Original Article

ISSN (O): 2456-7388; ISSN (P): 2617-5479

Norepinephrine and Phenylephrine for the Treatment of Hypotension During Spinal Anesthesia for Caesarean Section

Gagan Deep Singh[1], **Atanu Mukherjee**[1], **Deepika Bagga**[2]

[1]Associate Professor, Department of Anesthesia, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, India, [2]Final year MD Student, Department of Anesthesia, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, India.

Abstract

Background: To compare norepinephrine and phenylephrine for the treatment of hypotension during spinal anesthesia for caesarean section. **Subjects and Methods:** 104 American Society of Anesthesiologists I or II, primiparity, singleton, term pregnancy, elective caesarean section scheduled for spinal anesthesia were divided into two groups viz. Group P (phenylephrine) and group N (Norepinephrine). Following parameters such as systolic BP (SBP), Systolic blood pressure; HR: Heart rate; incidence of requirement for extra bolus, time to first extra bolus, and frequency of extra bolus, incidence of bradycardia was recorded. **Results:** The incidence of nausea, vomiting and dizziness was higher in group N as compared to group M. A significant difference was observed in two groups ($P< 0.05$). Time to first extra bolus was 5.2 minutes in group N and 5.7 minutes in group M, frequency of extra bolus was seen 1 in each group and incidence of bradycardia was seen among 2 in group N and 8 in group M. A non- significant difference was observed ($P> 0.05$). **Conclusion:** A greater SBP and a lower incidence of bradycardia with norepinephrine compared to phenylephrine for the management of maternal hypotension during elective cesarean section with spinal anesthesia.

Keywords: Cardiac output, cesarean section, Systolic blood pressure, Stroke volume

Corresponding Author: Gagan Deep Singh, Associate Professor, Department of Anesthesia, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, India.
E-mail: gagandeepsingh974@gmail.com

Received: 08 April 2021 **Revised: 03 June 2021** **Accepted: 12 June 2021** **Published: 25 June 2021**

Introduction

Maternal hypotension is a common complication during cesarean section with spinal anesthesia, which can possibly result from a synergy of reduced venous return, reduced cardiac output (CO), or decreased peripheral vascular resistance.[1] It usually leads to adverse maternal outcomes such as nausea, vomiting, and dizziness.[2] Besides, compromised placental perfusion raises the concerns of fetal acidosis, hypoxia, and even postnatal neurological injury. Thus, effective prevention or treatment of maternal hypotension is of great clinical significance.[3,4]

Phenylephrine is commonly used to maintain blood pressure during spinal anesthesia for cesarean delivery.[5] However, because phenylephrine is a potent α-adrenergic receptor agonist without β-adrenergic receptor activity at usual clinical doses, its use is often associated with a dose-related reflexive slowing of maternal heart rate (HR) and a corresponding decrease in cardiac output (CO).[6,7] Although the clinical significance of these decreases in HR and CO in healthy patients with unstressed fetuses is unknown, concern has been expressed that there may be potential for harm in the presence of a compromised fetus.[8] Norepinephrine has pharmacologic properties that suggest it may be a useful alternative to phenylephrine. Norepinephrine is a potent α-adrenergic receptor agonist, but unlike phenylephrine, it is also a relatively weak agonist at β-adrenergic receptors.[9] Unlike phenylephrine, norepinephrine has weak b receptor agonistic properties, other than a-receptor agonism property.[10] Our previous work systematically discussed its feasibility as a substitution of phenylephrine based on available limited clinical trials and suggested it is a promising alternative for phenylephrine in obstetric anesthesia.[11] Besides, use of intermittent intravenous norepinephrine bolus seems feasible to prevent spinal induced hypotension in obstetric patients without presence of obvious side effects.[12] Considering this, the present study was initiated with the aim to compare norepinephrine and phenylephrine for the treatment of hypotension during spinal anesthesia for caesarean section.

Subjects and Methods

This study involves 104 American Society of Anesthesiologists I or II, primiparity, singleton, term pregnancy, elective caesarean section scheduled for spinal anesthesia. Exclusion criteria was <18 years, PIH, patients taking anti- depressants and those unwilling to participate. The study duration was 6 months.

Following random allocation, patients were divided into two groups viz. Group P (phenylephrine) and group N (Norepinephrine). Group P received 100 μg of phenylephrine and group N received 8 μg of Norepinephrine. Following parameters such as systolic BP (SBP), Systolic blood pressure; HR: Heart rate; incidence of requirement for extra bolus, time to first extra bolus, and frequency of extra bolus, incidence of bradycardia, bradycardia comorbid with hypotension, and hypertension were recorded. Maternal side effects and neonatal outcomes were collected too. Statistical analysis was done by SPSS software. The variables were compared between the groups by Student's paired t-test.

Results

Table 1: Parturient characteristics

Parameters	Group N	Group M	P value
Age (Years)	32.5	31.1	>0.05
Height (cm)	165.2	166.5	>0.05
Weight (Kg)	72.1	72.3	>0.05
Gestational age (day)	280.5	278.4	>0.05
Estimated blood loss (mL)	485.2	480.4	>0.05

Mean age of patients in group N was 32.5 years and in group M was 31.1 years, height was 165.2 cm and in group M was 166.5 cm, weight was 72.1 kg in group N and 72.3 Kg in group M, gestational age was 280.5 days in group N and 278.4 days in group M and estimated blood loss was 485.2 ml in group N and 480.4 ml in group M. A non- significant difference was observed (P> 0.05) [Table 1].

Baseline SBP was 118.6 mm Hg in group N and 116.5 mm Hg in group M, baseline HR was 85.2 beats/min in group N and 85.0 beats/min in group M. Incidence of need for extra bolus was seen in 35 in group N and 32 in group M. Time to first extra bolus was 5.2 minutes in group N and 5.7 minutes in group M, frequency of extra bolus was seen 1 in each group and incidence of bradycardia was seen among 2 in group N and 8 in group M. A non- significant difference was observed (P> 0.05) [Table 2].

Table 2: Maternal hemodynamics

Items	Group N	Group M	P value
Baseline SBP (mm Hg)	118.6	116.5	>0.05
Baseline HR (beats/min)	85.2	85.0	>0.05
Incidence of need for extra bolus	35.1	32.2	>0.05
Time to first extra bolus (min)	5.2	5.7	>0.05
Frequency of extra bolus	1	1	>0.05
Incidence of bradycardia	2	8	>0.05

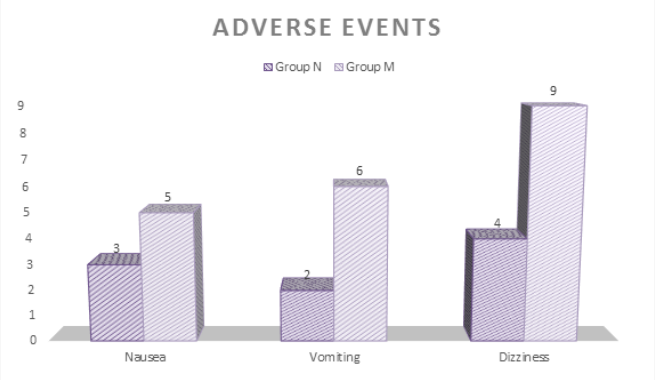

Figure 1: Adverse events

The incidence of nausea, vomiting and dizziness was higher in group N as compared to group M. A significant difference was observed in two groups (P< 0.05) [Figure 1].

Discussion

We compared compare norepinephrine and phenylephrine for the treatment of hypotension during spinal anesthesia for caesarean section. We observed that mean age of patients in group N was 32.5 years and in group M was 31.1 years, height was 165.2 cm and in group M was 166.5 cm, weight was 72.1 kg in group N and 72.3 Kg in group M, gestational age was 280.5 days in group N and 278.4 days in group M and estimated blood loss was 485.2 ml in group N and 480.4 ml in group M. The typical hemodynamic response to spinal anesthesia in parturients is a decrease in SBP with a compensatory increase in HR and CO; thus, immediate treatment with an α-adrenergic agonist is appropriate and recommended.[13] Phenylephrine has become

the agent most commonly recommended although alternatives such as metaraminol are also effective.[14,15] A limitation of the use of pure α-adrenergic drugs such as phenylephrine is that they have a dose-related tendency to decrease HR and CO, which can occur even without marked increases in blood pressure above baseline. Concern has been expressed that this decrease in CO may adversely affect uteroplacental perfusion. For that, a drug such as norepinephrine may potentially be advantageous. Norepinephrine has both direct positive chronotropic and reflexive negative chronotropic actions with the overall effect on HR considered to be approximately neutral.[16]

A study by Ngan et al,[17] 104 healthy patients having cesarean delivery under spinal anesthesia were randomized to have systolic blood pressure maintained with a computer-controlled infusion of norepinephrine 5 μg/ml or phenylephrine 100 μg/ml. Normalized cardiac output 5min after induction was greater in the norepinephrine group versus the phenylephrine group 94.3 to 116.7% versus 93.8%. From induction until uterine incision, for norepinephrine versus phenylephrine, systolic blood pressure were similar, heart rate were greater, and the incidence of bradycardia was smaller. Neonatal outcome was similar between groups. It was pointed that when given by computer-controlled infusion during spinal anesthesia for cesarean delivery, norepinephrine was effective for maintaining blood pressure and was associated with greater heart rate compared with phenylephrine.

It was obtained that Baseline SBP was 118.6 mm Hg in group N and 116.5 mm Hg in group M, baseline HR was 85.2 beats/min in group N and 85.0 beats/min in group M. Wang et al,[18] included 102 women allocated to receive prophylactic 8 mg norepinephrine (group N; n = 52) or 100 mg phenylephrine (group P; n = 50) immediately post-spinal anesthesia, followed by an extra bolus of the same dosage until delivery whenever maternal systolic blood pressure became lower than 80% of the baseline. Furthermore, the incidence of bradycardia was lower in group N than in group P (2% vs. 14%, P = 0.023), along with an overall higher standardized heart rate (78.8 $\pm$ 11.6 vs. 75.0 $\pm$ 7.3 beats/min, P = 0.049). Other hemodynamics, as well as maternal side effects and neonatal outcomes, were similar in two groups (P > 0.05).

Incidence of need for extra bolus was seen in 35 in group N and 32 in group M. Time to first extra bolus was 5.2 minutes in group N and 5.7 minutes in group M, frequency of extra bolus was seen 1 in each group and incidence of bradycardia was seen among 2 in group N and 8 in group M. Xu et al,[19] in their study Three RCTs in 4 reports published between 2015 and 2018 were finally identified with a total of 294 parturients. They found there was no difference in effectiveness between norepinephrine and phenylephrine for the treatment of maternal hypotension and there was no difference in the occurrence of hypertension. Of note, compared to the phenylephrine group, parturients in the norepinephrine group were less likely to experience bradycardia and IONV. Further, we did not observe a difference between the two vasopressors in the incidence of neonatal Apgar scores < 7 at 1 and 5 minutes or in umbilical vein (UV) blood gas. However, evidence is insufficient to draw conclusions regarding the better BP control precision with the use of norepinephrine.

Conclusion

Study results shows a greater SBP and a lower incidence of bradycardia with norepinephrine compared to phenylephrine for the management of maternal hypotension during elective cesarean section with spinal anesthesia.

References

1. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev. 2006;(4):2251. Available from: https://doi.org/10.1002/14651858.cd002251.pub2.
2. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, et al. Hemodynamic Effects of Ephedrine, Phenylephrine, and the Coadministration of Phenylephrine with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery. Anesthesiology. 2009;111(4):753–765. Available from: https://dx.doi.org/10.1097/aln.0b013e3181b437e0.
3. Langesaeter E, Rosseland LA, Stubhaug A. Continuous Invasive Blood Pressure and Cardiac Output Monitoring During Cesarean Delivery: A Randomized, Double-Blind Comparison of Low-dose versus High-Dose Spinal Anesthesia With Intravenous Phenylephrine or Placebo Infusion. Obstetric Anesthesia Digest. 2009;29(2):94–95. Available from: https://dx.doi.org/10.1097/01.aoa.0000350635.88043.d2.
4. Allen TK, George RB, White WD, Muir HA, Habib AS. A Double-Blind, Placebo-Controlled Trial of Four Fixed Rate Infusion Regimens of Phenylephrine for Hemodynamic Support During Spinal Anesthesia for Cesarean Delivery. Anesth Analg. 2010;111(5):1221–1229. Available from: https://dx.doi.org/10.1213/ane.0b013e3181e1db21.
5. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The Dose-Dependent Effects of Phenylephrine for Elective Cesarean Delivery Under Spinal Anesthesia. Anesth Analg. 2010;111(5):1230–1237. Available from: https://dx.doi.org/10.1213/ane.0b013e3181f2eae1.
6. Heesen M, Klöhr S, Rossaint R, Straube S. Prophylactic phenylephrine for caesarean section under spinal anaesthesia: systematic review and meta-analysis. Anaesthesia. 2014;69(2):143–165. Available from: https://dx.doi.org/10.1111/anae.12445.
7. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia.

2018;73(1):71–92. Available from: https://dx.doi.org/10.1111/anae.14080.
8. Allen TK, Muir HA, George RB, Habib AS. A survey of the management of spinal-induced hypotension for scheduled cesarean delivery. Int J Obstet Anesth. 2009;18(4):356–361. Available from: https://dx.doi.org/10.1016/j.ijoa.2009.03.014.
9. Onwochei DN, Kee WDN, Fung L, Downey K, Ye XY, Carvalho JCA. Norepinephrine Intermittent Intravenous Boluses to Prevent Hypotension During Spinal Anesthesia for Cesarean Delivery: A Sequential Allocation Dose-Finding Study. Anesth Analg. 2017;125(1):212–218. Available from: https://dx.doi.org/10.1213/ane.0000000000001846.
10. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990;300(6719):230–235. Available from: https://dx.doi.org/10.1136/bmj.300.6719.230.
11. Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and Maternal Effects of Phenylephrine and Ephedrine during Spinal Anesthesia for Cesarean Delivery. Anesthesiology. 2002;97(6):1582–1590. Available from: https://dx.doi.org/10.1097/00000542-200212000-00034.
12. Poterman M, Vos JJ, Vereecke HEM, Struys MMRF, Vanoverschelde H, Scheeren TWL, et al. Differential effects of phenylephrine and norepinephrine on peripheral tissue oxygenation during general anaesthesia. Eur J Anaesthesiol. 2015;32(8):571–580. Available from: https://dx.doi.org/10.1097/eja.0000000000000247.
13. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*. Crit Care Med. 2012;40(12):3146–3153. Available from: https://dx.doi.org/10.1097/ccm.0b013e318260c6c3.
14. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*. Crit Care Med. 2011;39(4):689–694. Available from: https://dx.doi.org/10.1097/ccm.0b013e318206d2a3.
15. Macarthur A, Riley ET. Obstetric Anesthesia Controversies: Vasopressor Choice for Postspinal Hypotension During Cesarean Delivery. Int Anesthesiol Clin. 2007;45(1):115–132. Available from: https://dx.doi.org/10.1097/aia.0b013e31802b8d53.
16. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*. Crit Care Med. 2011;39(4):689–694. Available from: https://dx.doi.org/10.1097/ccm.0b013e318206d2a3.
17. Kee WDN, Lee SWY, Ng FF, Tan PE, Khaw KS. Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery. Anesthesiology. 2015;122(4):736–745. Available from: https://dx.doi.org/10.1097/aln.0000000000000601.
18. Wang X, Mao M, Zhang SS, Wang ZH, Xu SQ, Shen XF. Bolus norepinephrine and phenylephrine for maternal hypotension during elective cesarean section with spinal anesthesia: a randomized, double-blinded study. Chin Med J (Engl). 2020;133(5):509–516. Available from: https://dx.doi.org/10.1097/CM9.0000000000000621.
19. Xu S, Shen X, Liu S, Yang J, Wang X. Efficacy and safety of norepinephrine versus phenylephrine for the management of maternal hypotension during cesarean delivery with spinal anesthesia: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(5):14331. Available from: https://doi.org/10.1097/md.0000000000014331.

How to cite this article: Singh GD, Mukherjee A, Bagga D. Norepinephrine and Phenylephrine for the Treatment of Hypotension During Spinal Anesthesia for Caesarean Section. Acad. Anesthesiol. Int. 2021;6(1):148-151.

DOI: dx.doi.org/10.21276/aan.2021.6.1.26

Source of Support: Nil, **Conflict of Interest:** None declared.