

## Appraisal of the Effect of Norepinephrine Versus Phenylephrine on Blood Pressure and Heart Rate During Spinal Anaesthesia for a Caesarean Section; A Quasi-Experimental Study

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### ABSTRACT

**Objectives:** To compare the effects of Norepinephrine and Phenylephrine on blood pressure and heart rate during spinal anaesthesia for caesarean section.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Department of Anaesthesia Combined Military Hospital, Multan Pakistan, from May to Nov 2019.

**Methodology:** Women (age: 18 to 45 years) with singleton pregnancy planned for caesarean section in spinal anaesthesia were included. Women with pregnancy-induced hypertension, placenta previa, placenta accreta, diabetes mellitus, and any other cardiovascular disease were excluded. After distribution into groups, Group-A was given a 20µg Norepinephrine bolus, and Group-B was given a 50µg bolus of Phenylephrine just after spinal anaesthesia. At five time points, systolic, diastolic, and mean blood pressures and heart rate were measured: baseline, block of the highest sensory level, oxytocin injection, delivery, and operation completion. If hypotension developed, the same rescue drug was repeated. Bradycardia was countered by 0.5 mg of Atropine.

**Results:** The frequency of hypotension in the Norepinephrine group was 5 (16.67%), and in the Phenylephrine Group, it was 19 (63.33%) ( $p=0.0001$ ). The frequency of bradycardia in the Norepinephrine Group was 6 (20%), and in the Phenylephrine Group, it was 17 (56.67%) ( $p=0.003$ ).

**Conclusion:** The frequency of hypotension and bradycardia is less after prophylactic 20 µg of Norepinephrine during spinal anaesthesia for a caesarean section than 50 µg of Phenylephrine.

**Keywords:** Bradycardia, Hypotension, Spinal anaesthesia.

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### INTRODUCTION

Spinal anaesthesia has become the standard of choice in almost all patients undergoing caesarean section because of its low cost, easy induction, and excellent efficacy.<sup>1</sup> It eliminates the most prevalent hazards of general anaesthesia, such as aspiration, difficulties in intubation, and undesirable consequences of general anaesthetics on the foetus. More than 80% of caesarean sections are now performed under spinal anaesthesia.<sup>2</sup> Nevertheless, spinal anaesthesia is not without side effects. One of the major adverse effects of spinal anaesthesia is hypotension which occurs in about 60-70% of patients after induction of spinal anaesthesia.<sup>3,4</sup> Hypotension is caused by the preganglionic sympathetic blockade. The vasodilation caused by spinal block-induced sympatholytic induces hypotension in mothers. The reduced systolic pressure can impair uterine blood flow and foetal circulation,

resulting in foetal hypoxia and acidosis.<sup>5</sup> For more than 50 years, medical researchers have studied hypotension following caesarean sections done under spinal anaesthesia. In different studies, the incidence of hypotension under spinal anaesthesia for caesarean delivery ranges from 7.4% to 74.1%. Prolonged hypotension, if left untreated, is associated with organ ischemia, reduction in placental blood flow, and loss of consciousness.<sup>5</sup> Fluid administration, use of vasopressors and compression of lower limbs are commonly employed strategies to prevent hypotension.<sup>6</sup>

Phenylephrine is the favoured medication for hypotension in caesarean births because it induces less foetal acidosis than Ephedrine. However, this medicine has a disadvantage in that it lowers the heart rate (HR) and cardiac output, which may have a detrimental effect on maternal and foetal parameters. Norepinephrine is a powerful vasopressor that also has  $\beta$ -adrenergic effects. Norepinephrine infusion has recently been proposed as a replacement for Phenylephrine in treating hypotension after caesarean

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birth caused by spinal anaesthesia.<sup>7</sup> Norepinephrine can also be used to treat hypotension accounting for its  $\alpha$ -adrenergic properties. It is associated with decreased incidence of bradycardia compared to Phenylephrine,<sup>8</sup> and results in better cardiac output and HR.<sup>9</sup>

Nothing less to say that there is very limited data in Pakistan regarding recommendations for using Norepinephrine in women undergoing caesarean section. The rationale of this study was to compare the effects of Norepinephrine and Phenylephrine on maternal HR and blood pressure (BP) in our setups such that Norepinephrine may or may not be recommended for use in Pakistani medical settings.

## METHODOLOGY

It was a double-blinded quasi-experimental study carried out at the Department of Anesthesia, Combined Military Hospital Multan Pakistan, from May to November 2019. The sample size was calculated by the World Health Organization sample size calculator for hypothesis testing for two population proportions (one-sided) while keeping the level of significance at 5%, power of the test at 80 %, and anticipated hypotension proportion in the Phenylephrine Group as 66.6%,<sup>7</sup> and anticipated hypotension proportion in Norepinephrine group as 16.7%.<sup>7</sup> After approval from the Hospital Ethics Committee (ERC Certificate number: 13/Trg/2021), all women were included through non-probability consecutive sampling.

**Inclusion Criteria:** Women between 18 to 45 years, with singleton pregnancy who were booked for elective caesarean section in spinal anaesthesia were included in the study.

**Exclusion Criteria:** Women with a height of <150cm or >180cm, a weight of <50kg or >100kg, contraindications to spinal anaesthesia, a history of allergy to any of the drugs used in the trial, pregnancy-induced hypertension, placenta previa, placenta accreta, diabetes mellitus and any other cardiovascular disease were decided to be in the exclusion category.

All women had singleton term pregnancies and were classified in the American Society of Anaesthesiologists physical status-II. Written consent was taken after an overnight fast. In the operating room, an intravenous line was established with the 16-Gauge cannula, and 500mL of Ringer's Lactate was administered before surgery. All women were subjected to standard monitoring, which included electrocardiography, pulse oximetry, body temperature assessment, and non-invasive hemodynamic monitoring.

Women were divided into two Groups by lottery method. Group-A was administered Norepinephrine, and Group-B was given Phenylephrine. To ensure blinding, the researcher placed each drug in a consecutively numbered envelope and handed it over to the anaesthetist introducing spinal anaesthesia.

The spinal anaesthesia was induced in a sitting position. A 25-gauge lumbar puncture needle was used to provide spinal anaesthetic at the L3–4 level. Following the confirmation of the cerebrospinal fluid, 12.5mg (2.5ml of 0.5%) Bupivacaine was administered. After injection, the patient lay supine with a wedge under the right hip. Pinpricking with a 23-gauge needle was used to determine block level, which was kept within the T4–6 range. The medications under study were then given to both groups. Group-A was given a 20  $\mu$ g Norepinephrine bolus, and Group B was given a bolus of 50  $\mu$ g Phenylephrine. The parameters were recorded till the procedure was completed. At five time points, systolic, diastolic, mean BP, and HR were measured: baseline, block of the highest sensory level, oxytocin injection, delivery, and operation completion. If hypotension developed, the same rescue drug was repeated. Bradycardia was countered by 0.5 mg of Atropine.

The data was recorded on the proforma and transferred to Statistical Package for Social Sciences version 24.0 (for windows) for statistical analysis. Descriptive statistics were used for qualitative and quantitative variables. The qualitative variables like hypotension and bradycardia were measured as frequency and percentages. Quantitative variables like age, BP, and HR readings were presented as mean  $\pm$  standard deviation. The frequency of hypotension and bradycardia was compared by Pearson's chi-squared test. The *p*-value of  $\leq 0.05$  was taken as significant.

## RESULTS

The total sample was composed of 60 women after applying the exclusion criteria. Thirty women were in Group-A while 30 were in Group-B. The mean age of the sample was 28.6 $\pm$ 4.6 years (range: 18 to 45 years). The mean age of women in Group-A was 28.5 $\pm$ 4.4 years, and in Group-B, it was 28.7 $\pm$ 4.9 years. The majority of the women, i.e. 33 (55.0%), were between 18 to 30 years in both groups. The mean systolic BP in Group-A was 128.53 $\pm$ 9.55 mmHg, and the mean systolic BP in Group-B was 103.36 $\pm$ 7.51 mmHg. The mean diastolic BP in Group-A was 82.44 $\pm$ 5.71 mmHg, and the mean diastolic BP in Group-B was 72.42 $\pm$ 4.89 mmHg. The mean HR in

Group-A was  $71.59 \pm 7.21$ /min, while the mean HR in Group-B was  $54.78 \pm 6.63$ /min.

Hypotension was observed in five (16.67%) women in the Norepinephrine Group and 19 (63.33%) women in the Phenylephrine Group ( $p=0.0001$ ). The frequency of bradycardia was found in six (20.0%) women in the Norepinephrine Group and 17 (56.67%) women in the Phenylephrine Group ( $p=0.003$ ), shown in Table-I.

**Table-I: Comparison of Hypotension and Bradycardia Between the Two Study Groups(n=60)**

Complications	Group-A (n=30) n (%)	Group-B (n=30) n (%)	p-value
<b>Hypotension</b>			
Present	5 (16.67)	19 (63.33)	0.001
Absent	25 (83.33)	11 (36.67)	
<b>Bradycardia</b>			
Present	6 (20.00)	17 (56.67)	0.003
Absent	24 (80.00)	13 (43.33)	

## DISCUSSION

Mother hypotension is a physiological reaction to a spinal anaesthetic after caesarean birth that interposes unfavourable maternal responses such as nausea, vomiting, dizziness, and even cardiovascular collapse. Furthermore, foetal acidosis, hypoxia, and even brain damage after birth are all concerns when placental perfusion is reduced. Keeping that in view, successful prevention and management of maternal hypotension after spinal anaesthesia is critical in the operation theatre. The vasopressor of the first choice to treat maternal hypotension during obstetric anaesthesia is Phenylephrine. However, more recently, Norepinephrine has gained popularity as a substitute vasopressor for Phenylephrine. Nevertheless, the clinical evidence to recommend its use is still weak.<sup>3</sup>

This study compared the prophylactic doses of Norepinephrine and Phenylephrine in terms of hypotension and bradycardia following caesarean section under spinal anaesthesia. In our study, the frequency of hypotension was considerably lower in the Norepinephrine Group (16.67%), parallel to the Phenylephrine group (63.33%) ( $p=0.001$ ). Similarly, the frequency of bradycardia was significantly reduced (20.0%) in the Norepinephrine Group as measured up against the Phenylephrine group (56.67%) ( $p=0.003$ ). Ngan Kee *et al.*<sup>8</sup> were the leading researchers to disclose the use of Norepinephrine to sustain BP during caesarean delivery under spinal anaesthesia in 2015. They found that Norepinephrine produced

higher HR and cardiac output using computer-controlled infusion while having a similar BP maintaining effect as Phenylephrine. Vallejo *et al.*<sup>9</sup> assessed  $6 \mu\text{g}/\text{kg}/\text{h}$  of Phenylephrine in counteracting hypotension during spinal anaesthesia with  $3 \mu\text{g}/\text{kg}/\text{h}$  of Norepinephrine for elective caesarean delivery; the percentage of women who needed rescue vasopressor boluses was similar in both groups, so they deemed Norepinephrine as a replacement for Phenylephrine.

Chen *et al.*<sup>7</sup> in a randomized controlled trial (RCT), showed that the Norepinephrine treated group had a lower frequency (16.7%) of falls in BP than the control group (66.7%) ( $p \leq 0.001$ ), which also demonstrated a dramatic fall in BP from 122.4 to 91.7 mmHg with a  $p$ -value of  $< 0.001$ . Dong *et al.*<sup>10</sup> in another trial, witnessed that Norepinephrine was associated with fewer side effects than Phenylephrine. One difference was regarding HR in that the Norepinephrine group had a lower rate of bradycardia (18.4%) than the Phenylephrine group (55.8%,  $p < 0.001$ ).<sup>10</sup> In another study, 50 patients receiving an elective caesarean section under spinal anaesthesia were divided into two groups. To treat spinal hypotension, Group-P patients were given a  $50 \mu\text{g}$  intravenous bolus of Phenylephrine and Group-N patients received a  $4 \mu\text{g}$  intravenous bolus of Norepinephrine. In Group-N, the number of vasopressor boluses needed to treat hypotension was considerably lower ( $1.40 \pm 0.577$  vs  $2.28 \pm 1.061$ ,  $p=0.001$ ). Although Group-P had a higher rate of bradycardia, the change was not statistically meaningful (4% vs 20%,  $p=0.192$ ). Adverse effects in the mother, such as nausea, vomiting, and shivering, were similar in both groups. The foetal tissues in both groups were likewise equivalent.<sup>11</sup>

Norepinephrine was shown to be 11 times more powerful than Phenylephrine in research by Mohta *et al.*<sup>12</sup> and  $100 \mu\text{g}$  of Phenylephrine was comparable to  $9 \mu\text{g}$  of Norepinephrine. Sharkey *et al.*<sup>13</sup> evaluated bolus dosages of Phenylephrine ( $100 \mu\text{g}$ ) in comparison with Norepinephrine ( $6 \mu\text{g}$ ) and concluded that Norepinephrine had improved hemodynamic management during caesarean delivery due to fewer HR variations. Compared to Ephedrine and Phenylephrine, an intermittent bolus dosage of Norepinephrine was shown to be a strong medication for treating spinal hypotension.<sup>14,15</sup> In a comprehensive review and meta-analysis, Xu *et al.*<sup>16</sup> found that Norepinephrine and Phenylephrine had equivalent effectiveness in controlling maternal hypotension.

When compared to the Phenylephrine group, Anusornatanawat *et al.*<sup>17</sup> found that the Norepinephrine group had a reduced incidence of bradycardia. In the current study, the occurrence of bradycardia in the Norepinephrine group was consistently 20%, much less than in the Phenylephrine group (56.67%). These findings suggest that Norepinephrine is more effective than Phenylephrine in counteracting bradycardia. Dong *et al.*<sup>10</sup> in another RCT showed that Norepinephrine was associated with fewer side effects than Phenylephrine. The Norepinephrine Group had a lower rate of bradycardia (18.4%) than the Phenylephrine group (55.8%,  $p < 0.001$ ).

Poterman *et al.*<sup>18</sup> found that Phenylephrine 100µg/min and Norepinephrine 10µg/min had the same anti-hypotensive effect. According to Onwochei *et al.*<sup>19</sup> Norepinephrine was harmless for local tissue perfusion because it is diluted before use and supplied in a flowing fluid for a short period, lowering the danger of tissue ischemia. Furthermore, an identical strength of Norepinephrine infusion or bolus has a hypothetically comparable vasoconstrictive efficacy to the presently utilized Phenylephrine. Therefore, the danger should be similar. Additionally, a prior study found that spinal anaesthesia enhanced skin perfusion, which the administration of Norepinephrine did not counter. Overall, the findings imply that typical infusion or bolus dosages of Norepinephrine have no deleterious effect on local tissue perfusion in patients with spinal anaesthesia. Levophed (the commercially available Norepinephrine) does not mention that it should be given centrally, simply that it must be delivered through a big vein, if possible, the antecubital vein.<sup>21</sup>

While these reports advocate the effectiveness and safety of Norepinephrine, the best dosing and administration idea is still argued. Compared to equipotent Phenylephrine infusion or Norepinephrine bolus, either computer-controlled closed-loop feedback infusion or manually controlled variable rate infusion of Norepinephrine gives extra accurate BP regulation. However, smart pumps or greater physician assistance are required for such infusion regimens, which are unavailable at all institutions. Furthermore, a new agreed declaration states that hypotension is common and that vasopressors should be taken often, if not prophylactically.<sup>22</sup> When contrasted to a reactive bolus, a prophylactic fixed-rate infusion is linked with reduced hemodynamic fluctuation and fewer maternal adverse effects. Separate groups have explored the best

possible preset infusion rate for Norepinephrine alone,<sup>7,9,23</sup> or in comparison with Phenylephrine,<sup>8</sup> with doses ranging from 1.5 to 15 µg/min (for a 60 kg parturient). The results revealed that a dosage of 3-5 µg/min is usually adequate, with larger doses (10-15 µg/min) causing hypertension in parturients.

The findings of our study have further strengthened the conclusion that Norepinephrine is far better than Phenylephrine in controlling hypotension and bradycardia during elective caesarean section and thus should replace Phenylephrine in our hospitals for use in elective caesarean sections. The double-blind design is the strength of this study. Further studies to include a larger sample size to observe the effects of Norepinephrine are also recommended.

#### LIMITATION OF THE STUDY

The sample size in our study was small, thus reducing the strength of assumptions made through this study.

#### CONCLUSION

This study concluded that the frequency of hypotension and bradycardia is less after prophylactic 20µg of Norepinephrine during spinal anaesthesia for a caesarean section than 50µg of Phenylephrine. Consequently, we recommend that a prophylactic dose of Norepinephrine in patients during spinal anaesthesia should be used routinely in our general practice to prevent hypotension and bradycardia and manage patients undergoing spinal anaesthesia.

**Conflict of Interest:** None.

#### Author's Contribution

HI: Main Author, AH: Data collector, HR: Data analysis, SBA: Discussion/reference, ZA: Literature review, Proof Reading.

#### REFERENCES

1. Wani SA, Pandit BH, Din MU, Nissa WU, Ashraf A, Bashir S, et al. Comparative study to evaluate the effect of colloid coloadung versus crystalloid coloadung for prevention of spinal anaesthesia induced hypotension and effect on fetal Apgar score in patients undergoing elective lower segment caesarean section: a prospective observational study. *Int J Reprod Contracept Obstet Gynecol* 2018; 7(5): 1868-1875.
2. McDonnell NJ, Paech MJ, Muchatuta NA, Hillyard S, Nathan EA. A randomised double-blind trial of phenylephrine and metaraminol infusions for prevention of hypotension during spinal and combined spinal-epidural anaesthesia for elective caesarean section. *Anaesthesia* 2017; 72(5): 609-617.
3. Mercier FJ, Augè M, Hoffmann C, Fischer C, Le Gouez A. Maternal hypotension during spinal anaesthesia for caesarean delivery. *Minerva Anesthesiol* 2013; 79(1): 62-73.
4. Langesæter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anesthesiol* 2011; 24(3): 242-248.
5. Macarthur A, Riley ET. Obstetric anaesthesia controversies: vasopressor choice for postspinal hypotension during caesarean delivery. *Int Anesthesiol Clin* 2007; 45(1): 115-132.

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6. Chooi C, Cox JJ, Lumb RS, Middleton P, Chemali M, Emmett RS, et al. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev* 2017; 8(8): CD002251.
  7. Chen D, Qi X, Huang X, Xu Y, Qiu F, Yan Y, et al. Efficacy and Safety of Different Norepinephrine Regimens for Prevention of Spinal Hypotension in Caesarean Section: A Randomized Trial. *Biomed Res Int* 2018; 2018(1): 2708175.
  8. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of BP during spinal anesthesia for caesarean delivery. *Anesthesiology* 2015; 122(4): 736-745.
  9. Vallejo MC, Attaallah AF, Elzamazny 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 caesarean delivery. *Int J Obstet Anesth* 2017; 29(1): 18-25.
  10. Dong L, Dong Q, Song X, Liu Y, Wang Y. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for caesarean section. *Int J Clin Exp Med* 2017; 10(8): 12315-12321.
  11. Puthenveetil N, Sivachalam SN, Rajan S, Paul J, Kumar L. Comparison of norepinephrine and phenylephrine boluses for the treatment of hypotension during spinal anaesthesia for caesarean section-A randomised controlled trial. *Indian J Anaesth* 2019; 63(12): 995-1000.
  12. Mohta M, Dubey M, Malhotra RK, 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(1): 25-31.
  13. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, Carvalho JCA. Comparison of Intermittent Intravenous Boluses of Phenylephrine and Norepinephrine to Prevent and Treat Spinal-Induced Hypotension in Caesarean Deliveries: Randomized Controlled Trial. *Anesth Analg* 2019; 129(5): 1312-1318.
  14. Elnabity AMA, Selim MF. Norepinephrine versus Ephedrine to Maintain Arterial Blood Pressure during Spinal Anesthesia for Caesarean Delivery: A Prospective Double-blinded Trial. *Anesth Essays Res* 2018; 12(1): 92-97.
  15. Wang X, Mao M, Liu S, Xu S, Yang J. A comparative study of bolus norepinephrine, phenylephrine, and ephedrine for the treatment of maternal hypotension in parturients with preeclampsia during caesarean delivery under spinal anesthesia. *Med Sci Monit* 2019; 25(1): 1093-1101.
  16. Xu S, Shen X, Liu S, Yang J, Wang X. Efficacy and safety of norepinephrine versus phenylephrine for the management of maternal hypotension during caesarean delivery with spinal anesthesia: A systematic review and meta-analysis. *Medicine (Baltimore)* 2019; 98(5): e14331.
  17. Anusornatanawat R, Uerpairojkit K, Thongthaweepon N, Charuluxananan S. Safety of Phenylephrine in Antihypotensive Treatment during Spinal Anesthesia for Caesarean Section. *J Med Assoc Thai* 2016; 99(2): 188-196.
  18. Poterman M, Vos JJ, Vereecke HE, Struys MM. Differential effects of phenylephrine and norepinephrine on peripheral tissue oxygenation during general anaesthesia: A randomised controlled trial. *Eur J Anaesthesiol* 2015; 32(8): 571-580.
  19. Onwochei DN, Ngan-Kee WD, Fung L. Norepinephrine Intermittent Intravenous Boluses to Prevent Hypotension During Spinal Anesthesia for Caesarean Delivery: A Sequential Allocation Dose-Finding Study. *Anesth Analg* 2017; 125(1): 212-218.
  20. Lecoq JP, Brichant JF, Lamy ML, Joris JL. Norepinephrine and ephedrine do not counteract the increase in cutaneous microcirculation induced by spinal anaesthesia. *Br J Anaesth* 2010; 105(2): 214-219.
  21. Wang X, Shen X, Liu S, Yang J, Xu S. The Efficacy and Safety of Norepinephrine and Its Feasibility as a Replacement for Phenylephrine to Manage Maternal Hypotension during Elective Caesarean Delivery under Spinal Anesthesia. *Biomed Res Int* 2018; 2018(1): 1869189.
  22. 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.
  23. Hasanin AM, Amin SM, Agiza NA, Elsayed MK, Refaat S. Norepinephrine Infusion for Preventing Postspinal Anesthesia Hypotension during Caesarean Delivery: A Randomized Dose-finding Trial. *Anesthesiology* 2019; 130(1): 55-62.
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