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Review

Norepinephrine versus phenylephrine for post-spinal hypotension during caesarean section

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Abstract

Background: **Currently, phenylephrine is the first-choice vasopressor for prevention and treatment of post-spinal hypotension in caesarean section. Phenylephrine is a potent α-adrenergic vasopressor with a dose-dependent reflex bradycardia and could in theory cause a drop in cardiac output and lower uteroplacental blood flow. Hence, there is an increased interest in the use of norepinephrine because of its weak β-adrenergic activity which can counteract the reflex bradycardia.**
Methods: **Using PRISMA guidelines, we conducted a literature search and identified 35 trials related to the comparison of norepinephrine with phenylephrine for the prevention and/or treatment of post-spinal hypotension during caesarean section.**
Results: **In the present review thirty-five trials were reviewed which compared norepinephrine with phenylephrine for the prevention and/or treatment of post-spinal hypotension during caesarean section. The characteristics of all these trials were summarized in Table I.**
The effect on maternal hemodynamics, maternal adverse events, and neonatal outcome were summarized in Tables II, III, IV and V.
Conclusion: **We concluded that in the healthy parturient delivering an expected healthy fetus via elective caesarean section there is increasing evidence to support norepinephrine as an effective and safe vasopressor in comparison to phenylephrine. Questions about the fetal safety of norepinephrine have been raised and therefore in high-risk populations (compromised fetuses, unhealthy parturients) and during emergency caesarean section, there is a need for more research before we can recommend the routine use of norepinephrine.**

Keywords: **Post-spinal hypotension, norepinephrine, phenylephrine, caesarean section, spinal anesthesia.**

Introduction

The preferred method of anesthesia for caesarean delivery is neuraxial anesthesia, either single-shot spinal (SSS), combined spinal-epidural (CSE), or epidural catheter top-up[1-3]. However, these techniques produce maternal hypotension. If left untreated, the incidence of hypotension can be 60-90%[4-7]. If not treated properly, post-spinal hypotension can lead to maternal and fetal adverse events. These can range from nausea and vomiting, dizziness, cardiovascular instability, and even cardiovascular collapse in the mother. For the fetus, the compromised uteroplacental perfusion caused by the post-spinal hypotension can cause fetal distress with acidemia and hypoxia. In severe cases this can even lead to postnatal neurological injury. Therefore, prevention and treatment of post-spinal hypotension is of the utmost importance for the wellbeing of the mother and the fetus[1-3].

Although different strategies have been suggested to prevent and treat hypotension, current international consensus guidelines published in 2018[1] support the use of vasopressors and more specifically phenylephrine as the preferred method of prevention and treatment of spinal induced hypotension in CS (caesarean section). Left lateral tilt and fluid co-loading are useful but are less effective than vasopressor therapy. The reason vasopressors are needed for the treatment of post-

spinal hypotension is the fact that the sympathetic block is the main cause of post-spinal hypotension. This sympathetic block causes vasodilatation in the arteries and arterioles of the affected region. Through a baroreflex the sympathetic arterial vascular tone in the unaffected regions is increased. The sympathetic block also causes a pooling of blood in the capacitance vessels of the venous reservoir.

If the sensory block is at or higher than T6, the hepatosplanchnic region is part of this venous reservoir and up to 20% of the circulating volume can pool in this reservoir. The best way to mobilize this blood volume and to counteract this vasodilatation is by using vasopressors[8].

A few decades ago, the vasopressor of choice was ephedrine. It has α and β adrenergic agonistic activity, causing a rise in peripheral vascular resistance to counteract the drop in peripheral vascular resistance caused by the sympathetic block, and a positive cardiac chronotropic and inotropic effect. One of the drawbacks of the use of ephedrine in obstetric anesthesia is the fact that it has a late onset of action (up to 2-3 minutes) which makes titrating it to keep the maternal blood pressure stable around its base value more challenging. However, more importantly ephedrine causes much more fetal acidosis compared to phenylephrine. This fetal acidosis is caused by crossing the placenta and direct β-adrenergic activation of the fetal metabolism. The fetal acidosis and fetal pH are important markers of fetal outcome[9-12].

These effects on the fetal metabolism are the main reason that in current practice phenylephrine has become the vasopressor of choice. Phenylephrine has a strong α-adrenergic effect, causing vasoconstriction and thus counteracting the vasodilation caused by the spinal anesthesia, without any β-adrenergic activity. In different studies it has shown to cause significantly less fetal acidosis compared to ephedrine[10,12]. The major drawback of phenylephrine is its dose-dependent, baroreceptor-mediated bradycardia. This bradycardia leads to a drop in maternal cardiac output, which theoretically can cause a drop in uteroplacental blood flow.

This is the reason that in the last few years there has been a search for other vasopressors in obstetric anesthesia, such as norepinephrine.

The reason for this is the fact that norepinephrine has a weak β-adrenergic effect in addition to its strong α-adrenergic effect. It is this weak β-adrenergic that possibly can counteract the baroreceptor mediated bradycardia. And thus, in theory leading to less bradycardia, a better cardiac output and thus a better uteroplacental blood flow. The main difference with ephedrine is that (endogenous) catecholamines do not easily cross the placenta. This can be seen in the landmark trial of Ngan Kee et al[18]. In this trial they had shown that the concentration of norepinephrine and epinephrine in the umbilical cord blood of newborns in the norepinephrine group was lower compared to the phenylephrine group.

We performed a narrative review of all studies comparing phenylephrine with norepinephrine for the prevention and management of post-spinal hypotension following spinal anesthesia. We also evaluated the effects on the fetus.

Methods

This literature review is in accordance with the PRISMA guidelines. For this literature review we conducted an article search using the following terms: norepinephrine AND phenylephrine AND caesarean section OR caesarean delivery AND spinal anesthesia OR neuraxial anesthesia AND hypotension. We planned to only include RCT in this review. Other reviews could be used to find additional sources but would not be included in this review. The search itself was conducted on several different search platforms: PubMed, Cochrane Library, and Wiley Online Library. The endpoint of this search was set to 31 December 2023. The first step was to filter out all the duplicates. Next, the titles and abstracts were scanned for usefulness. The full text of eligible articles was then read to decide whether to include the article in our review. In addition to the online search, we also scanned the reference list of the eligible articles to widen our search. There were no language restrictions for the eligible articles.

Results

Figure 1 reflects the PRISMA flow chart of included and excluded studies. The initial search revealed 580 records. In the end, 35 relevant trials were identified after removing duplicates, screening abstracts, and full texts. The exclusion criteria can also be found in Figure 1. Table I (see page 27) summarizes the relevant characteristics of the selected trials, including the number of participants in each group, the method of administration of the vasopressors (bolus versus infusion), and primary and secondary endpoints.

All thirty-five included trials studied the effect of norepinephrine compared to phenylephrine. All the included trials were RCTs published between 2015 and 2023. No meta-analyses were included in this review. Twenty-five RCT focused on norepinephrine's effect on maternal hemodynamics in healthy women with singleton pregnancies undergoing an elective caesarean section. Next, one article explored norepinephrine's impact on

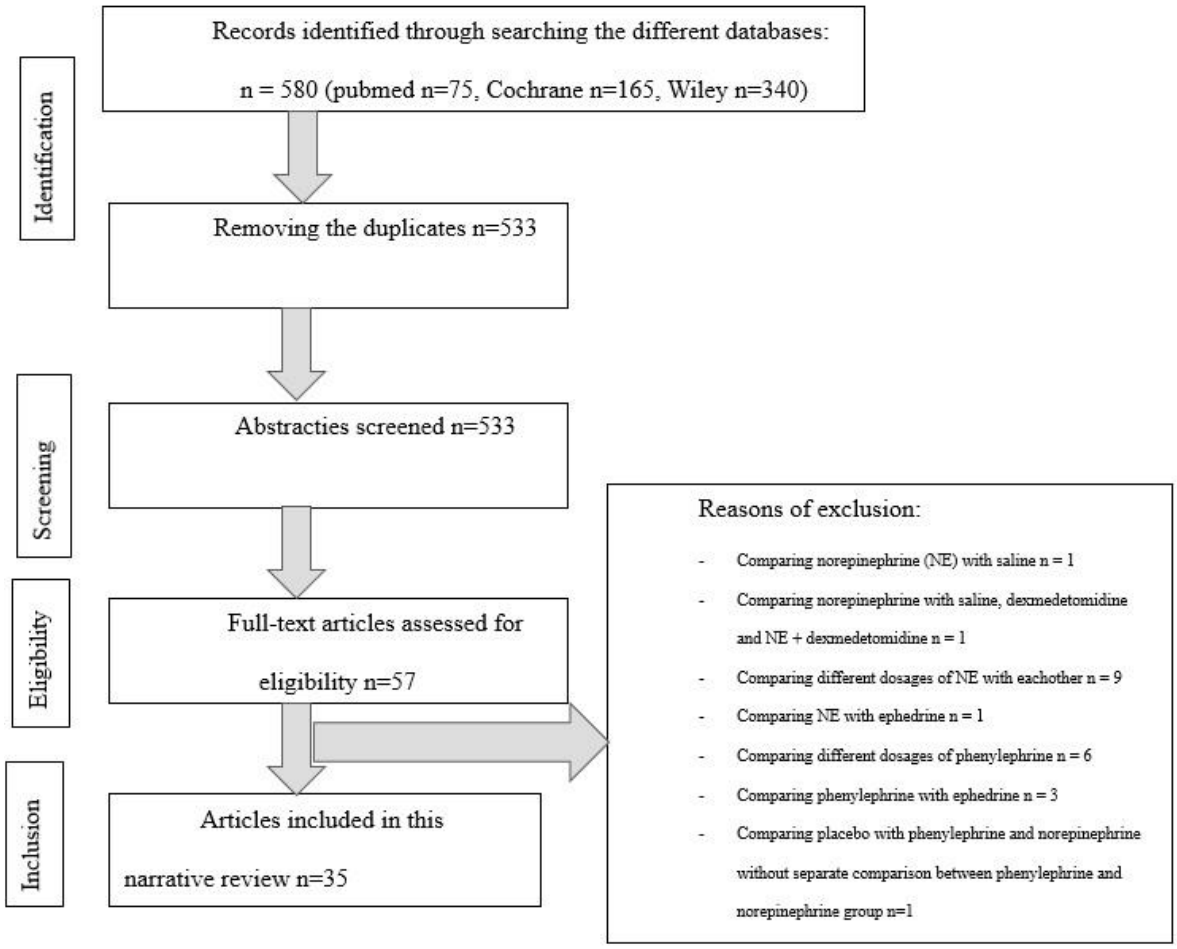

Fig. 1 — PRISMA Flowchart of inclusion of articles.

maternal hemodynamics in women undergoing elective caesarean section, either healthy or with mild pre-eclampsia. Two trials studied the effects of norepinephrine on the maternal hemodynamics in subjects with pre-eclampsia undergoing elective caesarean section, and one trial on fetal outcome in subjects with pre-eclampsia undergoing elective CS. Two trials examined norepinephrine's effect on maternal hemodynamics in women with twin pregnancies undergoing elective caesarean section. Lastly, four trials investigated the effect of norepinephrine on fetal outcome: two trials with healthy women undergoing elective caesarean section, one trial with healthy women undergoing either an elective or an emergency caesarean section and one trial with healthy women undergoing emergency caesarean section.

Twenty-two trials aimed to prevent maternal hypotension, while the other thirteen focused on the treatment of maternal hypotension.

Outcomes

Maternal hemodynamics

The effects of norepinephrine on maternal hemodynamics compared to phenylephrine are summarized in Table II.

Four studies determined the relative potency between the two vasopressors[13-16]. Three[13-15] studies used boluses, and one16 used a prophylactic fixed rate infusion with PE rescue boluses. Ngan Kee et al.15 found that for treatment of hypotension the ED50 of phenylephrine was 137 µg and norepinephrine was 10 µg, indicating a relative potency of 13.1:1. Guo et al.[14] found that the ED90 for prophylactic boluses was 90.9 µg for phenylephrine and 8 µg for norepinephrine, with a relative potency of 11.4:1. Motha et al.[13] reported that the optimal dose (ED95) for a bolus to treat post-spinal hypotension was 43.1 µg for phenylephrine and 3.7 µg for norepinephrine, with a relative potency of 11.6:1. Qian et al.16 found a relative potency of 6.03:1 for a fixed rate prophylactic infusion.

The relative potency is crucial for comparing two vasopressors at an equipotent dosage, to attribute differences in outcome to the vasopressors' efficacy, and not because it was given at a relatively higher dose compared to the other vasopressor[17]. Of the thirty-five studies, 15 used a relative potency between 11:1 and 13,3:1 and 3 trials[16,35,43] used a prophylactic infusion with a relative potency around 6.03:1. Eight studies used

Table I. — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2015. Ngan Kee et al.[18]	Double-blind RCT	101 Healthy Singleton pregnant women with elective CS (PE = 52 vs NE = 49)	Computer controlled closed loop infusion (Fixed Rate) of either PE infusion (100 µg ml^{-1}) or NE infusion (5 µg ml^{-1}) (starting at 30 ml h^{-1})	20:1	Prevention of hypotension (SBP < 80% baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after administration of spinal anesthesia until delivery	Cardiac output	Other maternal hemodynamic outcome measurements, maternal side effects neonatal outcome
2019 Mohta et al.[13]	Double-blind RCT	100 Healthy singleton pregnant women that developed post-spinal hypotension During elective CS (PE = 50 vs NE = 50)	Bolus of either PE (ranging from 30 µg to 100 µg) or NE (ranging from 3 µg to 6 µg)	11.3:1	Treatment of the first episode of hypotension SBP < 80% baseline or SBP < 100 mmHg)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE & PE dilution not mentioned type of NE used: NA	From just after administration of spinal anesthesia until delivery	Calculation of ED95 of PE and NE	ED50 of PE and NE, maternal hemodynamic outcome measurements, maternal side effects, neonatal outcome (Apgar score)
2019 Sharky et al.[31]	Double-blind RCT	112 healthy women with singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 56 vs NE = 56)	Intermittent boluses of either 100 µg PE or 6 µg NE, rescue boluses of ephedrine 10 mg when HR below 60 bpm or when SBP stayed < 80% for 2 consecutive readings despite administration of study drug	16.6:1	Prevention of hypotension (SBP < 80% baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 6 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after administration of spinal anesthesia until delivery	Incidence of brady-cardia (HR < 50 bpm)	Other maternal hemodynamic measurements, rescue dose of ephedrine, maternal side effects, Neonatal outcome (Apgar, UA and UV blood gas)
2023 Guo et al.[14]	Double blind RCT	80 healthy singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40)	Prophylactic PE (ranging from 37.5 µg to 100 µg) or NE (ranging from 3 µg to 9 µg) boluses	11.4:1	Prevention of hypotension (SBP <80%) of baseline	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 1 µg ml^{-1} PE dilution 12.5 µg ml^{-1}; type of NE used: NA	789	ED90 of PE and NE for prevention of hypotension	Maternal hemodynamic measurements, maternal side effects, neonatal outcome (UA blood gas, Apgar)
2020 Wang et al.[26]	Double blinded RCT	102 healthy parturients with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 50 vs NE = 52)	Bolus of PE (100 µg) or NE (8 µg) immediately after spinal anesthesia and boluses whenever hypotension occurred.	12.5:1	Treatment of hypotension (SBP < 80%)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 8 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until delivery	Maternal CO	Other maternal hemodynamic measurements, Incidence of need of extra Bolus, time to first extra bolus, maternal side effects, neonatal outcome (Apgar, UA and UV blood gas values)

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2022 Zhou et al.[21]	Double blinded RCT (Non-inferiority)	75 healthy singleton pregnant women undergoing CS under CSE anesthesia (PE = 25 vs NE = 25 vs Metaraminol = 25)	Metaraminol (500 µg ml^{-1}), PE (100 µg ml^{-1}) And NE (8 µg ml^{-1}) fixed rate infusion (30 ml h^{-1}) after initial bolus of 1 ml + rescue boluses of M 250 µg, PE 50 µg or NE 4 µg	12.5:1 (PE:NE) 5:1 (M:PE) 60:1 (M:NE)	Prevention of hypotension (SBP <80% of baseline)	CSE anesthesia; IV-line with 3-way stopcock was used for vasopressor administration; NE dilution 4 µg ml^{-1} for bolus and 8 µg ml^{-1} for infusion PE dilution 50 µg ml^{-1} for bolus & 100 µg ml^{-1}infusion; metaraminol dilution: 250 µg ml^{-1} for bolus and 500 µg ml^{-1} for infusion; type of NE used: NA	From just after spinal anesthesia until Delivery	UA pH	Other neonatal outcome, maternal hemodynamic measurements, maternal side effects
2017 Ngan Kee et al.[15]	Double blinded RCT	180 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 90 vs NE = 90)	Norepinephrine bolus (4-12 µg) or phenylephrine bolus (60-200 µg)	13:1	Treatment of the first episode of hypotension (SBP < 80%)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE & PE dilution not mentioned; type of NE used: NA	From just after spinal anesthesia until response measurement 60 sec after bolus injection	Dose response curves for PE and NE for treatment of first episode of hypotension	ED50, ED90, maternal heartrate
2019 Hasanin et al.[32]	Double blinded RCT	123 healthy pregnant women undergoing CS under spinal anesthesia (PE = 63 vs NE = 60)	Weight adjusted infusion Of PE (0.75 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) that was manually titrated + rescue boluses (50-100 µg PE vs 9-15 mg ephedrine vs 0.5 mg atropine)	15:1	Prevention of hypotension (SBP <80% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 4 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: norepinephrine bitartrate	From just after spinal anesthesia until the end of surgery	Incidence of post spinal hypotension	Incidence of severe post-spinal hypotension, other maternal hemodynamic measurements, maternal side effects, need of physician interventions neonatal outcome (blood gas values, Apgar score)
2017 Vallejo et al.[39]	Open-labelled RCT	81 Healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 38 vs NE = 43)	Weight adjusted infusion of PE (0.1 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses of PE 100 µg in both arms	2:1	Prevention of hypotension (SBP < 100% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution not mentioned; PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until Postoperatively transfer	Proportion of patients that needed rescue boluses	Other hemodynamic measurements, maternal side effects, Neonatal outcome (Apgar, blood gas values)

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2017 Ngan Kee et al.[33]	Double blinded RCT	101 healthy women undergoing elective CS under spinal anesthesia (PE = 52 vs NE = 49	Computer controlled closed loop infusion of PE (0-100 µg min^{-1}) or NE (0-5 µg min^{-1})	20:1	Prevention of hypotension (SBP < 100% of baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after start of spinal anesthesia until delivery	Median absolute performance error (MDAPE) = parameter for the inaccuracy of the BP control	MDPE (median of the values of PE (PE = difference between measured SBP and baseline value)), divergence, wobble
2023 de Queiroz et al.[42]	Double blinded RCT	72 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 37 vs NE = 35)	Rescue boluses of PE (100 µg) or NE (5 µg)	20:1	Treatment of hypotension (SBP < 90% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 20 µg ml^{-1}; type of NE used: norepinephrine hemitartrate	From start of spinal anesthesia until clamping of umbilical cord	Occurrence or absence of at least one episode of brady-cardia (HR between 40 & 60 bpm)	Number of episodes of bradycardia, occurrence of extreme bradycardia (< 40 bpm), occurrence of hypo- and hypertension (SBP > 120% of baseline value) neonatal outcome (Apgar, umbilical cord blood gas values),
2020 Theodoraki et al.[27]	Double blinded RCT	82 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 41 vs NE = 41)	Fixed rate infusion (30 ml h^{-1}) of either PE (50 µg min^{-1}) or NE (4 µg min^{-1}) started during spinal anesthesia	12.5:1	Prevention of hypotension (SBP < 80% of baseline value)	CSE anesthesia; separate IV was used for vasopressor administration with 3-way stopcock; NE dilution 8 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	Just after start of spinal anesthesia until 5 min after delivery of the fetus	Incidence of brady-cardia (HR < 60 bpm)	Hemodynamic measurements at specific moments, Incidence of hypotension or hypertension, need of rescue boluses, need to modify infusion, maternal adverse events, neonatal outcome (Apgar, UV blood gas values)
2019 Mohta et al.[34]	Double blinded RCT	90 healthy women singleton pregnancy (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 5 µg of NE	20:1	Treatment of hypotension (SBP < 80% of baseline value or SBP < 100 mmHg)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	Just after start of spinal anesthesia until delivery	Incidence of maternal brady-cardia (HR < 60 bpm) after vasopressor administration	Changes in maternal SBP after vasopressor administration, number of hypotensive episodes and hypertension, number of boluses needed to treat first episode, total vasopressor dose needed, maternal complications, neonatal outcome (Apgar, UA and UV blood gas values)

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2020 Biricik et al.[6]	Double blinded RCT	160 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40 vs E = 40 vs saline = 40)	Fixed rate (30 ml h^{-1}) infusion of either saline 0.9%, NE (5 µg ml^{-1}), E (5 µg ml^{-1}), PE 100 µg ml^{-1}) + rescue bolus of ephedrine	20:1 (PE:NE) 20:1 (PE: E) 1:1 (NE: E)	Treatment of hypotension (SBP < 80% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} E dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	Just after start of spinal anesthesia until end of surgery	Incidence of hypotension	Total number of hypotension episodes, number of patients requiring rescue boluses, total amount of ephedrine used, maternal side effects; neonatal outcome (Apgar, UV blood gas values)
2017 Dong et al.[40]	Double blinded RCT	126 healthy women with singleton undergoing elective CS under CSE anesthesia (PE = 64 vs NE = 62)	Prophylactic bolus of PE 50 µg vs NE 10 µg + rescue boluses PE 50 µg vs NE 10 µg	5:1	Prevention of hypotension (SBP < 80% of baseline value) + treatment of hypotension	CSE anesthesia; no separate IV was used for vasopressor administration; NE dilution 10 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: NA	Just after start of CSE anesthesia until delivery	Incidence of bradycardia (HR < 60 bpm)	SBP, HR, CO, IONV and neonatal outcome
2020 Cho et al.[41]	Double blinded RCT	44 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 22 vs NE = 22)	Rescue boluses of 100 µg PE vs 5 µg NE	20:1	Treatment of hypotension (SBP <80% of baseline value or < 90 mmHg)	CSE anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From start of spinal anesthesia until 5 min after delivery	Normalized CO	Other maternal hemodynamic measurements, maternal side effects, neonatal outcome
2022 Rai et al.[30]	Double blinded RCT	90 healthy women with singleton pregnancy undergoing elective CSE under spinal anesthesia (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 7.5 µg NE	13.3:1	Treatment of hypotension (SBP < 80% of baseline value	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 7.5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until delivery	UA pH	Incidence of hypotension, reactive hypertension, bradycardia, and tachycardia Vasopressor dose needed, maternal side effects, UA and UV blood gas values, Apgar score, birth weight, requirement of PPV, need to admission on NICU, neurobehavioral Scale

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2023 Priya et al.[22]	Double blinded RCT	156 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 78 vs NE = 78)	Prophylactic fixed rate infusion of PE 50 µg min^{-1} vs NE 5 µg min^{-1} + rescue boluses if needed (PE 50 µg vs NE 5 µg)	10:1	Prevention of hypotension (SBP < 80% of baseline value) + treatment of hypotension	Spinal anesthesia; separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until end of CS	Incidence of hypotension	Incidence of use of rescue boluses, overall dose of vasopressor given, bradycardia, tachycardia, hypertension, number of additional interventions, IONV, Apgar score
2019 Puthenveettil et al.[47]	Double blinded RCT	50 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25)	Rescue boluses of PE (50 µg) or NE infusion (4 µg)	12.5:1	Treatment of hypotension (SBP < 80% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 4 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until end of surgery	Number of IV boluses needed to treat spinal hypotension	Incidence of bradycardia, incidence of hypertension, incidence of nausea and vomiting, fetal outcome
2023 Ravichandrane et al.[35]	Double blinded RCT	130 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 65 vs NE = 65)	Prophylactic fixed rate infusion of either PE (25 µg min^{-1} or 5 µg min^{-1}) + rescue boluses of PE 25 µgin both groups	5:1	Prevention of hypotension (SBP < 80% of baseline value or SBP < 100 mmHg)	Spinal anesthesia; separate IV was used for vasopressor administration; NE dilution 20 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until end of surgery	Incidence of maternal hypotension	Incidence of bradycardia, reactive hypertension, IONV, requirement of rescue boluses; Apgar scores, umbilical cord blood gas values
2021 Ashraf et al.[44]	Double blinded RCT	75 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25 vs E = 25)	Weight adjusted prophylactic infusion of either PE (0.1 µg kg^{-1} min^{-1}), NE (0.05 µg kg^{-1} min^{-1}) or fixed rate ephedrine 1 mg min^{-1} infusion + rescue boluses of either 0.2 µg kg^{-1} PE, 0.1 µg kg^{-1} NE or 5 mg ephedrine.	2:1 PE:NE	Prevention of hypotension (SBP < 80% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution and PE dilution: NA; type of NE used: Levophrine®	From just after spinal anesthesia until end of surgery	Maternal MAP	Incidence of tachycardia, bradycardia, IONV, neonatal outcome, incidence of hypertension, physician, need of anti-emetic drugs
2022 Tiwari et al.[28]	RCT (blinding was not specifically mentioned	126 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 63 vs NE = 63)	Rescue boluses of either 50 µg of PE or 4 µg of NE	12.5:1	Treatment of hypotension (Specific cutoff value was not mentioned)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE & PE dilution: NA; type of NE used: NA	The intra-operative period (not more specifically mentioned)	Not specifically mentioned what their primary endpoint was	Looked at neonatal outcome, maternal side effects, number of vasopressor boluses needed, MAP, HR

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2021 Goel et al.[36]	Double-blinded RCT	200 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 100 vs NE = 100)	Variable rate infusion of either PE (100 µg ml^{-1}) or NE (5 µg ml^{-1}) both started at 30 ml h^{-1} + rescue boluses of 100 µg PE or 5 µg NE	20:1	Prevention of hypotension (Keeping SBP at 100% of baseline) + treatment of hypotension (SBP < 80% of baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 5 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until delivery	Episodes of hypotension	Other maternal hemodynamics, maternal side effects, neonatal outcome
2022 Mahzad et al.[37]	RCT (blinding not specifically mentioned)	45 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 15 vs NE = 15 vs ephedrine = 15)	Prophylactic bolus of either PE (40 µg), NE (5 µg) or ephedrine (5 mg)	8:1 PE:NE 125:1 ephedrine 1000:1 ephedrine: NE	Prevention of hypotension (< 70% of baseline value or below 90 mmHg)	Spinal anesthesia; separate IV was used for vasopressor administration; NE &' PE dilution: NA; type of NE used: NA	From just after spinal anesthesia until end of surgery	MAP Over time	HR over time Neonatal outcome Maternal side effects Incidence of hypotension, number of patients needing atropine bolus Number of vasopressor boluses
2022 Qian et al.[16]	Double blinded RCT	60 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 30 vs NE = 30)	Prophylactic infusion (Fixed rate) of PE (100 µg ml^{-1}) or NE (8 µg ml^{-1}) + rescue bolus of PE (50 µg) when hypotension occurred	6.03:1	Prevention of hypotension (SBP < 80% baseline value or SBP < 90 mmHg)	CSE anesthesia; no separate IV was used for vasopressor administration; NE dilution 8 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From just after spinal anesthesia until end of surgery	ED50	ED90, incidence of hypotension, hypertension, bradycardia, IONV, shivering, neonatal outcome
2023 Belin et al.[29]	Double-blinded RCT	124 women (healthy or with mild pre-eclampsia) undergoing elective CS under spinal anesthesia (PE = 62 vs NE = 62)	Manually adjusted variable rate infusion of either PE (50 µg ml^{-1}) or NE (5 µg ml^{-1}) starting at 0.5 µg kg^{-1} min^{-1} in PE vs 0.05 µg kg^{-1} min^{-1} in NE + rescue bolus of 5 mg ephedrine in case of persisted hypotension	10:1	Prevention of hypotension (SBP < 90% of baseline value before and < 80% of baseline value after delivery)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 10 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: norepinephrine tartrate (1 µg NE tartrate = 0.5 µg NE base)	From just after start of spinal anesthesia until stop of vasopressor (weaning of vasopressor started after delivery)	Evolution of cardiac index (CO divided by body surface area)	Evolution of SBP, MAP Evolution of HR, indexed SV indexed TVR Incidence of hypotension, bradycardia, hypertension, maternal side effects, neonatal outcome

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2019 Wang et al.[23]	Double-blind RCT	166 singleton pregnant women with pre-eclampsia with elective CS under spinal anesthesia (PE = 55 vs NE = 56 vs ephedrine = 55)	Intermittent bolus of NE 4 µg (NE group), bolus of 50 µg PE (PE group) or bolus of 4 mg ephedrine (E group)	12.5 PE:1NE 80 E:1PE 1000E:1NE	Treatment of hypotension (SBP < 80% baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 4 µg ml^{-1} PE dilution 100 µg ml^{-1}; ephedrine dilution= 4 $mg.ml^{-1}$; type of NE used: NA	From just after administration of spinal anesthesia until delivery	Overall maternal SBP and HR	Other maternal hemodynamic outcome measurements, maternal side effects neonatal outcome
2022 Guo et al.[24]	Double blind RCT	138 singleton pregnant women with pre-eclampsia undergoing elective CS under spinal anesthesia (PE 69 vs NE = 69)	Weight adjusted prophylactic infusion of PE (0.625 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses (PE 75 µg or NE 6 µg)	13.1:1	Prevention of hypotension (SBP < 80% of baseline)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 6 µg ml^{-1} PE dilution 75 µg ml^{-1}; type of NE used: NA	Unclear (At least 15 min Starting after administration of spinal anesthesia	Incidence of brady-cardia (HR <60 bpm)	Other maternal hemodynamic measurements, rescue Boluses needed, maternal side effects, Neonatal outcome (Apgar, UA blood gas)
2021 Mohta et al.[25]	Double blinded RCT	86 women with singleton pregnancy and pre-eclampsia (PE = 43 vs NE = 43)	Rescue boluses of PE (50 µg) or NE (4 µg)	12.5:1	Treatment of hypotension (SBP < 80% of baseline value or < 100 mmHg)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 4 µg ml^{-1} PE dilution 50 µg ml^{-1}; type of NE used: NA	Just after start of spinal anesthesia until delivery	UA pH	Neonatal outcome (Apgar, other blood gas values) number of hypotensive episodes, vasopressor need, Incidence of tachycardia, bradycardia, hypertension Maternal complications
2022 Du et al.[46]	Double blinded RCT	62 healthy parturients with twin pregnancy undergoing elective CS under spinal anesthesia (PE = 31 vs NE = 31)	Fixed rate infusion at 60 ml h^{-1} of PE (75 µg ml^{-1}) or NE (6 µg ml^{-1}) + rescue boluses of PE (75 µg) or NE (6 µg)	12.5:1	Prevention of hypotension (SBP < 80% of baseline) And maintaining SBP around baseline	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 6 µg ml^{-1} PE dilution 75 µg ml^{-1}; type of NE used: norepinephrine bitartrate	From just after spinal anesthesia until 10 minutes later	Changes in maternal CO	Other hemodynamic measurements, maternal side effects; neonatal outcomes
2022 Chen et al.[20]	Double blinded RCT	100 healthy women with twin pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of PE (40 µg min^{-1}) or NE (3.2 µg min^{-1})	12.5:1	Prevention of hypotension	Spinal anesthesia; separate IV was used for vasopressor administration; NE dilution 8 µg ml^{-1} PE dilution 100 µg ml^{-1}; type of NE used: NA	From start of spinal anesthesia until delivery of second twin	Change in HR en BP	Maternal adverse events, neonatal outcome (Apgar, umbilical blood gas values)

Table I (Continued). — Characteristics of the eligible studies comparing norepinephrine with phenylephrine.

Year and Author	Type of study design	Study population	Intervention	Potency ratio (PE:NE)	Prevention /Treatment	Details regarding the anesthesia plan	Duration of observation	Primary endpoint	Secondary Endpoints
2022 Liu et al.[43]	Double blinded RCT	78 healthy women with singleton pregnancy undergoing CS under CSE anesthesia (PE = 26 vs NE = 26 vs metaraminol = 26)	Weight adjusted infusion of either PE (0.54 μg $kg^{-1}min^{-1}$), NE 0.08 μg kg^{-1} min^{-1}) or metaraminol (2 μg kg^{-1} min^{-1})	6.75:1 (PE:NE) 25:1 (M:NE) 3.7 (M:PE)	Prevention of hypotension (SBP < 80% of baseline value or SBP < 90 mmHg)	CSE anesthesia; no separate IV was used for vasopressor administration; NE dilution 16 μg ml^{-1} PE dilution 108 μg ml^{-1} metaraminol dilution 400 μg ml^{-1}; type of NE used: NA	Just after placement of epidural catheter until delivery	UA pH	Other neonatal blood gas values, Apgar score, Incidence of hypotension, SBP within 12 minutes after spinal injection, maternal side effects (hypertension, IONV, bradycardia Number of rescue boluses given
2022 Singh et al.[45]	Double blinded RCT	100 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of either PE (100 μg min^{-1}) or NE (5 μg min^{-1}) + rescue boluses of PE (60 μg) or NE (6 μg)	20:1 For infusion 10:1 for rescue boluses	Prevention of hypotension (SBP < 90% of baseline value)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 6 μg ml^{-1} for infusion & bolus, PE dilution 120 μg $ml^{-1}$for infusion & 60 μg $ml^{-1}$for bolus; type of NE used: NA	From just after spinal anesthesia until delivery	UA base excess	Fetal acidosis, Apgar score < 8, need for Neonatal resuscitation, Incidence of maternal bradycardia, Incidence of IONV, total vasopressor dose, number of women needing rescue interventions
2020 Ngan Kee et al.[38]	Double blinded non-inferiority RCT	664 healthy women undergoing CS (531 elective and 133 non-elective) under spinal or CSE anesthesia (elective: PE = 265 vs NE = 266; non-elective: PE 67 vs NE = 66)	Fixed rate infusion of either PE (100 μg min^{-1}) or NE (6 μg min^{-1}) and/ or rescue boluses of PE (100 μg) or NE (6 μg)	16.67:1	Prevention or treatment of hypotension (SBP < 100 mm Hg) (Depending on preference of anesthetist in charge)	Spinal or CSE anesthesia; no separate IV was used for vasopressor administration; NE dilution 6 μg ml^{-1} PE dilution 100 μg ml^{-1}; type of NE used: NA	From induction of anesthesia until end of surgery	UA pH	UA and UV blood gas values, Apgar scores, Incidence of bradycardia (HR < 60 bpm), Incidence of hypotension (SBP < 100 mmHg), volume of vasopressor, Incidence of IONV
2022 Mohta et al.[19]	Double blinded RCT	100 healthy women with singleton pregnancy undergoing emergency CS under spinal anesthesia (for actual or potential compromised status of fetus) (PE = 50 vs NE = 50)	Rescue boluses of either PE (100 μg) or NE (8 μg)	12.5:1	Treatment of hypotension (SBP < 100 mmHg)	Spinal anesthesia; no separate IV was used for vasopressor administration; NE dilution 8 μg ml^{-1} PE dilution 100 μg ml^{-1}; type of NE used: NA	From just after spinal injection until delivery	UA pH	Apgar scores, Incidence of fetal acidosis, admission to NICU, number of vasopressor boluses given, number of hypotensive episodes, Incidence of bradycardia, tachycardia, arrhythmias, IONV other maternal adverse events

RCT: randomized control trials, CS: caesarean section, IV: intravenous, PE: phenylephrine, NE: norepinephrine, E: epinephrine, BP: blood pressure SBP: systolic blood pressure, G: gauge, HR: heart rate IONV: intra-operative nausea and vomiting, bpm: beats per minute, CSE: combined spinal and epidural, UA: umbilical artery, UV umbilical vein, NICU: neonatal intensive care unit, ED: effective dose; (PE =n) = number of people in the final analysis of PE group; (NE=n) = number of people in the final analysis of norepinephrine group.

Table II. — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2015. Ngan Kee et al.[18]	101 Healthy Singleton pregnant women with elective CS (PE = 52 vs NE = 49)	Computer controlled closed loop infusion (Fixed Rate) of either PE infusion (100 µg ml^{-1}) or NE infusion (5 µg ml^{-1}) (starting at 30 ml h^{-1})	Greater in NE group vs PE group ($p = 0.039$) Incidence of bradycardia (HR < 60 bpm) greater in PE vs NE (55.8 vs 18.4%) ($p < 0.001$)	SBP is similar between NE and PE P = 0.36)	Normalized CO at 5 min: median 102.7% in NE vs 93.8% in PE (P = 0.004) CO over time: greater in NE vs PE group ($p < 0.001$)	SVR was lower in NE vs PE group ($p < 0.001$) No significant difference in SV	NA	The rate was greater in NE group vs PE group ($p = 0.002$)
2019 Mohta et al.[13]	100 Healthy singleton pregnant women that developed post-spinal hypotension During elective CS (PE = 50 vs NE = 50)	Bolus of either PE (ranging from 30 µg to 100 µg) or NE (ranging from 3 µg to 6 µg)	HR at first episode of hypotension 99.1 bpm in PE vs 98.2 bpm in NE (p=0.82) HR at 1 min After vasopressor administration 79.7 bpm in PE vs 85.3 bpm in NE (p= 0.13) Bradycardia at 1 min (4 patients in PE vs 5 patients in NE group) ($p > 0.05$)	SBP at first episode of hypotension (98.5 mmHg In PE vs 99.8 mmHg in NE) ($p = 0.48$) SBP at 1 minute after vasopressor administration (114.8 mmHg in PE vs 114.3 mmHg in NE) ($p = 0.83$) More than 1 episode of hypotension 42% in PE vs 38% in NE (p=0.838)	NA	Time to develop hypotension ($p = 0.95$)	NA	NA (ED determination study)
2019 Sharky et al.[31]	112 healthy women with singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 56 vs NE = 56)	Intermittent boluses of either 100 µg PE or 6 µg NE, rescue boluses of ephedrine 10 mg when HR below 60 bpm or when SBP stayed < 80% for 2 consecutive readings despite administration of study drug	Incidence of bradycardia (HR < 50 bpm) 10.7% in NE vs 37.5% in PE ($p < 0.001$) distribution of bradycardia episodes= significantly higher in PE vs NE (p=0.007) Incidence of multiple episodes of bradycardia: 19.6% in PE vs 3.6% in NE (p=0.008)	Incidence of hypotension: 38% in NE vs 39% in PE (p=0.9)	NA	NA	NA	Proportion of patients needing rescue boluses of ephedrine: 7.2% in NE vs 21.4% in PE ($p < 0.03$) number of vasopressor boluses needed until delivery 9 in NE vs 8 in PE (p=0.19)
2023 Guo et al.[14]	80 healthy singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40)	Prophylactic PE (ranging from 37.5 µg to 100 µg) or NE (ranging from 3 µg to 9 µg) boluses	Incidence of bradycardia (HR < 60 bpm): 2.5% in NE vs 20% in PE (p=0.034)	Incidence of hypotension (SBP < 80% of baseline value) 27.5% in PE vs 27.5% in NE (p=1.0) Incidence of severe hypotension (SBP < 60% of baseline value) 1 in PE vs 0 in NE (p=1.0)	NA	NA	NA	Number of vasopressor boluses needed: 1 in NE vs 2 in PE (p=0.332)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2020 Wang et al.[26]	102 healthy parturients with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 50 vs NE = 52)	Bolus of PE (100 µg) or NE (8 µg) immediately after spinal anesthesia and boluses whenever hypotension occurred.	Incidence of bradycardia (HR < 60 bpm) 2% in NE vs 14% in PE (p=0.023) Standardized HR 78.8 bpm in NE vs 75 bpm in PE (p=0.049) Relative change in HR in comparison with baseline value: -6.7% vs – 12.1% (p=0.0036)	Standardized SBP 97.1 mmHg in NE vs 95 mmHg in PE (p=0.17)	Standardized CO 5.8 L min^{-1} in NE vs 5.3 L min^{-1} in PE group (p=0.02) Relative change in CO in comparison with baseline value: + 4% vs – 5.7% (p=0.0029)	Standardized SV: 73.6 ml in NE vs 60 ml in PE (p< 0.001) Standardized TRP 875 dyne*s cm^{-5} in NE vs 996 dyne*s cm^{-5} in PE (p< 0.001) Relative change in SV in comparison with baseline value: +2% vs – 2.2 % (p<0.001) Relative change in TPR in comparison with baseline value: -35% vs – 27.8% (p<0.001)	NA	Total dosage of vasopressor 16 µg (8-40 µg) in NE vs 100 µg (100-400 µg) Atropine required 0 in NE vs 2 in PE (p=0.49)
2022 Zhou et al.[21]	75 healthy singleton pregnant women undergoing CS under CSE anesthesia (PE = 25 vs NE = 25 vs Metaraminol = 25)	Metaraminol (500 µg ml^{-1}), PE (100 µg ml^{-1}) And NE (8 µg ml^{-1}) fixed rate infusion (30 ml h^{-1}) after initial bolus of 1 ml + rescue boluses of M 250 µg, PE 50 µg or NE 4 µg	Bradycardia 4% in M group vs 12% in PE group vs 0% in NE group (p=0.15)	Hypotension 4% in M group vs 20% in PE vs 32% in NE group (overall P=0.0388 M vs PE p=0.087, M vs NE p = 0.01, PE vs NE p=0.0169)	NA	NA	NA	Number of rescue boluses 0 in M vs 0 in PE vs 0 in NE (overall p=0.042, M vs PE p=0.38, M vs NE p=0.039, PE vs NE p=0.99)
2017 Ngan Kee et al.[15]	180 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 90 vs NE = 90)	Norepinephrine bolus (4-12 µg) or phenylephrine bolus (60-200 µg)	Median magnitude of decrease of HR after administration of vasopressor was greater in PE group vs NE group (p=0.036)	NA	NA	NA	NA	Measurement of ED50: 10 µg For NE and 137 µg For PE And ED90 18 µg For NE and 239 µg for PE (for treatment of first episode of hypotension)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2019 Hasanin et al.[32]	123 healthy pregnant women undergoing CS under spinal anesthesia (PE = 63 vs NE = 60)	Weight adjusted infusion Of PE (0.75 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) that was manually titrated + rescue boluses (50-100 µg PE vs 9-15 mg ephedrine vs 0.5 mg atropine)	Incidence of bradycardia 13% in NE vs 21% in PE group (p=0.3) No significant difference in HR at any time between the groups	Hypotension (SBP<80% Of baseline value) 30% in NE vs 32% in PE (p=0.8) Severe hypotension (SBP <60% of baseline value) 13% vs 18% (p=0.6) Post delivery hypotension 3% in NE vs 3% in PE (p=0.9) No significant difference in SBP at any timepoint	NA	NA	NA	Rescue ephedrine Requirements 0 mg in NE vs 0 mg in PE (p=0.07) Rescue PE requirements 0 mg in NE vs 0 mg in PE (p=0.3) Atropine requirements 0 mg in NE vs 0 mg in PE (p=0.3) Number of physician interventions 0 in NE vs 1 in PE (p=0.001)
2017 Vallejo et al.[39]	81 Healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 38 vs NE = 43)	Weight adjusted infusion of PE (0.1 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses of PE 100 µg in both arms	Incidence of bradycardia 23.7% in PE vs 18.6% in NE group (p=0.58) No significant difference between HR in PE vs NE group (p=0.17)	No significant difference between PE and NE group for SBP (p=0.25) and DBP (p=0.15)	No significant difference in CO between PE and NE group (P=0.5)	No significant difference in cardiac index (p=0.84), SV (P=0.5) SVR (p=0.54) between PE and NE group	NA	Rescue boluses ephedrine: 0 mg in PE vs 0 mg in NE (p=0.1) Rescue boluses PE: 50 µg in PE vs 100 µg in NE (p=0.73); proportion of patients needed rescue boluses ephedrine 23.7% in PE vs 2.3% in NE group (p<0.01)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2017 Ngan Kee et al.[33]	101 healthy women undergoing elective CS under spinal anesthesia (PE = 52 vs NE = 49	Computer controlled closed loop infusion of PE (0-100 µg min^{-1}) or NE (0-5 µg min^{-1})	Minimum recorded heart rate: 59 bpm vs 65 bpm (p=0.001) Incidence of bradycardia: 29 in PE vs 9 in NE (p<0.001)	Incidence of hypotension 7.7% in PE vs 8.2% in NE (p=0.93)	NA	NA	MDAPE: 4.70 in PE vs 3.79 in NE (p=0.028) (more precise BP control in NE group) MDPE: 2.61 in PE vs 0.75 in NE (p=0.002) (BP was maintained at lower values in NE group) Wobble: 3.39 in PE vs 2.85 in NE (p=0.028) No significant difference in divergence between the groups	Total vasopressor volume: 10.4 ml in PE vs 14.3 ml in NE (p=0.12)
2023 de Queiroz et al.[42]	72 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 37 vs NE = 35)	Rescue boluses of PE (100 µg) or NE (5 µg)	Incidence of at least 1 episode of bradycardia (HR < 60 bpm) 70.3% in PE vs 51.4% in NE group (p=0.16) Incidence extreme bradycardia (HR < 40 bpm) 13.5% in PE vs 2.9% in NE (p=0.19)	Significant more boluses needed in NE vs PE with corresponded to more hypotensive episodes	NA	NA	NA	Number of boluses per patient 5 in PE vs 8 in NE (p=0.01)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2020 Theodoraki et al.[27]	82 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 41 vs NE = 41)	Fixed rate infusion (30 ml h^{-1}) of either PE (50 µg min^{-1}) or NE (4 µg min^{-1}) started during spinal anesthesia	Incidence of bradycardia: 31.7% in PE vs 4.8% in NE (p=0.004) Standardized HR over time 81.9 bpm in PE vs 86.7 bpm in NE (p=0.012)	Standardized SBP over time 116 mmHg in PE vs 115.4in NE group (p=0.789) Standardized DBP over time 61.3 mmHg in PE vs 60.3 mmHg in NE group (p=0.551) Standardized MAP over time: 84.2 mmHg in PE vs 83.4 mmHg in NE (p=0.629)	NA	NA	NA	Incidence of need to use atropine for treatment of bradycardia 24.3% in PE vs 2.4% in NE (p=0.01) number of atropine boluses significantly higher in PE (p=0.004) Total amount of atropine needed was significantly higher in PE group (p=0.004) No difference in use of ephedrine between the groups Incidence of requirement of physician interventions to lower infusion rate 39% in PE vs 14.6% in NE (p=0.025)
2019 Mohta et al.[34]	90 healthy women singleton pregnancy (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 5 µg of NE	Incidence of bradycardia 37.8% in PE vs 22.2% in NE group (p=0.167) Incidence of need to treat bradycardia: 6.6% in PE vs 2.2% in NE (p=0.1) No significant difference in overall HR in the first 10 min or in HR at any given timepoint between PE and NE group HR 1 min after vasopressor administration: 76.8 bpm vs 88.3 bpm (p=0.034)	number of hypotensive episodes 2 in PE vs 1 in NE group (p=0.06) No significant difference in overall SBP in the first 10 min or in SBP at any given timepoint between PE and NE group	NA	NA		total number of vasopressor boluses: 2 in PE vs 1 in NE group (p=0.01) number vasopressor boluses needed to treat first episode of hypotension: 1 in PE vs 1 in NE (p=0.09)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2020 Biricik et al.[6]	160 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40 vs E = 40 vs saline = 40)	Fixed rate (30 ml h^{-1}) infusion of either saline 0.9%, NE (5 µg ml^{-1}), E (5 µg ml^{-1}), PE 100 µg ml^{-1}) + rescue bolus of ephedrine	Incidence of bradycardia: 12.5% in saline group vs 15% in PE vs 12.5% in NE vs 7.5% in E (p=0.752)	Perioperative SBP, DBP and MAP were not Significantly different between the groups Incidence of hypotension: 67.5% in PE vs 70% in NE vs 72.5% in E vs 80% in saline group (p=0.625) No significant difference in number of hypotensive episodes	NA	NA	NA	Incidence of need of ephedrine rescue boluses: 65% in saline group vs 22.5% in PE vs 42.5% in NE vs 45% in E (P=0.001 for PE vs saline) p>0.05 when comparing PE, NE and E groups Mean atropine consumption: 62.5 µg in saline group vs 75 µg in PE group vs 37.5 µg in E group vs 62.5 µg in NE group (p=0.77)
2017 Dong et al.[40]	126 healthy women with singleton undergoing elective CS under CSE anesthesia (PE = 64 vs NE = 62)	Prophylactic bolus of PE 50 µg vs NE 10 µg + rescue boluses PE 50 µg vs NE 10 µg	HR was significantly higher in NE group vs PE group at 2 min and 4 min after CSE anesthesia (p< 0.05)	No significant differences In SBP between the two group (p> 0.05)	CO at 5 min was significantly higher in NE vs PE group (p<0.05) at other moments CO was not significantly different	NA	NA	Incidence of women needing rescue boluses: 5% in PE vs 8% in NE group (p=0.5)
2020 Cho et al.[41]	44 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 22 vs NE = 22)	Rescue boluses of 100 µg PE vs 5 µg NE	Serial changes in HR were not significantly different between the two groups Incidence of bradycardia: 32% in PE vs 22% in NE (p=0.736)	Serial changes in SBP were comparable between the two groups (p=0.175)	Normalized CO: significantly higher in NE then PE (p<0.001)	Normalized SV: overall SV was significantly higher in NE then in PE group (p=0.002) TPR: no overall difference between groups (p=0.726)	NA	Median volume of study drug (ml) administered: 2 ml in PE vs 3 ml in NE (p=0.043)
2022 Rai et al.[30]	90 healthy women with singleton pregnancy undergoing elective CSE under spinal anesthesia (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 7.5 µg NE	Decrease in HR from baseline: 14 bpm in PE vs 5 bpm in NE (p=0.014) Incidence of bradycardia (< 60 bpm) 33.3% in PE vs 8.9% in NE (p=0.009) Incidence of extreme bradycardia (<45 bpm) 17.8% in PE vs 2.2% in NE	Maximum SBP 140.2 mmHg in PE vs 127 mmHg in NE (p=0.002) Duration of hypotension: 1.29 min in PE vs 1.29 min in NE (p=0.475)	NA	NA	NA	Number of vasopressor doses: 1 in PE vs 1 in NE (p=0.161) Time to first vasopressor 5.2 min in PE vs 4.4 min in NE (p=0.584)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2023 Priya et al.[22]	156 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 78 vs NE = 78)	Prophylactic fixed rate infusion of PE 50 µg min^{-1} vs NE 5 µg min^{-1} + rescue boluses if needed (PE 50 µg vs NE 5 µg)	Incidence of bradycardia: 21.8% in PE vs 3.8% in NE (p=0.053)	Incidence of hypotension: 26.8% in PE vs 17.9% NE group (p=0.182) Trend of changes in SBP was comparable between the two groups (p>0.05), changes in DBP were comparable between the two groups (p> 0.05)	NA	NA	NA	Total dose of vasopressor used: 1227.56 µg in PE vs 125.96 µg in NE group (p=0.147) Number of patients needing rescue boluses: 20.5% in PE vs 17.9% in NE (p=0.340) Number of patients needing atropine 6.4% in PE vs 0% in NE (p=0.162) Overall number of physician interventions: 27 in PE vs 24 in NE group (p=0.154)
2019 Puthenveettil et al.[47]	50 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25)	Rescue boluses of PE (50 µg) or NE (4 µg)	Incidence of bradycardia: 20% in PE vs 4% in NE (p=0.192)	NA	NA	NA	NA	Number of boluses needed to treat hypotension 2.28 in PE vs 1.40 in NE (p=0.001)
2023 Ravichandrane et al.[35]	130 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 65 vs NE = 65)	Prophylactic fixed rate infusion of either PE (25 µg min^{-1} or 5 µg min^{-1}) + rescue boluses of PE 25 µgin both groups	Incidence of bradycardia (HR < 50 bpm) 12.3% in PE vs 10.7% in NE (p=0.46) Pre-delivery HR: 88.6 bpm in PE vs 81.8 bpm in NE (p=0.26) Post delivery HR: 85.3 bpm in PE vs 86.4 bpm in NE (p=0.74)	Incidence of hypotension 33.8% in PE vs 26.1% in NE (p=0.85) Pre-delivery SBP: 115.3 mmHg in PE vs 123.4 mmHg in NE (p=0.04) Post-delivery SBP: 113.3 mmHg in PE vs 115.7 mmHg in NE (p=0.19)	NA	NA	NA	Number of rescue boluses needed 1 in PE vs 1 in NE (p=0.48)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2021 Ashraf et al.[44]	75 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25 vs E = 25)	Weight adjusted prophylactic infusion of either PE (0.1 µg $kg^{-1} min^{-1}$), NE (0.05 µg $kg^{-1} min^{-1}$) or fixed rate ephedrine 1 mg min^{-1} infusion + rescue boluses of either 0.2 µg kg^{-1} PE, 0.1 µg kg^{-1} NE or 5 mg ephedrine.	HR increased significantly in ephedrine group in comparison to PE and NE group; At most time points HR was significantly higher in the NE group in comparison to PE group Incidence of bradycardia: 16% in PE vs 8% in NE vs 0% in ephedrine (p=0.114)	MAP was significantly higher in ephedrine group in comparison to PE and NE MAP was significantly higher in PE vs NE at many time points	NA	NA	NA	Number of rescue boluses needed: 2 in PE vs 2 in NE vs 4 in ephedrine (p=0.891)
2022 Tiwari et al.[28]	126 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 63 vs NE = 63)	Rescue boluses of either 50 µg of PE or 4 µg of NE	Incidence of bradycardia 19.04% in PE vs 4.76% in NE group (p=0.03); comparing HR overtime between the two groups showed no significant differences between the two groups	No significantly difference of MAP at any time point was noted	NA	NA	NA	Number of vasopressor boluses needed: 2.36 in PE vs 1.42 in NE (p=0.02)
2021 Goel et al.[36]	200 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 100 vs NE = 100)	Variable rate infusion of either PE (100 µg ml^{-1}) or NE (5 µg ml^{-1}) both started at 30 ml h^{-1} + rescue boluses of 100 µg PE or 5 µg NE	HR was significantly higher over time in NE vs PE group (p=0.017) Incidence of bradycardia: 16% in PE vs 1% in NE (p=0.001)	Incidence of At least 1 episodes of hypotension: 13% in PE vs 9% in NE (p=0.363) Values of SBP over time: until 6 min SBP was significantly lower in PE group (p<0.05), SBP from minute 6 until delivery were comparable between the two groups	NA	NA	NA	Number of patients receiving atropine: 7 in PE vs 1 in NE group Number of patients receiving 1 or more rescue boluses: 10 in PE vs 4 in NE (p=0.247) Total amount of vasopressor volume given: 3.7 ml in PE vs 3.7 ml in NE (p=0.660) Total amount of drugs used in µg 370 µg in PE vs 18.4 µg in NE (p<0.001)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2022 Mahzad et al.[37]	45 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 15 vs NE = 15 vs ephedrine = 15)	Prophylactic bolus of either PE (40 µg), NE (5 µg) or ephedrine (5 mg)	HR increased significantly higher in ephedrine group (p=0.001) NE had the most stable effect on HR, PE caused the most decrease in HR Incidence of bradycardia: 34% in PE vs 0% in NE vs 0% in ephedrine (p=0.0036)	MAP over time was not significantly different between the three groups, at specific moments there was a significant difference in MAP (from 2 min until 60 min), MAP of NE was most constant of the three groups Incidence of hypotension: 0% in PE v 0% in NE v 27% in ephedrine (p=0.0124)	NA	NA	NA	Number of vasopressor boluses: 0% in PE vs 0% in NE vs 27% in ephedrine (p=0.0124)
2022 Qian et al.[16]	60 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 30 vs NE = 30)	Prophylactic infusion (Fixed rate) of PE (100 µg ml^{-1}) or NE (8 µg ml^{-1}) + rescue bolus of PE (50 µg) when hypotension occurred	Incidence of bradycardia 0% in PE vs 0% in NE	Incidence of hypotension: 40% in PE vs 46.7% in NE (p=0.60)	NA	NA	NA	ED50 for a continues infusion for prevention of hypotension:0.061 µg kg^{-1} min^{-1} for NE and 0.368 µg kg^{-1} min^{-1} for PE Relative potency 6.03:1 ED50 (probit regression) 0.059 µg kg^{-1} min^{-1} for NE and 0.330 µg kg^{-1} min^{-1} for PE; ED90 (probit regression) 0.08 µg kg^{-1} min^{-1} for NE and 0.449 µg kg^{-1} min^{-1} for PE

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2023 Belin et al.[29]	124 women (healthy or with mild pre-eclampsia) undergoing elective CS under spinal anesthesia (PE = 62 vs NE = 62)	Manually adjusted variable rate infusion of either PE (50 µg ml^{-1}) or NE (5 µg ml^{-1}) starting at 0.5 µg kg^{-1} min^{-1} in PE vs 0.05 µg kg^{-1} min^{-1} in NE + rescue bolus of 5 mg ephedrine in case of persisted hypotension	No significantly difference in HR over time until umbilical cord clamping between the two groups No significantly difference in HR over time after umbilical cord clamping between the two groups Incidence of bradycardia: 12.3% in PE vs 10.1% in NE before clamping (p=0.52) and 18.9% in PE vs 15% in NE after clamping (p=0.40)	No significantly difference in SBP Or MAP over time until umbilical cord clamping between the two groups (except MAP at T4: significantly higher in NE (p>0.05) No significantly difference in SBP or MAP over time after clamping between the two groups Time below SBP <80% of baseline value: 8.5% in PE v 2.3% in NE (p=0.006) before clamping and 20.9% in PE vs 24.7% in NE after clamping (p=0.38)	CI was maintained between 81-88% of baseline value from T4 until umbilical cord clamping in PE group vs 90-110% of baseline value in NE group (p=0.001)	Indexed SV between 100-110% of baseline value in PE vs 120% in NE (not significantly different except at T4, higher in NE), in first 20 min after clamping indexed SV was comparable between the two groups Indexed TVR was not significantly different from start until umbilical cord clamping between the two groups or in first 20 min after clamping (accept at 2 min, significantly higher in PE)	NA	Max infusion rate 63 ml h^{-1} in PE vs 57 ml h^{-1} in NE (p=0.015) Need of atropine boluses 1.6% in PE vs 3.2% in NE (p=0.99) Need of ephedrine boluses: 8.1% in PE v 3.2% in NE (p=0.44)
2019 Wang et al.[23]	166 singleton pregnant women with pre-eclampsia with elective CS under spinal anesthesia (PE = 55 vs NE = 56 vs ephedrine = 55)	Intermittent bolus of NE 4 µg (NE group), bolus of 50 µg PE (PE group) or bolus of 4 mg ephedrine (E group)	Standardized HR: 76.6 bpm in PE vs 80.5 bpm in NE (p=0.04) 80.5 bpm in NE vs. 84.9 bpm in E (p=0.02) 76.6 bpm in PE vs 84.9 bpm in E (p<0.05) Incidence of bradycardia: 21.8% in PE vs 3.6% in NE (p=0.004)	Overall SBP was similar in all 3 groups, no significant differences in number of hypotension episodes	NA	NA	NA	No significant differences in total number of vasopressor boluses between the 3 groups

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2022 Guo et al.[24]	138 singleton pregnant women with pre-eclampsia undergoing elective CS under spinal anesthesia (PE 69 vs NE = 69)	Weight adjusted prophylactic infusion of PE (0.625 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses (PE 75 µg or NE 6 µg)	Incidence of bradycardia 24.6% in PE vs 7.2% in NE (p=0.005)	Incidence of hypotension 14.5% in PE vs 15.9% in NE (p=0.813) Incidence of severe hypotension 4.4% in PE vs 5.8% in NE (p=0.698)	NA	NA	MDPE for HR: -13.5% in PE vs -5.3% in NE (p<0.001) MDAPE for HR 15.1% in PE vs 8.7% in NE (p<0.001) MDPE fir SBP -7.6% in PE vs -8.5% in NE (p=0.49) MDAPE for SBP 8.8% in PE vs 9.4% in NE (p=0.86)	Number of rescue blouses needed: 2 in PE vs 2 in NE (p=0.918)
2021 Mohta et al.[25]	86 women with singleton pregnancy and pre-eclampsia (PE = 43 vs NE = 43)	Rescue boluses of PE (50 µg) or NE (4 µg)	HR was significantly lower in PE vs NE in first 5 min (p=0.0026) Number of bradycardia episodes after vasopressor use: 1 in PE vs 0 in NE (p=1)	Overall SBP was not significantly different between PE and NE groups (p=0.344) Median number of hypotensive episodes 1 in PE vs 2 in NE (p=0.014)	NA	NA	NA	Median number of boluses needed to treat first episode of hypotension: 1 in PE vs 1 in NE (p=0.011), it was significantly higher in PE than in NE Total number of vasopressor boluses 2 in PE vs 2 in NE (p=0.411)
2022 Du et al.[46]	62 healthy parturients with twin pregnancy undergoing elective CS under spinal anesthesia (PE = 31 vs NE = 31)	Fixed rate infusion at 60 ml h^{-1} of PE (75 µg ml^{-1}) or NE (6 µg ml^{-1}) + rescue boluses of PE (75 µg) or NE (6 µg)	AUC HR PE vs NE (p=0.997) Incidence of bradycardia (HR < 60 bpm): 69% in PE vs 24.2% in NE (p<0.001)	AUC SBP PE vs NE (p=0.057) Incidence of hypotension 44.8% in PE vs 41.4% in NE group)	AUC of CO PE vs NE p=0.889	AUC SVR PE vs NE (p=0.416)	NA	Total volume of study drug: 7 ml in PE vs 9 ml in NE (p=0.079)

Table II (Continued). — Efficacy of norepinephrine on maternal hemodynamics in comparison to phenylephrine.

Year and Author	Study population	Intervention	Effect on HR	Effect on BP	Effect on CO	Effect on other hemodynamic measurements	Performance error	Measurements related to dosage & number of rescue boluses*
2022 Chen et al.[20]	100 healthy women with twin pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of PE (40 µg min^{-1}) or NE (3.2 µg min^{-1})	Standardized AUC of HR 74 bpm in PE vs 78 bpm NE (p=0.0567) Incidence of bradycardia (HR < 60 bpm): 30% in PE vs 6% in NE (p=0.002)	Standardized AUC of SBP in PE vs NE (p=0.0013) Incidence of hypotension: 6% in PE vs 24% in NE (p=0.012)	NA	NA	NA	Incidence of need of atropine administration: 6% in PE vs 0% in NE (p=0.242) Total volume of vasopressor given: 8.5 ml in PE vs 9.9 ml in NE (p=0.006) Requirement of physician intervention in PE vs NE (p=0.695)
2022 Liu et al.[43]	78 healthy women with singleton pregnancy undergoing CS under CSE anesthesia (PE = 26 vs NE = 26 vs metaraminol = 26)	Weight adjusted infusion of either PE (0.54 µg $kg^{-1}min^{-1}$), NE 0.08 µg $kg^{-1}min^{-1}$) or metaraminol (2 µg $kg^{-1}min^{-1}$)	Incidence of bradycardia: 8% in PE vs 0% in NE vs 0% in M group (p=0.13)	Incidence of hypotension: 12% in PE vs 38% in NE vs 27% in M (p=0.08) Significantly difference in SBP over time (p<0.001) Significant difference in SBP between the 3 groups (p=0.007) Only PE had significantly higher SBP in comparison to M group Time to first hypotensive episode not significantly different between the groups (p=0.06)	NA	NA	NA	Rescue boluses needed 8% in PE vs 8% in NE vs 8% in M

CS = caesarean section, HR = heart rate, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, CO = cardiac output, PE = phenylephrine, NE = norepinephrine SV = stroke volume, SVR = systemic vascular resistance, NA = not available TRP = total peripheral resistance;, CI = cardiac index, bpm = beats per minute; NA = not available.
*Total dosage of vasopressor given: if significantly different relative potency between PE and NE chosen in the study is possibly incorrect. ** p value < 0.05 is statistically significant; (PE =n) = number of people in the final analysis of PE group; (NE=n) = number of people in the final analysis of norepinephrine group.

a relative potency of 20:1, which was suggested to be incorrect by Ngan Kee et al.18, who observed that the volume of norepinephrine needed was significantly higher than phenylephrine, suggesting that this relative potency was incorrect. Two studies used a relative potency of 16.6:1, one used 15:1 and one used a relative potency of 10:1. The remaining studies used a relative potency higher than 10:1. The exact relative potencies of the trials can be looked up in Table I.

Systolic blood pressure

Among the 15 studies with a relative potency between 11:1-13.3:1, two found a higher incidence of hypotension in the norepinephrine group[19-20], one found more hypotensive episodes in the phenylephrine group[20], and four found no difference[14,23-25]. In the remaining studies the incidence of hypotension was not mentioned. Severe hypotension (SBP < 60% of baseline value) was comparable between both vasopressors in two studies[14,24]. Six trials[13,19,24,25-27] found the systolic blood pressure, systolic blood pressure over time and changes in systolic blood pressure to be comparable. Two trials[27,28] found the MAP and MAP over time to be comparable One trial[30] looked at the duration of hypotension and found it to be comparable between both groups.

Three trials that used an infusion with a relative potency around 6.03:1 found mixed results, with Ravichandrane et al[35] reporting a significantly higher systolic blood pressure pre-delivery in the norepinephrine group, while Qian et al.[16] and Liu et al.[43] found no significant difference in the incidence of hypotension.

In the other 17 trials, twelve found a similar incidence of hypotension in both groups[6,16,22,29,31-38], reported a similar incidence of severe hypotension, and nine trials found comparable systolic blood pressure or systolic blood pressure over time[6,18,22,29,32,34,39-41]. Three trials[6,22,39] found comparable diastolic blood pressure or changes in diastolic blood pressure. Three trials found a comparable MAP between both groups[6,29,37].

One trial reported a significantly higher systolic blood pressure during the first 6 minutes in the norepinephrine group[36]. After those six minutes, there was no significant difference between both vasopressors. One trial found the systolic blood pressure to be significantly higher in the norepinephrine group before delivery[35], with no significant difference after delivery.

In contrast, two trials found a significantly higher incidence of hypotension in the NE group[42-43]; and found a significantly higher MAP in the phenylephrine group at certain time points[44-45]. One trial found both systolic and diastolic pressure to be significantly higher in the PE group[45].

Twenty-four trials examined the incidence of reactive hypertension (see Table III). Two trials[21,30] found a significant higher incidence of reactive hypertension in the phenylephrine group. The remaining twenty-two found a comparable incidence.

Heart rate

In the trials with a relative potency between 11:1-13:1, nine found a significantly lower incidence of bradycardia in the NE group[14,20,23-24,26-28,30,46], three studies found the standardized heart rate to be significantly higher in the NE group[23,26,27], and two studies noted significantly fewer changes in heart rate in the NE group[26,30].

One study found that the heart rate decrease after vasopressor administration was significantly lower in the NE group[15].

In contrast, three trials found the incidence of bradycardia to be comparable between both vasopressors[21,25,47]; one trial found the heart rate over time to be comparable[25], and two studies found the heart rate after vasopressor administration to be comparable[13,25]. Two studies found the area under the curve for heart rate to be comparable between both vasopressors[39,40].

Of the three trials with a relative potency around 6.03:1 the incidence of bradycardia was not significantly different between both vasopressors

In the trials with less optimal relative potency, seven studies found a significantly lower incidence of bradycardia in the NE group[18,31,33,36-38,45], two found a significantly lower minimal heart rate in the PE group[33,37], four trials found the heart rate to be significantly higher in the NE group at some timepoints[18,36,40,44], and one trial found the heart rate after vasopressor administration to be significantly higher in the NE group[34].

Eight studies found no significant difference in the incidence of bradycardia[6,22,29,32,34,39,41-42], two trials found a comparable heart rate[35,39], and in three found the heart over time to be comparable[29,32,34].

Eight trials looked at the incidence of tachycardia[19,22,23,25,30,31,44,47], finding no significant difference between both vasopressors.

Four trials investigated the arrhythmia incidence, with three[19,25,34] finding no significant difference and one reporting more premature ventricular contractions in the NE group[35].

Cardiac output

Six studies examined the cardiac output, with four finding it significantly higher in the NE group[18,26,29,41] and two finding no significant difference[39,46].

Table III. — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2015. Ngan Kee et al.[18]	101 Healthy Singleton pregnant women with elective CS (PE = 52 vs NE = 49)	Computer controlled closed loop infusion (Fixed Rate) of either PE infusion (100 µg ml^{-1}) or NE infusion (5 µg ml^{-1}) (starting at 30 ml h^{-1})	6.1% in NE vs. 3.8% in PE (p = 0.67)	NA	NA	NA	NA	NA
2019 Mohta et al.[13]	100 Healthy singleton pregnant women that developed post-spinal hypotension During elective CS (PE = 50 vs NE = 50)	Bolus of either PE (ranging from 30 µg to 100 µg) or NE (ranging from 3 µg to 6 µg)	Nausea 6% in NE vs 10% in PE group (p = 0.51) Vomiting 2% in NE vs 6% in PE (p = 0.612)	0 vs 0	0 vs 0	NA	NA	NA
2019 Sharky et al.[31]	112 healthy women with singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 56 vs NE = 56)	Intermittent boluses of either 100 µg PE or 6 µg NE, rescue boluses of ephedrine 10 mg when HR below 60 bpm or when SBP stayed < 80% for 2 consecutive readings despite administration of study drug	Nausea: 32.1% in PE vs 27.3% in NE (p=0.57) Vomiting 7.1% in PE vs 1.8% in NE (p=0.17)	NA	No adverse events of extravasation or tissue ischemia in PE or NE group	10.7% in PE vs 10.7% in NE (p=0.99)	12.5% in PE vs 10.7% in NE (p=0.76)	NA
2023 Guo et al.[14]	80 healthy singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40)	Prophylactic PE (ranging from 37.5 µg to 100 µg) or NE (ranging from 3 µg to 9 µg) boluses	Nausea 7.5% in NE vs 10% in PE (p= 1) Vomiting 5% in NE vs 2.5% in PE (p=1.0)	NA	NA	5% in NE vs. 2.5% in PE (p=1)	NA	NA
2020 Wang et al.[26]	102 healthy parturients with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 50 vs NE = 52)	Bolus of PE (100 µg) or NE (8 µg) immediately after spinal anesthesia and boluses whenever hypotension occurred.	Nausea 4% in NE vs 8% in PE (p=0.43) Vomiting (0% in NE vs 2% in PE) (p=0.50)	0 in NE vs. 0 in PE (p>0.99)	NA	NA	NA	NA
2022 Zhou et al.[21]	75 healthy singleton pregnant women undergoing CS under CSE anesthesia (PE = 25 vs NE = 25 vs Metaraminol = 25)	Metaraminol (500 µg ml^{-1}), PE (100 µg ml^{-1}) And NE (8 µg ml^{-1}) fixed rate infusion (30 ml h^{-1}) after initial bolus of 1 ml + rescue boluses of M 250 µg, PE 50 µg or NE 4 µg	Nausea 4% in M group vs 8% in PE group vs 4% in NE group (overall p=0.8071) Vomiting: 0% in all groups	0% in M group vs 0% in PE group vs 8% in NE group: p=0.14	NA	68% in M group vs 36% in PE vs 8% in NE group (P<0.0001; M vs PE p=0.02, M vs NE p<0.0001, PE vs NE p=0.0169)	NA	NA
2017 Ngan Kee et al.[15]	180 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 90 vs NE = 90)	Norepinephrine bolus (4-12 µg) or phenylephrine bolus (60-200 µg)	NA	NA	NA	NA	NA	NA

Table III (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2019 Hasanin et al.[32]	123 healthy pregnant women undergoing CS under spinal anesthesia (PE = 63 vs NE = 60)	Weight adjusted infusion Of PE (0.75 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) that was manually titrated + rescue boluses (50-100 µg PE vs 9-15 mg ephedrine vs 0.5 mg atropine)	Nausea 15% in NE vs 6% in PE (p=0.1) Vomiting 5% in NE vs 2% in PE (p=0.4)	NA	NA	12% in NE vs. 24% in PE (P=0.1)	NA	NA
2017 Vallejo et al.[39]	81 Healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 38 vs NE = 43)	Weight adjusted infusion of PE (0.1 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses of PE 100 µg in both arms	Incidence of nausea 63.2% in PE vs 51.2% in NE (p=0.28) Incidence of emesis 26.3% in PE vs 16.3% in NE group (p <0.001)	NA	NA	1 in PE vs 2 in NE group	NA	NA
2017 Ngan Kee et al.[33]	101 healthy women undergoing elective CS under spinal anesthesia (PE = 52 vs NE = 49	Computer controlled closed loop infusion of PE (0-100 µg min^{-1}) or NE (0-5 µg min^{-1})	Incidence of IONV: 3.8% in PE vs 6.1% in NE (p=0.67)	NA	NA	Incidence of hypertension 17.3% in PE vs 8.2% in NE (p=0.1	NA	NA
2023 de Queiroz et al.[42]	72 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 37 vs NE = 35)	Rescue boluses of PE (100 µg) or NE (5 µg)	NA	NA	NA	Incidence of hypertension 51.3% in PE vs 34.3% in NE (p=0.22) number of hypertensive episodes 1 in PE vs 0 in NE (p=0.1)	NA	NA
2020 Theodoraki et al.[27]	82 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 41 vs NE = 41)	Fixed rate infusion (30 ml h^{-1}) of either PE (50 µg min^{-1}) or NE (4 µg min^{-1}) started during spinal anesthesia	NA	NA	NA	Incidence of reactive hypertension 7.3% in PE vs 4.8% in NE (p=1.000)	NA	NA
2019 Mohta et al.[34]	90 healthy women singleton pregnancy (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 5 µg of NE	Number of women with nausea: 4 in PE vs 3 in NE (P=1) Number of women with vomiting: 1 in PE vs 2 in NE (P=1)	Number of women with dizziness: 0 in PE group vs 1 in NE group (p=1)	NA	Incidence of reactive hypertension: 2.2% in PE vs 4.4% in NE group (p=0.56)	NA	0 in PE vs 0 in NE

Table III (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2020 Biricik et al.[6]	160 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40 vs E = 40 vs saline = 40)	Fixed rate (30 ml h^{-1}) infusion of either saline 0.9%, NE (5 µg ml^{-1}), E (5 µg ml^{-1}), PE 100 µg ml^{-1}) + rescue bolus of ephedrine	Incidence of nausea 20% in saline group vs 12.5% in PE vs 17.5% in NE vs 12.5% in E group (p=0.734) Incidence of vomiting: 15% in saline group vs 7.5% in PE vs 12.5% in E vs 8% in NE group (p=0.452)	NA	NA	NA	NA	NA
2017 Dong et al.[40]	126 healthy women with singleton undergoing elective CS under CSE anesthesia (PE = 64 vs NE = 62)	Prophylactic bolus of PE 50 µg vs NE 10 µg + rescue boluses PE 50 µg vs NE 10 µg	Incidence of nausea: 3% in PE vs 5% in NE group (p=0.68)	NA	NA	Incidence: 3% in PE vs 5% in NE group (p=0.68)	NA	NA
2020 Cho et al.[41]	44 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 22 vs NE = 22)	Rescue boluses of 100 µg PE vs 5 µg NE	Incidence of IONV (9% in PE vs 4.5% in NE (p=1.000)	NA	NA	NA	NA	NA
2022 Rai et al.[30]	90 healthy women with singleton pregnancy undergoing elective CSE under spinal anesthesia (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 7.5 µg NE	Nausea 17.8% in PE vs 8.9% in NE (p > 0.05) Vomiting: 2.2% in PE vs 6.7% in NE (p > 0.05)	Dizziness: 17.8 in PE vs 2.2% in NE (p=0.03)	NA	28.9% in PE vs 4.4% in NE (p=0.003)	0 in PE vs 0 in NE	NA
2023 Priya et al.[22]	156 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 78 vs NE = 78)	Prophylactic fixed rate infusion of PE 50 µg min^{-1} vs NE 5 µg min^{-1} + rescue boluses if needed (PE 50 µg vs NE 5 µg)	NA	NA	NA	Incidence: 12.8% in PE vs 23.1% in NE (p=0.290)	Incidence: 2.6% in PE vs 6.4 in NE (p=0.241)	NA
2019 Puthenveettil et al.[47]	50 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25)	Rescue boluses of PE (50 µg) or NE infusion (4 µg)	Incidence of IONV: 8% in PE vs 8% in NE group (p=0.695)	NA	Shivering: 4% in PE vs 16% in NE (p=0.174)	Incidence: 0 in PE vs 0 in NE	0 in PE vs 0 in NE	NA
2023 Ravichandrane et al.[35]	130 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 65 vs NE = 65)	Prophylactic fixed rate infusion of either PE (25 µg min^{-1} or 5 µg min^{-1}) + rescue boluses of PE 25 µgin both groups	Incidence of nausea: 9.2% in PE vs 4.6% in NE (p=0.49)	NA	NA	Number of patients with hypertension: 0 in PE vs 3 in NE group (p=0.08)	NA	Premature ventricular concentration: 0 patients in PE vs 7 patients in NE (P=0.006)

Table III (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2021 Ashraf et al.[44]	75 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25 vs E = 25)	Weight adjusted prophylactic infusion of either PE (0.1 µg kg^{-1} min^{-1}), NE (0.05 µg kg^{-1} min^{-1}) or fixed rate ephedrine 1 mg min^{-1} infusion + rescue boluses of either 0.2 µg kg^{-1} PE, 0.1 µg kg^{-1} NE or 5 mg ephedrine.	Incidence of nausea: 8% in PE vs 0% in NE vs 8% in ephedrine (p=0.348) Vomiting: 4% in PE vs 0% in NE vs 8% in ephedrine (p=0.353) Need for anti-emetic medication: 12% in PE vs 0% in NE vs 16% in ephedrine (p=0.129)	NA	NA	Incidence: 0% in PE vs 0% in NE vs 8% in ephedrine (p=0.128)	Incidence: 0% in PE vs 0% in NE vs 12% in ephedrine (p=0.044)	NA
2022 Tiwari et al.[28]	126 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 63 vs NE = 63)	Rescue boluses of either 50 µg of PE or 4 µg of NE	Incidence 7.93% in PE vs 7.93 in NE	NA	Incidence of shivering: 7.93% in PE vs 15.87% in NE (p=0.05)	NA	NA	NA
2021 Goel et al.[36]	200 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 100 vs NE = 100)	Variable rate infusion of either PE (100 µg ml^{-1}) or NE (5 µg ml^{-1}) both started at 30 ml h^{-1} + rescue boluses of 100 µg PE or 5 µg NE	Incidence of nausea: 11% in PE Vs 7% in NE (p=0.323) Incidence of vomiting (0 in PE vs 0 in NE)	NA	NA	Incidence 4% in PE vs 3% in NE (p>0.05)	NA	NA
2022 Mahzad et al.[37]	45 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 15 vs NE = 15 vs ephedrine = 15)	Prophylactic bolus of either PE (40 µg), NE (5 µg) or ephedrine (5 mg)	Incidence of nausea: 20% in PE vs 0% in NE vs 6% in ephedrine (p=0.1465) Incidence of vomiting: 0% in PE vs 0% in NE vs 0% in ephedrine	NA	NA	NA	NA	NA
2022 Qian et al.[16]	60 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 30 vs NE = 30)	Prophylactic infusion (Fixed rate) of PE (100 µg ml^{-1}) or NE (8 µg ml^{-1}) + rescue bolus of PE (50 µg) when hypotension occurred	IONV 16.7% in PE vs 13.3% in NE (p=1.0)	NA	Incidence of shivering: 40% in PE vs 33.3% in NE (p=0.59)	Incidence: 6.7% in PE vs 0% in NE (p=0.47)	NA	NA

Table III (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2023 Belin et al.[29]	124 women (healthy or with mild pre-eclampsia) undergoing elective CS under spinal anesthesia (PE = 62 vs NE = 62)	Manually adjusted variable rate infusion of either PE (50 µg ml^{-1}) or NE (5 µg ml^{-1}) starting at 0.5 µg kg^{-1} min^{-1} in PE vs 0.05 µg kg^{-1} min^{-1} in NE + rescue bolus of 5 mg ephedrine in case of persisted hypotension	Incidence of IONV: 30% in PE vs 40% in NE group (p=0.26)	Incidence: 4.8% in PE v 8.1% in NE (p=0.72)	NA	% of time spent with SBP > 140 mmHg until umbilical cord clamping: 6.9% in PE vs 7.2% in NE (p=0.94) % of time spent with SBP > 140 mmHg after umbilical cord clamping: 0.9% in PE vs 0.9% in NE (p=0.92)	NA	NA
2019 Wang et al.[23]	166 singleton pregnant women with pre-eclampsia with elective CS under spinal anesthesia (PE = 55 vs NE = 56 vs ephedrine = 55)	Intermittent bolus of NE 4 µg (NE group), bolus of 50 µg PE (PE group) or bolus of 4 mg ephedrine (E group)	Incidence of nausea: 5.5% in PE vs 3.6% in NE vs 9.1% in E (not significantly different between groups) Incidence of vomiting: 1.8% in PE vs 1.8% in NE vs 11% in E (not significantly different between groups) Incidence IONV 5.4% in NE vs 20% in E (p=0.02)	Incidence of dizziness: 1.8% in PE vs 0% in NE vs 3.6% in E (not significantly different)	Shivering: 3.6% in PE vs 7.1% in NE vs 5.5% in E (not significantly different)	0 in PE vs. 0 in NE vs. 0 in E	Incidence of tachycardia: 16.1 in PE vs 14.6 in NE vs 36.4% in E (PE vs NE p>0.05; PE vs E p<0.05; NE vs E p<0.05)	NA
2022 Guo et al.[24]	138 singleton pregnant women with pre-eclampsia undergoing elective CS under spinal anesthesia (PE 69 vs NE = 69)	Weight adjusted prophylactic infusion of PE (0.625 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses (PE 75 µg or NE 6 µg)	Incidence of nausea: 5.8% in PE vs 7.3% in NE (p=0.73) Incidence of vomiting: 2.9% in PE vs 2.9 in NE (p=1.00)	NA	NA	Incidence of hypertension 2.9% in PE vs 4.4% in NE (p=0.649)	NA	NA

Table III (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: maternal adverse events.

Year And Author	Study population	Intervention	IONV	Dizziness	Other side effects	Hypertension	Tachycardia	Arrhythmia
2021 Mohta et al.[25]	86 women with singleton pregnancy and pre-eclampsia (PE = 43 vs NE = 43)	Rescue boluses of PE (50 µg) or NE (4 µg)	Incidence of nausea: 1 in PE vs 1 in NE group (In both cases related to hypotension) Incidence of vomiting: 0 in PE vs 0 in NE group	Incidence of dizziness: 0 in PE vs 0 in NE group	Incidence of other side effects: 0 in PE vs 0 in NE	0 in PE vs 0 in NE group	0 in PE vs 0 in NE group	0 in PE vs 0 in NE group
2022 Du et al.[46]	62 healthy parturients with twin pregnancy undergoing elective CS under spinal anesthesia (PE = 31 vs NE = 31)	Fixed rate infusion at 60 ml h^{-1} of PE (75 µg ml^{-1}) or NE (6 µg ml^{-1}) + rescue boluses of PE (75 µg) or NE (6 µg)	Incidence of IONV: 24.1% in PE vs 31% in NE group (p=0.065)	NA	NA	Incidence of hypertension: 58.6% in PE vs 34.5% in NE group (p=0.065)	NA	NA
2022 Chen et al.[20]	100 healthy women with twin pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of PE (40 µg min^{-1}) or NE (3.2 µg min^{-1})	Incidence of IONV: 2% in PE vs 4% in NE group (p=1)	NA	NA	Incidence of hypertension: 26% in PE vs 12% in NE (p=0.074)	NA	NA
2022 Liu et al.[43]	78 healthy women with singleton pregnancy undergoing CS under CSE anesthesia (PE = 26 vs NE = 26 vs metaraminol = 26)	Weight adjusted infusion of either PE (0.54 µg $kg^{-1}min^{-1}$), NE 0.08 µg $kg^{-1}min^{-1}$) or metaraminol (2 µg $kg^{-1}min^{-1}$)	Incidence of IONV 8% in PE vs 23% in NE vs 15% in M (p=0.31)	NA	NA	Incidence of hypertension 4% in PE vs 0% in NE vs 0% in M (p=0.36)	NA	NA
2022 Singh et al.[45]	100 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of either PE (100 µg min^{-1}) or NE (5 µg min^{-1}) + rescue boluses of PE (60 µg) or NE (6 µg)	IONV not significantly different between PE and NE group Antiemetics needed in 14% in PE vs 20% in NE	NA	NA	11 women in PE group, NA for NE group	NA	NA
2020 Ngan Kee et al.[38]	664 healthy women undergoing CS (531 elective and 133 non-elective) under spinal or CSE anesthesia (elective: PE = 265 vs NE = 266; non- elective: PE 67 vs NE = 66)	Fixed rate infusion of either PE (100 µg min^{-1}) or NE (6 µg min^{-1}) and/or rescue boluses of PE (100 µg) or NE (6 µg)	Incidence of IONV 24% in PE vs 27% in NE (p=0.29)	NA	NA	NA	NA	NA
2022 Mohta et al.[19]	100 healthy women with singleton pregnancy undergoing emergency CS under spinal anesthesia (for actual or potential compromised status of fetus) (PE = 50 vs NE = 50)	Rescue boluses of either PE (100 µg) or NE (8 µg)	Incidence of IONV was not significantly different between PE and NE group (Nausea: 10% in PE vs 6% in NE; vomiting: 4% in PE vs 2% in NE)	NA	NA	NA	Incidence of tachycardia 6% in PE vs 6% in NE (p=0.817)	0 in PE vs 0 in NE

CS = caesarean section, IONV = intra operative nausea and vomiting, NE = norepinephrine; PE = phenylephrine M = metaraminol E=epinephrine NA = not available; (PE =n) = number of people in the final analysis of PE group; (NE=n) = number of people in the final analysis of norepinephrine group.

However, the study of Vallejo et al[39] had a biased study design (open labelled and a relative potency of 2:1) so no conclusion can be drawn out of his results. One study found the cardiac output to be significantly higher at minute 5 and comparable at other time points[40].

Other hemodynamic variables

Six studies looked at other hemodynamic variables, more specifically the stroke volume and systemic vascular resistance[18,26,29,39,41,46]. One of those six trials was the trial of Vallejo et al[39] and because of its biased design we can't interpreted the results of that trial. Two trials found comparable SV between both groups[18,29], while two trials found it to be significantly higher in the norepinephrine group[26,41]. Three trials[29,41,46] found a comparable SVR between both groups, whilst two trials[18,26] found the SVR to be significantly higher in the PE group.

Performance error

Ngan Kee et al.33 found that NE could control the blood pressure more precisely. Guo et al24 found that NE could control the heart rate and blood pressure more precisely compared to PE.

Maternal adverse events

The first step to evaluate the safety of norepinephrine for use as vasopressor in caesarean section is to look at the maternal adverse events. Table III summarizes all adverse events considered in the thirty-five included articles.

The most looked at maternal adverse event is intraoperative nausea and vomiting (IONV). Only the trial by Vallejo et al.[39] found a significantly higher incidence of vomiting in the phenylephrine group, but because of the biased trial design it is not possible to interpret these results. All the other trials found a comparable incidence of IONV between both vasopressors.

Two studies looked at the use of anti-emetic medication and both did not find a significant difference between the norepinephrine and phenylephrine group[44,45].

Another adverse event caused by cerebral hypo-perfusion is dizziness. The incidence of dizziness was studied in eight trials[13,19,21,23,26, 29,30,34]. Only Rai et al.[30] found a significantly higher incidence of dizziness in the phenylephrine group. The other seven trials did not find a significant difference in the incidence of dizziness between both vasopressors[13,19,21,23,26,29,34].

No trial mentioned a higher incidence of tissue damage after extravasation of norepinephrine compared to phenylephrine.

Neonatal outcome

The neonatal outcomes of all the different trials are summarized in Table IV.

Of the thirty-five included trials neonatal outcome was a primary outcome in only seven trials[19,21,25,30,38,43,45], and in twenty-seven trials it was a secondary outcome[6,13-16,18,20,22-24,26-29,31,32,34-37,39-42,44,46,47]. Ngan Kee et al. did not evaluate neonatal outcome in the study where they evaluated their automated infusion system[33]. This is because this trial re-analyzed the data of their 2015 trial and only applied a performance error analysis to assess the relative performance for maintaining BP of phenylephrine compared to norepinephrine.

Apgar score

Out of the seven trials that had neonatal outcome as their primary outcome, no significant difference was found between both groups regarding the Apgar score.

In the other trials no significant difference was found regarding the Apgar score between both groups. In the trial of Priya et al.[28] 1 neonate in the NE group had an Apgar score less than 6 at five minutes versus 0 in the PE group, but the p-value was not given.

Umbilical arterial blood gas values and fetal acidosis

All umbilical cord blood gas values are summarized in Table IV. The most important umbilical arterial blood gas values are summarized separately in Table V. In most trials no significant difference was found in these umbilical arterial blood gas values. The trials of Singh et al.[45] and Ravichandrane et al.[35] found the umbilical arterial HCO3- to be significantly higher in the norepinephrine group. Singh et al.[45] also found the umbilical arterial base excess to be significantly better in the norepinephrine group compared to the phenylephrine group. In contrast Mohta et al.[34] found an umbilical arterial pH that was significantly lower in the norepinephrine group compared to the phenylephrine group. Not a single trial found a significant difference in the incidence of fetal acidosis between both vasopressors.

Other outcome measurements

Five trials compared the NICU admission rates between the two groups[20,24,25,30,45].
No significant difference was seen between both vasopressors regarding NICU admission, with Rai et al.[30] not calculating the p-value for NICU admission.

Rai et al.[30] found a significant higher neurobehavioral score after 24 and 48 hours in the norepinephrine group.

Table IV. — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2015. Ngan Kee et al.[18]	101 Healthy Singleton pregnant women with elective CS (PE = 52 vs NE = 49)	Computer controlled closed loop infusion (Fixed Rate) of either PE infusion (100 µg ml^{-1}) or NE infusion (5 µg ml^{-1}) (starting at 30 ml h^{-1})	<8 after 1 min 0 vs 0 <8 after 5 min 0 vs 0	7.30 in NE vs. 7.29 in PE (P = 0.45)	0 vs 0	UV pH 7.35 in NE vs 7.34 in PE (p=0.031) oxygen content UV 12.7 ml dl^{-1} in NE vs 11.8 ml dl^{-1} in PE (p = 0.047) UA PCO2, PO2 base excess oxygen content and UV PCO2, PO2 base excess were not significantly different between NE and PE group	UA plasma concentration of epinephrine 400 pg ml^{-1} in PE vs 281 pg ml^{-1} in NE (p = 0.042) UA plasma concentration of norepinephrine 2.178 in PE vs 1.756 pg ml^{-1} in NE (p = 0.035) UA plasma concentration of glucose 46 mg dl^{-1} in PE vs 53 mg dl^{-1} in NE (p < 0.001) UA plasma concentration of lactate (P = 0.088) UV plasma concentration of epinephrine 40 pg ml^{-1} vs 23 pg ml^{-1} (p = 0.16) UV plasma concentration of norepinephrine 457 pg ml^{-1} in PE vs 347 pg ml^{-1} in NE (p = 0.031) UV plasma concentration of glucose 51 mg dl^{-1} in PE vs 56 mg dl^{-1} in NE (p < 0.001) UV plasma concentration of lactate (p=0.33)
2019 Mohta et al.[13]	100 Healthy singleton pregnant women that developed post-spinal hypotension During elective CS (PE = 50 vs NE = 50)	Bolus of either PE (ranging from 30 µg to 100 µg) or NE (ranging from 3 µg to 6 µg)	Comparable at 1 min (p =1) Comparable at 5 min (p = 1)	NA	NA	NA	Birth weight 2.7 kg in PE vs 2.6 kg in NE (p=0.214)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2019 Sharky et al.[31]	112 healthy women with singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 56 vs NE = 56)	Intermittent boluses of either 100 µg PE or 6 µg NE, rescue boluses of ephedrine 10 mg when HR below 60 bpm or when SBP stayed < 80% for 2 consecutive readings despite administration of study drug	At 1 min: 9 in PE vs 9 in NE (p=0.72) At 5 min 9 in PE vs 9 in NE (p=0.32)	7.25 in PE vs 7.24 in NE (p=0.82)	NA	UA PCO2, UA PO2, UA HCO3, UA base access, UV pH, UV PCO2, UV PO2, UV HCO3 UV base excess were al not significantly different between NE and PE groups	NA
2023 Guo et al.[14]	80 healthy singleton pregnant women undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40)	Prophylactic PE (ranging from 37.5 µg to 100 µg) or NE (ranging from 3 µg to 9 µg) boluses	At 1 min 9 in NE vs 9 in PE (p=1.0) < 7 at 1 min 0 in NE vs 1 in PE (p=1.0) At 5 min 10 in NE vs 10 in PE (p=1.0) < 7 at 5 min 0 in NE vs 0 in PE (p=1.0)	7.36 In NE vs 7.35 in PE group (p=0.456)	0 in NE vs. 0 in PE (p=1.0)	UA PCO2, UA PO2, UA base excess were not significantly different between NE and PE group	NA
2020 Wang et al.[26]	102 healthy parturients with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 50 vs NE = 52)	Bolus of PE (100 µg) or NE (8 µg) immediately after spinal anesthesia and boluses whenever hypotension occurred.	At 1 min 10 in NE vs 10 in PE (p=0.97) At 5 min: 10 in NE vs 10 in PE (p=0.19) Incidence of Apgar < 7 at 1 min: 0 in NE vs 0 in PE (p>0.99) Apgar < 7 at 5 min: 0 in NE vs 0 in PE (p>0.99)	7.32 in NE vs. 7.32 in PE (p=0.23)	Incidence: 0 in NE vs 0 in PE (p>0.99)	UA Glucose plasma concentration: 3.5 mmol L^{-1} in NE vs 3.3 mmol L^{-1} in PE (p=0.046) UV glucose plasma concentration 4.4 mmol L^{-1} in NE vs 4.2 mmol L^{-1} (p=0.042) All other blood gas values were not significantly different between NE and PE (UA PO2, PCO2, HCO3, base access, lactate plasma concentration, UV pH, pO2, pCO2, HCO3, base excess, lactate plasma concentration)	Birth weight 3402 gr in NE vs 3492 gr in PE (p=0.97)
2022 Zhou et al.[21]	75 healthy singleton pregnant women undergoing CS under CSE anesthesia (PE = 25 vs NE = 25 vs Metaraminol = 25)	Metaraminol (500 µg ml^{-1}), PE (100 µg ml^{-1}) And NE (8 µg ml^{-1}) fixed rate infusion (30 ml h^{-1}) after initial bolus of 1 ml + rescue boluses of M 250 µg, PE 50 µg or NE 4 µg	Apgar at 1 min 10 in M vs 10 in PE vs 10 in NE p=0.77 Apgar at 5 min 10 in M vs 10 in PE vs 10 in NE p=0.60	7.32 in M group vs 7.31 in PE vs 7.31 in NE group (p=0.548) M and PE are non-inferior in comparison with NE	NA	UA pO2 Significantly higher in M vs NE (p=0.02) No difference in other values (UA pCO2, base excess, lactate concentration UV pH; pCO2, pO2, base excess, lactate concentration)	NA

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2017 Ngan Kee et al.[15]	180 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 90 vs NE = 90)	Norepinephrine bolus (4-12 µg) or phenylephrine bolus (60-200 µg)	Apgar score < 7 at 1 min: 1 in PE vs 0 in NE group Apgar score < 8 at 5 min: 0 in PE vs 0 in NE Significance of the differences was not determined	No comparison was made between the different groups	5 neonates in PE vs 4 neonates in NE groups	Data was given but no comparison was made between the different groups	NA
2019 Hasanin et al.[32]	123 healthy pregnant women undergoing CS under spinal anesthesia (PE = 63 vs NE = 60)	Weight adjusted infusion Of PE (0.75 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) that was manually titrated + rescue boluses (50-100 µg PE vs 9-15 mg ephedrine vs 0.5 mg atropine)	At 1 min: 8 in NE vs 8 in PE (p=0.74) At 5 min 10 in NE vs 10 in PE (p=0.3)	7.31 In NE vs. 7.30 in PE (p=0.2)	NA	No significant differences in other values between NE and PE group (UA pCO2, UA pO2, UA HCO3)	NA
2017 Vallejo et al.[39]	81 Healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 38 vs NE = 43)	Weight adjusted infusion of PE (0.1 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses of PE 100 µg in both arms	Incidence of Apgar < 7 at 1 min 6 in PE vs 6 in NE group (p=0.82) Incidence of Apgar < 7 at 5 min 2 in PE vs 1 in NE group (p=0.48)	UA pH not measured only UV	NA	UV pH 7.30 in PE vs 7.27 in NE group (P=0.42) UV PCO2 54 mmHg in PE vs 24 mmHg in NE (p=0.32) UVpO2 51 mmHg n PE vs 56 mmHg in NE (p=0.46) UV HCO3 23 mEq l^{-1} in PE vs 20.3 mEq l^{-1} in NE (p=0.56) UV base excess 4.3 mEq l^{-1} in PE vs 4.3 mEq l^{-1} in NE (p=0.74)	NA
2017 Ngan Kee et al.[33]	101 healthy women undergoing elective CS under spinal anesthesia (PE = 52 vs NE = 49	Computer controlled closed loop infusion of PE (0-100 µg min^{-1}) or NE (0-5 µg min^{-1})	NA	NA	NA	NA	NA
2023 de Queiroz et al.[42]	72 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 37 vs NE = 35)	Rescue boluses of PE (100 µg) or NE (5 µg)	Apgar score at 1 min: 9 in PE vs 9 in NE group (p=0.23) Apgar score at 5 min: 9 in PE vs 9 in NE group (p=0.34)	7.25 in PE vs 7.28 in NE (p=0.15)	0 in PE vs 0 in NE group	UA and UV pCO2, pO2, HCO3, base excess, lactate plasma concentration, glucose plasma concentration were all not significantly different between PE and NE group UV pH 7.27 in PE vs 7.31 in NE group (p=0.04)	NA

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2020 Theodoraki et al.[27]	82 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 41 vs NE = 41)	Fixed rate infusion (30 ml h^{-1}) of either PE (50 µg min^{-1}) or NE (4 µg min^{-1}) started during spinal anesthesia	Apgar score at 1 min: 9 in PE vs 9 in NE (P=0.714) Apgar score at 5 min 9 in PE vs 9 in NE (0.663) Incidence of Apgar < 7 at 1 min: 0 in PE vs 0 in NE Incidence of Apgar < 9 at 5 min: 0 in PE vs 0 in NE	Only UV blood was used (UV pH 7.34 in PE vs 7.35 in NE (p=0.027))	0 in PE vs 0 in NE group	UV HCO3 22.6 mEq L^{-1} in PE vs 24 mEq l in NE (p=0.014) UV base excess: -2.2 mEq L^{-1} in PE vs -0.7 mEq L^{-1} in NE (p=0.037) UV glucose plasma concentration: 68 mg dL^{-1} in PE vs 71 mg dL^{-1} in NE (0.019) All other measured values (UV pO2, UV pCO2, UV lactate plasma concentration) were not significantly different between PE and NE group	Birth weight: 3126 gr in PE vs 3282 gr in NE group (p=0.147)
2019 Mohta et al.[34]	90 healthy women singleton pregnancy (PE = 45 vs NE = 45)	Rescue boluses of 100 µg PE or 5 µg of NE	Apgar score at 1 min: 9 in PE vs 9 in NE (p=1.0) Apgar score at 5 min 9 PE vs 9 NE (p=0.54)	7.29 in PE vs 7.25 in NE group (p=0.03)	Incidence of fetal acidosis: 15.6% in PE vs 13.3% in NE group (p=0.77)	UA HCO3: 24.3 mmol L^{-1} in PE vs 22.5 mmol L^{-1} in NE (p=0.04) UA base excess -2.8 mmol L^{-1} in PE vs -5.2 mmol L^{-1}in NE (p=0.02) UV HCO3: 23.7 mmol L^{-1} in PE vs 21.2 mmol L^{-1} in NE (p=0.006) UV base excess: -2.1 mmol L^{-1} in PE vs -5.1 mmol L^{-1} in NE (p=0.008) Other measurements (UA pO2, UA pCO2, UV pH, UV pO2, UV pCO2) were not significantly different between PE and NE group	Birth weight: 2.9 kg in PE vs 2.9 kg in NE group (p=0.62)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2020 Biricik et al.[6]	160 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 40 vs NE = 40 vs E = 40 vs saline = 40)	Fixed rate (30 ml h^{-1}) infusion of either saline 0.9%, NE (5 µg ml^{-1}), E (5 µg ml^{-1}), PE 100 µg ml^{-1}) + rescue bolus of ephedrine	Apgar score at 1 min: 8 in saline group vs 8 in PE vs 8 in NE vs 9 in E (overall p=0.001), compared with saline only E was significantly different Apgar score at 5 min: 9 in saline vs 9.5 in PE vs 9 in NE vs 10 in E (overall p=0.016), compared to saline only E was significantly different	Only UV blood was analyzed (UV pH: 7.3 in S vs 7.31 in PE vs 7.34 in NE vs 7.32 in E, overall p=0.016, compared to saline all groups had significantly different UV pH)	NA	UV pCO2 (p=0.151) and UV pO2 (p=0.273) were not significantly different UV base excess: -4.7 mmol L^{-1} in saline group vs -4.3 mmol L^{-1} in PE vs -1.25 mmol in NE vs-3.35 mmol L^{-1} in E (overall p=0.001); all groups were significantly different when compared to saline group	NA
2017 Dong et al.[40]	126 healthy women with singleton undergoing elective CS under CSE anesthesia (PE = 64 vs NE = 62)	Prophylactic bolus of PE 50 µg vs NE 10 µg + rescue boluses PE 50 µg vs NE 10 µg	Apgar score < 8 at 1 min: 0 in PE vs 0 in NE group Apgar score < 8 at 5 min: 0 in PE vs 0 in NE	7.31 in PE vs 7.29 in NE (p=0.49)	0 in PE vs 0 in NE group	UA pO2 (p=0.33), UA pCO2 (p=0.64), UA base excess (p=0.79), UA lactate plasma concentration (p=0.25) UV pH (p=0.21), UV pO2 (p=0.42), UV pCO2 (p=0.69), UV base excess (p=0.28), UV lactate plasma concentration (p=0.09) are all not significantly different between the two groups	NA
2020 Cho et al.[41]	44 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 22 vs NE = 22)	Rescue boluses of 100 µg PE vs 5 µg NE	Apgar score < 7 at 1 min: 9% in PE vs 18 in NE group (p=0.664) Apgar score < 7 at 5 min: 0 in PE vs 0 in NE (p=1.000)	7.32 in PE vs 7.31 in NE (0.383)	NA	UA PCO2 (p=0.212), UA PO2 (p=0.212) and UA base excess (p=0.819) were not significantly different between the two groups	Birth weight: 3.0 kg in PE vs 3.0 kg in NE (P=0.993)
2022 Rai et al.[30]	90 healthy women with singleton pregnancy undergoing elective CSE under spinal anesthesia (PE = 45 vs NE= 45)	Rescue boluses of 100 µg PE or 7.5 µg NE	Apgar score at 1 min: 8 in PE vs 9 in NE (p=0.312) Apgar score at 5 min: 9 in PE vs 9 in NE (p=0.650) Apgar score at 10 min: 9 in PE vs 9 in NE (p=0.161)	7.27 in PE vs 7.30 in NE (p=0.128)	0 in PE vs 0 in NE	UA pO2 (p=0.53), pCO2, HCO3-, base excess UV pH, pO2, pCO2 HCO3-, base excess were all not significantly different between PE and NE	NICU admission 1 in PE vs 1 in NE Neurobehavioral score: comparable at 2-4h (p=0.057), significant higher in NE at time 24h (p=0.007) and 48h (p=0.002) Birth weight 2.7 kg vs 2.7 kg (p=0.803)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2023 Priya et al.[22]	156 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 78 vs NE = 78)	Prophylactic fixed rate infusion of PE 50 µg min^{-1} vs NE 5 µg min^{-1} + rescue boluses if needed (PE 50 µg vs NE 5 µg)	Apgar score > 8 at 1 min: 83.3% in PE vs 84.6% in NE (p>0.05) Apgar score > 8 at 5 min was not significantly different (p=0.16) Apgar score < 6 at 5 min: 0% in PE vs 1.2% in NE group	NA	NA	NA	NA
2019 Puthenveettil et al.[47]	50 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25)	Rescue boluses of PE (50 µg) or NE infusion (4 µg)	Apgar score at 1 min: 7.92 in PE vs 8 in NE (p=0.538) Apgar score at 5 min: 8.88 in PE vs 8.92 in NE (p=0.646)	UV pH 7.318 in PE vs 7.320 in NE (p=0.850) (no UA blood was analyzed in this study)	NA	UV pCO2 (p=0.108); UV pO2 (p=0.264); UV lactate plasma concentration (p=0.538)	NA
2023 Ravichandrane et al.[35]	130 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 65 vs NE = 65)	Prophylactic fixed rate infusion of either PE (25 µg min^{-1} or 5 µg min^{-1}) + rescue boluses of PE 25 µgin both groups	Apgar score at 1 min 8.5 in PE vs 8.7 in NE (p=0.176) Apgar score at 5 min 9.7 in PE vs 9.7 in NE (p=0.608)	7.29 in PE vs 7.30 in NE	NA	Subgroup analysis of UA pH in neonates of mother with bradycardia: 7.26 in PE vs 7.29 in NE (p=0.052) UA pCO2 (p=0.706) was not significantly different between the two groups UA HCO3- (p=0.022) was significantly higher in NE compared to PE group	NA
2021 Ashraf et al.[44]	75 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 25 vs NE = 25 vs E = 25)	Weight adjusted prophylactic infusion of either PE (0.1 µg kg^{-1} min^{-1}), NE (0.05 µg kg^{-1} min^{-1}) or fixed rate ephedrine 1 mg min^{-1} infusion + rescue boluses of either 0.2 µg kg^{-1} PE, 0.1 µg kg^{-1} NE or 5 mg ephedrine.	Apgar score at 1 min: 9 in PE vs 9 in NE vs 8 in ephedrine (p=0.809) Apgar score at 5 min: 9 in PE vs 9 in NE vs 9 in ephedrine (p=0.883)	7.38 in PE vs. 7.37 in NE vs. 7.33 in ephedrine (p=0.001)	Incidence: 0% in PE vs 0% in NE vs 8% in ephedrine (p=0.128)	UA pO2 was significantly different between the groups (27.5 mmHg in PE vs 25.94 in NE vs 25.2 in ephedrine) (p=0.012) UA HCO3- was significantly different between the groups (23.88 PE vs 23.15 in NE vs 22.8 in ephedrine) (p=0.016) No significant difference in UA pCO2 between the groups (p=0.703)	NA

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2022 Tiwari et al.[28]	126 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 63 vs NE = 63)	Rescue boluses of either 50 µg of PE or 4 µg of NE	Apgar score at 1 min: 8.01 in PE vs 7.92 in NE (p=0.26) Apgar score at 5 min: 8.91 in PE vs 8.87 in NE (p=0.39)	Only UV blood was collected UV pH 7.32 in PE vs 7.39 in NE (p=0.07)	NA	UV pO2 (p=0.08), UV pCO2 (p=0.12) and UV lactate plasma concentration (p=0.19) were not significantly different between the two groups	NA
2021 Goel et al.[36]	200 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 100 vs NE = 100)	Variable rate infusion of either PE (100 µg ml^{-1}) or NE (5 µg ml^{-1}) both started at 30 ml h^{-1} + rescue boluses of 100 µg PE or 5 µg NE	Apgar score 1 min and at 5 min were not significantly different between the two groups Apgar score < 8: 0 in PE vs 0 in NE group	NA	NA	NA	NA
2022 Mahzad et al.[37]	45 healthy women with singleton pregnancy undergoing elective CS under spinal anesthesia (PE = 15 vs NE = 15 vs ephedrine = 15)	Prophylactic bolus of either PE (40 µg), NE (5 µg) or ephedrine (5 mg)	NA	7.38 in PE vs 7.38 in NE vs 7.34 in ephedrine group (Overall p=0.009; NE vs ephedrine p=0.033, PE vs ephedrine p=0.013; PE vs NE p=0.929)	Acidosis was significantly higher in ephedrine group in comparison with the other groups (p=0.043)	UA pCO2 was not significantly different (p=0.816) UA HCO3- was significantly different between the groups (p=0.016)	NA
2022 Qian et al.[16]	60 healthy women with singleton pregnancy undergoing elective CS under CSE anesthesia (PE = 30 vs NE = 30)	Prophylactic infusion (Fixed rate) of PE (100 µg ml^{-1}) or NE (8 µg ml^{-1}) + rescue bolus of PE (50 µg) when hypotension occurred	Apgar score at 1 min: 10 in PE vs 10 in NE (0.52) Apgar score at 5 min; 10 in PE vs 10 in NE (p=0.49)	7.31 in PE vs. 7.33 in NE (p=0.13)	NA	NA	Neonatal weight 3394 in PE vs 3377 in NE (p=0.87)
2023 Belin et al.[29]	124 women (healthy or with mild pre-eclampsia) undergoing elective CS under spinal anesthesia (PE = 62 vs NE = 62)	Manually adjusted variable rate infusion of either PE (50 µg ml^{-1}) or NE (5 µg ml^{-1}) starting at 0.5 µg kg^{-1} min^{-1} in PE vs 0.05 µg kg^{-1} min^{-1} in NE + rescue bolus of 5 mg ephedrine in case of persisted hypotension	Apgar score < 7 at 1 min: 4.6% in PE vs 3.2% in NE (p>0.99) Apgar score < 7 at 5 min: 0% in PE vs 1.6% in NE (p=0.49) Apgar score < 7 at 10 min: 0% in PE vs 0% in NE	7.29 in PE vs. 7.30 in NE (p=0.22)	(Here described as UA pH < 7): 0 in PE vs 3.2% in NE (p=0.23)	UA pO2, UA pCO2, UA lactate concentration, UA glycemia, were not significantly different between groups	Glycemia at 1h after birth 48 mg dL^{-1} in PE vs 47 mg dL^{-1} in NE (p=0.86) Severe hypoglycemia at 1h after birth in neonates with mothers with gestational diabetes: 19.6% in PE vs 4.1% in NE (p=0.02)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2019 Wang et al.[23]	166 singleton pregnant women with pre-eclampsia with elective CS under spinal anesthesia (PE = 55 vs NE = 56 vs ephedrine = 55)	Intermittent bolus of NE 4 µg (NE group), bolus of 50 µg PE (PE group) or bolus of 4 mg ephedrine (E group)	Apgar score at 1 min: 9 in PE vs 9 in NE vs 9 in E Apgar score at 5 min: 10 in NE vs 10 in E Incidence of Apgar < 7 at 1 min: 9.1% in PE vs 7.1% in NE vs 9.1% in E (not significantly different) Incidence of Apgar < 9 at 5 min: 0 in all groups	7.32 in PE vs. 7.32 in NE vs. 7.31 in E (PE vs. E $p<0.05$, PE vs. NE $p>0.05$, NE vs. E $p<0.05$)	Incidence of fetal acidosis is 0 in all groups	No significant differences in blood gas values between PE and NE UA pO2 13.5 mmHg in PE vs 14.5 mmHg in NE vs 15.2 mmHg in E (only PE vs E is significantly different) UA pCO2 is not significantly different between the groups (50.8 in PE vs 50.9 in NE vs 50.4 in E) UA glucose concentration is not significantly different between the groups UA lactate is significantly higher in E (1.8 mmol L^{-1}) vs NE (1.2 mmol L^{-1}) and in E (1.8 mmol L^{-1}) vs PE (1.3 mmol L^{-1}) UA HCO3-: 24.1 mEq L^{-1} in E vs 21.8 mEq L^{-1} in NE vs 22.2 mEq L^{-1} in PE ($p<0.05$ in E vs NE and E vs PE) UA base excess 0.2 in PE vs -0.2 in NE vs -1.3 in E (significantly higher in NE vs E and in PE vs E)	Birth weight: 3446 gr in PE vs 3402 gr in NE vs 3492 gr in E (no significant differences)
2022 Guo et al.[24]	138 singleton pregnant women with pre-eclampsia undergoing elective CS under spinal anesthesia (PE 69 vs NE = 69)	Weight adjusted prophylactic infusion of PE (0.625 µg kg^{-1} min^{-1}) or NE (0.05 µg kg^{-1} min^{-1}) + rescue boluses (PE 75 µg or NE 6 µg)	Apgar score at 1 min 8 in PE vs 9 in NE (p=0.532) Apgar score at 5 min 9 in PE vs 9 in NE (p=0.496) Apgar score < 7 at 1 min 1.5% in PE vs 2.9% in NE (p=0.559) Apgar score < 7 at 5 min 0% in PE vs 0% in NE)	7.31 in PE vs 7.31 in NE (p=0.607)	Incidence of fetal acidosis: 5.8% in PE vs 7.3% in NE (p=0.73)	No significant differences between PE and NE group for pCO2, pO2 and base excess	Admission at NICU 55.1% in PE vs 50.7% in NE (p=0.609)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2021 Mohta et al.[25]	86 women with singleton pregnancy and pre-eclampsia (PE = 43 vs NE = 43)	Rescue boluses of PE (50 µg) or NE (4 µg)	Apgar score at 1 min: 9 in PE vs 9 in NE (p=0.77) Apgar score at 5 min: 10 in PE vs 10 in NE (p=1.0)	7.26 in PE vs 7.27 in NE (p=0.903)	Incidence of fetal acidosis: 5 in PE vs 4 in NE (p=0.693)	No significant differences in other blood gas values (UA pO2, pCO2, O2 saturation, HCO3-base excess, UV pH, pCO2, HCO3-, base excess) except for UV pO2 29.5 mmHg in PE vs 39 mmHg in NE (p=0.003) and UV O2 saturation:49.6% in PE vs 64.4% in NE (p=0.001)	Birth weight 2.6 kg in PE vs 2.7 kg in NE (p=0.511)
2022 Du et al.[46]	62 healthy parturients with twin pregnancy undergoing elective CS under spinal anesthesia (PE = 31 vs NE = 31)	Fixed rate infusion at 60 ml h^{-1} of PE (75 µg ml^{-1}) or NE (6 µg ml^{-1}) + rescue boluses of PE (75 µg) or NE (6 µg)	Apgar score at 1 min twin A: 9 in PE vs 9 in NE (p=0.605) Apgar score at 1 min twin B 9 in PE vs 9 in NE (p=0.463) Apgar score at 5 min twin A 10 in PE vs 10 in NE (p=0.119) Apgar score at 5 min twin B 10 in PE vs 10 in NE (p=0.766)	Only UV blood was analyzed because of the technical difficultly of obtaining UA blood in twins (UV pH 7.34 in PE vs 7.34 in NE (p=0.743) for twin A and 7.31 in PE vs 7.30 in NE (p=0.407) for twin B)	NA	UV pO2, UV pCO2 and UV HCO3 were not significantly different between PE and NE group for twin A UV pO2, UV pCO2 and UV HCO3 were not significantly different between PE and NE group for twin B	NA
2022 Chen et al.[20]	100 healthy women with twin pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of PE (40 µg min^{-1}) or NE (3.2 µg min^{-1})	Apgar at 1 min: 10 in PE vs 10 in NE (p=0.764) Apgar at 5 min 10 in PE vs 10 in NE (p=0.562) Apgar at 10 min 10 in PE vs 10 in NE (p=0.156)	7.295 in PE vs 7.292 in NE (p=0.538)	18.8% in PE vs 21.7% in NE (p=0.681)	UA glucose plasma concentration: 2.71 mmol L^{-1} In PE vs 2.92 mmol L^{-1} in NE (p=0.015) and UV glucose plasma concentration: 3.18 mmol L^{-1} in PE vs 3.39 mmol L^{-1} in NE (p=0.02) UA pCO2, UA pO2, UA base excess, UA SO2%, UA lactate plasma concentration, UV pH, UV pCO2, UV pO2, UV base excess, UV SO2%, UV lactate plasma concentration were all not significantly different between PE and NE group	NICU admission 30% in PE vs 27% in NE (p=0.638) Birth weight: 2389 gr in PE vs 2493 gr in NE (p=0.043)

Table IV (Continued). — Safety of norepinephrine during caesarean section in comparison to phenylephrine: neonatal outcome.

Year And Author	Study population	Intervention	Apgar Score	UA pH	Fetal acidosis (= UA/UV pH <7.2)	Other blood gas values	Other measurements
2022 Liu et al.[43]	78 healthy women with singleton pregnancy undergoing CS under CSE anesthesia (PE = 26 vs NE = 26 vs metaraminol = 26)	Weight adjusted infusion of either PE (0.54 µg $kg^{-1}min^{-1}$), NE 0.08 µg $kg^{-1}min^{-1}$) or metaraminol (2 µg $kg^{-1}min^{-1}$)	Apgar score < 7 at 1 min 0% in PE vs 0% in NE vs 0% in M group Apgar score < 7 at 5 min 0% in PE vs 0% in NE vs 0% in M group	7.33 in PE vs. 7.33 in NE vs. 7.33 in M (p=0.99) (PE vs. NE p=0.89, PE vs. M p=0.96, NE vs. M p=0.93)	NA	No significant difference in UA pO2 (p=0.21), pCO2 (p=0.39), base excess (p=0.06), lactate plasma concentration (p=0.26), HCO3- (p=0.18), UV pH (p=0.5), pO2 (p=0.59), pCO2 (p=0.59), base excess (p=0.09), lactate plasma concentration (p=0.39), HCO3- (p=0.23)	NA
2022 Singh et al.[45]	100 healthy women with singleton pregnancy undergoing CS under spinal anesthesia (PE = 50 vs NE = 50)	Fixed rate infusion of either PE (100 µg min^{-1}) or NE (5 µg min^{-1}) + rescue boluses of PE (60 µg) or NE (6 µg)	Apgar score < 8 at 1 min 16% in PE vs 12% in NE group (p=0.86) Apgar score < 8 at 5 min: 14% in PE vs 10% in NE group (p=0.54)	pH 7.3 in PE vs 7.3 in NE group (p=0.1)	Incidence of fetal acidosis 54% in PE vs 36% in NE (p=0.07)	UA Base excess -6.9 mmol L^{-1} in PE vs -5.5 mmol L^{-1} in NE (p=0.014) UA HCO3- 18.9 mEq L^{-1} in PE .vs 20.3 mEq L^{-1} in NE (p=0.03) UA pO2 (p=0.5), UA pCO2 (p=0.3) UA lactate plasma concentration (p=0.8) did not significantly differ	Admission to NICU: 0 in PE vs. 0 in NE Incidence of need of immediate resuscitation: 0 in PE vs 0 in NE
2020 Ngan Kee et al.[38]	664 healthy women undergoing CS (531 elective and 133 non-elective) under spinal or CSE anesthesia (elective: PE = 265 vs NE = 266; non- elective: PE 67 vs NE = 66)	Fixed rate infusion of either PE (100 µg min^{-1}) or NE (6 µg min^{-1}) and/or rescue boluses of PE (100 µg) or NE (6 µg)	Apgar score < 7 at 1 min; 28% in PE vs 27% in NE (p=0.73) Apgar score <7 at 5 min: 0% in PE vs 1% in NE (p=0.12)	7.286 in PE vs 7.289 in NE (p=0.57) (NE not inferior to PE in total group and elective subgroup, but not in non-elective subgroup	NA	No significant differences in other blood gas values (UA pCO2 (p=0.95), UA pO2 (p=0.60), UA base excess (p=0.48), UV pH (p=0.22), UV pCO2 (p=0.72), UV pO2 (p=0.63), UV base excess (p=0.40))	Birth weight 3.02 kg in PE vs 3 kg in NE (p=0.67)
2022 Mohta et al.[19]	100 healthy women with singleton pregnancy undergoing emergency CS under spinal anesthesia (for actual or potential compromised status of fetus) (PE = 50 vs NE = 50)	Rescue boluses of either PE (100 µg) or NE (8 µg)	Apgar score at 1 min: 9 in PE vs 9 in NE (P=0.099) Apgar score at 5 min: 9 in PE vs 10 in NE (p=0.28) Incidence of Apgar score < 7: 2% in PE vs 2% in NE (p>0.99)	7.251 in PE group vs 7.252 in NE group (p=0.953)	Incidence of fetal acidosis 18.8% in PE vs 21.7% in NE group (p=0.681)	No significant difference in other blood gas values (UA pO2 (p=0.825), pCO2 (p=0.215), O2 sat (p=0.624), HCO3- (p=0.453), base excess (p=0.596), UV pH (p=0.827), pCO2 (p=0.194), pO2 (p=0.88), O2 sat (p=0.741), HCO3- (p=0.276), base excess (p=0.729), pCO2 difference (p=0.681))	Neonatal birth weight: 2.349 kg in PE vs 2.421 kg in NE (p=0.526) Incidence of NICU admission: 24% in PE vs 14% in NE (p=0.202) Median duration in NICU: 2 in PE vs 2 in NE (p=0.826)

CS = caesarean section, UV= umbilical vein, UA= umbilical artery, NE = norepinephrine, PE = phenylephrine, M = metaraminol, E = epinephrine; pCO2= partial pressure of CO2, pO2 = partial pressure of O2, O2 sat= O2 saturation, HCO3-= bicarbonate; NA = not available; (PE =n) = number of people in the final analysis of PE group; (NE=n) = number of people in the final analysis of norepinephrine group.

Table V. — Summary of the results of most important blood gas values looked at in all reviewed trials.

Year And Author	Group	Umbilical artery pH	Umbilical artery $HCO3^-$	Umbilical artery base excess	Incidence of fetal acidosis (pH < 7.20)
2015. Ngan Kee et al.[18]	PE group	7.29 [7.28-7.32]	NA	-2.4 [-4.2 to -0.8]	0%
	NE group	7.30 [7.28-7.33]	NA	-2.0 [-3.7 to -1.0]	0%
2019 Mohta et al.[13]	PE group	NA	NA	NA	NA
	NE group	NA	NA	NA	NA
2019 Sharky et al.[31]	PE group	7.25 ± 0.05	25 (2)	-2.8 [-4.0 to -1.7]	NA
	NE group	7.24 ± 0.08	25 (2)	-2.5 [-4.1 to -1.5]	NA
2023 Guo et al.[14]	PE group	7.35 ± 0.03	NA	-2.9 ± 1.5	0%
	NE group	7.36 ± 0.03	NA	-2.7 ± 1.5	0%
2020 Wang et al.[26]	PE group	7.32 [7.25-7.37]	21.2 [19.7 -23.5]	-0.22 [-4.6 to 3.1]	0%
	NE group	7.32 [7.24-7.36]	22.2 [17.4 -26.3]	0.24 [-6 to 3.3]	0%
2022 Zhou et al.[21]	PE group *	7.31 ± 0.03	NA	-1.86 ±1.55	NA
	NE group *	7.31 ± 0.03	NA	-1.92±1.20	NA
2017 Ngan Kee et al.[15]	PE group (6 different dosage groups) *	60 µg: 7.30 ± 0.06 80 µg: 7.31 ± 0.05 100 µg: 7.27 ± 0.05 120 µg: 7.30 ± 0.09 160 µg: 7.29 ± 0.07 200 µg: 7.29 ± 0.03	NA	60 µg: -4.4 ± 3.3 80 µg: - 5.5 ± 4.1 100 µg: -5.3 ± 3.5 120 µg: -3.8 ± 3.2 160 µg: - 5.1 ± 3.7 200 µg: - 4.9 ± 2.5	4.4%
	NE group(6 different dosage groups) *	4 µg: 7.30 ± 0.04 5 µg: 7.28 ±0.03 6 µg: 7.31 ± 0.02 8 µg: 7.28 ± 0.05 10 µg: 7.26 ± 0.06 12 µg: 7.32 ± 0.06	NA	4 µg: -3.6 ± 2.0 5 µg: -4.1 ± 2.6 6 µg: -3.3 ± 2.5 8 µg: -5.6 ± 3.6 10 µg: -5.3 ±2.8 12 µg: -4.1 ± 3.3	5.5%
2019 Hasanin et al.[32]	PE group	7.30 [7.25-7.33]	24 ± 2	NA	NA
	NE group	7.31 [7.27 – 7.34]	23 ± 2	NA	NA
2017 Vallejo et al.[39]	PE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
2017 Ngan Kee et al.[33]	PE group	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome
	NE group	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome	This trial did not look at neonatal outcome
2023 de Queiroz et al.[42]	PE group	7.25 ± 0.08	18.0 [16.7 – 21.3]	- 3.9 ± 3.29	0%
	NE group	7.28 ± 0.07	20.2 [18.3 – 21.3]	- 3.6 ± 2.88	0%
2020 Theodoraki et al.[27]	PE group	NA, only UV blood was	NA, only UV blood was analysed	NA, only UV blood was analysed	0%
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	0%

Table V (Continued). — Summary of the results of most important blood gas values looked at in all reviewed trials.

2019 Mohta et al.[34]	PE group	7.29 ± 0.07 (+)	24.3±3.8 (+)	- 2.8±4.3 (+)	15.6%
	NE group	7.25 ± 0.10	22.5±3.7	- 5.2±5.4	13.3%
2020 Biricik et al.[6]	PE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
2017 Dong et al.[40]	PE group	7.29 [7.28-7.31]	NA	-2.3 [-4.1 to -0.5]	0%
	NE group	7.31 [7.28-7.32]	NA	-1.9 [-3.2 to -0.6]	0%
2020 Cho et al.[41]	PE group	7.32 [7.30-7.33]	NA	-1.73 [-2.31 to -1.15]	NA
	NE group	7.31[7.29-7.31]	NA	-1.83 [-2.53 to -1.13]	NA
2022 Rai et al.[30]	PE group	7.27 ± 0.05	20.52 ± 3.40	-3.14 ± 2.27	0%
	NE group	7.30 ± 0.05	22.7 ± 9.06	- 3.13 ± 2.55	0%
2023 Priya et al.[22]	PE group	NA	NA	NA	NA
	NE group	NA	NA	NA	NA
2019 Puthenveettil et al.[47]	PE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed
2023 Ravichandrane et al.[35]	PE group	7.29 ± 0.06	20.4 ± 2.3	NA	NA
	NE group	7.30 ± 0.05	21.5 ± 2.9 (+)	NA	NA
2021 Ashraf et al.[44]	PE group	7.38 ± 0.03	23.88 ± 1.34	NA	0%
	NE group	7.37 ± 0.03	23.15 ± 0.76	NA	0%
2022 Tiwari et al.[28]	PE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA
2021 Goel et al.[36]	PE group	NA	NA	NA	NA
	NE group	NA	NA	NA	NA
2022 Mahzad et al.[37]	PE group	7.38 ± 0.02	23.4 ± 1.18	NA	NA
	NE group	7.38 ± 0.02	23.73 ± 1.1	NA	NA
2022 Qian et al.[16]	PE group	7.31 ± 0.04	NA	NA	NA
	NE group	7.33 ± 0.05	NA	NA	NA
2023 Belin et al.[29]	PE group	7.29 [7.26-7.31]	NA	-1.5 [-2.7 to -0.5]	0%
	NE group	7.30 [7.25-7.32]	NA	-1.0 [-2.1 to -0.1]	3.2%
2019 Wang et al.[23]	PE group	7.32 ± 0.02	21.8 ± 1.1	-0.2 ± 1.6	0%
	NE group	7.32 ± 0.02	22.2 ± 1.5	0.2 ± 1.9	0%
2022 Guo et al.[24]	PE group	7.31 ± 0.06	NA	- 3.6 ± 1.9	5.8%
	NE group	7.31 ± 0.07	NA	- 3.9 ± 1.9	7.3%
2021 Mohta et al.[19]	PE group	7.251 ± 0.081	21.5 ± 4.3	- 5.5 ± 4.8	9/48 = 18.8%
	NE group	7.252 ± 0.082	22.2 ± 4.4	- 4.9 ± 5.2	10/46 = 21.7%

Table V (Continued). — Summary of the results of most important blood gas values looked at in all reviewed trials.

2022 Du et al.[46]	PE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed
	NE group	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed	NA, only UV blood was analysed
2022 Chen et al.[20]	PE group	7.295 ± 0.035	NA	-2.93 ± 1.91	1.1%
	NE group	7.292 ± 0.036	NA	-3.09 ± 1.99	2.3%
2022 Liu et al.[43]	PE group	7.33 ± 0.03	22.4 ± 1.7	-0.11 ± 2.61	NA
	NE group	7.33 ± 0.04	23 ± 1.4	1.13 ± 1.71	NA
2022 Singh et al.[45]	PE group	7.3 ± 0.05	18.9 ± 3.2	-6.9 ± 3.1	54% (acidosis defined as UA BE > -6 mmol L^{-1})
	NE group	7.3 ± 0.06	20.3 ± 3.1 (+)	-5.5 ± 3.3 (+)	36% (acidosis defined as UA BE > -6 mmol L^{-1})
2020 Ngan Kee et al.[38]	PE group	7.286 ± 0.048	NA	-5.0 ± 2.8	NA
	NE group	7.289 ± 0.049	NA	-4.8 ± 2.7	NA
2022 Mohta et al.[25]	PE group	7.26 ± 0.06	21.0 ± 3.6	4.1 ± 6.0	12.8%
	NE group	7.27 ± 0.06	21.2 ± 3.4	1.8 ± 6.6	10%

UV= umbilical vein, UA= umbilical artery, NE = norepinephrine, PE = phenylephrine, HCO3-= bicarbonate (mmol L-1 or mEq L-1), BE = base excess (mEq L-1 or mmol L-1); NA = not available
Values are median [interquartile range]; mean ±SD
*: no specific comparison between the phenylephrine and norepinephrine was made in this multi-arm trial
(+): result was significantly higher than the other group in this trial.

Belin et al.[29] found a higher incidence of severe hypoglycemia in neonates with mothers with gestational diabetes coming out of the phenylephrine group.

Discussion

Phenylephrine is currently the preferred vasopressor to prevent and manage spinal-induced hypotension during caesarean sections (CS). However, norepinephrine has emerged as a potential alternative. For norepinephrine to be considered a viable substitute, it must demonstrate equivalent or superior efficacy in preventing and managing hypotension and ensuring safety for both mother and neonate.

Understanding and finding the relative potency between norepinephrine and phenylephrine is crucial for an accurate comparison between both vasopressors. Like mentioned in the results only four trials looked into the relative potency of norepinephrine and phenylephrine[13-16]. Three trials evaluated the relative potency of norepinephrine and phenylephrine[13-15] when given as boluses, and only one[16] looked at the relative potency when given as a fixed rate prophylactic infusion. Given this small number of trials more research is needed on the relative potency of phenylephrine and norepinephrine, especially regarding prophylactic infusions, as these are currently considered superior by international consensus[1]. Another drawback of most of the included trials is the fact that only five of the thirty-five included trials mention that they worked with NE concentration as NE tartrate (knowing 1 μg of NE tartrate is equal to 0.5 μg of NE base); all other trials made no mention of the fact that they used norepinephrine base or norepinephrine tartrate. Since some countries use NE tartrate as a standard to express NE concentration while the rest of the world uses NE base as the standard, it is difficult and sometimes confusing to compare the NE concentrations and relative potencies across the different studies[58].

A few trials looked into the optimal dose of phenylephrine and norepinephrine to prevent and treat post-spinal hypotension. Kinsella et al.[1] used the trial by Allen et al.[48] in their international consensus for the ideal dose of a prophylactic phenylephrine infusion. Allen et al.[48] found that the optimal dose for prevention of post-spinal hypotension to be 25-50 μg min-1. A more recent study of Xiao et al.[49] found that the ED50 and ED95 of a prophylactic phenylephrine infusion was 0.31 μg kg-1 min-1 and 0.54 μg kg-1 min-1. For a 70 kg weighing woman this was in range with the study by Allen et al.[48]

Onwochei et al.[50] found the ED90 of norepinephrine bolus to prevent hypotension to be 6 μg. Wei et al.[51] found the optimal infusion for prevention of hypotension to be 0.07 μg kg-1 min-1. Hasanin et al.[52] found the optimal infusion rate of norepinephrine to prevent post-spinal hypotension to be 0.05-0.075 μg kg-1 min-1. Fu et al.[53] found the optimal infusion rate to prevent hypotension in CSE anesthesia to be 0.08 μg kg-1 min-1.

The primary outcome in these thirty-five varied, with seven focusing on neonatal outcome and the rest focusing on maternal outcomes.

In the studies focused on maternal outcome, there was considerable variation regarding which parameter was ideal for assessing maternal hemodynamics. Of the thirty-five trials there were six trials that looked directly at the cardiac output and four of them found a better cardiac output in the norepinephrine group. Two trials found no significant difference in the cardiac output of both groups. One of those two trials was the trial of Vallejo et al[39]. As previously mentioned because of its biased study design no conclusions can be drawn out of those results.

Regarding heart rate no trial reported a significantly lower heart rate or a higher incidence of bradycardia in the norepinephrine group. Out of the trials that looked at the heart rate they either found no significant difference between both vasopressors (in fourteen trials) or found the heart rate or the incidence of bradycardia to be significantly better in the norepinephrine group (in eighteen trials).

If we look at the blood pressure control Ngan Kee et al.[33] found that the blood pressure was better controlled with norepinephrine than with phenylephrine in their closed-looped infusion system. Out of the other thirty-four trials most trials found a comparable blood pressure control in both groups or a better control in the norepinephrine group. Six trials found a higher incidence of hypotension or a lower blood pressure in the norepinephrine group[19-20,42-45]. Out of those six trials four trials had the maternal hemodynamics as a secondary outcome so it cannot be said with certainty that they were sufficiently powered to make a statement about maternal hemodynamics. The two other trials[42,44] used a relative potency of 2:1 and 20:1 which were proven to be incorrect.

Something important to mention is that almost half the included trials used boluses for prevention or treatment of post-spinal hypotension. Just like with phenylephrine some recent studies suggest a prophylactic infusion is superior compared to intermittent boluses. It maintains a better hemodynamics with less hypotensive episodes[59,60].

Hemodynamic results evaluating heart rate, blood pressure and cardiac output therefore seem to suggest norepinephrine might be similar or even superior to phenylephrine to prevent and manage post-spinal hypotension during CS. However, most studies seemed to focus on healthy women undergoing elective CS, highlighting a need for more research on non-elective, non-singleton, and non-healthy pregnancies.

Regarding maternal safety outcomes, no trial found a higher incidence of IONV or reactive hypertension in the norepinephrine group. Also, the incidence of dizziness, shivering, tachycardia and arrhythmias were similar between both groups in most trials, whit a few exceptions mentioned earlier.

Another important safety concern with a lot of anesthesiologists is the fact that norepinephrine can cause necrotic damage during extravasation. Not a single trial reported necrotic tissue damage. Medlej et al.[54] found that there is no higher incidence of ischemic tissue damage that needs a medical intervention when norepinephrine was given in hypotensive patients with a maximum rate of 30 µg min-1 for an average of 32 hours. During caesarean section, the infusion rate of norepinephrine is much lower than 30 µg min-1 and the duration of norepinephrine administration during caesarean section is much shorter. Thus, if you use a large-bore venous access with a low concentration of norepinephrine, like for example 1 mg diluted in a 100 ml NaCl infusion (10 µg ml-1), on a continuesly running crystalloid infusion there is no reason not to give norepinephrine via a peripheral infusion.

To conclude, there is no increased incidence of maternal adverse events in the norepinephrine group in comparison to the phenylephrine group.

In terms of fetal and neonatal safety, Mohta et al.[34] found a significantly lower arterial pH in the norepinephrine group in comparison to the phenylephrine group. Wang et al.[55] tried to give a few possible explanations for these aberrant results. The first was that the relative potency used in this trial was 20:1. Because of this chosen relative potency and the earlier trial of Ngan Kee et al.[17] they expected a higher need of norepinephrine boluses, but the opposite was true with a significant lower need of norepinephrine boluses compared to phenylephrine boluses.

With these two facts combined they suggested that the overall blood pressure in the norepinephrine group was maintained at a lower value but one that was still above the 80% of the baseline value cutoff.

But more importantly to mention is the fact that this lower pH was not accompanied by a higher incidence of fetal acidosis or a significant difference in Apgar score.

A last thing to mention is the fact that these results were not replicated in any of the trials that looked at neonatal outcome as their primary outcome.

Conclusion

In healthy subjects there is increased evidence that norepinephrine is a valuable alternative to phenylephrine to be the first-choice vasopressor for elective caesarean section. Norepinephrine can maintain blood pressure as good as phenylephrine with a higher heart rate and a higher cardiac output than phenylephrine. Maternal side effects are similar between both vasopressors. Further study is required to establish fetal and neonatal safety.

In other circumstances, like emergency section, compromised fetuses, non-healthy parturients, there is still not enough available data to make a definitive conclusion of the advantages of norepinephrine. So, more research under these circumstances is needed because it is in those circumstances that a maintenance of a good uteroplacental flow is of the utmost importance for the already compromised fetuses. And so, it is in these circumstances that there is the biggest possible advantage of norepinephrine with its weak β-adrenergic effect to maintain the cardiac output and in doing so the uteroplacental flow.

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