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META-ANALYSIS

Vasopressors for managing maternal hypotension during cesarean section under spinal anesthesia: A systematic review and network meta-analysis

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Abstract

Introduction: Spinal anesthesia during elective cesarean section often induces maternal hypotension, and vasopressors are the most reliable agents to counteract this. We conducted a systematic review and network meta-analysis to compare and specifically evaluate the efficacy of vasopressors in preventing maternal hypotension (effectiveness) and decreasing fetal acidosis (safety) in parturients undergoing spinal anesthesia for cesarean section. **Methods**: We performed a systematic and comprehensive search to identify all randomized controlled studies on vasopressors to manage maternal hypotension during cesarean section under spinal anesthesia, which had been published until June 30, 2019 and updated until September 20, 2020. A network meta-analysis was conducted to combine direct and indirect comparisons of vasopressors. The primary outcomes included minimum systolic blood pressure, the incidence of hypotension, and fetal acidosis. Stata SE 15.0 was used for the meta-analysis. **Results**: Forty-five studies (n = 3,369) with six different vasopressors injected using various methods were included. Based on the surface under the cumulative ranking curve (SUCRA) value, intravenous (IV) continuous infusion of mephentermine (SUCRA value 83.4%) was the most efficacious vasopressor with the lowest incidence of hypotension, followed by continuous infusion of ephedrine with norepinephrine bolus (81.6%) and norepinephrine (76.4%). Compared with an IV bolus injection, all analyzed vasopressors were more effective when they were infused continuously for managing maternal hypotension. In terms of safety, only angiotensin II as an IV continuous infusion (94.7%) was efficacious in preventing fetal acidosis, resulting in a pH closer to 7.4, and there were no significant differences in umbilical arterial pH between the test and control groups. **Conclusion**: Clinicians should continuously infuse vasopressors to manage maternal hypotension during cesarean section under spinal anesthesia. According to SUCRA, norepinephrine administered as an IV continuous infusion was the third most efficacious vasopressor with the lowest incidence of maternal hypotension, and it could be a potential alternative to phenylephrine. Meanwhile, only angiotensin II administered as an IV continuous infusion caused less umbilical arterial acidosis than the control group.

Keywords

Spinal anesthesia; Cesarean section; Hypotension; Meta-analysis; Systematic review; Vasopressors

1. Introduction

Spinal anesthesia offers a rapid onset and reliable surgical anesthesia with a failure rate of $< 1\%$ [1, 2]. However, the risk of maternal hypotension is higher with spinal anesthesia than with epidural anesthesia. This is because spinal anesthesia results in a rapid sympathetic vasomotor blockade that causes arteriolar vasodilation and decreases systemic vascular resistance, which is impossible to titrate [3]. Therefore, spinal anesthesia lowers not only maternal mean arterial blood pressure, but also reduces uteroplacental perfusion, leading to a low Apgar score and fetal acidosis. Previous studies on spinal-induced maternal hypotension have reported an incidence rate of up to 80% in the absence of prophylaxis [4–6].

The use of vasopressors is the most reliable method for counteracting spinal anesthesia-induced hypotension [7]. Vasopressors act on α1-, β1-, and β2-adrenoreceptors in the heart and vascular systems. The physiological response of these adrenoreceptor agonists depends on the type and location of the receptors. Vasoconstriction is mainly mediated by α1-receptors. However, some vasopressors can also directly or

indirectly stimulate β1- and/or β2-receptors, leading to positive inotropic (increasing cardiac contractility) and/or positive chronotropic (increasing heart rate [HR]) effects. The complex hemodynamic effects of various vasoconstrictors depend on the relative stimulation of these adrenoreceptors. In contrast, cardiovascular reflex responses to vasopressors may result in other changes, including unwanted reflex bradycardia.

Ephedrine has been the first-line agent used in obstetric anesthesia for many decades [8]. However, recent clinical trials have demonstrated that compared with ephedrine, phenylephrine, which has a potent direct α1 effect, decreases the risk of fetal acidosis [9, 10]. However, pH and base excess values are still within the normal range in many studies, and no differences in the incidence of true fetal acidosis and neonatal morbidities have been reported in systematic reviews of randomized controlled trials (RCTs) of ephedrine versus phenylephrine [11, 12].

Phenylephrine is a pure vasoconstrictor; thus, its use is often associated with reflex bradycardia and a consequent decrease in cardiac output (CO). CO is an important requisite for oxygen delivery to peripheral tissues, including the placenta, and hence is more important than BP itself, especially under conditions of fetal hypoxemia during delivery. Responding to this emerging information, some investigators have suggested using norepinephrine as a potential alternative to phenylephrine [13]. Norepinephrine is not only a potent α1-adrenergic agonist, but also a relatively mild β1-agonist; therefore, it increases both HR and cardiac contractility. Hence, norepinephrine might be an effective vasopressor for maintaining maternal BP and CO during spinal anesthesia [13].

The ideal vasopressor would not only maintain maternal hemodynamic stability but also have minimal detrimental effects on the uteroplacental blood flow and neonatal clinical outcomes. However, it is not clear which vasopressor more effective during cesarean section for parturients and fetuses. Thus, we conducted a network meta-analysis (NMA) to compare and specifically evaluate the efficacy of vasopressors in simultaneously preventing maternal hypotension and decreasing fetal acidosis in women undergoing spinal anesthesia for elective cesarean section.

2. Methods

We developed a protocol for this systematic review and NMA according to the preferred reporting requirements for a systematic review and meta-analysis protocol (PRISMA-P) statement [14]. The protocol was registered with the PROSPERO network (registration number: CRD42018111852; www.crd.york.ac.uk/prospero) on October 18, 2018, and published it in a peer-reviewed journal [15]. This systematic review and NMA of vasopressors for the management of maternal hypotension during cesarean section under spinal anesthesia was performed according to the protocol recommended by the Cochrane Collaboration [16] and has been reported according to the PRISMA extension for NMA guidelines [17].

2.1 Search strategy

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar using search terms related to vasopressors for the management of maternal hypotension during cesarean section under spinal anesthesia for articles published until June 30, 2019 and updated until September 20, 2020. Search terms used for MEDLINE and EMBASE are listed in the appendix. Two authors screened the titles and abstracts of the retrieved articles. Reference lists were imported to Endnote software 8.1 (Thompson Reuters, CA, USA), and duplicate articles were removed. Additional relevant articles were identified by scanning the reference lists of articles obtained from the original search.

2.2 Inclusion and exclusion criteria

We included only RCTs that compared two or more vasopressors for the management of maternal hypotension during cesarean section under spinal anesthesia.

The PICO-SD information was composed as follows:

1. Patients (P): all parturients receiving cesarean section under spinal anesthesia.
2. Intervention (I): vasopressors to treat or prevent hypotension in parturients receiving cesarean section, which might be injected using different methods (intravenous [IV] bolus vs. IV continuous infusion) or via different routes (intramuscular [IM] vs. IV).
3. Comparison (C): the same vasopressor injected using different methods or routes, other vasopressors using the same method, placebos, or no treatment.
4. Outcome measurements (O): the primary outcomes were maximum and minimum systolic blood pressures (SBPs), incidence of hypertension and hypotension during cesarean section, and pH of the umbilical artery or vein. The secondary outcomes were incidence of bradycardia, tachycardia, and neonatal Apgar score.
5. Study design (SD): RCTs

Ineligible studies had the following features:

1. Review articles, case reports, case series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other non-relevant studies.
2. Studies that failed to report the outcomes of interest.
3. Dose-finding studies, for instance, those that used an up-and-down sequential method or compared different doses of a single vasopressor.

There were neither language limitations nor date restrictions in our study.

2.3 Study selection

The titles and abstracts identified through the search strategy described above were reviewed independently by two investigators. To minimize data duplication due to multiple reporting, papers by the same author, organization, or country were compared. For articles determined to be eligible based on the title or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least one author were retrieved, and the full text was evaluated. Articles meeting the inclusion

criteria were assessed separately by two authors, and any disagreements were resolved through discussion. In cases where an agreement could not be reached, the dispute was resolved with the help of a third investigator. If the authors were similar or incidence data were extracted from the same database, the study period was assessed. If the study periods overlapped, only the most recent study was included.

2.4 Data extraction

Using a standardized extraction form, the following data were extracted independently by two investigators: (1) title, (2) name of the first author, (3) name of the journal, (4) year of publication, (5) SD, (6) types of vasopressors, (7) dose of vasopressors, (8) country, (9) risk of bias (ROB), (10) inclusion criteria, (11) exclusion criteria, (12) age, (13) number of subjects, (14) the highest value of SBP during the study period (SMP_{max}), (15) the lowest SBP during the study period (SBP_{min}), (16) incidence of hypertension during the study period, (17) incidence of hypotension during the study period, (18) pH of the umbilical artery or vein, (19) incidence of bradycardia during the study period, (20) incidence of tachycardia during the study period, and (21) neonatal Apgar score.

The definitions of hypotension, hypertension, bradycardia, and tachycardia were based on the values defined in each study. If the information was inadequate, attempts were made to contact the study authors, and additional information was requested. If unsuccessful, missing information was calculated from the available data if possible or was extracted from figures using the open-source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net).

The reference lists were divided into two halves. Two investigators completed data extraction, one for each half of the reference list. Data extraction forms were then cross-checked to verify the accuracy and consistency of the extracted data.

2.5 Study quality assessment.

The quality of the studies was independently assessed by two investigators using the ROB tool, according to the Review Manager (version 5.3, The Cochrane Collaboration, Oxford, UK). Quality was evaluated using the following potential sources of bias: sequence generation, allocation concealment, blinding of participants or outcome assessor, incomplete data, and selective reporting. The methodology for each study was graded as "high", "low" or "unclear" to reflect the ROB [16].

2.6 Statistical analysis

Ad-hoc tables were designed to summarize data from the included studies to show their key characteristics and any important questions related to the review objectives. After extracting the data, reviewers determined the feasibility of the meta-analysis.

A multiple treatment comparison NMA is a meta-analysis generalization method that includes both direct and indirect RCT comparisons of treatments. A random-effects NMA based on a frequentist framework was performed using Stata software (version 15; StataCorp LP, College Station, TX, USA) based on *mvmeta* with NMA graphical tools developed by Chaimani and colleagues [18].

Before conducting NMA, we evaluated the transitivity assumptions by examining the comparability of ROB (all versus removing high ROB for randomization, allocation concealment, and blinding of the outcome assessors), demographic characteristics, and types of vasopressors as potential treatment effect modifiers across comparisons.

A network plot linking all included vasopressors was formed to indicate the types of vasopressors, the number of parturients under different vasopressors, and the level of pair-wise comparisons. The nodes show vasopressors being compared, and the edges show the available direct comparisons among the vasopressors. The nodes and edges were weighted based on the number of parturients and the inverse of the standard error of effect.

Contribution plots presented the percentage contribution of each estimate in the summary estimate and the entire network. We displayed the contribution percentage of each comparison by weighted squares in a contribution plot.

We evaluated the consistency assumption for the entire network using the design-by-treatment interaction model. We also evaluated each closed loop in the network to discern local inconsistencies between the direct and indirect effect estimates for the same comparison. For each loop, we estimated the inconsistency factor as the absolute difference between the direct and indirect estimates for each paired comparison in the loop [19].

The mean summary effects with a confidence interval (CI) are presented together with their predictive intervals (PrIs) to facilitate interpretation of the results considering the magnitude of heterogeneity. PrIs provide an interval that is expected to encompass the estimate of a future study.

A rankogram and cumulative ranking curve were drawn for each vasopressor. Rankogram plots are the probabilities for treatments to assume a possible rank. We used the surface under the cumulative ranking curve (SUCRA) values to present the hierarchy of vasopressors for the primary and secondary outcomes. SUCRA is a relative ranking measure that accounts for uncertainty in the treatment order or, in other words, accounts for both the location and variance of all relative treatment effects. A higher SUCRA value is regarded as a better result for individual interventions [20].

A comparison-adjusted funnel plot was used to assess the presence of small-study effects [21].

3. Results

3.1 Study selection

We initially retrieved 240 articles from MEDLINE, EMBASE, CENTRAL, and Google Scholar, in addition to a manual search, and the flow diagram is depicted in Fig. 1. After removing duplicated articles from among 219 potentially eligible articles, we finally included 45 RCTs with 3,369 participants [9, 13, 22–64]. These RCTs were conducted in 15 countries, with the United States contributing to the highest number (12 articles, Table 1). All articles were reported in English, except for two: one in French [31] and the other in Portuguese [29].

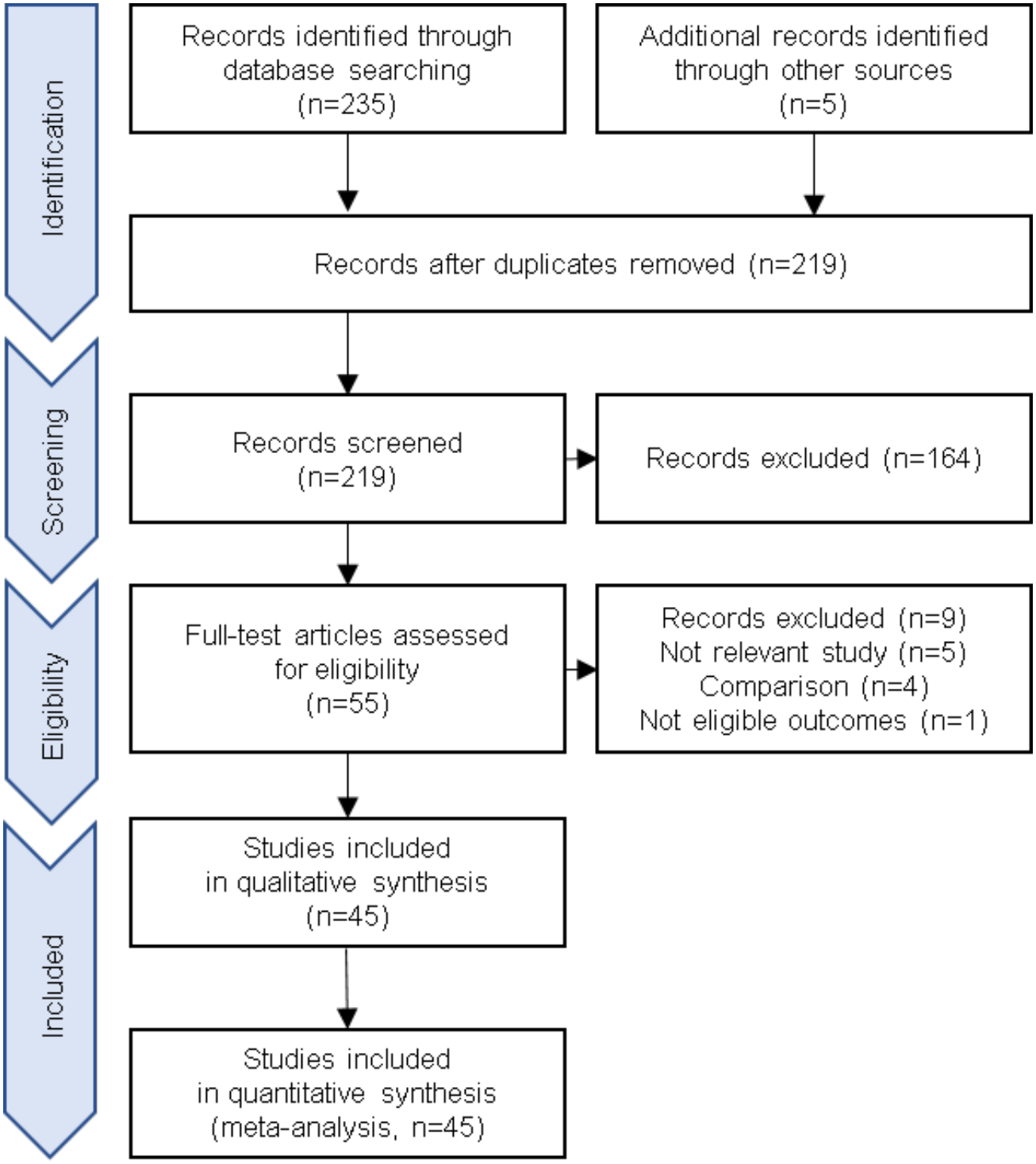

FIGURE 1. PRISMA flow diagram of study selection process.

3.2 Study characteristics

In papers published since 1976, we identified six types of vasopressors and 14 different management modalities (in total, 94 directly compared groups) to treat or prevent hypotension in parturients during cesarean section under spinal anesthesia (Fig. 2). These vasopressors were ephedrine, phenylephrine, angiotensin II, metaraminol, mephentermine, and norepinephrine. Ephedrine (36/94, 38.3%) was the most commonly studied vasopressor among these published trials, followed by phenylephrine (31/94, 33.0%). In terms of management modalities, ephedrine IV continuous infusion (20/94, 21.3%) was the most commonly studied, followed by phenylephrine IV continuous infusion (18/94, 19.1%), ephedrine IV bolus (14/94, 14.9%), and phenylephrine IV bolus (13/94, 13.8%). Although various endpoints were measured in all included studies (Fig. 3), the Apgar score was the most commonly measured endpoint (36/45 studies, 80.0%), followed by umbilical arterial blood gas analysis (34/45, 75.6%) and the incidence of hypotension (32/45, 71.1%).

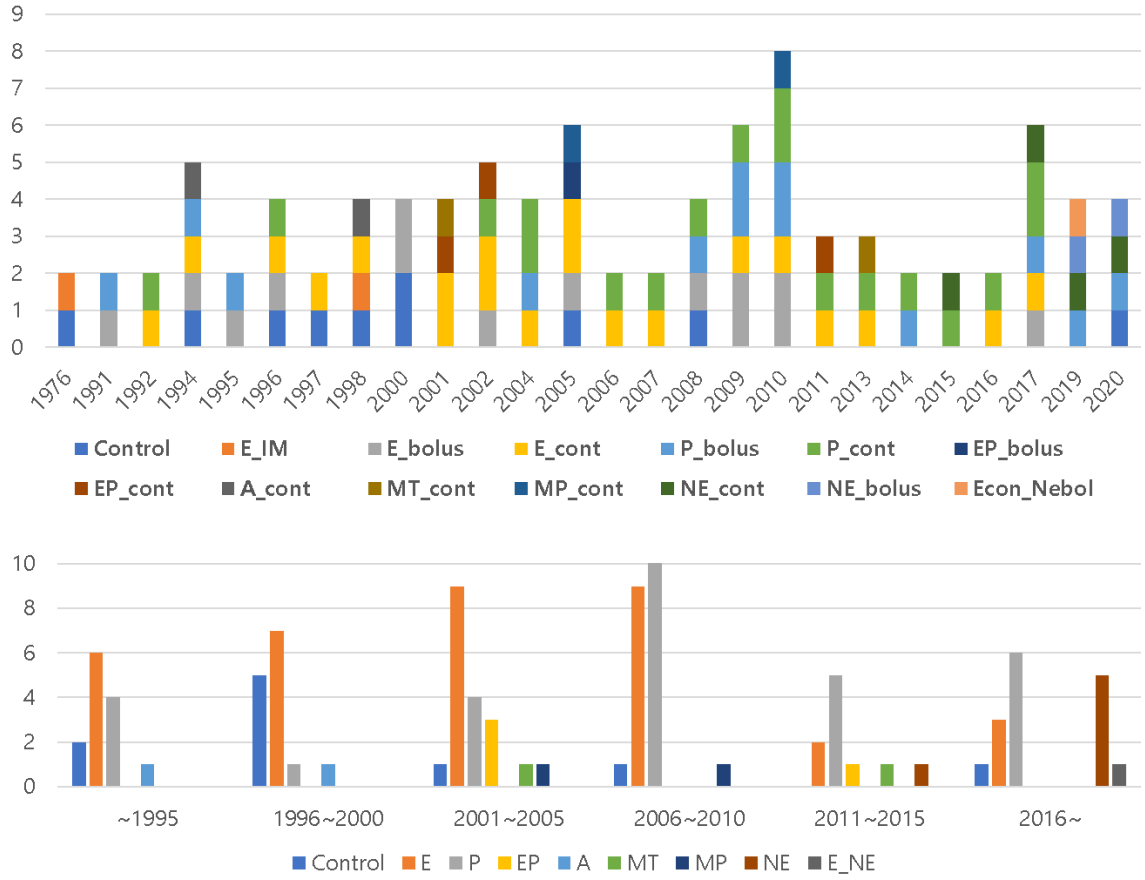

FIGURE 2. History of management modality types and frequencies. Y-axis shows the number of the articles that studied each vasopressor. (A) Yearly trend of the number of the articles including the way and route of injection for each vasopressor. (B) The changes of studied vasopressors over time.

3.3 Study quality assessment

The ROB assessment of the included studies using the Cochrane tool is presented in Table 2. Only four studies had a low ROB in all domains. The most common risk was the incomplete blinding of participants and personnel (8/45 studies, 17.8%). However, its effect on the statistical analysis might be limited because most of the measured endpoints were objective outcomes such as vital signs or results of laboratory studies, except for nausea. Furthermore, most of the data collection (42/45, 93.3%) was completed as scheduled because the studies were conducted during the time of anesthesia in the operating room. In terms of selective outcome reporting, many study protocols (36/45, 80%) were not registered with the clinical registry before enrollment, especially the studies published before 2006. The network plots for all measured endpoints are documented in the supplementary data (Fig. S1).

3.4 Synthesis of results

This study aimed to compare and specifically evaluate different vasopressors in terms of effectiveness in managing maternal hypotension and ensuring safety by avoiding adverse maternal and fetal outcomes. To this end, we selected the incidence of hypotension (iHypo) and lowest SBP (SBP_{min}) as representative indicators of effectiveness. Umbilical arterial pH and Apgar score were chosen as representative indicators of safety in this analysis. All data for statistical analysis, except for these indicators, are presented in the supplements. In most studies, the control groups were performed only fluid loading, although the total injection volume was different.

(1) Effectiveness

Incidence of hypotension: In total, 31 studies (2,266 patients) measured the incidence of hypotension, although the definition of hypotension was different among the included studies. The network plot of all eligible comparisons for this endpoint is depicted in Fig. 4A. Although all 14 management modalities (nodes) were connected to the network, four nodes (control, ephedrine IV bolus, ephedrine IV continuous infusion, and phenylephrine IV continuous infusion) were compared more than the other 10 nodes. Evaluation of the network inconsistency using the design-by-treatment interaction model suggested no evidence of statistically significant inconsistency ($\chi^2(9) = 11.22$, $P = 0.2612$).

The expected mean rankings and SUCRA values for each management modality are depicted in Fig. 5A. According to the SUCRA value, when compared to the control, mephentermine IV continuous infusion (SUCRA value: 83.4%) was the most efficacious modality with the lowest incidence of hypotension, followed by continuous infusion of ephedrine with norepinephrine bolus (81.6%), norepinephrine (76.4%), ephedrine mixed with phenylephrine (75.2%), phenylephrine

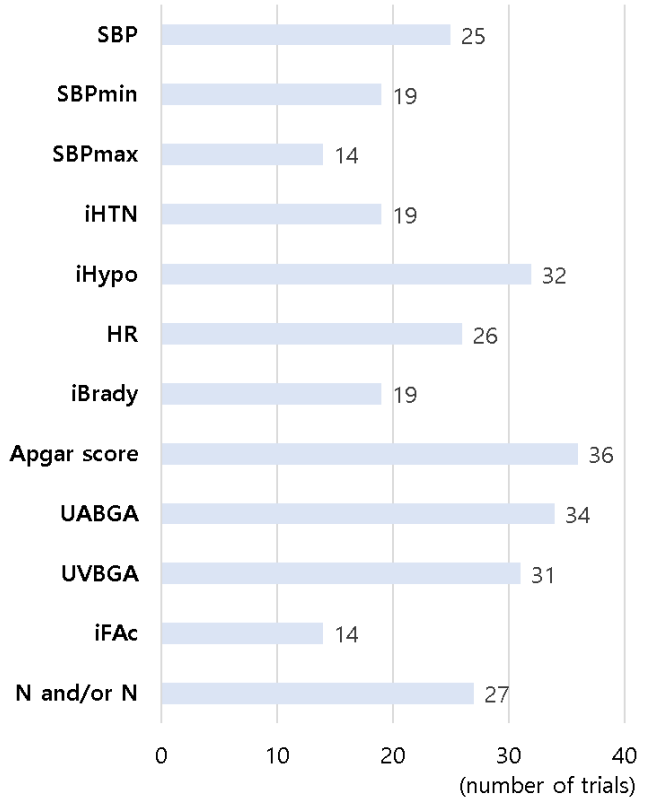

FIGURE 3. Various endpoints that were frequently measured in all of the included studies. Abbreviation: SBP = systolic blood pressure; SBP_{min} = minimum systolic blood pressure; SBP_{max} = maximum systolic blood pressure; iHTN = incidence of hypertension; iHypo = incidence of hypotension; HR = heart rate; iBrady = incidence of bradycardia; UABGA = umbilical arterial blood gas analysis; UVBGA = umbilical venous blood gas analysis; iFAc = incidence of fetal acidosis; N = nausea; V = vomiting.

(74.7%), and angiotensin II (68.4%) IV continuous infusion in the order of effectiveness. The predictive interval plot (Fig. 6A) showed that all analyzed vasopressors were more effective than the control only when they were infused continuously and injected intramuscularly. On the other hand, no bolus injection of the studied vasopressors did not show such an effect.

Minimum SBP (SBP_{min}): A total of 30 studies (2,577 patients) measured SBP_{min}, although the total duration (150 s to 60 min) and time interval (20 s to 5 min) of BP measurements varied considerably among the studies. The network plot of all eligible comparisons for this endpoint is depicted in Fig. 4B. Although all 14 nodes were connected to the network, two nodes (ephedrine IV continuous infusion and phenylephrine IV continuous infusion) were compared more than the other 12. Evaluation of the network inconsistency suggested no evidence of statistically significant inconsistency ($\chi^2(7) = 5.97$, $P = 0.5427$).

The expected mean rankings and SUCRA values for each management modality are depicted in Fig. 5B. According to the SUCRA value, when compared to the control, phenylephrine IV continuous infusion (SUCRA value: 85.5 %) was the most efficacious in maintaining higher SBP_{min}, followed by ephedrine mixed with phenylephrine (83.3%) IV continuous infusion and ephedrine IM injection (81.6%) in the order of effectiveness. The predictive interval plot (Fig. 6B) showed that the three interventions described above were significantly more effective than the control.

(2) Safety

Umbilical arterial pH: A total of 34 studies (2,434 patients) sampled umbilical arterial blood for gas analysis. The network plot of all eligible comparisons for this endpoint is depicted in Fig. 4C. Thirteen management modalities, except the ephedrine IM injection, were connected to the network. Four nodes (ephedrine IV bolus and continuous infusion, phenylephrine IV bolus, and continuous infusion) were compared more than the other nine nodes. Evaluation of the network inconsistency suggested no evidence of statistically significant inconsistency ($\chi^2(10) = 18.99$, $P = 0.0404$), and in the inconsistency plot, all 95% confidence intervals (Cis) included zero, which means that there was no local inconsistency in the loop.

The expected mean rankings and SUCRA values of each intervention are shown in Fig. 5C. According to the SUCRA value, when compared to the control, angiotensin II as an IV continuous infusion (SUCRA value 94.7%) was the most efficacious, resulting in a pH closer to 7.4. On the CI plot, angiotensin II as IV continuous infusion was the only vasopressor with a statistically significant difference in the umbilical arterial pH when compared to the control (Fig. 6C, 95% CI [0.00, 0.12], Supplementary Table S10).

Apgar score: A total of 20 studies (1,638 patients) measured Apgar scores at 1 min and 5 min after delivery. The network plot of all eligible comparisons for this endpoint is depicted in Fig. 4D, E. Twelve management modalities, except ephedrine IM injection and norepinephrine IV continuous infusion, were connected to the network. The two trials used norepinephrine IV continuous infusion as a management modality and documented the Apgar score only as a categorical variable. Therefore, we could not include it in the statistical analysis. Evaluation of the network inconsistency suggested no evidence of statistically significant inconsistency (1 min Apgar score: $\chi^2(7) = 3.41$, $P = 0.8448$, 5 min Apgar score: $\chi^2(7) = 1.02$, $P = 0.9945$).

The expected mean rankings and SUCRA values for each intervention are depicted in Fig. 5D, E. According to the SUCRA value, when compared to the control, metaraminol IV continuous infusion (SUCRA value: 78.7% in 1 min, 97.0% in 5 min) was ranked the most efficacious for its higher 1 min and 5 min Apgar scores. However, in the case of 1 min Apgar score, there was no statistical significance as per the predictive interval plot (Fig. 6D). In contrast, the 5 min Apgar score showed a statistically significant difference (Fig. 6E, 95% CI [0.05, 2.03]).

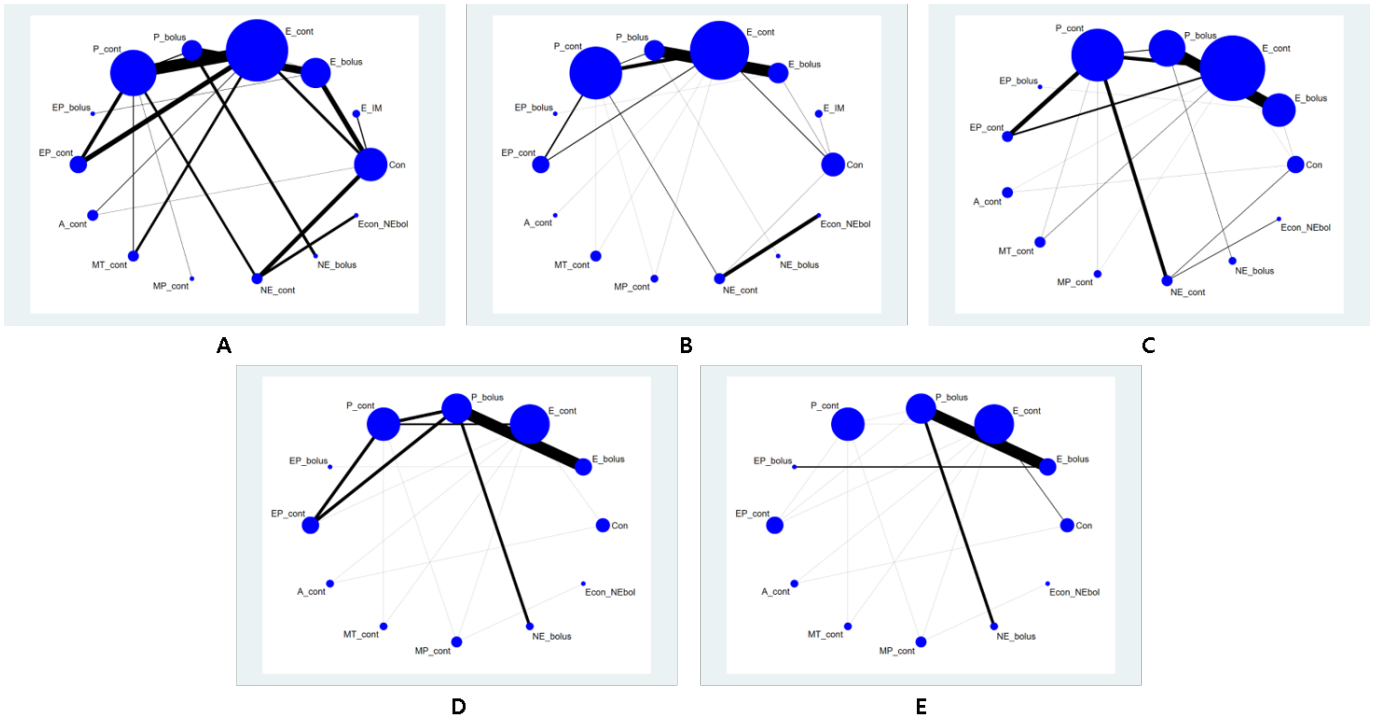

FIGURE 4. Network plots of the major endpoints. The nodes show vasopressors being compared, and the edges show the available direct comparisons among the vasopressors. The nodes and edges are weighed on the basis of the number of parturients and inverse of standard error of effect. (A) Incidence of hypotension, (B) Minimum systolic blood pressure (SBPmin), (C) Umbilical arterial pH, (D) 1 min Apgar score, (E) 5 min Apgar score.

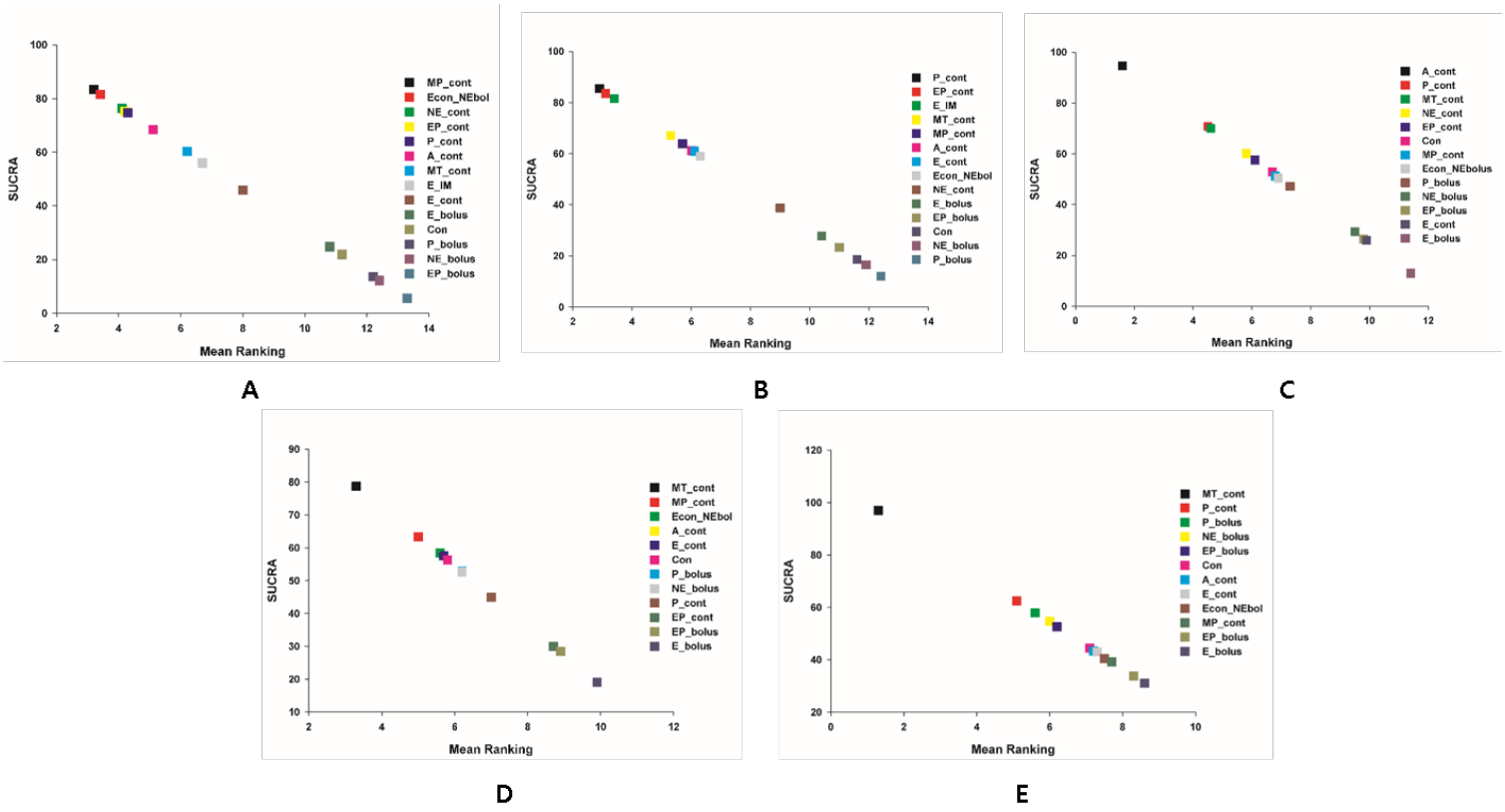

FIGURE 5. SUCRA (surface of under cumulative ranking curve) mean effectiveness ranking of major endpoints. (A) Incidence of hypotension, (B) Minimum systolic blood pressure (SBPmin), (C) Umbilical arterial pH, (D) 1 min Apgar score, (E) 5 min Apgar score.

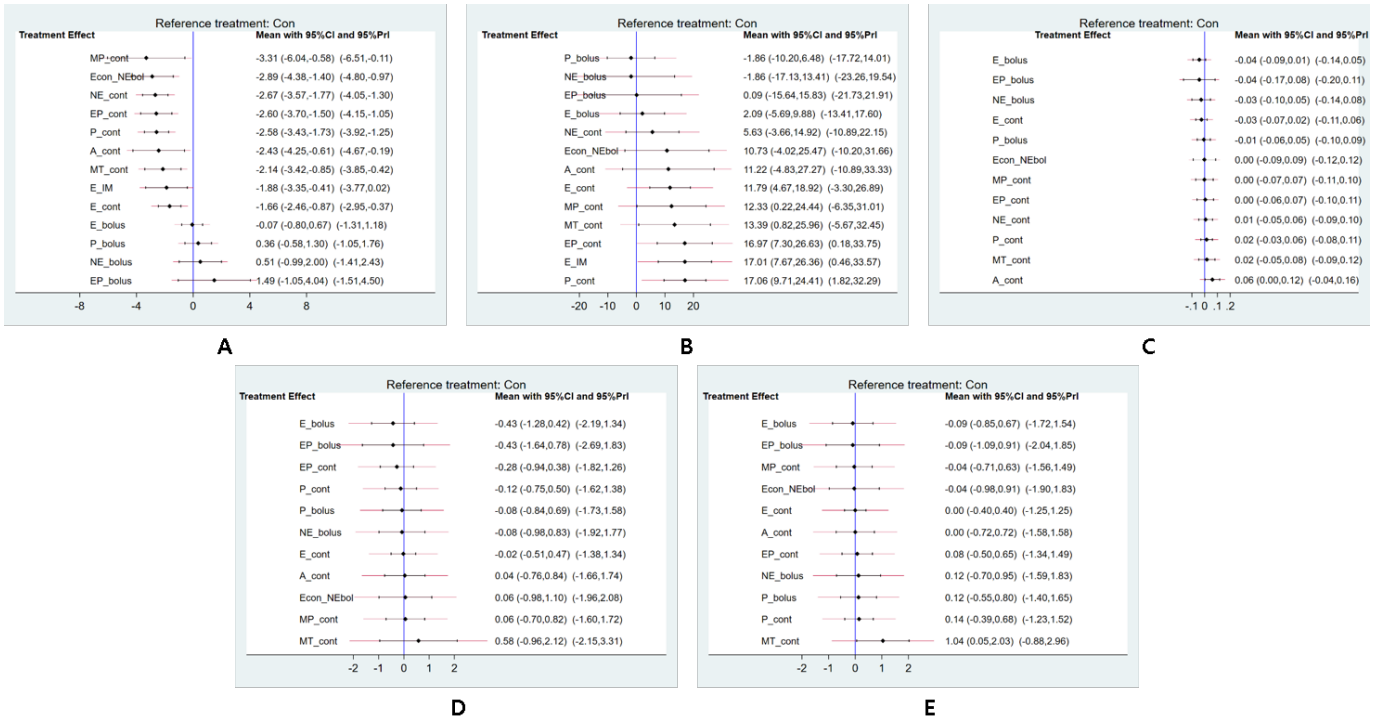

FIGURE 6. Predictive interval plots between each management modalities and control group. A) Incidence of hypotension, (B) Minimum systolic blood pressure (SBPmin), (C) Umbilical arterial pH, (D) 1 min Apgar score, (E) 5 min Apgar score.

4. Discussion

An optimal management strategy for maternal hypotension during cesarean section under spinal anesthesia has been one of the central issues concerning the field of obstetric anesthesia. The optimal strategy should not cause fetal acidosis and, at the same time, avoid maternal complications such as nausea and vomiting. Several attempts have been made to identify the best management strategy, including the types of vasopressors, methods of administration, and their optimal dose. However, a consensus has not been reached. From the literature, we identified six types of vasopressors: ephedrine, phenylephrine, angiotensin II, metaraminol, mephentermine, and norepinephrine. Before 2005, most RCTs compared ephedrine with other vasopressors (Fig. 2B). However, in 2012, a systematic review and cumulative meta-analysis found that compared with phenylephrine, ephedrine use was associated with an increased risk of fetal acidosis [10]. Thereafter, studies have focused more on phenylephrine than on ephedrine, especially since 2015 (Fig. 2B). Some authors have recently conducted RCTs to compare the effect of norepinephrine in preventing maternal hypotension and to determine the optimal infusion dose [13, 60–64].

NMA can increase the precision of the estimates and produce a relative ranking of all treatments for the studied outcome by integrating direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator) [18]. This will provide researchers with valuable information for decision making. In this NMA, we included only RCTs that directly compared two or more vasopressors for the management of maternal hypotension and did not include dose-finding studies, for instance, those that used an up-and-down sequential method or compared different doses of one vasopressor. The main results of this systematic review and NMA are as follows.

(1) All analyzed vasopressors were more effective when infused continuously than when injected as an IV bolus, even when injected several times with multiple intermittent boluses.

(2) Compared to the control, angiotensin II as an IV continuous infusion was the only effective vasopressor that caused less umbilical arterial acidosis than the control group. However, there was no statistically significant difference between the 1 min and 5 min Apgar scores.

4.1 Effectiveness

Our results show that IV continuous infusion of all vasopressors described above and IM injection of ephedrine are more effective than the control in lowering the incidence of maternal hypotension. In addition, the full predictive interval plot of the incidence of hypotension, presented in the supplements (Fig. S7), shows that these are more effective than an IV bolus injection of vasopressors. The predictive interval is a range of values that predict the values of new observations based on the existing model. Therefore, we suggest the abovementioned strategies to be more effective than the control, although more trials must be conducted in the future to prove the same. Consequently, we can conclude that clinicians should continuously infuse vasopressors for prophylaxis or treatment of maternal hypotension during cesarean section under spinal anesthesia.

TABLE 1. A summary of characteristics of included studies for the network meta-analysis.

ID	Author Year	Country	Management	No. of patients	Purpose P/T	Definition of hypotension	Total dose*	Endpoints
1	[22]	USA	Control E 50 mg IM	9 8	P	SBP < 100 torr	No statement	SBP, SBP_{min}, iHypo, Apgar score, UVBGA, N or V
2	[23]	USA	E 5 mg IV bolus P 40 μg IV bolus	29 31	T	Any decrease of baseline SBP	41 ± 4 mg 335 ± 31 μg	iHypo, Apgar score, UABGA, UVBGA, N or V
3	[24]	Finland	E 50 μg/hr IV P 1 mg/hr IV	9 8	P	Fall in SBP > 10 mmHg from the baseline	No statement	SBP, DBP, iHypo, HR, Apgar score, UABGA, UVBGA
4	[25]	USA	E 5 mg IV bolus P 40 μg IV bolus	16 14	T	SBP < 100 mmHg or < 90% of baseline	36.2 ± 22.7 mg 258.5 ± 138.2 μg	UABGA, UVBGA, iFAc
5	[26]	USA	Control E 10 mg/hr IV A II 1~33 ng/kg/min IV	10 10 10	P	SBP < 70% of baseline	No statement	MBP, iHypo, Apgar score, UABGA, UVBGA, iFAc, N and/or V
6	[27]	USA	E 5 mg IV bolus P 40 μg IV bolus	20 20	T	SBP < 100 mmHg	39.5 ± 18.5 mg 364 ± 149 μg	Apgar score, UABGA, UVBGA
7	[28]	USA	Control E 10 mg IV bolus	30 92	T	SBP ≤ 100 mmHg	0.18 ± 0.03 mg/kg 0.33 ± 0.02 mg/kg	SBP_{min}, iHypo, Apgar score, UABGA, iFAc, V
8	[29]	USA	E 50~75 mg/hr IV P 1.15 mg/hr IV	19 19	T	SBP < 80% of baseline	No statement	SBP, SBP_{min}, iHypo, HR, iBrady, Apgar score, UABGA, iFAc
9	[30]	UK	Control E 0.25 mg/kg IV	23 23	P	SBP < 80% of baseline	14.8 ± 12.0 mg 30.7 ± 7.47 mg	SBP, iHypo, HR, Apgar score, UABGA, UVBGA, N or V
10	[31]	USA	A II 10 ng/kg/min IV E 5 μg/kg/min	29 25	P	SBP < 90% of baseline	500 ± 320 ng/kg 790 ± 640 μg/kg	SBP, iHTN, iHypo, HR, iBrady, Apgar score, UABGA, UVBGA, N or V
11	[32]	South Africa	Control E 35 mg IM	20 20	P	SBP < 100 mmHg or < 70% of baseline		SBP_{min}, SBP_{max}, iHTN, iHypo, iTachy, Apgar score, UVBGA
12	[33]	USA	Control E 10 mg IV bolus	20 20	P	SBP < 80% of baseline	31.25 ± 16.53 mg 29.5 ± 18.7 mg	MBP, iHypo, HR, Apgar score
13	[34]	Belgium	Control E 5 mg IV bolus	24 24	T	SBP < 100 mmHg or < 70% of baseline	No statement	SBP_{min}, iHypo, Apgar score, iFAc
14	[35]	USA	E 2 mg/min IV EP (E 2 mg/min + P 10 μg/min) IV	20 19	P	SBP < 100 mmHg or < 80% of baseline	68 ± 23 mg E41 ± 21 mg P 178 ± 81 μg	SBP, SBP_{min}, SBP_{max}, iHTN, iHypo, HR, Apgar score, UABGA, UVBGA, V
15	[36]	Hong Kong	E 5 mg/min IV MT 0.25 mg/min IV P 0~4 mg/hr IV	25 25 48	T	SBP < 90% of baseline	50.0 ± 25.1 mg 3.1 ± 0.9 mg	SBP, SBP_{min}, SBP_{max}, iHypo, HR, Apgar score, UABGA, UVBGA, iFAc, N or V
16	[37]	UK	E 0~120 mg/hr IV EP (E 0~2 mg/hr + P 0~60 mg/hr) IV	50 49	P	SBP < 80% of baseline	No statement	SBP, SBP_{min}, iHypo, HR, iBrady, Apgar score, UABGA, UVBGA, iFAc, N

TABLE 1. Continued

ID	Author Year	Country	Management	No. of patients	Purpose P/T	Definition of hypotension	Total dose*	Endpoints
17	[38]	Turkey	E 2.5~5 mg/min IV E 10 mg IV bolus	15 15	P	SBP < 80% of baseline	33.5 ± 7.7 mg 29.7 ± 8.5 mg	SBP, iHypo, HR, UABGA, UVBGA, N
18	[39]	UK	E 2 mg/ml, P 67 μg/ml, 2.5~40 ml/hr IV	30 30	P	SBP < 80% of baseline	39.2(29.5-43.9) mg 0.97(0.68-1.28) mg	SBP_{min}, SBP_{max}, MBP, iHTN, iHypo, iBrady, iTachy
19	[40]	Hong Kong	P 100 μg/min IV P 100 μg IV bolus	26 24	P	SBP < 80% of baseline	No statement	SBP_{min}, SBP_{max}, iHTN, HR, Apgar score, UABGA, UVBGA, N & V
20	[41]	Nigeria	Control (Prehydration) E 1.5 mg/min	30 30	P	SBP < 80% of baseline	9.8 ± 5.5 mg 39.8 ± 6.0 mg	SBP, iHTN, iHypo, HR, Apgar score, iBrady, iTachy, N, V
21	[42]	India	E 2.5 mg/min MP 2.5 mg/min	30 30	T	SBP ≤ 80% of baseline or < 100 mmHg	19.9 ± 11.45 mg 17.2 ± 10.38 mg	SBP, SBP_{max}, HR, iBrady, Apgar score, UABGA, UVBGA, iFAc, N or V
22	[43]	USA	E 10 mg IV bolus EP (E10 mg+P40 μg) IV bolus	20 20	P	SBP < 80% of baseline or < 100 mmHg	29.25 ± 18.5 mg E 25.25 ± 8.5 mg P 101 ± 34 μg	SBP_{min}, SBP_{max}, iHypo, Apgar score, UABGA, UVBGA
23	[44]	UK	E 10~100 mg/hr IV P 0.1~1 mg/hr IV	40 40	P	SBP < 75% of baseline or < 100 mmHg	39.64 ± 6.33 mg 496.45 ± 78.3 μg	UABGA, N
24	[39]	UK	E 45~180 mg/hr IV P 1~4 mg/hr IV	27 27	P	SBP < 80% of baseline	9(7-23) mg 0.63(0.43-0.96) μg	SBP_{min}, SBP_{max}, MBP, iHTN, iHypo, Apgar score, UABGA, UVBGA
25	[45]	Norway	Control P 0.25 μg/kg/min IV	40 40	P	SBP < 90 mmHg	No statement	SBP, MBP, DBP, HR, CO, SVR, SV
26	[46]	Hong Kong	E 10 mg IV bolus P 100 μg IV bolus	102 102	T	SBP < 100 mmHg	No statement	SBP_{min}, SBP_{max}, iHypo, UABGA, UVBGA, N or V
27	[47]	South Africa	E 10 mg IV bolus P 80 μg IV bolus	20 20	T	SBP < 80% of baseline	No statement	MBP, MBP_{max}, HR, Apgar score, UABGA, N & V
28	[48]	Brazil	E 10 mg IV bolus P 80 μg IV bolus	30 30	P	SBP ≤ 80% of baseline	14 mg 186 μg	iHypo, iBrady, Apgar score, UABGA, UVBGA
29	[49]	Hong Kong	E 8 mg/min IV P 100 μg/min IV	52 52	P	SBP < 80% of baseline	62.3(44.8-79.2) mg 1300(960-1690) μg	SBP_{min}, SBP_{max}, iHTN, iHypo, iBrady, Apgar score, UABGA, UVBGA, N or V
30	[50]	Nigeria	E 5 mg IV bolus P 100 μg IV bolus	31 31	T	SBP < 70% of baseline or < 100 mmHg	No statement	SBP, iHTN, iHypo, Apgar score, N
31	[51]	France	E 195 mg/hr IV P 2.5 mg/hr IV	20 20	P	SBP < 90% of baseline	68 ± 25 mg 1.1 ± 0.4 mg	HR, QTc, Apgar score, UABGA, UVBGA
32	[52]	India	P 50 μg/min IV MP 600 μg/min IV	30 30	P	SBP ≤ 80% of baseline or < 100 mmHg		SBP, iHTN, iHypo, HR, iBrady, Apgar score, UABGA, UVBGA, N, V
33	[53]	India	E 6 mg IV bolus P 100 μg IV bolus	30 30	T	SBP ≤ 80% of baseline	12.5 ± 5.1 mg 0.16 ± 0.06 mg	SBP, SBP_{min}, SBP_{max}, iHTN, HR, iTachy, iBrady, Apgar score, UABGA, UVBGA

TABLE 1. Continued

ID	Author Year	Country	Management	No. of patients	Purpose P/T	Definition of hypotension	Total dose*	Endpoints
34	[54]	India	E 3 mg/ml P 100 μg/ml EP (E1.5 mg+ P50 μg)/ml 20~80 ml/hr IV	29 31 33	P	SBP < 80% of baseline	No statement	SBP, iHTN, iHypo, iTachy, iBrady, Apgar score, N
35	[55]	India	E 2.5 mg/min IV MT 0.25 mg/min IV P 15 μg/min	26 27 32	P	SBP < 80% of baseline	39.3 $\pm$ 14.6 mg 1.7 $\pm$ 0.9 mg 283.6 $\pm$ 99.8 μg	SBP, iHTN, iHypo, HR, iBrady, Apgar score, UABGA, UVBGA, iFAc, N & V
36	[56]	Lebanon	P 0.75 μg/kg/min IV P 100 μg IV bolus	40 39	P T	SBP < 80% of baseline and < 100 mmHg	1533 $\pm$ 519 μg 313 $\pm$ 214 μg	SBP, iHTN, iHypo, HR, iBrady, Apgar score, UABGA, UVBGA, N or V
37	[13]	Hong Kong	P 0~100 μg/min IV NE 0~5 μg/min IV	52 49	P	SBP < 80% of baseline	No statement	SBP, HR, iBrady, Apgar score, UABGA, UVBGA, iFAc, N or V
38	[57]	India	E 2.5 mg/min IV P 30 μg/min IV	45 45	P	SBP < 90% of baseline	No statement	SBP, iHTN, iHypo, HR, iBrady, UABGA, UVBGA
39	[58]	UK	E 5 mg/min IV P 100 μg/min IV	20 20	P	SBP < 80% of baseline	62.5 $\pm$ 4.77 mg 2.23 $\pm$ 0.45 μg	SBP, HR, UABGA, UVBGA, iFAc
40	[59]	Thailand	E 6 mg IV bolus P 100 μg IV bolus	177 177	T	SBP < 80% of baseline	12(6-60) mg 100(100-200) μg	SBP_{min}, Apgar score, Neonatal capillary blood glucose/lactate/amphetamine
41	[60]	USA	P 100 μg/kg/min IV NE 0.05 μg/kg/min IV	38 43	P	SBP < baseline	No statement	SBP, DBP, HR, iHypo, iBrady, CO, CI, SV, SVR, Apgar score, UVBGA, N
42	[61]	Inidia	P 100 μg IV bolus NE 5 μg IV bolus	45 45	T	SBP $\leq$ 80% of baseline or < 100 mmHg	200(100-300) μg 5(5-10) μg	SBP, SBP_{min}, SBP_{max}, HR, iBrady, iHTN, Apgar score, iFAc, UABGA, UVBGA
43	[62]	China	E 4 mg/min IV + NE 8 μg bolus NE 4 μg/min IV +NE 8 μg bolus	49 48	P	SBP < 80% of baseline	E 25(20-30.5) mg NE 0(0-8) μg NE 25(20-30.5) μg	SBP, SBP_{min}, SBP_{max}, iHTN, iHypo, HR, iBrady, iTachy, Apgar score, UABGA, iFAc, N, V
44	[63]	China	Control NE 0.05 μg/kg/min IV	98 97	P	SBP < 80% of baseline	No statement	SBP, SBP_{min}, SBP_{max}, iHTN, iHypo, HR, iBrady, UABGA, N, V
45	[64]	China	P 100 μg/ml IV bolus NE 8 μg/min IV bolus	50 52	T	SBP < 80% of baseline	100(100-400) 16(8-40)	iHTN, iHypo, Apgar score, UABGA, UVBGA, iFAc, N, V

** Data are expressed as mean $\pm$ SD or median (interquartile range).* ***Abbreviations:*** *E = ephedrine; P = phenylephrine; EP = ephedrine mixed with phenylephrine; A II = angiotensin II; MT = metaraminol; MP = mephentermine; NE = norepinephrine; Purpose (P = Prevention, T = Treatment); SBP = systolic blood pressure; SBP_{min} = minimum systolic blood pressure; SBP_{max} = maximum systolic blood pressure; SBP_{mean} = mean systolic blood pressure; MBP = mean blood pressure; MBP_{max} = highest mean blood pressure; DBP = diastolic BP; iHTN = incidence of hypertension; iHypo = incidence of hypotension; HR = heart rate; iTachy = incidence of tachycardia; iBrady = incidence of bradycardia; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance; SV = stroke volume; UABGA = umbilical arterial blood gas analysis; UVBGA = umbilical venous blood gas analysis; iFAc = incidence of fetal acidosis; N = nausea; V = vomiting.*

TABLE 2. Summary of risk of bias assessment.

ID	Author, Year	Sequence generation		Allocation concealment		Blinding of participants, personnel		Blinding of outcome assessors		Incomplete data		Selective outcome reporting		Other source of bias	
1	[22]	unclear	no specific statement	unclear	no specific statement	high	different injection number	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
2	[23]	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement, but same volume	unclear	no specific statement	low	1/60 excluded	unclear	not predefined	unclear	no statement of sample size & equipotency
3	[24]	unclear	no specific statement	low	randomization list	low	both blinded	low	blinded	unclear	2/19 excluded	unclear	not predefined	unclear	no statement of sample size & equipotency
4	[25]	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement	unclear	4/30 excluded	unclear	not predefined	unclear	no statement of sample size & equipotency
5	[26]	unclear	no specific statement	unclear	no specific statement	high	different drug volume	unclear	no specific statement	low	2/32 excluded	unclear	not predefined	unclear	no statement of sample size & equipotency
6	[27]	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement, but same volume	unclear	no specific statement	low	4/44 excluded	unclear	not predefined	unclear	no statement of sample size & equipotency
7	[28]	unclear	no specific statement	unclear	no specific statement	high	different injection number	unclear	no specific statement	low	no exclusion	unclear	not predefined	high	discrepancy in sample size
8	[29]	unclear	no specific statement	low	opaque envelope	low	both blinded	low	blinded	low	2/40 excluded	unclear	not predefined	unclear	no statement of equipotency
9	[30]	unclear	no specific statement	unclear	no specific statement	high	no prehydration in study group	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
10	[31]	unclear	no specific statement	low	opaque envelope	high	different drug volume	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of equipotency
11	[32]	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement, but same volume	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
12	[33]	unclear	no specific statement	low	sealed envelope	low	both blinded	low	automatically recorded	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
13	[34]	unclear	no specific statement	unclear	no specific statement	unclear	no specific statement, but same volume	unclear	no specific statement	low	2/50 excluded	unclear	not predefined	unclear	no statement of sample size
14	[35]	low	random table /c stratification	low	sealed envelope	low	both blinded	unclear	no specific statement	low	3/42 excluded	unclear	not predefined	low	none
15	[36]	low	shuffled	low	sealed envelope	low	both blinded	low	automatically downloaded	low	4/42 partially excluded	unclear	not predefined	low	none
16	[37]	unclear	no specific statement	low	envelope selection	low	both blinded	low	blinded	low	3/147 partially excluded	unclear	not predefined	low	none
17	[38]	unclear	no specific statement	low	sealed envelope	high	discrepancy in injection type	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
18	[39]	unclear	no specific statement	low	envelope selection	low	both blinded	unclear	no specific statement	low	no exclusion	unclear	not predefined	low	none
19	[40]	low	computer generated code	low	sealed envelope	low	both blinded	low	automatically downloaded	low	no exclusion	unclear	not predefined	low	none
20	[41]	unclear	no specific statement	low	blind balloting	high	no prehydration in study group	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of sample size
21	[42]	unclear	no specific statement	low	sealed envelope	low	both blinded	unclear	no specific statement	low	no exclusion	unclear	not predefined	unclear	no statement of equipotency
22	[43]	unclear	no specific statement	low	sealed envelope	low	both blinded	low	blinded	low	3/43 excluded	unclear	not predefined	low	none
23	[44]	low	computer-generated code	low	computer-generated code	low	both blinded	low	blinded	low	6/80 excluded	unclear	not predefined	unclear	no statement of equipotency

TABLE 2. Continued

ID	Author, Year	Sequence generation		Allocation concealment		Blinding of participants, personnel		Blinding of outcome assessors		Incomplete data		Selective outcome reporting		Other source of bias	
24	[39]	low	computer-generated code	low	computer-generated code	low	both blinded	low	blinded	low	no exclusion	low	predefined	low	none
25	[45]	low	list of random numbers	low	sealed envelope	low	both blinded	low	blinded	low	no exclusion	unclear	not predefined	low	none
26	[46]	low	computer-generated code	low	sealed envelope	low	both blinded	low	blinded	low	no exclusion	low	predefined	unclear	no statement of equipotency
27	[47]	low	block randomization	low	sealed envelope	low	both blinded	low	blinded	low	2/40 excluded	unclear	not predefined	unclear	no statement of equipotency
28	[48]	low	computer-generated code	low	sealed envelope	low	both blinded	low	blinded	low	no exclusion	unclear	not predefined	unclear	no statement of equipotency
29	[49]	low	computer-generated code	low	sealed envelope	low	both blinded	low	blinded	low	no exclusion	low	predefined	low	none
30	[50]	low	coded sealed envelope	low	coded sealed envelope	low	both blinded	low	blinded	low	no exclusion	unclear	not predefined	unclear	no statement of sample size & equipotency
31	[51]	low	online calculator	unclear	no specific statement	low	blinded	low	blinded	low	no exclusion	unclear	not predefined	low	none
32	[52]	unclear	no specific statement	low	sealed envelope	low	both blinded	low	blinded	low	2/60 excluded in fetal parameters	unclear	not predefined	low	none
33	[53]	low	computer-generated number	low	allocation after hypotension	unclear	no specific statement, but same volume	low	blinded	low	no exclusion	unclear	not predefined	unclear	no statement of equipotency
34	[54]	low	computer-generated number	low	sealed opaque envelope	low	both blinded	low	blinded	high	39/132 dropout	unclear	not predefined	unclear	no statement of equipotency
35	[55]	low	computer-generated code	low	sealed envelope	low	both blinded	low	blinded	low	5/90 excluded	unclear	not predefined	unclear	no statement of equipotency
36	[56]	low	computer-generated number	low	sealed opaque envelope	low	both blinded	low	blinded	low	1/80 excluded	low	predefined	low	none
37	[13]	low	on-line random number generator	low	opaque envelope	low	both blinded	low	blinded	low	3/104 excluded	low	predefined	low	none
38	[57]	low	computer-generated number	low	sealed opaque envelope	low	both blinded	low	blinded	low	4/94 exclude	unclear	not predefined	low	none
39	[58]	low	computer-generated number	low	sealed opaque envelope	low	both blinded	low	blinded	low	6/46 exclude, but enough power	unclear	not predefined	unclear	no statement of equipotency
40	[59]	low	computer-generated number	low	sealed opaque envelope	high	discrepancy in injection volume	unclear	no specific statement	low	no exclusion	low	predefined	unclear	no statement of equipotency
41	[60]	low	computer-generated table	low	sealed opaque envelope	low	both blinded	low	blinded	low	4/85 exclude	low	predefined	unclear	no statement of equipotency
42	[61]	low	Computer-generated table	low	Sealed opaque envelope	low	Both blinded	low	blinded	low	No exclusion	unclear	not predefined	unclear	no statement of equipotency
43	[62]	low	computer-generated number	low	Sealed opaque envelope	low	Both blinded	low	blinded	low	1/142 exclude	low	predefined	unclear	no statement of equipotency
44	[63]	low	computer-generated sequence	low	Sealed opaque envelope	low	Both blinded	low	blinded	low	5/200 exclude	low	predefined	unclear	no statement of equipotency
45	[64]	low	computer-generated number	unclear	no specific statement	low	Both blinded	low	blinded	low	9/102 exclude	unclear	not predefined	low	none

In terms of minimum SBP, an IM injection of ephedrine, IV continuous infusion of phenylephrine, ephedrine mixed with phenylephrine, metaraminol, mephentermine, and ephedrine were more effective than the control in maintaining SBP higher. According to the SUCRA value, phenylephrine IV continuous infusion is the most efficacious strategy. Considering the predictive interval, only IM injection of ephedrine, IV continuous infusion of phenylephrine and ephedrine mixed with phenylephrine remained more effective than the control.

We believe that this discrepancy is because of the differences in the definition of maternal hypotension among the included studies (Table 1). Some trials defined it as a fixed value such as SBP 100 mmHg, and others defined it as a relative cut-off ratio, such as SBP $<$ 70-100% of baseline. Therefore, the results, such as the incidence of hypotension and minimum SBP, can differ. For this reason, we considered the incidence of hypotension to be a more meaningful endpoint. In addition, the dose of vasopressors varied among the included studies. For example, in the case of fixed-rate infusion, ephedrine was infused at a rate of 10 - 480 mg/h and phenylephrine within the range of 0.9-6 mg/h. Both of these could be a source of between-study heterogeneity.

Norepinephrine is an emerging vasopressor in the field of obstetric anesthesia as a potential alternative to phenylephrine. Norepinephrine is a potent α1-adrenergic agonist and has a relatively modest β1-agonist activity. Therefore, it is expected to be effective in maintaining maternal BP and in increasing CO during spinal anesthesia [13]. Although CO has not been clearly shown to correlate with regional uteroplacental blood flow, maintaining or increasing CO may improve oxygen delivery to the placenta and fetus, which may be beneficial, especially in circumstances of fetal hypoxemia. According to our results, although continuous infusion of norepinephrine IV was ranked the third most efficacious vasopressor that had the lowest incidence of maternal hypotension, only mephentermine [52] and Econ_NEbol (ephedrine IV continuous infusion with norepinephrine intermittent bolus injection) [62] have been studied in each article. However, there was no significant difference when compared with an IV continuous infusion of other vasopressors, except for ephedrine. In addition, the full predictive interval plot of the minimum SBP, presented in the supplements (Fig. S7A), showed no significant difference between norepinephrine and other vasopressors administered as an IV continuous infusion. These results agree with those of two previous trials that compared phenylephrine with norepinephrine IV continuous infusion [13, 60]. In those trials, SBP was observed to be similar between the two groups from induction until uterine incision. Nevertheless, this requires a closer examination and future studies to determine the optimal infusion rate and dosing strategy of norepinephrine for maintaining SBP might change the existing notions.

4.2 Safety

One of the hazardous effects of maternal hypotension after spinal anesthesia is a decrease in uteroplacental blood flow. This may lead to fetal acidosis and a low Apgar score after delivery. However, only 15 trials reported the incidence of fetal acidosis (pH $<$ 7.2 or 7.25) and 34 trials reported the results of umbilical arterial pH. The risk of neonatal morbidity is inversely related to pH [65]. Umbilical venous cord blood reflects the combined effect of maternal acid-base status and placental function, whereas umbilical arterial cord blood reflects the neonatal acid-base status. Therefore, we selected umbilical arterial pH as one of the representative indicators of safety.

Our analysis shows that angiotensin II as an IV continuous infusion is the only method to effectively maintain a significantly higher umbilical arterial pH (closer to 7.4) (Fig. 6C). Angiotensin II is a potent vasopressor that is reported to have fewer vasoconstrictive effects on the uteroplacental vascular bed than on the systemic vascular bed [26]. Vincent RD *et al.* showed that angiotensin II infusion maintained maternal SBP during spinal anesthesia without increasing maternal HR or causing fetal acidosis [31]. Therefore, it is a potentially advantageous strategy for preventing maternal hypotension during spinal anesthesia, although only two trials directly compared angiotensin II with the others [26, 31].

According to the full predictive interval plot of the umbilical arterial pH presented in the supplements (Fig. S7G), an IV continuous infusion of phenylephrine was more effective in maintaining a higher pH than ephedrine IV continuous infusion (95% CI, [0.02-0.06]) and IV bolus injection (95% CI, [0.02-0.10]). This finding is in agreement with that of previous studies, [9, 10] which confirmed that maternal administration of ephedrine induces higher fetal metabolism than phenylephrine. As a result, it induces higher umbilical arterial carbon dioxide tension (pCO_2), lower blood pH, lower blood glucose levels, and higher lactate levels in the neonatal umbilical artery compared with the maternal administration of phenylephrine [40]. Conversely, when we analyzed this further in accordance with the predictive interval, there were no significant differences between the two groups (95% PrI ephedrine IV continuous infusion [-0.04-0.12] and IV bolus injection [-0.03-0.15]), which means that statistical significance could have been altered as described above.

Moreover, in terms of Apgar score, although compared to the control metaraminol IV continuous infusion was ranked the most effective management modality resulting in higher 1 min and 5 min Apgar scores, only the 5 min Apgar scores were statistically significant according to the predictive interval plot (95% CI [0.05-2.03]). Moreover, it was estimated that statistical significance could change if more trials were to be conducted in the future (95% PrI [-0.88-2.96]) (Fig. 6D, E). Even angiotensin II had no statistical significance with respect to the 1 min and 5 min Apgar scores. Generally, umbilical cord blood gas analysis is more reliable than routine clinical assessment at birth using the Apgar scoring system [66]. The Apgar score is affected by numerous factors such as the type of delivery, maternal sedation or anesthesia, congenital malformations, gestational age, pH of the umbilical cord blood, lactate concentration, and interobserver variability [67, 68]. Therefore, it is important to recognize the limitations of the Apgar score. This corresponds closely with the results of many previous studies that did not show a statistical difference in Apgar scores.

4.3 Limitations

The present systematic review and NMA had several limitations. Because this was a meta-analysis, if the included studies were sub-optimally conducted or already had a type of bias, the resulting errors would definitely be reflected in this analysis. To begin with, many included studies did not conduct a power analysis for calculating the adequate sample size (14/45, 31.1%). Although all included studies compared the effect of two or more vasopressors as a management modality for preventing or treating maternal hypotension, many included studies did not select the dose of each vasopressor depending on their own equipotency ratio of evidence (21/45, 46.7%). Furthermore, the dose spectrums of injected vasopressors were very wide, as described above. These factors could influence the observed incidence of hypotension and minimum SBP and could potentially act as confounding factors for assessing effectiveness. Therefore, future studies in this subject should be designed based on the equipotent dose of each vasopressor.

5. Conclusions

Based on available evidence, IV continuous infusion of all analyzed vasopressors was more effective than the control or IV bolus injection in lowering the incidence of maternal hypotension during cesarean section under spinal anesthesia. Therefore, clinicians should continuously infuse vasopressors for managing maternal hypotension in this scenario. In contrast, angiotensin II, as an IV continuous infusion, was the only effective strategy that caused less umbilical arterial acidosis than the control group. However, there was no statistically significant difference between the 1 min and 5 min Apgar scores.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1331118035765739520/attachment/SV2020090701_Supplementary%20material.docx.

REFERENCES

[1] Riley ET, Cohen SE, Macario A, Desai JB, Ratner EF. Spinal versus epidural anesthesia for cesarean section: a comparison of time efficiency, costs, charges, and complications. Anesthesia and Analgesia. 1995; 80: 709-712.

[2] Fettes PD, Jansson JR, Wildsmith JA. Failed spinal anaesthesia: mechanisms, management, and prevention. The British Journal of Anaesthesia. 2009; 102: 739-748.

[3] Dyer RA, Biccard BM. Ephedrine for spinal hypotension during elective caesarean section: the final nail in the coffin? Acta Anaesthesiologica Scandinavica. 2012; 56: 807-809.

[4] Clark RB, Thompson DS, Thompson CH. Prevention of spinal hypotension associated with Cesarean section. Anesthesiology. 1976; 45: 670-674.

[5] Hall PA, Bennett A, Wilkes MP, Lewis M. Spinal anaesthesia for caesarean section: comparison of infusions of phenylephrine and ephedrine. The British Journal of Anaesthesia. 1994; 73: 471-474.

[6] Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. Anesthesia and Analgesia. 1982; 61: 839-842.

[7] Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database of Systematic Reviews. 2006; 4: Cd002251.

[8] Ralston DH, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology. 1974; 40: 354-370.

[9] Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2002; 97: 1582-1590.

[10] Veeser M, Hofmann T, Roth R, Klöhr S, Rossaint R, Heesen M. Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis. Acta Anaesthesiologica Scandinavica. 2012; 56: 810-816.

[11] Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesthesia and Analgesia. 2002; 94: 920-926.

[12] Heesen M, Kolhr S, Rossaint R, Traube S. Prophylactic phenylephrine for caesarean section under spinal anaesthesia: systematic review and meta-analysis. Anaesthesia. 2014; 69: 143-165.

[13] Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology. 2015; 122: 736-745.

[14] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. PRISMA-P Group: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. British Medical Journal (Clinical Research Edition). 2015; 350: g7647.

[15] Ryu C, Choi GJ, Park YH, Kang H. Vasopressors for the management of maternal hypotension during cesarean section under spinal anesthesia: A systematic review and network meta-analysis protocol. Medicine. 2019; 98: e13947.

[16] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Chichester, England, Wiley-Blackwell, 2008.

[17] Cornell JE. The PRISMA extension for network meta-analysis: bringing clarity and guidance to the reporting of systematic reviews incorporating network meta-analyses. Annals of Internal Medicine. 2015; 162: 797-798.

[18] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013; 8: e76654.
[19] White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods. 2012; 3: 111-125.
[20] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of Clinical Epidemiology. 2011; 64: 163-171.
[21] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. British Medical Journal (Clinical Research Edition). 2011; 342: d549.
[22] Gutsche BB. Prophylactic ephedrine preceding spinal analgesia for cesarean section. Anesthesiology. 1976; 45: 462-465.
[23] Moran DH, Perillo M, LaPorta RF, Bader AM, Datta S. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. Journal of Clinical Anesthesia. 1991; 3: 301-305.
[24] Alahuhta S, Räsänen J, Jouppila P, Jouppila R, Hollmén AI. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section. Effects on uteroplacental and fetal haemodynamics. The International Journal of Obstetric Anesthesia. 1992; 1: 129-134.
[25] Pierce ET, Carr DB, Datta S. Effects of ephedrine and phenylephrine on maternal and fetal artrial natriuretic peptide levels during elective cesarean section. Acta Anaesthesiologica Scandinavica. 1994; 38: 48-51.
[26] 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. American Journal of Obstetrics and Gynecology. 1994; 171: 734-739.
[27] LaPorta RF, Arthur GR, Datta S. Phenylephrine in treating maternal hypotension due to spinal anaesthesia for caesarean delivery: effects on neonatal catecholamine concentrations, acid base status and Apgar scores. Acta Anaesthesiologica Scandinavica. 1995; 39: 901-905.
[28] Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap LC 3rd. Fetal effects of prophylactic ephedrine and maternal hypotension during regional anesthesia for cesarean section. Journal of Maternal-Fetal & Neonatal Medicine. 1996; 5: 579-584.
[29] Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. British Journal of Anaesthesia. 1996; 76: 61-65.
[30] 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: 908-913.
[31] Vincent RD Jr, Werhan CF, Norman PF, Shih GH, Chestnut DH, Ray T, *et al*. Prophylactic angiotensin II infusion during spinal anesthesia for elective cesarean delivery. Anesthesiology. 1998; 88: 1475-1479.
[32] Webb AA, Shipton EA. Re-evaluation of i.m. ephedrine as prophylaxis against hypotension associated with spinal anaesthesia for Caesarean section. Canadian Journal of Anesthesia. 1998; 45: 367-369.
[33] Tsen LC, Boosalis P, Segal S, Datta S, Bader AM. Hemodynamic effects of simultaneous administration of intravenous ephedrine and spinal anesthesia for cesarean delivery. Journal of Clinical Anesthesia. 2000; 12: 378-382.
[34] 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. Anesthesia and Analgesia. 2000; 90: 324-327.
[35] Mercier FJ, Riley ET, Frederickson WL, Roger-Christoph S, Benhamou D, Cohen SE. Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section. Anesthesiology. 2001; 95: 668-674.
[36] 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: 307-313.
[37] Cooper DW, Jeyaraj L, Hynd R, Thompson R, Meek T, Ryall DM, *et al*. Evidence that intravenous vasopressors can affect rostral spread of spinal anesthesia in pregnancy. Anesthesiology. 2004; 101: 28-33.
[38] Turkoz A, Togal T, Gokdeniz R, Toprak HI, Ersoy O. Effectiveness of intravenous ephedrine infusion during spinal anaesthesia for caesarean section based on maternal hypotension, neonatal acid-base status and lactate levels. Anaesthesia and Intensive Care Medicine. 2002; 30: 316-320.
[39] Cooper DW, Gibb SC, Meek T, Owen S, Kokri MS, Malik AT, *et al*. Effect of intravenous vasopressor on spread of spinal anaesthesia and fetal acid-base equilibrium. British Journal of Anaesthesia. 2007; 98: 649-656.
[40] Ngan Kee WD, Khaw KS, Ng FF, Lee BB. Prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesthesia and Analgesia. 2004; 98: 815-821.
[41] Desalu I, Kushimo OT. Is ephedrine infusion more effective at preventing hypotension than traditional prehydration during spinal anaesthesia for caesarean section in African parturients? International Journal of Obstetric Anesthesia. 2005; 14: 294-299.
[42] Kansai A, Mohta M, Sethi AK, yagi A, Kumar P. Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section. Anaesthesia. 2005; 60: 28-34.
[43] Loughrey JP, Yao N, Datta S, Segal S, Pian-Smith M, Tsen LC. Hemodynamic effects of spinal anesthesia and simultaneous intravenous bolus of combined phenylephrine and ephedrine versus ephedrine for cesarean delivery. International Journal of Obstetric Anesthesia. 2005; 14: 43-47.
[44] Saravanan S, Kocarev M, Wilson RC, Watkins E, Columb MO, Lyons G. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. British Journal of Anaesthesia. 2006; 96: 95-99.
[45] Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology. 2008; 109: 856-863.
[46] Ngan Kee WD, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section. Anaesthesia. 2008; 63: 1319-1326.
[47] Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, *et al*. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology. 2009; 111: 753-765.
[48] Magalhães E, Govêia CS, de Araúdio Ladeira LC, Nascimento BG, Kluthcouski SM. Ephedrine versus phenylephrine: prevention of hypotension during spinal block for cesarean section and effects on the fetus. Brazilian Journal of Anesthesiology. 2009; 59: 11-20.
[49] Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2009; 111: 506-512.
[50] Adigun TA, Amanor-Boadu SD, Soyannwo OA. Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia. African Journal of Medicine and Medical Sciences. 2010; 39: 13-20.
[51] Guillon A, Leyre S, Remérand F, Taihlan B, Perrotin F, Fusciardi J, *et al*. Modification of Tp-e and QTc intervals during caesarean section under spinal anaesthesia. Anaesthesia. 2010; 65: 337-342.
[52] Mohta M, Janani SS, Sethi AK, Agarwal D, Tyagi A. Comparison of phenylephrine hydrochloride and mephentermine sulphate for prevention of post spinal hypotension. Anaesthesia. 2010; 65: 1200-1205.
[53] Prakash S, Pramanik V, Chellani H, Salhan S, Gogia AR. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomized study. International Journal of Obstetric Anesthesia. 2010; 19: 24-30.
[54] Das S, Mukhopadhyay S, Mandal M, Mandal S, Basu SR. A comparative study of infusions of phenylephrine, ephedrine and phenylephrine plus ephedrine on maternal haemodynamics in elective caesarean section. Indian Journal of Anaesthesia. 2011; 55: 578-583.
[55] Bhardwaj N, Jain K, Arora S, Bharti N. A comparison of three vasopressors for tight control of maternal blood pressure during cesarean section under spinal anesthesia: Effect on maternal and fetal outcome. Journal of Anaesthesiology Clinical Pharmacology. 2013; 29: 26-31.

[56] Siddik-Sayyid SM, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for cesarean delivery. Anesthesia and Analgesia. 2014; 118: 611-618.

[57] Jain K, Makkar JK, Subramani Vp S, Gander S, Kumar P. A randomized trial comparing prophylactic phenylephrine and ephedrine infusion during spinal anesthesia for emergency cesarean delivery in cases of acute fetal compromise. Journal of Clinical Anesthesia. 2016; 34: 208-215.

[58] Mon W, Stewart A, Fernando R, Ashpole K, El-Wahab N, MacDonald S, *et al*. Cardiac output changes with phenhlephrine and ephedrine infusions during spinal anesthesia for cesarean section: A randomized, double-blind trial. Journal of Clinical Anesthesia. 2017; 37: 43-48.

[59] Uerpairojkit K, Anusorntanawat R, Sirisabya A, Chaichalothorn M, Charuluxananan S. Neonatal effects after vasopressor during spinal anesthesia for cesarean section: a multicenter, randomized controlled trial. International Journal of Obstetric Anesthesia. 2017; 32: 41-47.

[60] Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, *et al*. An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. International Journal of Obstetric Anesthesia. 2017; 29: 18-25.

[61] Mohta M, Garg A, Chilkoti GT, Malhotra RK. A randomised controlled trial of phenylephrine and noradrenaline boluses for treatment of postspinal hypotension during elective caesarean section. Anaesthesia. 2019; 74: 850-855.

[62] Xu S, Mao M, Zhang S, Qian R, Shen X, Shen J, *et al*. A randomized double-blind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective caesarean section under spinal anesthesia: A CONSORT-compliant article. Medicine. 2019; 98: e18311.

[63] Chen Y, Guo L, Shi Y, Ma G, Xue W, He L, *et al*. Norepinephrine prophylaxis for postspinal anesthesia hypotension in parturient undergoing caesarean section: a randomized, controlled trial. Archives of Gynecology and Obstetrics. 2020; 302: 829-836.

[64] Wang X, Mao M, Zhang S, Wang ZH, Xu SQ, Shen XF. Bolus norepinephrine and phenylephrine for maternal hypotension during elective caesarean section with spinal anesthesia: a randomized, double-blinded study. Chinese Medical Journal (English) 2020; 133: 509-516.

[65] Andres RL, Saade G, Gilstrap LC, Wilkins I, Witlin A, Zlatnik F, *et al*. Association between umbilical blood gas parameters and neonatal morbidity and death in neonates with pathologic fetal acidemia. American Journal of Obstetrics and Gynecology. 1999; 181: 867-871.

[66] Sykes GS, Molloy PM, Johnson P, Gu W, Ashworth F, Stirrat GM, *et al*. Do Apgar scores indicate asphyxia? Lancet 1982; 27: 494-496.

[67] Kostro M, Jacyna N, Gluszczak-Idziakowska E, Sułek-Kamas K, Jakiel G, Wilińska M. Factors affecting the differentiation of the Apgar score and the biochemical correlation of fetal well-being, a prospective observational clinical study. Developmental Period Medicine. 2018; 22: 238-246.

[68] American College of Obstetrics and Gynecology. Task Force on Neonatal Encephalopathy: American Academy of Pediatrics. Neonatal Encephalopathy and Neurologic Oucome, 2^{nd} edition. Washington, DC: American College of Obstetricians and Gynecologists, 2014.

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