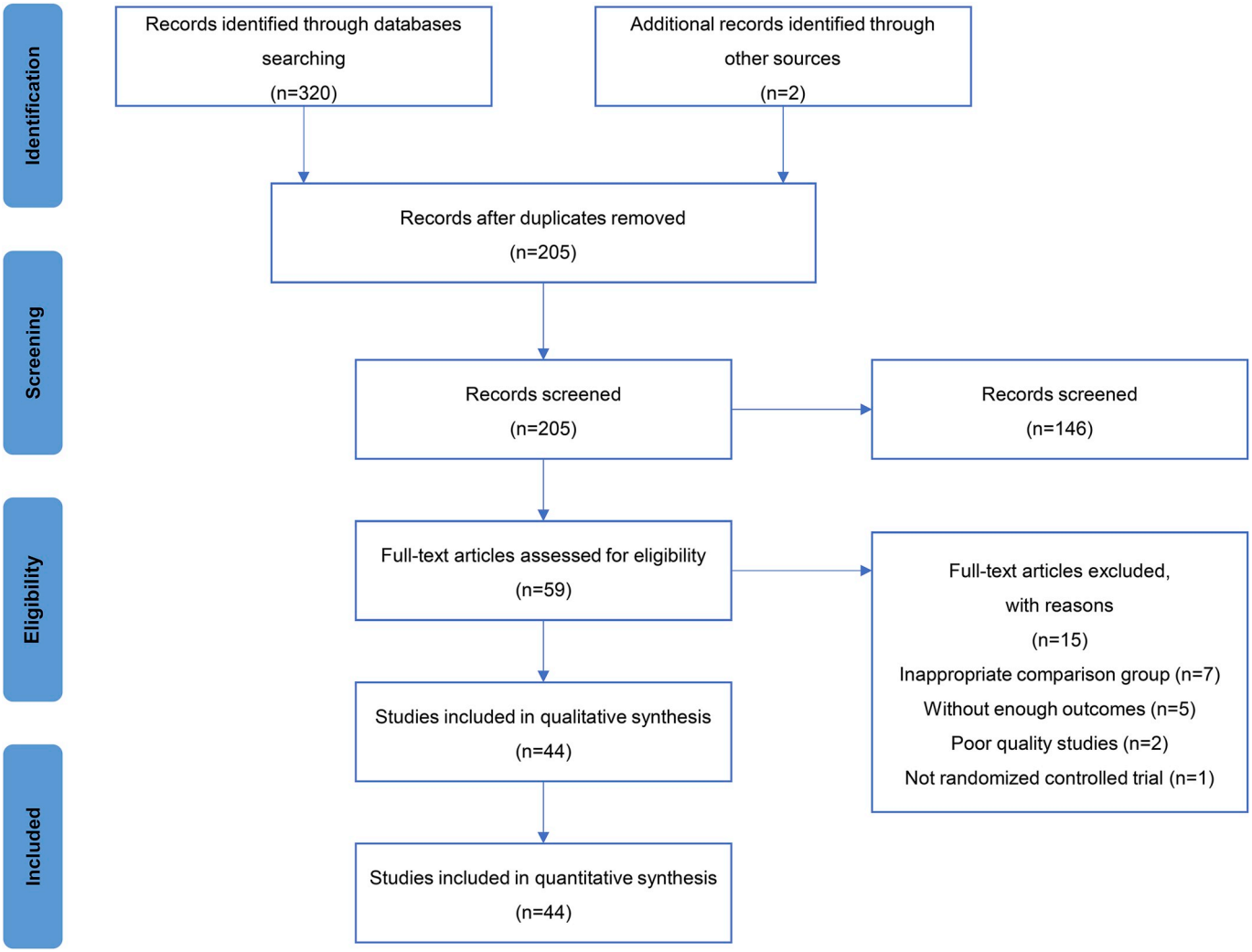

Fig. 1. Flow diagram of articles retrieval.

and robust [23]. When cumulative z-curves cross the TSA boundaries for benefit and harm, the futility area or the required information size (RIS), then a conclusive result can be obtained and no more trials are required in the meta-analysis. Otherwise, more trials should be included to obtain a more reliable result. We calculated the RIS according to the TSA handbook [24] by α (0.05), β (0.20), the incidence of the primary outcome, and a relative risk reduction (20%). Because of limited trials, we only performed TSA of the primary outcome (the incidence of hypotension) in elective cesarean delivery.

3. Results

3.1. Study selection

Study selection was conducted according to the PRISMA statement and a total of 322 articles were retrieved (Fig. 1). After excluding the repeated trials and irrelevant records, 59 studies were assessed via full-text review. Fifteen studies were excluded and 44 studies were included in the final quantitative synthesis.

3.2. Study characteristics

The basic information of every contained trial is displayed in Table 1. Among the 44 included studies [3,5–9,11–15,25–57], 36 studies [3,5,7–9,25–39,41–43,45–57] contained healthy mothers undergoing elective cesarean delivery, 3 studies [6,11,12] contained only emergency cesarean delivery, 3 studies [13–15] contained parturients with pre-eclampsia, and 2 studies [40,44] contained both elective and emergency surgery. For different goals of vasoactive drugs, 28 studies [3,5,8,9,11–13,26,27,30–35,37,42–53] used the drugs to prevent hypotension and 16 studies [6,7,14,15,25,28,29,36,38–41,54–57] used the drugs to treat hypotension. Thirty-three studies applied prehydration [3,5–9,13,14,25–33,36,38–45,47,50,52,53,55–57], with crystalloid or colloid volumes ranging from 500 to 2000 ml before anesthesia, and 11 studies [11,12,15,34,35,37,46,48,49,51,54] did not apply prehydration.

3.3. Risk of bias

The bias results are displayed in Fig. 2. Most trials had a low or moderate risk of bias, only one trial [3] had a high blinding of participants bias, and two trials [13,46] had a high selective reporting bias.

3.4. Elective cesarean delivery

Primary outcome: The incidence of hypotension. Eighteen studies reported the incidence of hypotension. Hypotension was not statistically significant between the two groups (RR 0.83, 95% CI 0.66 to 1.05, I^2 = 57%) (Fig. 3). According to the subgroup analysis, the difference was also insignificant in the hypotension treatment group, the with prehydration group and the without prehydration group, but it was significant in the hypotension prevention group (RR 0.69, 95% CI 0.49

Table 1
Characteristics of included studies.

Study	Country	Patient Number Phenylephrine/ ephedrine	Spinal Anesthesia Protocol	Outcomes	Surgery Type	Prehydration (Yes or No)	Prevention or treatment of hypotension
Moran 1991[25]	USA	31/29	Bupivacaine 7.5–15 mg,L2-3 or L3-4 interspace.	Maternal haemodynamics, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Treatment
Alahuhta 1992[26]	Finland	8/9	Bupivacaine 11.5–3 mg bupivacaine, L3-4 interspace	Maternal haemodynamics, Ultrasound measurements, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Hall 1994[27]	UK	10/10	Bupivacaine15 mg, L2-3 or L3-4 interspace	Maternal haemodynamics, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Pierce 1994[28]	USA	13/13	Bupivacaine 7.5–15 mg with 10 μg fentanyl, L2-3 or L3-4 interspace.	Materanl and fetal ANP, UA and UV blood gase values	Elective cesarean delivery	Yes	Treatment
LaPorta 1995[29]	USA	20/20	Bupivacaine 7.5–15 mg	Maternal venous, UA and UV catecholamine; UA and UV blood gase values. Apgar scores	Elective cesarean delivery	Yes	Treatment
Thomas 1996[7]	UK	19/19	Bupivacaine12.5 mg, L2-3 or L3-4 interspace	Maternal haemodynamics, UA and UV blood gas values, Apgar scores, Umbilical artery pulsatility index,CO	Elective cesarean delivery	Yes	Treatment
Ayorinde 2001[30]	UK	27/27	Bupivacaine 11 mg with 20 μg fentanyl, L2-3 or L3-4 interspace	Maternal haemodynamics; UV pH, Apgar scores.	Elective cesarean delivery	Yes	Prevention
Cooper1 2002[8]	UK	48/50	Bupivacaine10–12.5 mg with 10–20 μg fentanyl, interspace.	Maternal haemodynamics,nausea, vomit; UV pH, Apgar scores.	Elective cesarean delivery	Yes	Prevention
Saravanan 2006[31]	UK	40/40	Bupivacaine 13 mg with diamorphine 400 mg, L2-3 interspace	Vasopressor dose, UA pH and BE, Maternal nausea and vomiting	Elective cesarean delivery	Yes	Prevention
Jung 2006[32]	Kroea	30/30	Bupivacaine 10 mg with 10 μg fentanyl, L3-4 or L4-5 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Cooper2 2007[33]	UK	27/27	Bupivacaine14 mg with 400 mg diamorphine, L3-L4 interspace	Materanl haemodynamics; Block height, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Ngan1 2008[34]	China (HK)	24/25	Bupivacaine 10 mg with fentanyl 15 μg, L3-4 or L4-5 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Ngan2 2008[11]	China (HK)	102/102	Bupivacaine 10–12 mg with fentanyl 15 μg, L3-4 or L4-5 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores	Emergency cesarean delivery	No	Prevention
Magalhaes 2009[35]	Brazil	30/30	Bupivacaine 10 mg with 3 μg sufentanil, L2-3 or L3-4 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Mahajan 2009[9]	India	28/28	Bupivacaine 10 mg, L2-3 or L3-4 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Dyer1 2009[36]	South Africa	20/20	Bupivacaine 10 mg with 10 μg fentanyl, L3-4 interspace	Maternal hemodynamics, UA and blood gase values, Apgar scores	Elective cesarean delivery	Yes	Treatment
Ngan3 2009[37]	China (HK)	52/52	Bupivacaine 10 mg with 15 μg fentanyl, L3-4 or L4-5 interspace	Maternal, UA and UV catecholamine; Maternal hemodynamics, UA and blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Adigun 2010[38]	Nigeria	31/31	Bupivacaine 12.5 mg, L3-4 interspace	Maternal hemodynamics, nausea, vomit, Apgar scores	Elective cesarean delivery	Yes	Treatment
Prakash 2010[39]	India	30/30	Bupivacaine 10 mg bupivacaine, L3-4 interspace	Maternal haemodynamics, nausea and vomit, UA and UV blood gase values, Apgar scores; Neurobehavioural testing	Elective cesarean delivery	Yes	Treatment
Bhattarai 2010[40]	India	30/30	Bupivacaine 10 mg bupivacaine, L3-4 interspace	Maternal hemodynamics, nausea, vomit, Apgar scores	Elective and emergency cesarean delivery, healthy parturients	Yes	Treatment
Gunda 2010[41]	India	50/50	Bupivacaine 8 mg, L3-4 interspace	Maternal hemodynamics, nausea, vomit, Apgar scores	Elective cesarean delivery	Yes	Treatment
Guillon 2010[42]	France	20/20	Bupivacaine 10 mg, 2.5 μg sufentanil, 0.1 mg morphine, L3-4 or L4-5 interspace	UA and UV pH, Apgar scores	Elective cesarean delivery	Yes	Prevention
Das 2011[43]	India	31/29	Bupivacaine 12.5 mg, L3-4 or L4-5 interspace	Maternal hemodynamics, nausea, vomit and Apgar scores	Elective cesarean delivery	Yes	Prevention

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Patient Number Phenylephrine/ ephedrine	Spinal Anesthesia Protocol	Outcomes	Surgery Type	Prehydration (Yes or No)	Prevention or treatment of hypotension
Alday 2011[44]	Spain	36/44	0.5% bupivacaine, 0.07 mg/cm (height) with 20 μg fentanyl,L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values	Elective and emergency cesarean delivery	Yes	Prevention
Li 2011[45]	China	20/20	Bupivacaine 7.5 mg with 25 μg fentanyl, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values	Elective cesarean delivery	Yes	Prevention
Wang 2011[46]	China	30/30	Bupivacaine 10 mg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Nazir 2012[47]	India	50/50	Bupivacaine 12.5 mg, L3-4 interspace	Maternal hemodynamics, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Yadav 2012[48]	India	50/50	Bupivacaine 12.5 mg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Bhardwaj 2013[49]	India	32/26	Bupivacaine 12.5 mg.	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values, Apgar scores, fetal acidosis	Elective cesarean delivery	No	Prevention
Quan 2013[50]	China	30/30	Bupivacaine 7.5 mg, L2-3 or L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values,	Elective cesarean delivery	Yes	Prevention
Aragao 2014[51]	Brazil	30/30	Bupivacaine 10 mg with 100 μg morphine, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	No	Prevention
Foss 2014[3]	Denmark	12/12	Bupivacaine 12 mg with fentanyl 10 μg, L2-3 or L3-4 interspace	Maternal ScO2 change, hemodynamics, fetal heart rate, UA and UV blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Moslemi 2015[52]	Iran	30/27	Bupivacaine 12.5 mg with sufentanil 2.5 μg, L3-4 or L4-5 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores	Elective cesarean delivery	Yes	Prevention
Guo 2015[53]	China	30/30	Bupivacaine 7.5 mg, L3-4 or L4-5 interspace	Ultrasound measurements, UA and UV blood gase values,	Elective cesarean delivery	Yes	Prevention
Natarajan 2015[54]	India	40/40	Bupivacaine 7.5 mg with 25 μg fentanyl, L3-4 or L4-5 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores	Elective cesarean delivery	No	Treatment
Siddiqui 2015[55]	Pakistan	100/100	Bupivacaine 10 mg with fentanyl 25 μg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, Apgar scores	Elective cesarean delivery	Yes	Treatment
Jain 2016[12]	India	45/45	Bupivacaine 10 mg with fentanyl 25 μg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores	Emergency cesarean delivery	No	Prevention
Soxhuku 2016[56]	Albania	101/101	Bupivacaine 12.5 mg with fentanyl 10 μg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores, fetal acidosis	Elective cesarean delivery	Yes	Treatment
Mohta 2016[6]	India	53/53	Bupivacaine 10–11 mg, L3-4 or L2-3 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores, fetal acidosis, NICU admission	Emergency cesarean delivery	Yes	Treatment
Higgins 2017[13]	USA	54/54	Bupivacaine 12 mg with fentanyl 15 μg and morphine 150 μg, L3-4 or L4-5 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores, fetal acidosis,	Parturients with pre-eclampsia	Yes	Prevention
Dyer2 2017[14]	South Africa	32/32	Bupivacaine 10–11 mg with fentanyl 10 μg, L3-4 interspace	UA blood gase values, Apgar scores, fetal acidosis,	Parturients with pre-eclampsia	Yes	Treatment
Mon 2017[5]	UK	20/20	Bupivacaine 11 mg with fentanyl 15 μg, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores, fetal acidosis	Elective cesarean delivery	Yes	Prevention
Vakili 2017[57]	Iran	60/60	Bupivacaine 12.5 mg with 15 μg fentanyl, L3-4 interspace	Maternal hemodynamics, nausea,vomit, UA blood gase values, Apgar scores	Elective cesarean delivery	Yes	Treatment
Dyer3 2018[15]	South Africa	10/10	Bupivacaine 10–11 mg with 10 μg fentanyl, L3-4 interspace	Maternal hemodynamics, UA blood gase values	Parturients with pre-eclampsia	No	Treatment

UA = Umbilical Artery; UV = Umbilical Vein; ANP = Atrial Natriuretic Peptide; CO = Cardiac Output; BE= Base Excess; ScO2 = Spectroscopy-determined Frontal Lobe Oxygenation; NICU = Neonatal Intensive Care Unit.

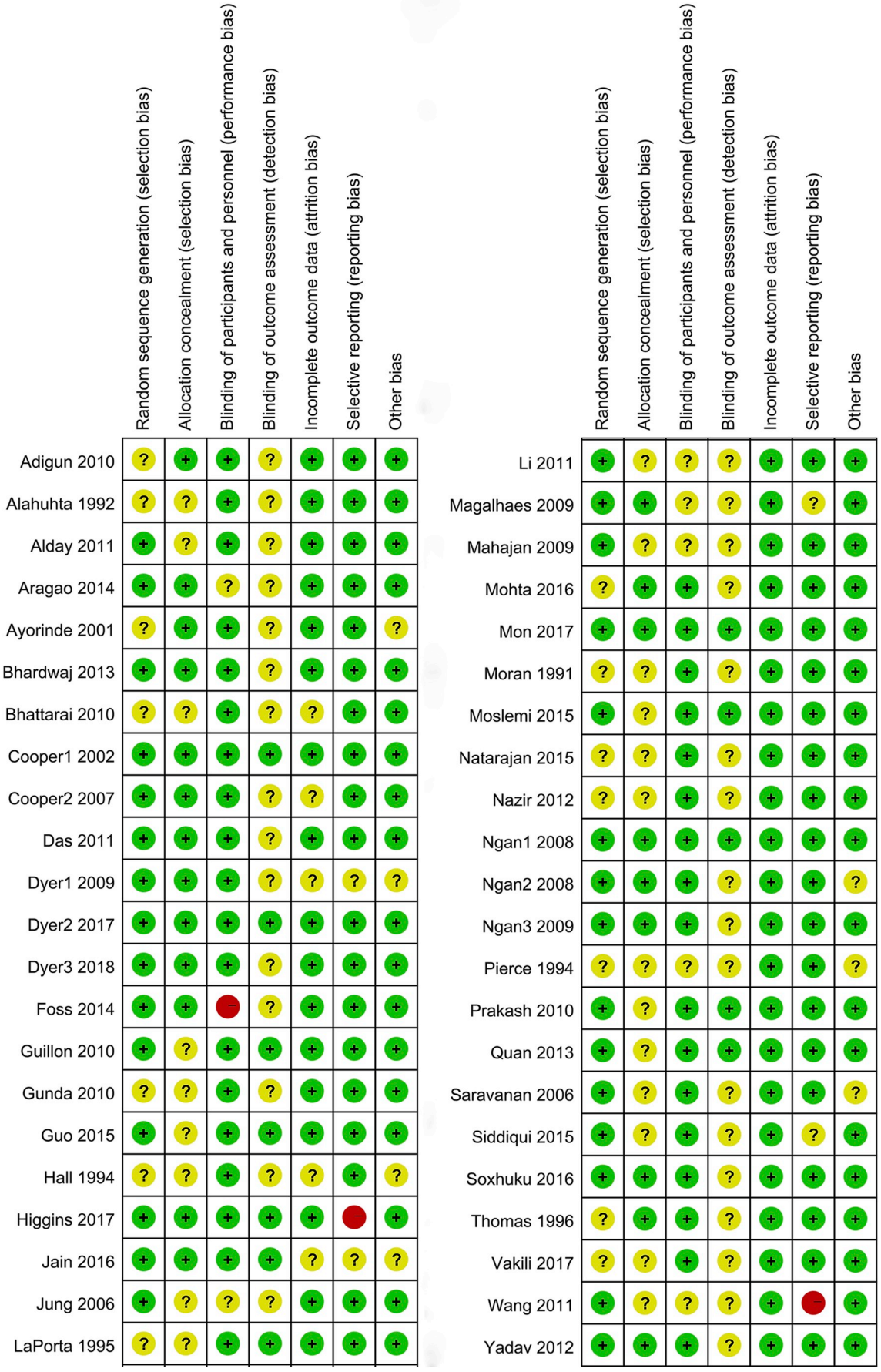

Fig. 2. Risk of bias assessed by the Cochrane risk of bias tool. + = low risk; ? = unclear risk; - = high risk.

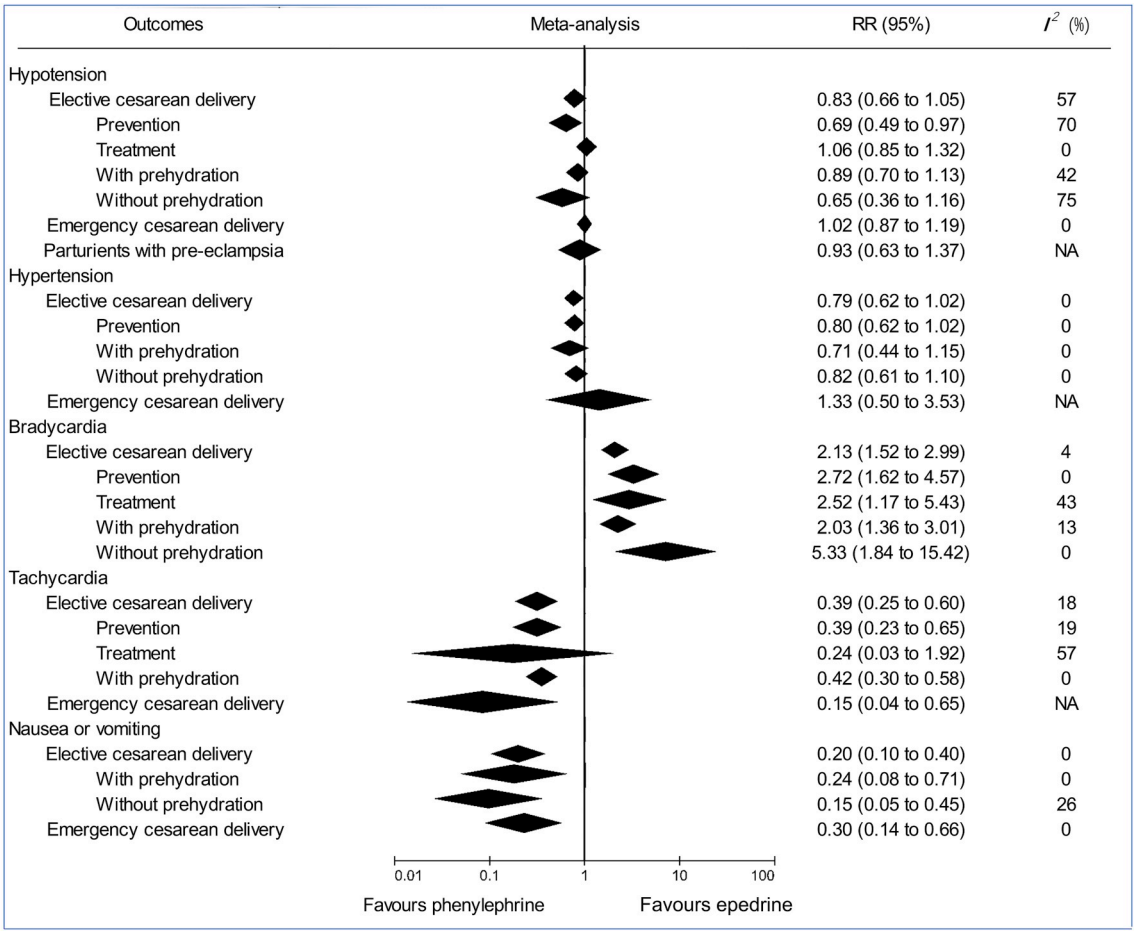

Fig. 3. Summary forest plot of maternal outcomes. RR = Relative Risk; NA = Not Applicable.

to 0.97).

3.4.1. Secondary outcomes

The overall incidence of hypertension was similar in the two groups (RR 0.79, 95% CI 0.62 to 1.02) (Fig. 3). The difference in hypertension was also insignificant in the following groups: prevention (RR 0.80, 95% CI 0.62 to 1.02), with prehydration (RR 0.71, 95% CI 0.44 to 1.15) and without prehydration (RR 0.82, 95% CI 0.61 to 1.10). The ephedrine group had a lower incidence of bradycardia (RR 2.13, 95% CI 1.52 to 2.99) and higher incidences of tachycardia (RR 0.39, 95% CI 0.25 to 0.60) and nausea or vomiting (RR 0.20, 95% CI 0.10 to 0.40) compared to the phenylephrine group.

Fetal outcomes with subgroup analysis are shown in Table 2. The phenylephrine group had a lower incidence of fetal acidosis (RR 0.18, 95% CI 0.06 to 0.48) and lower UA BE (WMD 1.09, 95% CI 0.57 to 1.60), UV BE (WMD 0.70, 95% CI 0.12 to 1.29), UA PaCO2 (WMD -4.52, 95% CI -6.00 to −3.04), UV PaCO2 (WMD -1.12, 95% CI -2.22 to −0.02), UA lactate (WMD -0.94, 95% CI -1.69 to −0.19) and UV lactate (WMD -0.62, 95% CI -1.20 to −0.05) levels compared to the ephedrine group. The phenylephrine group also had higher UA pH (WMD 0.04, 95% CI 0.03 to 0.06) and UV pH (WMD 0.02, 95% CI 0.02 to 0.03) values compared to the ephedrine group. No significant difference was found in the incidence of Apgar scores < 7 (1 min after birth) (RR 0.68, 95% CI 0.11 to 4.20) or UA PaO2 (WMD 0.13, 95% CI -0.70 to 0.96) and UV PaO2 (WMD 0.01, 95% CI -1.21 to 1.24) levels.

3.5. Emergency cesarean delivery

Hypotension was reported in 2 studies [6,11] containing only parturients undergoing emergency cesarean delivery. No difference was found in the hypotension rate (RR 1.02, 95% CI 0.87 to 1.19). For other outcomes, the phenylephrine group had less tachycardia (RR 0.15, 95% CI 0.04 to 0.65) and nausea or vomiting (RR 0.20, 95% CI 0.10 to 0.40) and lower UA lactate (WMD -0.20, 95% CI -0.41 to −0.01) and UV lactate (WMD -0.20, 95% CI -0.39 to −0.01) levels compared to the ephedrine group. No significant difference was found in the following outcomes: hypertension (RR 1.33, 95% CI 0.50 to 3.53), fetal acidosis (RR 0.71, 95% CI 0.39 to 1.28), Apgar score < 7 (1 min after birth) (RR 1.00, 95% CI 0.06 to 15.77), and UA pH (WMD 0.00, 95% CI -0.01 to 0.01), UV pH (WMD 0.00, 95% CI -0.01 to 0.01), UA BE (WMD 0.46, 95% CI -0.23 to 1.14), UV BE (WMD 0.03, 95% CI -0.85 to 0.92), UA PaO2 (WMD -0.60, 95% CI -3.44 to 2.44), UV PaO2 (WMD -0.27, 95% CI -1.74 to 1.20), UA PaCO2 (WMD -0.23, 95% CI -1.78 to 1.32) and UV PaCO2 (WMD -0.27, 95% CI -1.74 to 1.20) levels.

3.6. Parturients with pre-eclampsia

Three trials [13–15] included only parturients with pre-eclampsia, and the incidence of hypotension was reported in 1 trial [13]. No significant difference between the groups was found in the hypotension rate (RR 0.93, 95% CI 0.63 to 1.37), the incidence of an Apgar score < 7 at 1 min after birth (RR 1.20, 95% CI 0.61 to 2.37), or UA pH (WMD -0.01, 95% CI -0.04 to 0.03), UV pH (WMD -0.01, 95% CI -0.03 to 0.01), UA BE (WMD 0.29, 95% CI -0.89 to 1.47), UV BE (WMD -0.71, 95% CI -2.55 to 1.13), UA PaO2 (WMD -1.30, 95% CI -3.29 to 0.70), UA PaCO2 (WMD -0.37, 95% CI -3.21 to 2.47), UV PaCO2 (WMD 3.66, 95% CI -1.41 to 8.73), UA lactate (WMD -0.25, 95% CI -0.74 to 0.23) and UV lactate (WMD -0.13, 95% CI -1.25 to 0.99) levels. The phenylephrine

Table 2
Summary meta-analysis and heteroeneity of fetal outcomes.

Outomes	No. Patients	No. Studies	RR or WMD (95% CI)	*P* value	I^2 (%)
Fetal acidosis*					
Elective cesarean delivery †	569	8	0.18 (0.06–0.48)	0.0007	0
Prevention †	269	5	0.16 (0.06–0.47)	0.0008	0
Treatment	300	3	0.33 (0.01–7.7.)	0.49	NA
With prehydration	511	7	0.18 (0.06–0.48)		
Without prehydration	58	1	NA	NA	NA
Emergency cesarean delivery	196	2	0.71 (0.39–1.28)	0.25	0
Apgar score < 7, 1min*					
Elective cesarean delivery	224	3	0.68 (0.11–4.20)	0.67	0
Emergency cesarean delivery	204	1	1.00 (0.06–15.77)	1.00	NA
Parturients with pre-eclampsia	64	1	1.20 (0.61–2.37)	0.60	NA
UA pH					
Elective cesarean delivery†	1839	29	0.04 (0.03–0.06)	< 0.00001	95
Prevention †	1253	21	0.05 (0.03–0.07)	< 0.00001	89
Treatment †	586	8	0.03 (0.01–0.05)	< 0.00001	98
With prehydration †	1351	22	0.04 (0.03–0.05)	< 0.00001	95
Without prehydration †	488	7	0.06 (0.03–0.09)	< 0.00001	89
Emergency cesarean delivery †	400	3	0.00 (−0.01 to 0.01)	0.50	0
Parturients with pre-eclampsia	192	3	−0.01 (−0.04 to 0.03)	0.70	68
UV pH					
Elective cesarean delivery †	1235	23	0.02 (0.02–0.03)	< 0.00001	79
Prevention †	1049	19	0.03 (0.02–0.04)	< 0.00001	71
Treatment †	186	4	0.02 (0.00–0.03)	0.006	56
With prehydration †	808	17	0.02 (0.01–0.03)	< 0.0001	69
Without prehydration †	427	6	0.03 (0.01–0.04)	0.002	80
Emergency cesarean delivery	400	3	0.00 (−0.01 to 0.01)	0.70	0
Parturients with pre-eclampsia	172	2	−0.01 (−0.03 to 0.01)	0.41	0
UA BE					
Elective cesarean delivery †	1496	23	1.09 (0.57–1.60)	< 0.0001	96
Prevention †	936	16	1.03 (0.24–1.81)	< 0.00001	87
Treatment †	560	7	1.21 (0.40–2.01)	< 0.00001	98
With prehydration †	1168	18	0.87 (0.29–1.45)	0.03	97
Without prehydration †	328	5	2.01 (1.13–2.90)	< 0.00001	51
Emergency cesarean delivery	400	3	0.46 (−0.23 to 1.14)	0.19	23
Parturients with pre-eclampsia	192	3	0.29 (−0.89 to 1.47)	0.63	31
UV BE					
Elective cesarean delivery †	938	17	0.70 (0.12–1.29)	0.02	91
Prevention	778	14	0.75 (−0.14 to 1.65)	0.10	90
Treatment	160	3	0.29 (−0.86 to 1.45)	0.62	96
With prehydration	671	13	0.48 (−0.20 to 1.15)	0.17	92
Without prehydration †	267	4	1.42 (0.11–2.73)	0.03	78
Emergency cesarean delivery	400	3	0.03 (−0.85 to 0.92)	0.94	64
Parturients with pre-eclampsia	64	1	−0.71 (−2.55 to 1.13)	0.45	NA
UA PaO2					
Elective cesarean delivery	993	18	0.13 (−0.70 to 0.96)	0.76	67
Prevention	729	12	0.39 (−0.77 to 1.55)	0.51	62
Treatment	264	6	−0.29 (−1.63 to 1.06)	0.68	77
With prehydration	605	12	0.21 (−0.84 to 1.26)	0.69	72
Without prehydration	388	6	−0.05 (−1.50 to 1.41)	0.95	55
Emergency cesarean delivery	196	2	−0.60 (−3.44 to 2.24)	0.68	79
Parturients with pre-eclampsia	172	2	−1.30 (−3.29 to 0.70)	0.20	0
UV PaO2					
Elective cesarean delivery	934	17	0.01 (-1.21 to 1.24)	0.98	76
Prevention	748	13	0.08 (-1.64 to 1.79)	0.93	79
Treatment	186	4	-0.01 (-1.88 to 1.86)	0.99	64
With prehydration	607	12	0.93 (-0.56 to 2.42)	0.22	77
Without prehydration †	327	5	-2.05 (-3.82 to -0.27)	0.02	56
Emergency cesarean delivery	400	3	-0.27 (-1.74 to 1.20)	0.72	55
Parturients with pre-eclampsia †	172	2	-3.00 (-4.98 to -1.02)	0.003	0
UA PaCO2					
Elective cesarean delivery †	1160	21	-4.52 (-6.00 to -3.04)	< 0.00001	85
Prevention †	896	15	-5.74 (-8.58 to -2.91)	< 0.0001	86
Treatment †	264	6	-2.81 (-4.14 to -1.48)	< 0.0001	72
With prehydration †	772	15	-4.71 (-6.39 to -3.03)	< 0.00001	88
Without prehydration	388	6	-4.16 (-8.26 to -0.05)	0.05	78
Emergency cesarean delivery	400	3	-0.23 (-1.78 to 1.32)	0.77	14
Parturients with pre-eclampsia	172	2	-0.37 (-3.21 to 2.47)	0.80	1
UV PaCO2					
Elective cesarean delivery	1004	18	-1.12 (-2.22 to -0.02)	0.05	75
Prevention	818	14	-1.65 (-2.82 to -0.48)	0.006	61
Treatment	186	4	0.48 (-0.03 to 0.99)	0.07	0
With prehydration †	677	13	-1.41 (-2.72 to -0.11)	0.03	80
Without prehydration	327	5	-0.10 (-2.33 to 2.14)	0.93	51
Emergency cesarean delivery	400	3	-0.27 (-1.74 to 1.20)	0.72	55

(*continued on next page*)

Table 2 (*continued*)

Outomes	No. Patients	No. Studies	RR or WMD (95% CI)	*P* value	I^2 (%)
Parturients with pre-eclampsia	172	2	3.66 (-1.41 to 8.73)	0.16	67
UA Lactate					
Elective cesarean delivery †	150	3	-0.94 (-1.69 to -0.19)	0.01	85
Emergency cesarean delivery †	204	1	-0.20 (-0.41 to -0.01)	0.06	NA
Parturients with pre-eclampsia	84	2	-0.25 (-0.74 to 0.23)	0.31	0
UV Lactate					
Elective cesarean delivery †	130	3	-0.62 (-1.20 to -0.05)	0.03	85
Emergency cesarean delivery †	204	1	-0.20 (-0.39 to -0.01)	0.04	NA
Parturients with pre-eclampsia	64	1	-0.13 (-1.25 to 0.99)	0.82	NA

UA = Umbilical Artery; UV = Umbilical Vein; BE = Base Excess; RR = Relative Risk; WMD = Weighted Mean Difference; NA = Not Applicable; * Binary outcomes measured by RR and the remaining results were continuous outcomes measured by WMD; † Statistically significant outcomes (*P* value < 0.05).

group had lower UV PaO2 (WMD -3.00, 95% CI -4.98 to −1.02) levels compared to the ephedrine group.

3.7. Publication bias

We did publication bias of hypotension rate in parturients undergoing elective cesarean delivery. The funnel plot (Appendix 2) showed asymmetry owing to small study effects. The publication bias was confirmed by subsequent quantitative results of Begg test and Egger test (both *P* value less than 0.05). The trim and fill results showed that no new studies were added after 'trimming and filling', hence the publication bias influenced little on the final results. We also did a sensitivity analysis and the synthesized outcome remained unchanged after excluding one study each time. The sensitivity analysis result also demonstrated that the outcome result was robust (Appendix 2).

3.8. Trial sequential analysis

TSA was conducted for the primary outcome (maternal hypotension rate), and the RIS was 2523. The cumulative z-curve did not cross the TSA monitoring boundaries or reach the futility area (Fig. 4). The total information size of the 17 included studies was 1159, which did not fulfill the RIS. The results of the TSA demonstrated that more RCTs should be included to obtain a conclusive result.

4. Discussion

Our meta-analysis showed the following results. First, in elective cesarean delivery, the phenylephrine group had similar incidences of hypotension, hypertension, and Apgar score < 7 (1 min after birth), similar UA PaO2, UV PaO2 and UV PaCO2 levels, a higher incidence of bradycardia, higher UA and UV pH values, lower incidences of tachycardia, nausea or vomiting, and fetal acidosis, and lower UA BE, UV BE, UA lactate, UV lactate and UA PaCO2 levels compared to the ephedrine group. The abovementioned results changed very little after subgroup analysis according to prevention or treatment of hypotension and with or without prehydration. Second, in emergency surgery and in parturients with pre-eclampsia, the phenylephrine group maintained similar incidences of hypotension, hypertension, and Apgar score < 7 (1 min after birth), a higher incidence of bradycardia and lower incidences of tachycardia and nausea or vomiting. However, unlike the elective surgery patients, the following outcomes between groups were similar: incidence of fetal acidosis and the outcomes of acid-base equilibrium (UA pH, UV pH, UA BE, and UV BE).

Unlike the former meta-analysis by Lin [10] in 2012, our study contained not only healthy parturients under elective cesarean delivery, but also analyzed emergency surgery and parturients with pre-eclampsia. Lin's study included 15 RCTs of elective cesarean delivery and our meta-analysis contained 36 RCTs with subgroup analysis (different goals of vasopressors: treatment or prevention of hypotension; with or without prehydration before spinal anesthesia).

Phenylephrine, a pure α1 adrenergic receptor agonist, can elevate blood pressure by contracting the vascular smooth muscle. Therefore, heart rate will decline reflexively, and the incidence of hypotension will increase with its use. Ephedrine, a mixed α and β adrenergic receptor agonist, increases blood pressure mainly by activating β adrenergic receptors. Therefore, heart rate, myocardial contractility and cardiac output will improve after ephedrine administration [58]. The abovementioned theory could explain the higher incidence of bradycardia in the phenylephrine group and the higher incidence of tachycardia in the ephedrine group.

Our meta-analysis demonstrated that the incidence of intraoperative nausea or vomiting was less in the phenylephrine group. First, parasympathetic nerves were overactive after sympathetic nerve blockade due to spinal anesthesia and induced nausea or vomiting by activating gastrointestinal function. The overactive parasympathetic nerves were aggravated by β-adrenergic receptor agonism [59]. Second, although the incidence of hypotension did not differ between two groups, ephedrine has a longer onset time than phenylephrine, causing delayed treatment of hypotension, which was not detected by noninvasive blood pressure monitoring.

Our study showed that in elective cesarean delivery, phenylephrine use resulted in a lower fetal acidosis rate, a higher umbilical cord pH and a lower base excess compared to ephedrine use. An RCT conducted by Ngan Kee [37] showed that ephedrine had greater liposolubility than phenylephrine and more readily crossed the placenta. Therefore, fetal metabolism was also stimulated by β adrenergic receptor activation due to ephedrine administration, causing more acidic status in the fetuses.

Unlike in elective cesarean delivery, fetal acid-base equilibrium was not better with phenylephrine use in emergency surgery. Our meta-analysis found that the two groups had similar fetal acidosis rate and umbilical cord pH in the emergency surgery. A retrospective study demonstrated that the total dosage of ephedrine was related to worsening acid-base equilibrium [60]. The total dose of ephedrine used in emergency surgery seemed lower than that used in elective surgery [6,11,12] because less vasopressor support is required in laboring mothers compared to nonlaboring mothers.In our meta-analysis, the total dose of ephedrine used in emergency surgery was lower than that used in elective surgery [6,11,12], causing less ephedrine-related acidic status in the fetuses.

The basic physiological changes in pre-eclampsia are arteriole spasm and damaged vascular endothelial cells, causing reduced uteroplacental perfusion [61]. Research [62] has shown that parturients with pre-eclampsia exhibited a lower incidence of hypotension, and three studies showed that lower total doses of vasopressors were required for pre-eclamptic patients compared to those required for healthy mothers undergoing elective surgery [13–15]. Less vasopressor use was associated with a better fetal acid-base status [60], which is consistent with our results of similar fetal umbilical cord pH and BE values in pre-eclamptic mothers between the groups.

Some strengths exists in this meta-analysis. First, after searching the relatively comprehensive databases by appropriate searching strategies,

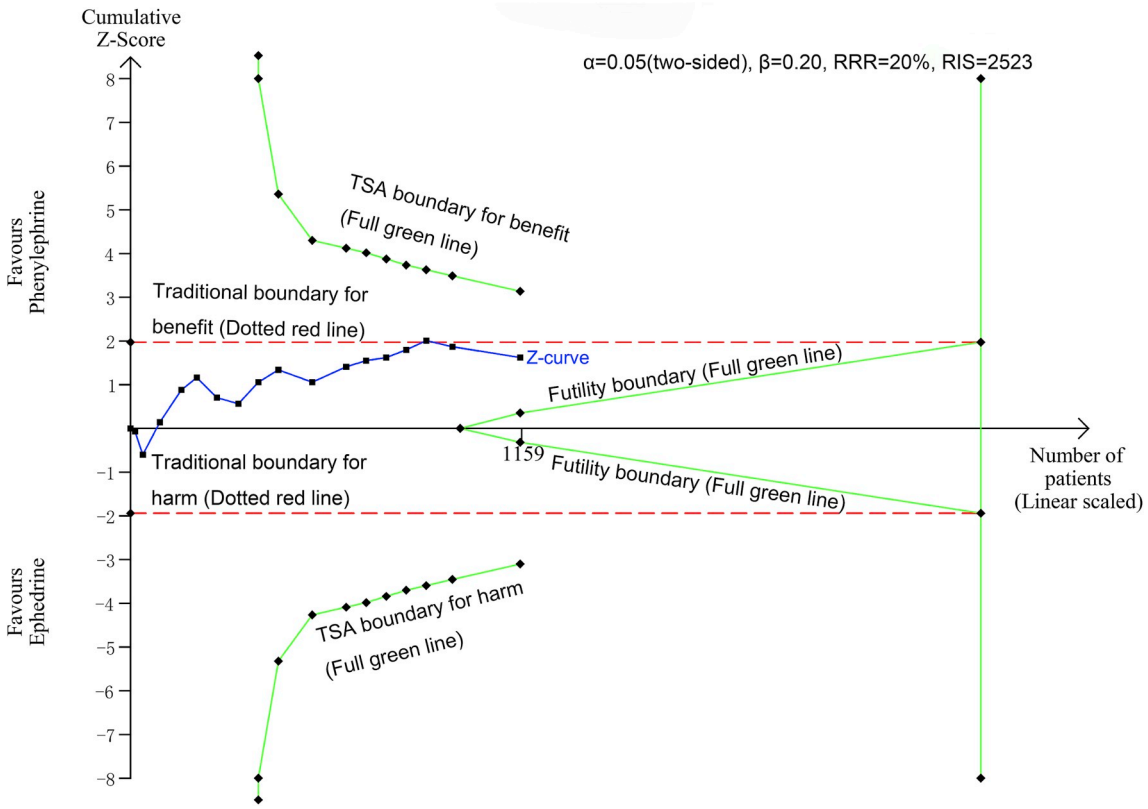

Fig. 4. Trial sequential analysis of 17 studies comparing a phenylephrine group with an ephedrine group for the primary outcome (hypotension). The X axis represents the total number of patients included. The Y axis represents the cumulative z-score. The two horizontal red lines represent the traditional monitoring boundary of the statistically significant threshold with z values of ± 1.96 (the upward red line for benefit and the downward red line for harm). The two curved green lines represent TSA monitoring boundaries. The inner wedge between the two sloping green lines represents the futility area. The vertical green line represents the required information size to draw a definitive conclusion calculated by α = 0.05 (two-sided), β = 0.20, RRR = 20% and the incidence of hypotension in the ephedrine group (41.04%). The z-curve represents synthetic outcomes after adding each study. Each dot on the z-curve represents one study. The result is confirmed when the z-curve crosses one of the TSA boundaries, the futility boundary or the RIS vertical line). TSA = Trial Sequential Analysis; RIS = Required Information Size; RRR = Relative Risk Reduction. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

RCTs were included, high quality study design, to minimize the selection bias. Second, appropriate statistical methods were used in this article. We not only used the conventional subgroup analysis and publication bias but also trial sequential analysis, evaluating the reliability of the conclusion. Third, 42 included studies involved not only elective cesarean delivery but also emergency surgery and parturients with pre-eclampsia, which was never reported in other meta-analysis.

Some limitations exists in this meta-analysis. First, the TSA outcome for the incidence of hypotension demonstrated that the cumulative z-curve did not cross the TSA monitoring boundaries or the futility area, and the cumulative sample size failed to fulfill the required information size. More trials are required to obtain a more conclusive result. Second, for the emergency cesarean delivery patients and the parturients with pre-eclampsia, the numbers of included studies were small, with three for each condition, and more RCTs involving emergency surgery, parturients with pre-eclampsia and other pregnancy-related complications should be included for a more comprehensive conclusion. Third, a publication bias existed for the incidence of hypotension due to small study effects. However, the subsequent trim and fill method showed that the publication bias had little impact on the stability of the final results. Finally, apart from elective cesarean delivery, we only included emergency cesarean delivery and parturients with pre-eclampsia. Subsequent analysis should discuss the two drugs in other circumstance such as fetal abnormality, parturients with diabetes, parturients with epilepsy, etc.

5. Conclusion

Our study revealed that phenylephrine and ephedrine were both effective in maintaining maternal hemodynamic balance in cesarean delivery. Fetal acid-base equilibrium was better controlled in the phenylephrine group in elective cesarean delivery, but not in emergency cesarean delivery or in parturients with pre-eclampsia. More trials should be included to fulfill the TSA requirements to achieve more conclusive results.

Ethical approval

This meta analysis was based on former studies and the ethical approval was not required in this meta analysis.

Sources of funding

None.

Author contribution

Chao Xu and Su Liu: study design, data collections, data analysis and writing.

HanBing Xiao and XiaoWei Guo: data collections and data analysis.

HanBing Xiao and DunYi Qi: Study design, data analysis and writing.

Conflicts of interest

None.

Trial registry number

This meta analysis was registered on PROSPERO. Registration Number: CRD42018087466.

Guarantor

DunYi Qi.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2018.10.039.

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