ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Comparison of norepinephrine and phenylephrine boluses during spinal anesthesia for cesarean delivery

Chandraleela Sundararajan[1], Chinthavali Sujatha[2], Arthi Asokan[3]

[1,2]Assistant Professor, [3]Associate Professor, Department of Anaesthesiology, Sri Venkateswaraa Medical College Hospital and Research Centre, Ariyur, Puducherry, India

Submission: 04-08-2022 Revision: 22-08-2022 Publication: 01-10-2022

ABSTRACT

Background: Cesarean sections are frequently carried out under spinal anesthesia (SA) to reduce the risk of neonatal drug transfer and airway difficulties associated with general anesthesia. Maternal hypotension is a typical consequence following SA, despite sufficient fluid loading. **Aims and Objectives:** The aim of this study was to evaluate the efficacy of norepinephrine and phenylephrine in treating spinal hypotension caused by cesarean delivery. **Materials and Methods:** This hospital-based interventional study was carried out at Sri Venkateswaraa Medical College Hospital and Research Centre, Ariyur, Puducherry from February 2020 to March 2022. Eighty patients were included in our trial and were split equally into two groups at random following approval by an ethical committee and written informed consent. Age, weight, height, and American Society of Anesthesiologists physical state of the patients was equivalent across the two groups. **Results:** In our study, mean age found in N group (25.96 ± 2.046) and P group (24.84 ± 1.748) which were insignificant. Vasopressor bolus dose needed for the treatment of hypotension was considerably less in Group N patients (1.71 ± 0.77 vs. 2.43 ± 1.01, P = 0.024). Group P had a higher incidence of bradycardia, although the difference was statistically insignificant (four patients vs. eight patients P = 0.242). The fetal parameters such as birth weight, umbilical PH, PCO, PO_2, and Apgar 1 and 5 min were comparable across the two groups, and no statistically significant differences were found.**Conclusion:** Intermittent norepinephrine boluses are a successful treatment for spinal hypotension during cesarean delivery. We found no evidence that norepinephrine had a detrimental effect on the newborn outcome as compared to phenylephrine, when used to maintain blood pressure during spinal and combined spinal-epidural anesthesia for cesarean birth.

Key words: Cesarean section; Spinal anesthesia; Phenylephrine; Norepinephrine; Hypotension

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v13i10.47232

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Nowadays, spinal anesthesia (SA) is frequently used during cesarean sections to reduce the danger of infant drug transfer during general anesthesia and to reduce the risk of respiratory problems.[1] Maternal hypotension is a typical consequence following SA, despite sufficient fluid loading. Hypotension can cause fetal hypoxia and acidosis, as well as nausea, vomiting, and dizziness in the mother. It can also reduce uterine blood flow. To prevent these harmful consequences on the mother and the newborn, hypotension must be treated quickly with intravenous (IV) fluids or a vasopressor.[2] Since it results in less fetal acidity than ephedrine, phenylephrine is recommended as the first-line medication to treat hypotension after cesarean delivery.[3] However, this medication's disadvantage is the decrease in heart rate (HR) and cardiac output, which could have a negative impact on both the mother and the fetus' outcomes. Norepinephrine is a strong vasopressor with adrenergic characteristics. Spinal-induced hypotension during cesarean delivery is currently being treated with norepinephrine infusion instead of phenylephrine.[4,5] Given that it has a smaller impact on HR

Address for Correspondence:
Dr. Chinthavali Sujatha, Assistant Professor, Department of Anaesthesiology, Sri Venkateswaraa Medical College Hospital and Research Centre, Ariyur - 605 107, Puducherry, India. **Mobile:** +91-8939012490. **E-mail:** sujathachinthavali@gmail.com

and cardiac output than phenylephrine, it might be more favourable.[6] It is found that 100 μg of phenylephrine is equivalent to 8 μg of norepinephrine.[7]

Norepinephrine has recently been studied as a vasopressor for maintaining arterial blood pressure during SA for cesarean delivery. Norepinephrine is a potent agonist of the alpha-adrenergic receptor and has comparable vasoconstrictor activity as phenylephrine. Contrary to phenylephrine, norepinephrine also has a small amount of beta-adrenergic receptor agonist activity, which prevents the baroreflexive reductions in HR and cardiac output that typically occur during unopposed stimulation of vascular alpha-adrenergic receptors. Consequently, when compared to phenylephrine, the use of norepinephrine may lead to higher maternal hemodynamic stability. Norepinephrine has also been recommended as the best vasopressor to be utilized during obstetric SA.[6,8] However, it is critical to rule out negative effects on neonatal outcome before norepinephrine may be totally approved for widespread clinical use. Umbilical arterial pH measurement is frequently employed as an objective indicator of the latter.[9]

Aims and objectives

The aim of this study was to evaluate the efficacy of norepinephrine and phenylephrine in treating spinal hypotension caused by cesarean delivery.

MATERIALS AND METHODS

This hospital-based interventional study was carried out at Sri Venkateswaraa Medical College Hospital and Research Centre, Ariyur, Puducherry from February 2020 to March 2022. All the selected patients were explained in detail about the purpose, procedure of the study, and possible side effects of the drugs being used as well as the procedure of SA. Following approval by the ethics committee, they were shown the letter of information on the study and written informed consent for the study and SA was taken in the local vernacular language.

Inclusion criteria

The study included individuals who were American Society of Anesthesiologists (ASA) physical Class I or II posted for an elective cesarean delivery under SA.

Exclusion criteria

Gestational age <36 weeks, multiple pregnancies, severe pregnancy-induced hypertension, eclampsia, epilepsy, diabetes mellitus, cardiac diseases, patient refusing for SA, and SA contraindications were not included in the investigation.

A multiparameters monitor (having electrocardiogram, SpO_2, and noninvasive BP) was attached to the patient and baseline parameters such as HR, mean arterial pressure (MAP), and systolic and diastolic blood pressure (SBP and DBP) were obtained.

Drugs were loaded by an anesthetist stationed in the recovery area. In a 10 mL coded syringe, norepinephrine and phenylephrine were diluted and loaded to give 4 mg/mL of norepinephrine (Adrenor, Samarth Life Sciences Pvt. Ltd, Mumbai, India) and 10 mg/mL of phenylephrine (Frenin, Samarth Life Sciences Pvt. Ltd., Mumbai, India).

All the participants were assigned a serial number 1−80 and divided into Group N or P as per the randomization protocol. The serial number of the participant with the group written against the number was placed in an opaque envelope which was opened, and the drug was prepared accordingly by a third-party anesthesiologist. In all patients, 18G IV access was secured, monitors were attached, intrathecal injection of injection bupivacaine (heavy) 2−2.4 mL was given in the sitting position after which immediately supine-left lateral 15° tilt position was given along with co-loading of ringers lactate at the rate of 10 mL/kg body weight. Patients were given an IV infusion of the study drug at 60 mL/h immediately after SA. The level to be achieved of SA was T4.

The baseline values of HR, MAP, SBP, and DBP were recorded. The same parameters were monitored at zero (at the time of giving SA), 2, 4, 6, 8, 10, 15, 20, 30, 45, and 60 min after SA. Hypotension (SBP <20% of baseline value) was intervened by an incremental dose of 1 mL bolus of the study drug. HR <60 beats/min was treated by IV glycopyrrolate 0.2 mg. immediately, after the delivery of the baby, the infusion dose was tapered gradually from 60 mL/h to 40 mL/h. The drug was immediately discontinued in the cases, where arrhythmia occurred. The drug was tapered before the delivery of the baby when there was an increase in SBP >20% of baseline by decreasing the rate of infusion from 60 mL/h to 40 mL/h in both groups. Unaware of the vasopressor use, a pediatrician recorded the patient's Apgar scores at 1 and 5 min. Blood gas analysis was performed on an umbilical vein sample taken at the time of delivery. PCO_2, bicarbonate, pH, and base excess were all examined. pH 7 was used to characterize fetal acidosis. Both the length of time between the uterine incision and the baby's delivery as well as the overall length of the surgery were recorded. There were also instances of nausea, vomiting, or dizziness brought on by maternal hypotension.

Statistical analysis

Forty patients in each group was determined to be the minimum sample size based on the mean and standard

deviation (1.80±0.48 vs. 2.4±0.43) with a 95% confidence and 80% power. In SPSS 22.0, the entire statistical analysis was completed (SPSS Inc., Chicago, USA). Results are shown as mean standard deviation for all continuous variables and frequency for categorical variables. The Pearson's Chi-square test with continuity correction was used to ascertain the relationship between two category variables. Using an independent sample t-test, the mean of continuous parameters for the two groups was compared. The average Apgar score within the groups was compared using a paired sample t-test at 1 and 5 min. Statistical significance was assigned to a difference with $P<0.05$.

RESULTS

In our study, mean age of N group (25.96±2.046) and P group (24.84±1.748) were not found to be significant. Other parameters such as height, weight, and gestation period (weeks) were also found to be insignificant. At 5 min, all patients had sufficient spinal block height above T5, and all groups had similar levels of dermatomal height. In addition, the length of the surgeries varied little between the groups (Table 1).

Patients in Group N required significantly fewer vasopressor boluses to treat hypotension (1.71 ± 0.77 vs. 2.43 ± 1.01, P=0.024). Although Group P had a higher incidence of bradycardia (four patients vs. eight patients, P=0.242), the difference was statistically insignificant. Both groups experienced similar levels of maternal problems, such as nausea/vomiting (four vs. five) and shivering (five vs. three) (Table 2).

Table 1: Characteristics of subjects

Demographic data	Group N (n=40)	Group P (n=40)	P value
Age (years)	25.96±2.046	24.84±1.748	0.129
Weight (kg)	65.92±9.387	63.88±8.62	0.7571
Height (cm)	155.84±6.479	156.00±5.51	0.295
Gestation (weeks)	38.1±1.24	38.3±1.12	0.0671
ASA1 (healthy), n (%)	17 (63)	14 (61)	
ASA2 (mild systemic disease), n (%)	10 (37)	9 (39)	0.573
Dermatomal block, n (%)			
T3	2 (5)	4 (10)	0.4721
T4	28 (70)	27 (67.5)	
T5	10 (25)	9 (22.5)	
Surgical time (min)			
Induction to delivery	9.76±2.82	10.74±2.33	0.231
Skin incision to delivery	5.34±1.70	5.44±1.51	0.208
Uterine incision to delivery	2.12±0.16	1.92±1.04	0.1958
Duration of surgery	67.60±9.43	70.12±8.56	0.716

ASA: American Society of Anesthesiologists

No statistical difference was seen in the fetal measures such as birth weight, umbilical PH, PCO, PO_2, and Apgar 1 and 5 min between the two groups (Table 3).

DISCUSSION

To address spinally induced hypotension during cesarean birth, our study examined the results of intermittent bolus dosages of phenylephrine and norepinephrine. The study's findings demonstrated that spinal hypotension can be effectively treated with intermittent IV norepinephrine boluses without having a negative impact on neonatal or maternal outcomes. When compared to phenylephrine, less number of norepinephrine boluses were required to keep the blood pressure stable.

Eighty patients from our study were divided into two equal groups by random selection. The patient demographics for the two groups were comparable in terms of age, height, weight, and ASA physical status.

Both the total amount of IV fluids transfused and intraoperative blood loss were comparable among the groups. In neither of the groups there were any instances of tachycardia.

Norepinephrine and phenylephrine have been compared in various other studies for BP maintenance during SA for cesarean delivery.[10-15]

It was observed that norepinephrine is 11 times more powerful than phenylephrine in a study by Mohta et al.,[11]

Table 2: Incidence of maternal hemodynamic abnormalities

Parameters	Group N (n=40)	Group P (n=40)	P value
Number of vasopressor boluses	1.71±0.77	2.43±1.01	0.0241
Hypotension	9	7	0.001*
Bradycardia	4	8	0.242
Hypertension	7	11	0.074
Nausea/vomiting	4	4	0.695
Shivering	5	3	0.174

*Significant P<0.05

Table 3: Fetal parameters

Fetal Parameters	Group N (n=40)	Group P (n=40)	P value
Birth weight (kg)	2.98±0.42	3.02±0.47	0.579
Umbilical pH	6.32±0.038	6.51±0.476	0.643
PCO	44.54±4.864	45.70±1.172	0.182
PO2	27.14±7.21	25.22±4.79	0.214
Lactates	1.42±0.43	2.18±1.44	0.128
Apgar (1 min)	7.6±0.041	7.92±0.640	0.381
Apgar (5 min)	8.22±0.277	8.54±0.332	0.462

and 100 µg of phenylephrine was about equivalent to 9 µg of norepinephrine.

When Sharkey et al.,[8] compared bolus dosages of norepinephrine 6 µg with phenylephrine 100 µg, they found that norepinephrine provided better hemodynamic control during cesarean birth due to less fluctuations in HR. When compared to phenylephrine and ephedrine, norepinephrine intermittent bolus dosage was demonstrated to be a potent treatment for spinal hypotension.[16,17] Norepinephrine and phenylephrine both had comparable efficacy in treating maternal hypotension, according to a review and meta-analysis by Xu et al.[18]

Norepinephrine infusions of 5 µg/mL were employed by Ngan Kee et al.,[6] and they discovered that they were effective at maintaining blood pressure without having a negative impact on neonatal outcomes. Norepinephrine prophylactic infusions were, additionally, employed to maintain maternal blood pressure without causing any negative newborn effects.[19]

CONCLUSION

Intermittent norepinephrine boluses are a successful treatment for spinal hypotension during cesarean delivery. We found no evidence that norepinephrine had a detrimental effect on the newborn outcome as compared to phenylephrine, when used to maintain blood pressure during spinal and combined spinal-epidural anesthesia for cesarean birth. Our findings add to the mounting body of proof that norepinephrine is a suitable agent for use in obstetric anesthesia.

ACKNOWLEDGMENT

We would like to acknowledge all the individuals who have extended their help and assistance throughout all aspects of our study.

REFERENCES

1. Kulkarni KR, Naik AG and Deshpande SG. Evaluation of antihypotensive techniques for cesarean section under spinal anesthesia: Rapid crystalloid hydration versus intravenous ephedrine. Anesth Essays Res. 2016;10(3):637-642.
   https://doi.org/10.4103/0259-1162.191118
2. Hasanin A, Mokhtar AM, Badawy AA and Fouad R. Post-spinal anesthesia hypotension during cesarean delivery, a review article. Egypt J Anaesth. 2017;33(2):189-193.
3. Xu C, Liu S, Huang Y, Guo X, Xiao H and Qi D. Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis. Int J Surg. 2018;60:48-59.
   https://doi.org/10.1016/j.ijsu.2018.10.039
4. Carvalho B and Dyer RA. Norepinephrine for spinal hypotension during cesarean delivery: Another paradigm shift? Anesthesiology. 2015;122(4):728-730.
   https://doi.org/10.1097/ALN.0000000000000602
5. Mets B. Should norepinephrine, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? Anesth Analg. 2016;122(5):1707-1714.
   https://doi.org/10.1213/ANE.0000000000001239
6. Ngan Kee WD, Lee SW, Ng FF, Tan PE and 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.
   https://doi.org/10.1097/ALN.0000000000000601
7. Kee WD. A Random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. Anesthesiology. 2017;127(6):934-941.
   https://doi.org/10.1097/ALN.0000000000001880
8. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J and Carvalho JC. Comparison of intermittent intravenous boluses of phenylephrine and norepinephrine to prevent and treat spinal-induced hypotension in cesarean deliveries: Randomized controlled trial. Anesth Analg. 2019;129(5):1312-1318.
   https://doi.org/10.1213/ANE.0000000000003704
9. Yeh P, Emary K and Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: Analysis of 51,519 consecutive validated samples. BJOG. 2012;119(7):824-831.
   https://doi.org/10.1111/j.1471-0528.2012.03335.x
10. Hasanin A, Amin S, Refaat S, Habib S, Zayed M, Abdelwahab Y, et al. Norepinephrine versus phenylephrine infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery: A randomised controlled trial. Anaesth Crit Care Pain Med. 2019;38(6):601-607.
    https://doi.org/10.1016/j.accpm.2019.03.005
11. Mohta M, Dubey M, Malhotra RK and Tyagi A. Comparison of the potency of phenylephrine and norepinephrine bolus doses used to treat post-spinal hypotension during elective caesarean section. Int J Obstet Anesth. 2019;38:25-31.
    https://doi.org/10.1016/j.ijoa.2018.12.002
12. Mohta M, Garg A, Chilkoti GT and Malhotra RK. A randomised controlled trial of phenylephrine and noradrenaline boluses for treatment of postspinal hypotension during elective caesarean section. Anaesthesia. 2019;74(7):850-855.
    https://doi.org/10.1111/anae.14675
13. Dong L, Dong Q, Song X, Liu Y and Wang Y. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for cesarean section. Int J Clin Exp Med. 2017;10(8):12315-12321.
14. Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, et al. An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. Int J Obstet Anesth. 2017;29:18-25.
    https://doi.org/10.1016/j.ijoa.2016.08.005
15. Wang X, Mao M, Zhang SS, Wang ZH, Xu SQ and 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.
    https://doi.org/10.1097/CM9.0000000000000621
16. Elnabtity AM and Selim MF. Norepinephrine versus ephedrine to maintain arterial blood pressure during spinal anesthesia for

cesarean delivery: A prospective double-blinded trial. Anesth Essays Res. 2018;12(1):92-97.

https://doi.org/10.4103/aer.AER_204_17

17. Wang X, Mao M, Liu S, Xu S and Yang J. A comparative study of bolus norepinephrine, phenylephrine, and ephedrine for the treatment of maternal hypotension in parturients with preeclampsia during cesarean delivery under spinal anesthesia. Med Sci Monit. 2019;25:1093-1101.

https://doi.org/10.12659/MSM.914143

18. Xu S, Shen X, Liu S, Yang J and 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):e14331.

https://doi.org/10.1097/MD.0000000000014331

19. Kee WD, Lee SW, Ng FF and Khaw KS. Prophylactic norepinephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesth Analg. 2018;126(6):1989-1994.

https://doi.org/10.1213/ANE.0000000000002243

Authors Contribution:
CS- Concept and design of the study, review of literature, original draft preparation, statistical analysis; **CS**- Review of literature, preparation of manuscript, statistical analysis and interpretation of results; and **AA**– Review, editing, interpretation of results and revision of manuscript.

Work attributed to:
Department of Anaesthesiology, Sri Venkateswaraa Medical College Hospital and Research Centre, Ariyur - 605 107, Puducherry, India.

Orcid ID:
Dr. Chinthavali Sujatha - https://orcid.org/0000-0002-8003-3544
Dr. Arthi Asokan - https://orcid.org/0000-0002-8928-7065

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