

Hemodynamic maintenance with norepinephrine in caesarean section under spinal anesthesia and its fetal outcome: a systematic review

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Unstructured abstract

Background: Postspinal hypotension is a frequent maternal complication in caesarean delivery under neuraxial anesthesia. Anesthesiologists have been using different vasopressors to maintain hemodynamics. Recent studies suggested beneficial effects of norepinephrine on maternal blood pressure and cardiac output, but little evidence exist on the neonatal outcome.

Objectives: This systematic review summarises recent evidence on neonatal outcome, such as umbilical arterial pH and base excess, after administration of norepinephrine during caesarean section.

Methods: A literature search on PubMed from 2010 to 2022 was performed and every article was reviewed on neonatal outcome, as primary endpoint and on maternal hemodynamics, as secondary endpoint. A total of 15 randomised controlled trials were included.

Results: Studies using a prophylactic infusion of norepinephrine show normal fetal blood gases. No evidence of fetal stress (pH < 7,20, base excess < -6) was assessed in the studies. Norepinephrine succeed in maintaining maternal hemodynamics. It is responsible for less bradycardia than phenylephrine and less tachycardia than ephedrine.

Conclusion: Our study suggests that norepinephrine, preferably as prophylactic infusion, is a safe vasopressor to prevent postspinal hypotension in caesarean section. No signs of fetal acidosis could be demonstrated in the recent studies.

Keywords: Caesarean section, norepinephrine, neonatal outcome

Abbreviations: BE: base excess, HR: heart rate, CS: caesarean section, NE: norepinephrine, PE: phenylephrine, BP: blood pressure.

Introduction

Postspinal hypotension is a frequent maternal complication in caesarean delivery under neuraxial anesthesia. Hypotension is caused by sympathetic block, vasodilation and reduced peripheral vascular resistance. It is the most frequent complication after spinal anesthesia in caesarean section. If no prophylactic measures are taken, the incidence can be as high as 62,1 – 89,7%¹. Severe or sustained hypotension contributes to maternal side effects such as nausea, vomiting, dizziness and even reduced placental blood flow. Because of discontinuation of fetal monitoring during caesarean section fetal stress is difficult to observe at this point. Therefore, maintaining maternal cardiac output and blood pressure is of primordial importance during spinal anesthesia.

Anesthesiologists have been using different methods for maintaining blood pressure. Nowadays the use of continuous phenylephrine is the golden standard. It can, however, due to its alpha-agonist effect, produce reflex bradycardia and can lower the cardiac output. Therefore, placental blood flow can be reduced with potential negative effects on fetal circulation²⁻⁴.

Previously ephedrine has also been used as a vasopressor to treat and prevent maternal hypotension. It has some favourable effects because of its alpha-and beta-adrenergic effects, but as Ngan Kee mentioned in his studies around this topic, ephedrine easily crosses the placental barrier and can produce fetal acidosis due to stimulation of fetal metabolism^{5,6}. From that time on, phenylephrine was considered the golden standard as vasopressor during caesarean section under spinal anesthesia.

But still, some concern about bradycardia and reduced cardiac output with phenylephrine remained.

In search for the ideal vasopressor, there is an increasing interest in the use of norepinephrine for maintaining the blood pressure during caesarean delivery under spinal anesthesia.

As norepinephrine has alpha and weak beta effects, less bradycardia occurs. In the last couple of years several studies already showed a good hemodynamic profile of norepinephrine, both used as continuous prophylactic infusion and as bolus regimen to treat postspinal hypotension^{3,4,7}.

Still some controversy exists concerning the safety profile of norepinephrine on the fetal outcome and parameters such as base excess, lactate and pH are still subject of further studies.

Methods

In this systematic review, we performed a literature search on Pubmed for articles from 2010 to 2022, given that recent studies have the most relevant and up-to-date information on this subject. Three search terms were inserted: caesarean section, norepinephrine and neonatal outcome. Relevant randomized controlled trials were reviewed before inclusion. Only English written literature is included and a free full text has to be available. Further selection process followed the PRISMA checklist and Cochrane guidelines⁸.

This literature search was performed in January 2023 by one reviewer and produced a list of 22 articles. One was excluded due to non-english language (Chinese) in the full text⁹, another

interesting article had no free full text available¹⁰.

The remaining 20 articles were screened by reading the full text. In three articles only fetal venous blood gases were determined and therefore not accepted for inclusion¹¹⁻¹³. As venous blood gases (blood coming from placenta to fetus) primarily provide information on the function of placenta, choice have been made to only include information of arterial blood samples. Two articles were screened but they did not cover the use of vasopressor during caesarean section as a primary study subject^{14,15}, and were therefore rejected.

As primary endpoints in this systematic review fetal pH and fetal base excess on arterial blood gas were used. Maternal hemodynamics and apgar scores were secondary endpoints. Fetal arterial lactate was not considered as a primary endpoint as only 4 studies documented about fetal lactate values at birth^{5,16-18}. Fetal acidosis is defined by fetal pH lower than 7,20 and/or base excess lower than -6 mmol/L, as normal base excess values for the newborn ranges from -3 to +1¹⁹.

For continuous variables, such as fetal pH and base excess, mean and 95% confidence intervals are described.

Results

A selection process is described in a flow diagram (Figure 1). We included 15 randomised controlled trials. Basic study characteristics are summed in Table I. Each study had its individual differences regarding the use of vasopressor (norepinephrine vs phenylephrine vs ephedrine), its dosage and also in the method of administration. This causes a big

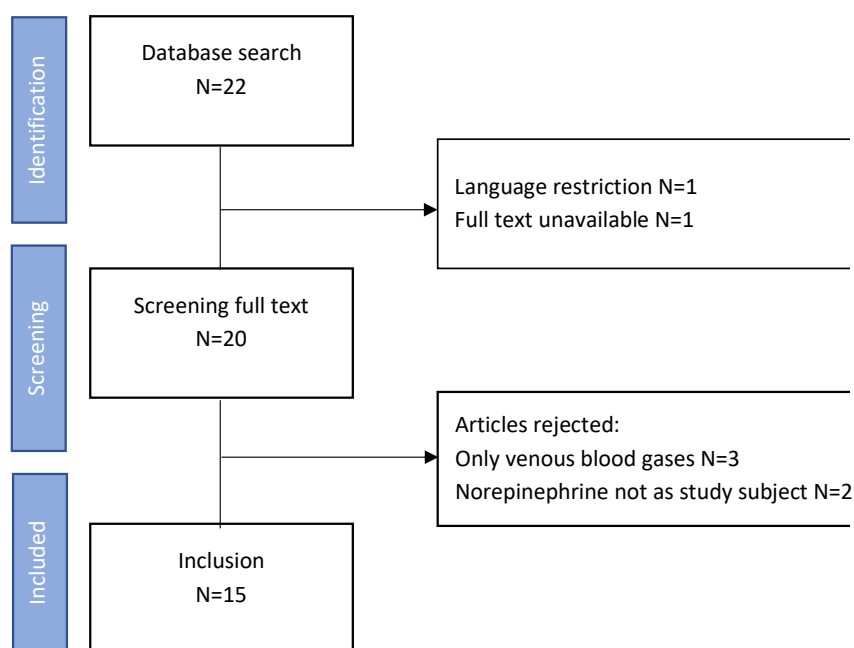


Fig. 1 — Inclusion flowchart.

Table I. — Study descriptives.

Authors, year	Number of subjects	Inclusion criteria	Methods	Outcome measures
Chen, 2020	195 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. placebo	1: Systolic BP 2: fetal art pH, BE
Chen, 2022	100 patients	Elective CS in twin pregnancy	Prophylactic infusion of NE vs. PE	1: maternal hemodynamics 2: neonatal outcome
Hasanin, 2019	123 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. PE	1: hypotension 2: other maternal hemodynamics and neonatal outcome
Hasanin, 2019	284 patients	Non-labour, elective CS	Prophylactic infusion of NE, dose-finding study	1: hypotension 2: other maternal hemodynamics and neonatal outcome
Liu, 2022	78 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. PE vs. metaraminol	1: fetal art pH 2: hemodynamic parameters
Mohta, 2019	90 patients	Non-labour, elective CS	Therapeutic bolus of NE vs. PE	1: maternal bradycardia 2: fetal art pH
Mohta, 2021	86 patients	CS in pre-eclamptic patients	Therapeutic bolus of NE vs. PE	1: fetal art pH 2: maternal hemodynamics
Mohta, 2022	100 patients	Emergency CS with fetal compromise	Therapeutic bolus of PE vs. NE	1: fetal art pH
Ngan Kee, 2015	104 patients	Non-labour, elective CS	Prophylactic, computer-controlled infusion of NE	1: cardiac output 2: blood pressure, neonatal outcome
Ngan Kee, 2020	668 patients	All CS (labour and non-labour, elective and emergent)	NE vs. PE (free choice of bolus, infusion, therapeutic and prophylactic)	1: fetal art pH
Singh, 2022	100 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. PE	1: fetal art BE
Sundararajan, 2020	144 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. leg wrapping vs. placebo	1: hypotension 2: other maternal hemodynamics and neonatal outcome.
Wang, 2020	102 patients	Non-labour, elective CS	Therapeutic bolus of NE vs. PE	1: cardiac output 2: other hemodynamic parameters, neonatal outcome
Xu, 2019	97 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. ephedrine	1: tachycardia 2: other hemodynamic parameters and fetal art pH, BE, lactate
Zhou, 2022	75 patients	Non-labour, elective CS	Prophylactic infusion of NE vs. PE vs. metaraminol	1: fetal art pH

NE: norepinephrine, PE: phenylephrine, CS: caesarean section, BE: base excess, BP: blood pressure.

heterogenicity in results but provides a rather broad overview of the effect on the neonatal outcome.

Neonatal outcome

Fetal acid-base status

Most studies included in this review use a prophylactic infusion of norepinephrine compared to phenylephrine. The first and most known researcher is Ngan Kee et al. In 2015 they published a study where a continuous computer titrated infusion of norepinephrine is used to maintain blood pressure

during elective caesarean section²⁰. In comparison to phenylephrine, they found no significant difference in umbilical arterial pH or base excess.

In the study of Liu¹⁶ a prophylactic administration of norepinephrine was compared to phenylephrine, both in continuous infusion in elective caesarean section. They found no difference in umbilical arterial pH (7.33 +/- 0.04 in the norepinephrine group vs. 7.33 +/- 0.03 in the phenylephrine group). Similar findings were seen in studies of Zhou et al.²¹, Chen et al.¹⁷ and Hasanin et al.²². These trials all compared continuous infusions of norepinephrine

to phenylephrine as prophylaxis for postspinal hypotension in elective caesarean sections.

In the trial of Singh¹⁹ a similar method was used to compare umbilical arterial pH and base excess in elective, non-labour caesarean sections. They used a prophylactic infusion of norepinephrine vs. phenylephrine and found no difference in arterial pH either (7.3 +/- 0.06 in the norepinephrine group vs. 7.3 +/- 0.05 in the phenylephrine group) but median umbilical arterial base excess was significantly higher in the noradrenaline group (-5.5 +/- 3.3 vs. -6.9 +/- 3.1 in the phenylephrine group). The study did not provide a clear interpretation of this finding and it could not be confirmed in other studies.

In contrast to the previous two studies, Ngan Kee et al.²³ included a large group of women (668 subjects) undergoing both elective and emergent caesarean sections and were randomized between phenylephrine and norepinephrine. The anesthesiologist was free to use a continuous infusion or bolus, in prophylactic or in therapeutic setting. This study is a non-inferiority study and umbilical arterial pH was non-inferior in the norepinephrine group (7.289 +/- 0.049 in norepinephrine group vs. 7.286 +/- 0.048 in the phenylephrine group). Base excess in this study did not show a significant difference either (-4.8 +/- 2.7 in the norepinephrine group vs. -5.0 +/- 2.8 in the phenylephrine group).

Some researchers used therapeutic boluses of norepinephrine instead of prophylactic infusions. One of them is Wang et al.¹⁸, they compared equivalent boluses of norepinephrine (8mcg) vs. phenylephrine (100mcg) and found no difference in umbilical arterial pH or in base excess.

To explore the safety profile of norepinephrine even more in depth, Mohta et al.²⁴ examined fetal outcome parameters in emergent caesarean sections because of fetal compromise. They used therapeutic boluses of norepinephrine (8mcg) vs. Phenylephrine (100mcg) to treat post-spinal hypotension in 100 patients. Both umbilical arterial pH (7.252 +/- 0.082 in norepinephrine group vs. 7.251 +/- 0.081 in phenylephrine group) and base excess (-4.9 +/- 5.2 in norepinephrine group vs. -5.5 +/- 4.8 in phenylephrine group) did not show any significant difference in this study.

In another study of Mohta et al.²⁵ therapeutic boluses of norepinephrine and phenylephrine were compared to examine the incidence of maternal bradycardia. This difference was not significant but as secondary endpoint they examined fetal arterial pH and it was significant lower in the norepinephrine group (7.25 +/- 0.10), compared to phenylephrine (7.29 +/- 0.07). Even though lower pH was seen, it never was below 7,20 so no acidosis occurred in this study.

In a last study of Mohta et al.²⁶ with therapeutic boluses of norepinephrine (4mcg) and phenylephrine (50mcg) no difference in fetal arterial pH or base excess was seen in pre-eclamptic patients (7,27 +/- 0,06 in norepinephrine group vs. 7,26 +/- 0,06 in phenylephrine group).

To provide a more complete risk analysis of norepinephrine on neonatal outcome, some researchers compared the use of norepinephrine with placebo (normal saline). Chen et al. 1 found, as a secondary outcome parameter, no evidence for a lower umbilical pH or base excess in norepinephrine (7.36 +/- 0.04 in norepinephrine group vs. 7.37 +/- 0.04 in the saline group). A similar study was performed by Sundararajan et al.²⁷. No difference was found between umbilical pH and base excess in both groups. Sidenote in these studies is that even in the normal saline group a bolus of norepinephrine (6mcg and 7,5mcg) is used to restore normotension when needed.

In this review we included a norepinephrine dose-finding study of Hasanin et al.²⁸. Even in the high dose group (0,075mcg/kg/min), no fetal acidosis could be demonstrated. Umbilical arterial pH was not significant different between the groups.

As already mentioned, ephedrine is known to have the possibility causing fetal acidosis compared to phenylephrine. Xu et al.⁵ made a comparison between ephedrine and norepinephrine and confirmed the previous hypothesis.

Apgar scores

All included studies provide data about Apgar scores as secondary endpoints. Apgar scores are determined at 1 minute and 5 minutes (and some at 10 minutes) after clamping the umbilical cord. Values below 7 at 1 minute and below 9 at 5 minutes are considered as low apgar scores. All of the included trials showed normal mean Apgar scores in all of the study groups.

Maternal hemodynamics

All studies previously mentioned with prophylactic administration of a vasopressor successfully managed to maintain maternal blood pressure.

In the pilot study of Ngan Kee et al.²⁰ they used, as previously mentioned, a computer-controlled infusion of norepinephrine or phenylephrine. Their primary outcome was cardiac output. At 5 minutes after administration of spinal anesthesia a normalization of cardiac output was greater in the norepinephrine group than in phenylephrine group. (median 102,7% vs. 93,8% with p= 0,004). Stroke volume was similar in both groups so they concluded that a slightly higher heart rate with norepinephrine can be beneficial in maintaining

Table II. — Neonatal outcome.

	Umbilical Artery pH			Umbilical Artery Base Excess		
	NE group	Placebo group	P-value	NE group	Placebo group	P-value
Norepinephrine vs placebo						
Chen, 2020	7,36 +/- 0,04	7,37 +/- 0,04	0,685	-2,99 +/- 1,41	-2,81 +/- 1,71	0,394
Sundararajan, 2020	7,37 +/- 0,04	7,36 +/- 0,04	0,667	-3,70 +/- 0,93	-3,51 +/- 0,93	0,191
Norepinephrine vs. Phenylephrine in prophylactic infusion						
	NE group	PE group	P-value	NE group	PE group	P-value
Liu, 2022	7,33 +/- 0,04	7,33 +/- 0,03	0,99	1,13 +/- 1,71	-0,11 +/- 2,61	0,06
Singh, 2022	7,3 +/- 0,06	7,3 +/- 0,05	0,1	-5,5 +/- 3,3	-6,9 +/- 3,1	0,014
Zhou, 2022	7,31 +/- 0,03	7,31 +/- 0,03	0,548	-1,44 +/- 1,65	-1,34 +/- 1,59	0,965
Chen, 2022	7,29 +/- 0,04	7,30 +/- 0,04	0,538	-3,09 +/- 1,99	-2,93 +/- 1,91	0,57
Hasanin, 2019	7,31 +/- 0,03	7,3 +/- 0,04	0,2	Not determined		
Ngan Kee, 2015	7,30 +/- 0,03	7,29 +/- 0,02	0,45	-2,0 +/- 1,35	-2,4 +/- 1,7	0,87
Norepinephrine vs. Phenylephrine in therapeutic bolus						
	NE group	PE group	P-value	NE group	PE group	P-value
Mohta, 2022	7,252 +/- 0,082	7,251 +/- 0,081	0,953	-4,9 +/- 5,2	-5,5 +/- 4,8	0,596
Mohta, 2019	7,25 +/- 0,10	7,29 +/- 0,07	0,03	-5,2 +/- 5,4	-2,8 +/- 4,3	0,02
Mohta, 2021	7,27 +/- 0,06	7,26 +/- 0,06	0,903	1,8 +/- 6,6	4,1 +/- 6,0	0,111
Wang, 2020	7,32 +/- 0,06	7,32 +/- 0,06	0,23	0,24 +/- 4,6	-0,22 +/- 3,7	0,22
Norepinephrine vs. Phenylephrine, free administration						
	NE group	PE group	P-value	NE group	PE group	P-value
Ngan Kee, 2020	7,289 +/- 0,049	7,286 +/- 0,048	0,57	-2,7 +/- 4,8	-5,0 +/- 2,8	0,48
Norepinephrine vs. Ephedrine in prophylactic infusion						
	NE group	Ephedrine group	P-value	NE group	Ephedrine group	P-value
Xu, 2019	7,33 +/- 0,02	7,32 +/- 0,03	0,15	0,36 +/- 1,6	-1,5 +/- 3,0	<0,001
Norepinephrine in dose-finding study						
	0,025 mcg/kg/min	0,050 mcg/kg/min	0,075 mcg/kg/min			
Hasanin, 2019	7,31 +/- 0,04	7,32 +/- 0,04	7,33 +/- 0,03	Not determined		

Mean values +/- standard deviation, NE: norepinephrine, PE: phenylephrine.

normal cardiac output. This study was performed in 2015 and at this stage more evidence was needed to evaluate norepinephrine as safe alternative to phenylephrine.

Afterwards several studies confirmed these findings, so did Hasanin et al.²² and Zhou et al.²¹. Blood pressure could easily be maintained with both infusions but heart rate was overall slightly higher in norepinephrine group due to beta-agonist activity, resulting in higher cardiac output.

In twin gestations maintaining cardiac output is even more of greater importance, because it is featured by a greater increase in cardiac output during pregnancy. Chen et al.¹⁷ compared a continuous infusion of norepinephrine to phenylephrine to examine the possible advantage of norepinephrine in twin gestation. This study failed to show an advantage of norepinephrine over phenylephrine but as the authors stated, the fixed rate of infusion was probably too low to fully prevent postspinal hypotension (3,2 mcg/min). After this trial more dose-finding studies followed²⁸, as the issue of equipotency between norepinephrine and phenylephrine has always been difficult for researchers.

In the study of Mohta et al.²⁵ not infusions but therapeutic boluses of norepinephrine were compared to phenylephrine. In both groups

baseline hemodynamic values were comparable but the incidence of bradycardia in the phenylephrine group was 37,8% vs. 22,2% in the norepinephrine group, which was a significant difference. When compared to ephedrine, norepinephrine results in less tachycardia, as stated in the study of Xu et al.⁵ (4,2 % of women had tachycardia (HR >100 bpm) in the norepinephrine group vs. 30,6% in the ephedrine group). There was no significant difference in episodes of hypotension in both groups.

With growing interest in the use of norepinephrine to maintain hemodynamics, not only healthy subjects were studied. Mohta et al.²⁶ performed a randomized controlled trial in 86 pre-eclamptic patients undergoing caesarean section. Therapeutic boluses of norepinephrine (4mcg) and phenylephrine (50mcg) were compared and these were equally effective in maintaining maternal hemodynamics. Although overall heart rate was lower in the phenylephrine group (p=0,026), but only 1 patient in this group developed bradycardia (HR <50).

Discussion

This study summarises recent evidence on neonatal outcome in caesarean section under spinal

anesthesia. Our goal is to give an overview of the safety profile of norepinephrine in the newborn after caesarean section.

All studies included give a different perspective on the subject because of their different study protocols. But the vast majority of data give the same conclusion, that norepinephrine is indeed a safe alternative to treat and prevent postspinal hypotension. In comparison to phenylephrine, it has an important advantage of reduction of bradycardia because of stimulation of beta-adrenergic vessels^{2,7,19}.

In this study we found no evidence that the use of norepinephrine contributes to fetal acidosis, a concern that was raised when anesthesiologists started using norepinephrine for postspinal hypotension in caesarean sections. This led to more studies about the safety profile of norepinephrine recent years. Only the study of Mohta et al.²⁵ suggested a lower umbilical arterial pH when boluses of norepinephrine were used, although this was only a secondary endpoint in the study and norepinephrine was used as therapeutic bolus in postspinal hypotension. We can therefore imagine that some level of hypotension was present and could possibly be responsible for a lower pH. This is a concern and a limitation of every study that used therapeutic vasopressors.

Most studies used a comparable technique to administer spinal anesthesia in lateral decubitus with hyperbaric bupivacaine 10 to 12mg and used a fluid loading with Ringer's lactate right after injecting the local anesthetic. As previously mentioned, vasopressor administration differed between the studies. Most studies used an infusion of norepinephrine of 4 to 6mcg/min. Therapeutic boluses were used in a dose of 4 to 8mcg norepinephrine. Therefore, limitation of equipotency is a major concern in comparing these studies.

We can conclude that no recent study can give evidence of a higher risk of fetal acidosis when norepinephrine is used during caesarean section under spinal anesthesia. Most important keynote is that postspinal hypotension must be avoided and it seems to be good clinical practice to use a prophylactic infusion of a vasopressor such as norepinephrine.

Still, more evidence is required to replace phenylephrine as golden standard during caesarean sections under spinal anesthesia.

Acknowledgments: There is no conflict of interest in this study.

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doi.org/10.56126/74.2.12