Comparison of prophylactic use of phenylephrine bolus versus norepinephrine bolus for the prevention of post-spinal hypotension in caesarean section



Thesis Submitted to

The Superior University Lahore

In Partial Fulfillment of the

Requirement for the Degree of

Master of Science in Allied Health Sciences

By

SAMINA SHARIF

SU91-MSAHW-S24-069

Session: 2024-2026

Faculty of Allied Health Sciences

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No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Faculty of Allied Health Sciences, The Superior University, Lahore in partial fulfillment of the requirements for the degree of Master of Science in the field of "**Allied Health Sciences"** in Faculty of Allied Health Sciences at The Superior University, Lahore.

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DEDICATION

This thesis is dedicated to my parents, whose unwavering support, unconditional love, and constant encouragement have been the foundation of my journey. Your sacrifices and belief in me have been my greatest strength.

To my family, thank you for being my pillars of support, for celebrating my successes, and for standing by me in times of struggle. Your presence has made this achievement all the more meaningful.

I am deeply grateful to each of you for inspiring me to reach higher and pursue my dreams.

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
ASA	American Society of Anesthesiologists
BP	Blood Pressure
bpm	Beats Per Minute
C/S	Caesarean Section
CO	Cardiac Output
DBP	Diastolic Blood Pressure
GA	Gestational Age
HR	Heart Rate
I.V	Intravenous
MAP	Mean Arterial Pressure
NIBP	Non-Invasive Blood Pressure
NE	Norepinephrine
PE	Phenylephrine
PONV	Postoperative Nausea and Vomiting
PSH	Post-Spinal Hypotension
SBP	Systolic Blood Pressure
SD	Standard Deviation
SpO_2	Peripheral Oxygen Saturation
SV	Stroke Volume
SVR	Systemic Vascular Resistance

ABSTRACT

Background: Post-spinal hypotension is a common complication during cesarean section under spinal anesthesia, leading to maternal and fetal adverse outcomes. Phenylephrine is widely used as a prophylactic vasopressor, but norepinephrine has recently emerged as a potential alternative with fewer side effects.

Objective: To compare the efficacy and safety of prophylactic phenylephrine versus norepinephrine bolus in preventing post-spinal hypotension in parturients undergoing elective cesarean section.

Methods: A total of 280 parturients were randomized to receive either prophylactic phenylephrine (n=140) or norepinephrine (n=140) immediately after spinal anesthesia. Demographic data, baseline hemodynamics, intraoperative episodes of hypotension and bradycardia, vasopressor requirements, and neonatal outcomes were recorded. Statistical analysis included chi-square tests for categorical variables, independent t-tests for continuous variables, and logistic regression to identify predictors of post-spinal hypotension. A p-value <0.05 was considered statistically significant.

Results: The incidence of hypotension was significantly lower in the norepinephrine group compared to phenylephrine (22.9% vs 37.1%, p=0.012). Bradycardia was more frequent with phenylephrine (15.7% vs 2.9%, $p<0.001$). Norepinephrine also reduced the need for rescue vasopressor doses (14.3% vs 27.1%, p=0.012) and the incidence of nausea/vomiting (10.0% vs 20.0%, p=0.031). There were no significant differences in shivering, neonatal NICU admission, APGAR scores, or birth weight between groups. Logistic regression identified norepinephrine as an independent protective factor against hypotension (OR 0.48, 95% CI 0.27–0.84, p=0.008). Patient satisfaction scores were slightly higher in the norepinephrine group (9.5 ± 0.8 vs 9.2 ± 1.0, p=0.02).

Conclusion: Prophylactic norepinephrine bolus is more effective than phenylephrine in preventing post-spinal hypotension in cesarean section, with lower incidence of bradycardia, rescue vasopressor requirements, and nausea/vomiting, without adverse neonatal effects. Norepinephrine may be considered a safer and more efficient alternative for maintaining maternal hemodynamic stability during cesarean delivery under spinal anesthesia.

Keywords: Norepinephrine, Phenylephrine, Post-spinal hypotension, Cesarean section, Spinal anesthesia, Maternal hemodynamics, Vasopressor

Chapter 1

INTRODUCTION

Elective cases Sometimes, rather than general anesthesia, the spinal anesthesia is used on the parturient in elective caesarean surgery (CS). Hypotension is occurring in approximately 80% of pregnant women due to pre- and post-synaptic neurone suppression in prevention of sympathetic post-synaptic neurones, consequent of reducing the systemic vascular resistance (1). Because the propensity of phenylephrine (PE), a pure alpha (a) agonist, is less to reduce fetal pH and base excess compared with ephedrine it is now the preferred vasopressor in the treatment of post-spinal hypotension. In theory, the developing fetus can be affected by bradycardia, which makes the heart of the mother produce less during pregnancy. In addition to some modifications to maternal HR, norepinephrine (NE), an a1 adrenergic agonist and a minor effect concentrating on beta (b)1 adrenergic agonist, has recently been proposed to use it. It has been widely held that constant high arterial blood pressure levels are the surest means of keeping some parts properly perfused. One of the adverse effects of spinal anesthesia (SA) is arterial hypotension though it demonstrates potential as a better procedure in comparison to general anesthesia. Spinal anesthesia-induced hypotension (SAIH) can be treated and prevented in several ways, and this paper will discuss them and assess the reasons behind them. The extent to which the sympathetic block caused by SA results in effects on the circulatory system is also correlated but not necessarily in a linear manner and differs greatly in different patients (2-5).

The quick dilation of blood vessels and arterial veins in areas where SA can influence the sympathetic nervous system results in a baroreflex to enhance the sympathetic artery vascular tone in areas unaffected by the blockage. This is because these compensatory mechanisms appear to be more effective in younger patients. The other hemodynamic consequence of the sympathetic obstruction of the venous reservoir by SA is the existence of blood in the capacitance pathways of the lower parts. At the equal or higher level of the sensory block T6, vasopressors can mobilize up to 20 percent of the circulating blood volume that is influenced by hepatosplanchnic pooling. The consequences of the imbalance of the

parasympathetic tone of SA are bradycardia and a decrease in blood pressure. The cause of this bradycardia/hypotension may be an interruption of the circulatory activity or an adaptive response, which is characterized by increasing the diastole duration to facilitate ventricular filling (7-10).

With the aid of the aortic and carotid baroreceptors, the Bezold-Jarisch reflex (BJR) and its cardioinhibitory receptors control the blood pressure in the arteries and follow the accepted physiological principles. Low blood volume increases the arterial blood pressure due to the activation of the baroreflex and reduction of the BJR activity. A rapid decrease in venous flow initiates the BJR in acute hypovolemia, including severe bleeding, which is the opposite effect that leads to the development of bradycardia and extended hypotension. The potential adaptive effect of bradycardia is that it helps to sustain a fixed diastolic filling time (11).

Approximately one out of every five non-obstetrical patients who experience bradycardia during SA does not experience significant complications provided they are treated soon. Since severe cases of bradycardia may readily lead to asystole, bradycardia due to SA is always an anteroom to hemodynamic failure (12). Cardiovascular output experiments under SA have indicated that the medication has a effect in two phases, whereby, it initially increases the cardiovascular output by lowering afterload through arterial vasodilatation (which peaks after approximately 7 minutes) and subsequently decreases the cardiovascular output by decreasing the preload. The reduced output of the heart in 15 percent to half of humanity is a cause of low pressure in the arteries. This reduction in the cardiac output can be further lowered in the elderly due to age related alterations like alterations in the diastolic relaxation and systolic operations (13).

The effects of SA on the cardiovascular system are hypotension in the arteries. Hypotension of the arteries intraoperative raises the likelihood of fatality or significant complications in the patients. The conventional medical literature definition of SAIH is a systolic reading of arterial blood pressure that is less than 80 percent of normal. In individuals aged 50 years and above, the incidence of SAIH is 75 as compared to 36 in the younger individuals. One of them is the high prevalence of SAIH among the elderly, despite the very low dosages of bupivacaine (7.5mg). The other threat that might worsen SAIH in the likelihood of altered homeostatic functions is, dysautonomia, or an increased deficiency of control over self-body mechanisms. This is more likely to happen in the patient experiencing rapid block

extension, with a problem of the neuro-humoral control of heart activity, and when anesthesia is involved simultaneously (14-16).

Phenylephrine is a common medication used to patients to minimize the chances of arterial hypotension post-operative period. it has instant agonistic interaction with a (1)- adrenergic receptor. Even though physiological investigations proved that a-adrenergic agonists raise afterload in the heart, and lower venous compliance, there exists a significant association between the initial state of venous return and the effect of phenylephrine on the heart output. In normal left ventricular function, left ventricular afterload increase does not alter cardiac output. According to Starling law, in case the intra-vascular volume status of the patient is good, it is possible to increase the cardiac output by mobilizing the fluid and enhancing the venous return base on phenylephrine. But it can increase sympathetic tone in people with impaired heart function thus leading to reduction in cardiac output and increase in arterial resistance (17).

There are some publications that mention that hypotension during SA procedures has been treated or prevented by using phenylephrine. A number of methods have been employed to administer phenylephrine. Pregnant women and the elderly respond better to the medicine and are more effective in avoiding arterial hypotension when compared to rescue therapy, which implies injecting phenylephrine 100 mg bolus every time the systolic pressure dropped to lower than 80% of that at the baseline. Conversely, undergoing a local anesthetic intrathecal injection followed by the administration of phenylephrine helps to keep the systolic blood pressure at least 80 percent of baseline and prevent complications. This would convey that in circumstances of preventive administration measures, a number of boluses are more preferable to fixed-rate continuous infusion. The advantages of the prophylactic use of variable-rate phenylephrine infusion are enhanced hemodynamic stability, reduced nausea and vomiting, and less intervention necessity to maintain the blood pressure. Also, research has indicated that closed-loop computer-controlled phenylephrine continuous infusion is more efficient than the manual continuous infusion in balancing blood pressure. Avoidance of the blood pressure decrease following SA can be attained by initiating a continuous rate adjusted intravenous infusion of phenylephrine immediately the intrathecal injection is injected. In situations where the blood pressure is less than 80 percent of zero, an unchanging rate of 50mg/minute and a frequent 100mg bolus seems suitable. Phenylephrine

repeated boluses can be administered as a preventive method in case the clinician does not know how to employ either of these two treatments (11).

Going back to the earlier discussion, Phenylephrine is a potent and pure a-adrenergic receptor agonist and is associated with cardiac output reduction in a dose-dependent manner. Due to the moderate propensity of norepinephrine to bind to b-adrenergic receptors, some of the authors have suggested it as possible solution. Recent randomized controlled studies compared norepinephrine with phenylephrine to be able to maintain a stable arterial blood pressure in elective caesarean surgery conducted on pregnant women under SA. The results were presented in 2018 in a study by Ngan Kee et al. Though continuous infusion of norepinephrine (5 mg/mL), which was controlled by a computer, had no effect on the outcomes of the baby, it reduced cardiac output and bradycardia and improved the regulation of blood pressure compared to the use of phenylephrine, presumably due to its action on b-receptors. Perhaps the best place to begin norepinephrine infusion at 0.07-0.08 mg kg 1 min 1 to prevent SAH following cesarean births. More studies should be conducted to establish whether phenylephrine or norepinephrine is better in the prevention of SA-induced hypotension. There is no urgency to change the current approach to the selection of vasopressor drugs even though the initial results are promising (12).

Nevertheless, in pregnant women, 90 percent of them are likely to develop hemodynamic abnormalities due to spinal anesthesia. Not only these changes endanger the health of the fetus, but also lead to several unpleasant side effects such as nausea, vomiting, and lightheadedness. Phenylephrine is an old a-receptor agonist which has been applied as a natural agent to prevent hypotension caused by spinal anesthesia particularly in caesarean operation. This drug is associated with severe side effects on the pregnant women who are comorbid with the condition, including bradycardia, heart depression, and cardiac output reduction (15). However, norepinephrine has a positive chronotropic effect on the heart besides stimulating the a and ss receptors. Consequently, it has recently become a popular substitute of phenylephrine in obstetric anesthesia. This research aimed at testing the effectiveness of phenylephrine and prophylactic norepinephrine since the elective cesarean sections sometimes require the use of spinal anesthesia (9).

Various meta-analyses have been conducted on the efficacy of various antihypertensive drugs to be used under spinal anesthesia, the comparative

advantages of phenylephrine and ephedrine and the methods to decrease the incidence of hypotension in the process. We however, found a very different line of thought since we studied these drugs at a different stage of usage, that of prevention. It is a well known fact that the administration of a agonists in the case of cesarean deliveries in spinal anesthesia can be considered a proactive measure to avoid such complications as hypotension. (11).

RATIONALE

Spinal anesthesia is associated with a number of advantages during a caesarean operation, which include a fast onset, complete immobility, and low medication transfer to the developing baby. It commonly goes along with maternal hypotension that afflict 70-80% of pregnant women and may lead to complications to both the mother and the unborn baby, including fetal acidosis, nausea, vomiting, vertigo, and reduced uteroplacental perfusion. The prevention of post-spinal hypotension should also be included in the anesthetic treatment of cesarean section.

A typical therapy in case of spinal-induced hypotension is pure a-adrenergic agonist and vasopressor phenylephrine. As administered, it corrects the systemic vascular resistance and stabilizes the maternal blood pressure. Nevertheless, it can cause reflex bradycardia and the decrease of cardiac output and thus, have adverse effects on uteroplacental perfusion due to the fact that it only acts in the a-adrenergic receptor.

One possible substitute is the a-adrenergic moderate b-adrenergic agonist norepinephrine. B-adrenergic activity of this substance prevents hypotension in addition to controlling heart rate and cardiac output. Recent studies have shown that norepinephrine can be used to improve hemodynamic stability and reduce the occurrence of bradycardia as compared to phenylephrine. Nonetheless, most of the studies that have been conducted so far have concentrated on norepinephrine infusions and none of them have explored bolus dosages of the two drugs on prophylaxis.

A study that enables the comparison of safety and effectiveness of norepinephrine bolus doses with those of phenylephrine is necessary since we are in need of a vasopressor that would be effective without posing threats to the health of the unborn child of the mother or the heart output of the mother. This study will seek to identify the existence of better hemodynamic stability at reduced adverse effects, and hence prevent post-spinal hypotension, in women undergoing caesarean sections using vasopressors.

OBJECTIVES

- To compare the efficacy of prophylactic phenylephrine bolus versus norepinephrine bolus in preventing post-spinal hypotension in women undergoing cesarean section under spinal anesthesia.

Chapter 2

LITERATURE REVIEW

When there is subarachnoid block, there are increased chances that maternal hypotension is experienced during a cesarean section. Prophylactic vasopressor therapy is becoming highly important when anesthetizing pregnant women with a subarachnoid block (3,4). The reason is that approximately 60% of mothers that undergo cesarean section experience post-spinal hypotension (PSH) without them. Some of the vasopressors that are used in PSH prophylaxis are ephedrine, norepinephrine (NE), and phenylephrine (PE) (3, 5). PE is the best vasopressor to aid in the management and prevention of PSH (5). PE is usually administered to individuals with cardiovascular issues or a low heart rate as it is a strong a adrenergic agonist with the ability to result in reflex bradycardia (6). Moreover, NE may be used as an alternative to PE in the obstetric group as it has a minimal impact on cardiac depression due to its weak b adrenergic agonistic effect (8). We are yet to gather sufficient information to draw out any conclusive conclusions about NE vs. PE. Ngan Kee et al. (9), in the comparison of the two drugs when they are utilized during a cesarean section. were using a computerized infusion. In an open-labeled study, Vallejo et al. compared the fixed-infusion of PE and NE in cesarean delivery (10).

The study by Sharma et al. was a randomised controlled trial (RCT) to determine a comparison of norepinephrine and phenylephrine boluses on the reduction of spinal-induced hypotension in the process of cesarean section. There were fifty patients who were to have an elective caesarean section under spinal anesthetic and the patients were randomly allotted to two equal groups. Group N and Group P received four mg intravenous boluses of norepinephrine and fifty mg intravenous boluses of phenylephrine respectively. The study with a p-value of 0.001 found that the norepinephrine group required significantly few vasopressor boluses (1.40 +- 0.577) as compared to the phenylephrine group. Bradycardia that occurred in the norepinephrine group (4) and that in the phenylephrine group (20) were statistically non different according to statistical analysis. Nor were there any disparities in neonatal outcomes or in the experience of shivering, vomiting, or nausea in the women. The researchers concluded that in caesarean sections, norepinephrine

intermittent boluses are safe in mothers and babies and effective in the treatment of caesarean-induced spinal-induced hypotension (5).

In a randomised controlled trial (RCT) by Singh et al., preventive norepinephrine (NE) and phenylephrine (PE) infusion was studied on how effective it is in the prevention of postspinal hypotension after cesarean delivery. The 130 pregnant women who were to undergo cesarean sections were randomized to one of the following spinal cord injections of 5mg/min NE, or 25mg/min PE. The sole outcome was the incidence of hypotension, whereas secondary events were maternal bradycardia, reactive hypertension, neonatal acid-base status, nausea, and vomiting and the requirement of atropine or rescue vasopressors. In the PE group, hypotension was found in 33.8 percent and in the NE group, it was found in 26.1 percent (P = 0.85). As it was found, NE was not inferior as the absolute risk difference was -7.7% (90% CI: -20.9 to 5.4) and the upper limit of the confidence interval was not bigger than the pre-established non-inferiority margin of 20%. Researchers discovered that preemptive NE infusion was equally good as PE infusion in the prevention of postspinal hypotension after the caesarean sections but it did not increase susceptibility to adverse effects on the mothers or the newborns (8).

Kothari et al. compared norepinephrine (NE) and phenylephrine (PE) infusions in terms of their equal effectiveness in preventing postspinal hypotension following a cesarean delivery through the randomised, double-blind controlled trial (RCT). During the spinal injection, 130 patients of elective cesarean delivery were randomly given either 5 mg/min NE or 25mg/min PE. The primary outcome was hypotension, and secondary outcome was the acid-base situation of the baby, maternal bradycardia, reactive hypertension, nausea, vomiting and need of rescue vasopressors or atropine. Hypotension was observed in 26.1 and 33.8 percent of NE patients and PE patients respectively with a p value of only 0.85. The upper limit of the 90% confidence interval was also contained in the 20% non-inferiority margin and the difference in absolute risk was 7.7%. The interval distribution was between -20.9 and 5.4. NE and PE infusions have the same effect on the prevention of postspinal hypotension, and the safety profile of both the mother and the newborn is similar (12).

Rao et al. developed a comparative observational study and examined the effectiveness of prophylactic bolus dose of noradrenaline and phenylephrine in the prevention of hypotension induced by spinal as well as the determination of fetal

outcomes following a cesarean delivery under the spinal anesthesia. 102 pregnant women participated in the study, 51 of them were administered with 100 ug of phenylephrine and 8 ug of noradrenaline right after spinal anesthesia. Further boluses were administered when needed to maintain systolic blood pressure (SBP) at 90 per cent or more of the baseline level. At one minute following spinal anesthesia, mean heart rates, systolic blood pressures, mean arterial pressures and diastolic pressures were significantly greater in the noradrenaline group than in the control group (90.1 vs. 87.3, 89.5 vs. 78.6 and 74.6, respectively) ($P < 0.05$). However, at subsequent periods of time, these differences were not statistically significant ($P>0.05$). The rates of maternal problems that took place in both groups were similar, i.e. bradycardia, hypotension, nausea, and vomiting and neonatal outcomes like Apgar scores. Noradrenaline and phenylephrine as prophylaxis have been shown to share the same benefits regarding prevention of spinal hypotension and improvement of initial hemodynamic stability (3).

Ahmed et al. conducted a double-blind randomized controlled trial (RCT) to determine the efficacy of norepinephrine and phenylephrine boluses in the prevention of spinal anesthesia to reduce spinal anesthesia-induced hypotension (SAH) in emergency caesarean births at Dr. Ruth K.M. Pfau Civil Hospital in Karachi. The pregnant women were divided in equal proportions into two groups and either were given 100 mg of phenylephrine (P) or 8 mg of norepinephrine (N). All the participants were selected randomly. The groups were comprised of sixty-two patients each. The primary objective was hypotension following spinal anesthesia, and the secondary objectives were the necessity of extra boluses of vasopressor, maternal issues, and baby Apgar scores. The rate of incidence of SAH was 56.5 and 37.1 in the phenylephrine and norepinephrine group respectively, $p = 0.031$. Also, the frequency of newborns with an Apgar score of < 7 at one minute was significantly different in the groups; the rate of newborns with phenylephrine was 33.9 times higher than that of norepinephrine (p-value = 0.0005). The authors discovered that prophylactic norepinephrine was better than phenylephrine (2) to use in emergency caesarean surgeries to improve the outcomes of infants and prevent the occurrence of SAH (12).

In the study by Wang et al., a prospective and randomized, double-blind study was conducted to study the outcomes of prophylactic norepinephrine and phenylephrine infusion to the fetus with the use of spinal anesthesia in the delivery of a baby

through cesarean section. 223 women, who had a single child born in a normal pregnancy and were scheduled to deliver an infant through elective cesarean delivery, were used in the study. To prevent the hypotension following spinal anesthesia, the participants were given a phenylephrine or norepinephrine infusion of 0.08 or 0.5 TMG/kg/min, respectively. The primary results were changes in fetal cardiac output and heart rate as measured noninvasively with Doppler ultrasonography before and after spinal anesthesia. To carry out the study, 90 subjects were norepinephrined and 93 phenylephrined. Six minutes after the subarachnoid block, the fetal cardiac output decreased significantly to generate a significant difference in fetal cardiac output between the two groups (mean difference 0.02 L/min; 95% CI, 0-0.04 L/min; $P < 0.05$), although not significantly different in the two groups. They did not identify any substantial adverse effects on fetal circulation or infant outcome and expected infusion of norepinephrine and phenylephrine at similar dosage produced the same impact on fetal heart rate and cardiac output (8).

To find out which prophylactic infusion; phenylephrine or norepinephrine was safer and more effective in prevention of post-spinal hypotension when using such prophylaxis in caesarean births induced by spinal anesthesia, Kumar et al. performed a randomised clinical trial (RCT). Profession Group P was infused with 0.75 mg/kg/min of phenylephrine and Group N with 0.05 mg/kg/min of norepinephrine. 164 ASA I and II pregnant women were randomly grouped in both groups. Some of the secondary outcomes included bradycardia, total rescue bolus dosages, maternal side effects, infant Apgar scores, post-spinal hypotension occurrence, reactive hypertension, severe hypotension and physician interventions. Both groups had similar incidences of severe hypotension (2.4% vs. 3.6% $p > 0.05$), incidence of post-spinal hypotension (29.3% in Group N vs. 24% in Group P; $p > 0.05$) and other maternal problems. The phenylephrine group however, needed medical interventions much more than the norepinephrine group (39% vs. 28; $p < 0.05$). At 1 and 5 minutes of age, the infants were found to perform well in both groups in terms of Apgar scale. Norepinephrine was also determined to be equally effective as phenylephrine in the prevention of post-spinal hypotension with similar hemodynamic stability and less medical treatments (11).

Li et al. conducted randomised dose-finding study that aimed at determining the effective dose (ED90), relative potency ratio of norepinephrine (NE) and

phenylephrine (PE) as preventive boluses to prevent hypotension after spinal anesthesia in caesarean deliveries. After the spinal anesthesia, 80 of the parturients previously scheduled to deliver via elective cesarean section were randomized to either PE or NE boluses. The ED90 of NE was 8.0 mg (95% CI: 7.1-11.0 mg), and PE was 90.9mg (95% CI: 82.0-123.9 mg). The proportion of the relative potency ratio was 11.4:1. This was through a sequential allocation method which is up and down. Secondary outcome measures indicated that bradycardia was much lower in the NE group (2.5% vs. 20%; P = 0.034) as compared to the PE. Conversely, several maternal and newborn outcomes were equally prevalent in both groups and they included; Apgar scores, hypotension, severe hypotension, nausea, vomiting and umbilical artery blood gas levels. The authors of the study determined that prophylactic boluses of 8 mg norepinephrine and 90 mg phenylephrine are effective inahoo preventing hypotension that is induced by spinal anesthesia. It is also interesting to mention that the bradycardia was less frequent in the presence of norepinephrine.

Moreover, due to its small b adrenergic agonistic effect, NE cannot exert cardiac depressing effect as compared to PE and therefore is a better alternative in the obstetric population (8,9). We do not have sufficient information to come up with any conclusive decision on NE vs. PE. Ngan Kee et al. (19) applied a computerized method of infusion to compare the two drugs in a caesarean section. In an open-labeled study by Vallejo et al., the fixed-infusion of PE and NE was compared in cesarean delivery (10). No randomized controlled trials assessing the efficiency of titration of the infusion of either one of the mentioned medications during a cesarean section were located.

Spinal anesthesia is the most widely and advised method of anesthesia used during cesarean births. Since the obstetric airway control may be challenging, this population does not need airway manipulation with the use of spinal anesthetic. Hypotension as a side effect caused by spinal anesthesia (SAH) in obstetric patients undergoing cesarean section is a frequent and potentially harmful side effect (56.8). Spinal anesthesia leads to sympathetic inhibition, resulting in vasodilation and decrease in venous return, which results in decreased cardiac output and systemic vascular resistance. The harmful feto-maternal effects are nausea, vomiting, fetal acidosis and in worst scenario, the blood pressure drop may cause intrauterine fetal death due to its ability to impair the uteroplacental blood flow.

To ensure that there is no hypotension due to spinal anesthesia, there are a number of strategies employed. Commonly, colloids are co-loaded, or crystalloids are preloaded with 10-15 ml/kg of crystalloids. It has been countered by numerous vasopressors which cause vasodilation. The preferred drug in the treatment of hypotension caused by spinal anesthesia is phenylephrine (4). Phenylephrine is an alpha-1 agonist that inhibits sympatholytic-induced vasodilation. It enhances the cardiac output and preserves preload. Phenylephrine has a dangerous side effect of reflex bradycardia (5).

Norepinephrine is a new vasopressor used to treat and prevent hypotension that is caused by the neuraxial anesthesia. It possesses another b1 effect and is a strong vasopressor. This would be a superior dual treatment than phenylephrine, potentially to offer more stable hemodynamics and thus may reduce the occurrence of reflex bradycardia and enhance cardiovascular stability in the mother. It has also been recently successfully utilized in addressing obstetric and geriatric populations in the treatment of hypotension that is a result of spinal anesthetic. Norepinephrine has been used as bolus doses and infusions seven times. Most of the studies involve the use of infusion pumps (8,9). Norepinephrine safe doses of bolus and infusion have been accurately calculated. Many researches on the bolus doses distribution have been conducted. Recent survey gave ED90 of prophylactic norepinephrine and phenylephrine boluses of 8.0 mg (95% CI 7.1-11.0 mg) and 90.9 mg (95% CI 82.0-123.9 mg), respectively (10, 11).

The outcome of the use of norepinephrine to treat hypotension induced by spinal anesthesia is similar when applied on the newborn (12,13). In a recent study, the hemodynamic parameters in parturients undergoing elective and emergency cesarean section were compared and the outcome indicated statistical difference between the two. 14. Norepinephrine has been administered with great success to reverse hypotension following the spinal anesthesia in individuals undergoing elective cesarean surgeries (15).

This paper aims to determine the efficacy of bolus norepinephrine and phenylephrine that are given before an emergency cesarean section. In the case of our country, being a developing country the extensive application of the medicine is financially beneficial, and the statistics were too weak in our area. The majority of the research has concerned elective cases with the use of infusion pumps; we examined the doses of the drug in bolus in emergency caesarean sections. This experiment will help

identify the optimal vasopressor among this high-risk group of patients by evaluating hemodynamic stability, adverse effects, and neonatal and maternal outcome.

The control of hypotension during spinal anesthesia in cesarean delivery is one of the biggest issues of obstetric anesthesia. The most effective way of preventing and treating hypotension in the post-spinal anesthesia mode of cesarean section is to administer vasopressors.

Ephedrine has been a preferred choice due to its ability to sustain the flow of blood to the uterus by its adrenergic beta-effect (11). The use of phenylephrine has also substituted the use of ephedrine because it was found to cause an acid-base imbalance in the fetus (21). The effect of phenylephrine on reducing maternal cardiac output could be a result of the capacity of this drug to induce bradycardia and raise the total vascular resistance. Despite glycopyrrolate being administered to the bradycardia induced by phenylephrine, its action is short-lived and may not always be effective (13).

Norepinephrine can be one of the potential alternatives to address these issues (14). Nevertheless, the safety of norepinephrine on the fetus remains disputable, and, thus, clinical studies that compare the two drugs to phenylephrine in this case are required. Greater likelihood of fetal acidity with use of spinal anesthetic is likely due to maternal hypotension or may be the effect of medications in treating or preventing hypotension. Ephedrine is an indirectly-acting agonist which stimulates a- and b-adrenergic receptors. As a survey has recently revealed, 95% of consultant obstetric anesthetists in the UK have only used vasopressor. The use of a-adrenergic drugs including phenylephrine was much less frequent. Previous studies on pregnant sheep have shown that using a-adrenergic agonists in the treatment of hypotension results in low uteroplacental perfusion relative to the use of ephedrine (16). Recent studies have demonstrated that phenylephrine is safe even in pregnant ewes (17). Ephedrine induces tachyphylaxis and has been linked to the acidosis of the fetus in prophylactic use (18). In recent years, a quantitative systematic review of trial comparing ephedrine and phenylephrine was published. 11 The two vasopressors were found to have equal impact on blood regulation but phenylephrine was reported to induce high blood pressure in the umbilical arteries compared to ephedrine at delivery. There were no differences in APGAR scores (appearance, pulse, grimace, activity, and respiration) under 7 at 1 and 5 minutes, and the rate of fetal acidosis (umbilical artery pH below 7.20) (13).

Unlike when ephedrine is used as the initial therapy, our convention revealed that the application of a combination of phenylephrine and ephedrine as the first-line vasopressor therapy was linked to a reduced frequency of fetal acidosis at birth (12). To ensure that the systolic arterial pressure of the mother remains at the normal range during spinal anesthesia, the incidence of fetal acidosis in elective cesarean delivery with administration of phenylephrine, ephedrine, or both should be compared. The maternal nausea and vomiting rates with the three infusions were compared in spinal anesthesia.

Chapter 3

METHODOLOGY

3.1. Research Design

A comparative cross-sectional study was conducted.

3.2. Clinical Settings

The study was carried out at Services Hospital Lahore.

3.3. Sample Size

With openEpi, a statistical program which is open-source, the sample size in this study was calculated by using a finite population formula where the total population size (N) was felt to be one million. The frequency of the outcome factor (p) in the population was established at 46.77 with an absolute precision (d) of +-5%. In this investigation, the design effect (DEFF) was applied since the cluster sampling was not applied. The above criteria were employed to estimate the sample required to achieve the confidence level of 95% and this was 280 people.

3.4. Sampling Technique

A convenience sampling technique was used.

3.5. Duration of Study

The duration of the study was four months.

3.6. Selection Criteria

3.6.1. Inclusion Criteria

- Pregnant women aged 18–40 years.
- Expectant women who are aged 18 to 40.
- ASA physical I or II. Single-term pregnancy (gestational age 37 weeks).
- Planned a spinal anesthetic elective cesarean section.
- Study participants that provided their informed permission in writing.

3.6.2. Exclusion Criteria

- Individuals who have a history of norepinephrine or phenylephrine hypersensitivity.
- Pre-existing pregnancy-related hypertensive diseases, such as chronic hypertension, eclampsia, or preeclampsia.
- Cardiovascular conditions, such as heart failure, ischemic heart disease, and arrhythmias.
- Endocrine conditions that impact blood pressure, such as hyperthyroidism and pheochromocytoma.

- Multiple pregnancies, such as triplets or twins.
- Cases of emergency cesarean sections.
- Individuals who are not suitable candidates for spinal anesthetic, such as those with coagulopathy, puncture site infections, or severe hypovolemia.
- Any vasoactive medication taken within 24 hours before surgery.
- Placenta previa and placental abruption are examples of known placental anomalies.
- Refusing to take part in the research.

3.7. Ethical Consideration

Assent of the Institutional Ethics Review Board was obtained before the implementation of the study. After a detailed explanation of the purpose of the study, the procedures, risks, and benefits of the study in a language to which they all could comprehend, the participants were required to sign an informed consent form. The participants were informed that their data will remain confidential and that it would not affect the treatment given in the study provided that they opt to drop out at any stage. The principles of the Declaration of Helsinki and Good Clinical Practice (GCP) were adhered to during the study execution.

3.8. Data Collection Procedure

The prospective data collection was initiated after the approval of the ethics committee of the hospital and the institutional review board of Superior University (IRB). Eligible parturients who met the inclusion criteria were recruited after signing their informed consent forms in writing. The identities and personal information of the participants were protected at all the stages.

Demographic information (maternity), intraoperative hemodynamic measurements, vasopressor requirement, neonatal outcomes (apgar and umbilical cord blood gas) and adverse events were all collected. All the data was entered into a pre-made proforma and stored safely to be analyzed. The patients were administered 10mg of metoclopramide and 50mg of ranitidine intravenously when they had fasted throughout the night. Non-invasive blood pressure, SpO2 and ECG monitors were attached to patients immediately they entered the operating room (OR). The patient was kept in a supine position with the left side tilted and three readings were taken at a 2 minutes interval to measure the baseline blood pressure and heart rate.

Following the insertion of an 18G IV cannula, coloading was done with 500 mL of lactated Ringer. External cardiotocography was used to monitor fetal heart rate up to

the commencement of the procedure. A qualified anesthesiologist injected the spinal injectate at L3-L4 with 150 ug of preservative-free morphine and 10 mg of hyperbaric bupivacaine. After block installation, the patients were put in the left lateral tilt and, as per group assignment, started to receive a 15 mL/h vasopressor infusion: The 1st group (PE group): 100 ug/mL of phenylephrine with 25 ug/min rate.

*Group 2 (NE group): 5 ug/min (20 ug/mL) of norepinephrine.

Spinal block failure was not found in either of the groups. The adequacy of SAB was evaluated by loss of cold sensation up to T4-T5 dermatome. Blood pressure and heart rate were recorded at one-minute intervals until delivery of the fetus. Then they were recorded after every five minutes until the process was complete. Hypotension was considered to be SBP less than 100 mmHg or [?]20% of the baseline. In case of necessity, 25 ug IV phenylephrine rescue boluses were administered. Because of reactive hypertension (>20 percent of changes in SBP compared to baseline), the infusion was halted. Atropine (0.3mg IV) was administered to correct bradycardia (HR <50bpm).

Postpartum Oxytocin (10IU in 500 mL NS) was started. Data were recorded at the time of uterine closure and termination of the study medication 4 mg of ondansetron IV and 1 g of paracetamol were administered before discharge. The primary goal of the study was to find out the frequency rates of hypotension in mothers after SAB. Secondary outcome was maternal bradycardia, reactive hypertension, nausea, vomiting, the necessity of using vasopressors or atropine, the acid-base condition of the newborn. Apgar was recorded after one and five minutes.

3.9. Data Analysis

All statistical analysis was done using IBM SPSS version 26.0 (SPSS Inc., Chicago, USA). Categorical data were represented using frequencies and percentages whereas the mean +- standard deviation was applied when representing continuous variables. Categorical variables were compared by means of Pearson Chi-square test with continuity correction. Independent samples t-tests were applied in order to compare the group means. Paired samples t-tests were used to compare apgar at 1 and 5 minutes in each group. The cut-off point of statistical significance was set to 0.05.

Chapter 4

RESULTS

The study population consisted mostly of women aged 25 to 34 old with 31.4 percent and 32.9 percent of women belonging to the 25-29 age group and 30-34 age group, 18.6 percent and 17.1 percent of women belonging to the 18-24 age group and 35-40 age group respectively. Concerning the BMI, 20.7 percent were normal in BMI, 32.1 percent were obese, and almost half (47.1) were overweight. Most of the participants (57.0%), were within 39-40 gestation periods, 27.0% were within 37-38 gestation periods and 14.3% had gone beyond 40 gestation weeks. Most of them were multigravida (58.6) as opposed to primigravida (41.4). Most ASAs (67.1) were of physical status I and 32.9% ASAs had a physical status of II. Only 1.4% stated that they were allergic to vasopressor, a minute percentage had a history of cardiovascular disease (3.6%), or high blood pressure (8.6%). No emergency cases were indicated and all the cesarean sections were elective.

Table 4.1 Study Characteristics and Demographics of the participants (n = 280)

Variable	**Category**	**Frequency (n)**	**Percentage (%)**
Age (years)	18–24	52	18.6
	25–29	88	31.4
	30–34	92	32.9
	35–40	48	17.1
BMI Category	Normal (18.5–24.9)	58	20.7
	Overweight (25–29.9)	132	47.1
	Obese (≥30)	90	32.1
Gestational Age (weeks)	37–38	78	27.9
	39–40	162	57.9
	>40	40	14.3
Parity	Primigravida	116	41.4
	Multigravida	164	58.6
ASA Status	I	188	67.1
	II	92	32.9

History of Hypertension	Yes	24	8.6
	No	256	91.4
History of Cardiovascular Disease	Yes	10	3.6
	No	270	96.4
Allergy to Vasopressors	Yes	4	1.4
	No	276	98.6
Indication for Cesarean	Elective	280	100
	Emergency	0	0

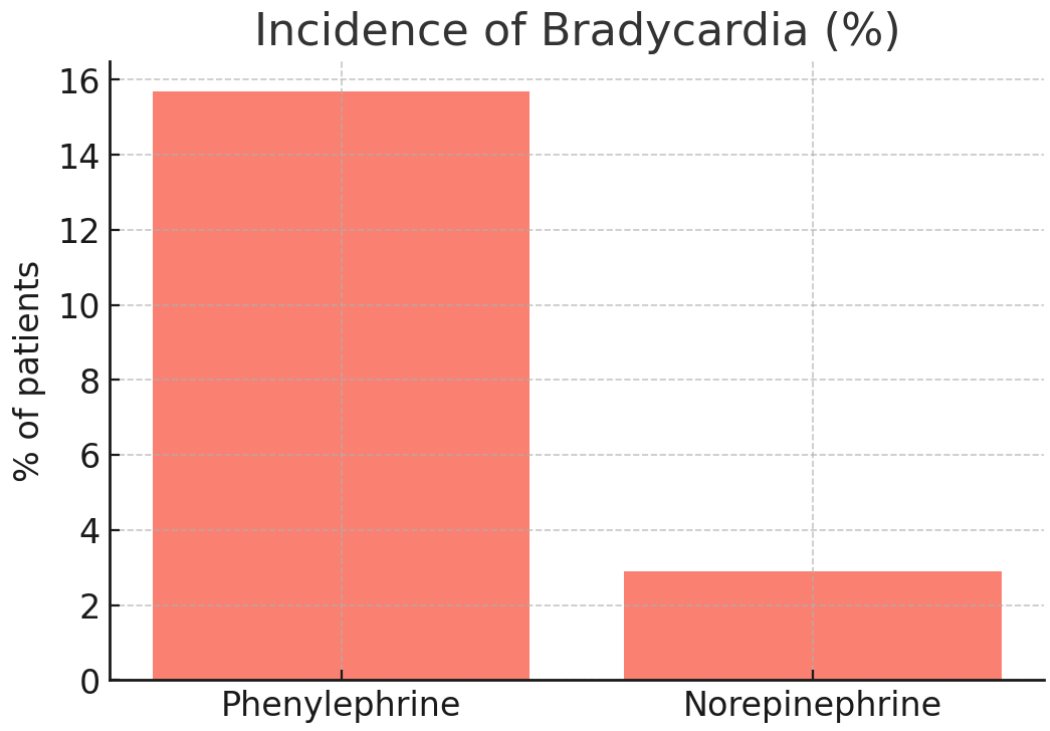


FIGURE 4.1 INCIDENCE OF BRADYCARDIA

The measured hemodynamic profile of the study population indicated that most of the participants had systolic blood pressures ranging between 120 and 129mmHg (39.3%), 110 and 119mmHg (35.0%), and lower percentages of systolic blood pressures were recorded between 100 and 109mmHg (13.6%) and [?]130mmHg (12.1%). Most of the diastolic blood pressure was in the 70-79 mmHg range (51.4), then 60-69 mmHg (27.1), and 80-89 mmHg (21.4). The commonest baseline heart rate was 80-89 bpm (47.9) then 70-79 bpm (33.6), and lastly 60-69 bpm (18.6). Regarding the delivery of preoperative medication, although most of them (77.1) did

not receive preoperative medications, 22.9 percent of subjects received preoperative medications.

Table 4.2 Preoperative Evaluation (n = 280) of the participants.

Variable	Category	Frequency (n)	Percentage (%)
Baseline Systolic BP (mmHg)	100–109	38	13.6
	110–119	98	35.0
	120–129	110	39.3
	≥130	34	12.1
Baseline Diastolic BP (mmHg)	60–69	76	27.1
	70–79	144	51.4
	80–89	60	21.4
Baseline Heart Rate (bpm)	70–79	94	33.6
	80–89	134	47.9
	≥90	52	18.6
Preoperative Medications Given	Yes	64	22.9
	No	216	77.1

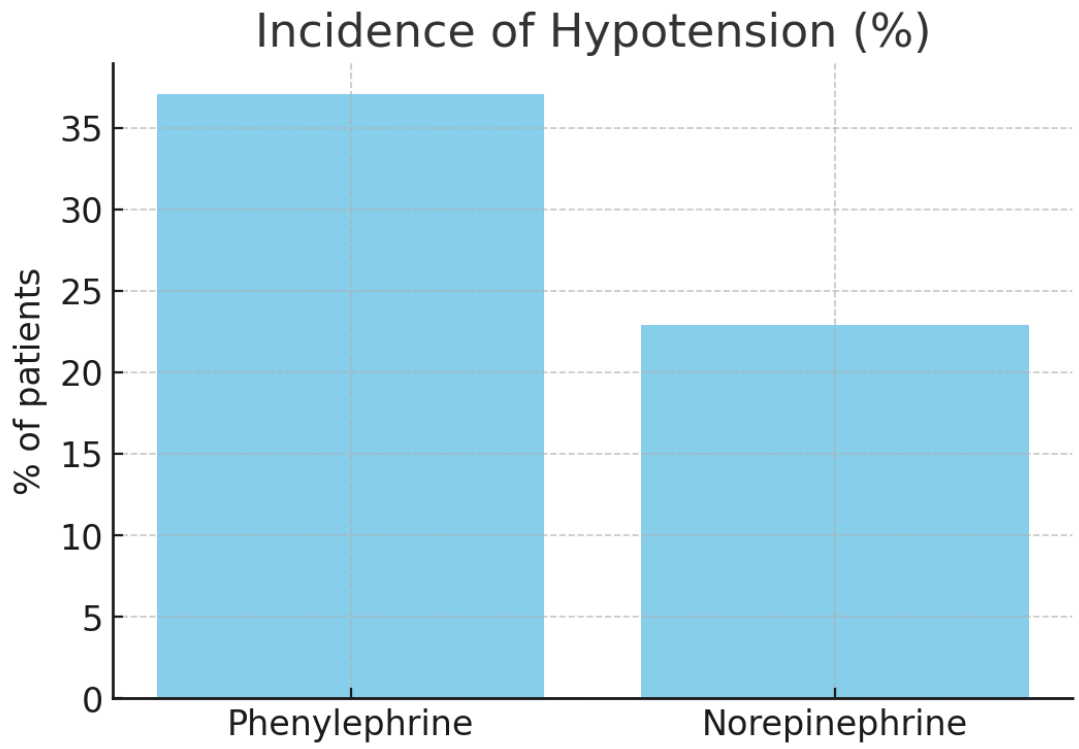


FIGURE 4.2 INCIDENCE OF HYPOTENSION

This group was administered prophylactic vasopressors in the same quantity as phenylephrine and norepinephrine (25:25). Those getting phenylephrine 62.9% got 80-100 mcg and 37.1% got 50-75 mcg and 42.9% got 4-6 mcg as compared to those getting norepinephrine 57.1% got 7-9 mcg and 42.9% got 4-6 mcg. The administration time was also variable with 13.6 percent of them administered two minutes after a spinal anesthesia, 39.3 percent right before it and 47.1 percent during spinal anesthesia. Pre-spinal IV fluids consisted of 500-999 mL (62.9%), 24.3% less than 500mL, 12.8% [?]1000mL; intraoperative fluids were 1000-1499mL (55.0%). Most patients (59.3 percent) were getting T4 spinal blocks, T5 (30.7 percent), and T6 (10.0 percent). Delivery occurred in 50.7% of cases (10-15 minutes of the spinal), and 30.0% had hypotension, and it was mostly in one episode (57.1%). Most patients had the lowest systolic and diastolic blood pressures of 80-89 mmHg (52.4%), and 50-59 mmHg (57.1%), respectively, and 20.7% of patients were receiving rescue vasopressors mostly phenylephrine (62.1%), and bradycardia was infrequent (9.3%). 15.0% of patients also experienced nausea or vomiting after surgery and 17.1% experienced shivering.

Table 4.3 Intraoperative Data of the participants (n = 280)

Variable	**Category**	**Frequency (n)**	**Percentage (%)**
Drug Administered Prophylactically	Phenylephrine	140	50.0
	Norepinephrine	140	50.0
Phenylephrine Dose (mcg) *(n = 140)*	50–75 mcg	52	37.1
	80–100 mcg	88	62.9
Norepinephrine Dose (mcg) *(n = 140)*	4–6 mcg	60	42.9
	7–9 mcg	80	57.1
Time of Administration	Immediately before spinal	110	39.3
	At time of spinal	132	47.1
	After spinal (<2	38	13.6

	min)		
IV Fluids Before Spinal (mL)	<500 mL	68	24.3
	500–999 mL	176	62.9
	≥1000 mL	36	12.8
IV Fluids During Surgery (mL)	500–999 mL	72	25.7
	1000–1499 mL	154	55.0
	≥1500 mL	54	19.3
Level of Spinal Block Achieved	T4	166	59.3
	T5	86	30.7
	T6	28	10.0
Time From Spinal to Delivery (minutes)	<10 min	88	31.4
	10–15 min	142	50.7
	>15 min	50	17.9
Hypotension Episodes	Yes	84	30.0
	No	196	70.0
Number of Hypotensive Episodes *(n = 84)*	1 episode	48	57.1
	2 episodes	26	31.0
	≥3 episodes	10	11.9
Lowest Systolic BP (mmHg) *(n = 84)*	70–79	22	26.2
	80–89	44	52.4
	90–99	18	21.4
Lowest Diastolic BP (mmHg) *(n = 84)*	40–49	20	23.8
	50–59	48	57.1
	≥60	16	19.1
Bradycardia (HR < 50 bpm)	Yes	26	9.3
	No	254	90.7

Need for Rescue Vasopressor	Yes	58	20.7
	No	222	79.3
Type of Rescue Drug *(n = 58)*	Phenylephrine	36	62.1
	Ephedrine	22	37.9
Nausea/Vomiting Observed	Yes	42	15.0
	No	238	85.0
Shivering Observed	Yes	48	17.1
	No	232	82.9

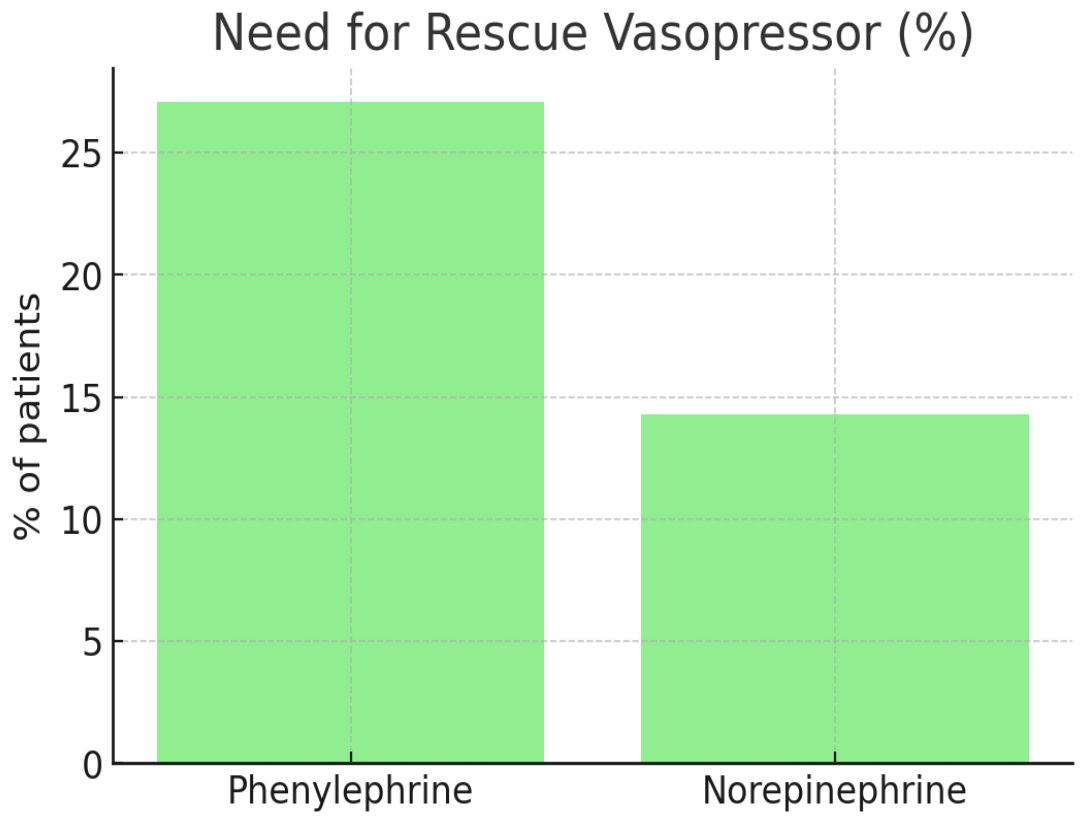


Figure 4.3 Need for Rescue vasopressor

The neonatal outcomes were mostly favorable with 80.0 percent of babies achieving an APGAR score of 9-10 at 1 minute and 100 percent of all babies achieving an APGAR score of 9-10 at 5 minutes. Most of the birth weights were between 2900-3299 g (50.0%), 3300-3800 g (32.9) and 2500-2899 g (17.1). Only a small portion of the newborns (4.3) had to undergo resuscitation and a small portion of those (3.6) were hospitalized to the intensive care unit. The key causes of NICU hospitalization

were transient tachypnea (40.0%), low birth weight (30.0%), meconium aspiration (20.0%), and sepsis assessment (10.0%). Overall, the majority of the newborns had no significant issues and average-first-outcome.

Table 4.4 Neonatal Outcomes (n = 280)

Variable	**Category**	**Frequency (n)**	**Percentage (%)**
APGAR Score at 1 Minute	7–8	56	20.0
	9–10	224	80.0
APGAR Score at 5 Minutes	9–10	280	100
Birth Weight (grams)	2500–2899 g	48	17.1
	2900–3299 g	140	50.0
	3300–3800 g	92	32.9
Neonatal Resuscitation Required	Yes	12	4.3
	No	268	95.7
Admission to NICU	Yes	10	3.6
	No	270	96.4
Reason for NICU Admission *(n = 10)*	Transient tachypnea	4	40.0
	Low birth weight	3	30.0
	Meconium aspiration	2	20.0
	Sepsis evaluation	1	10.0

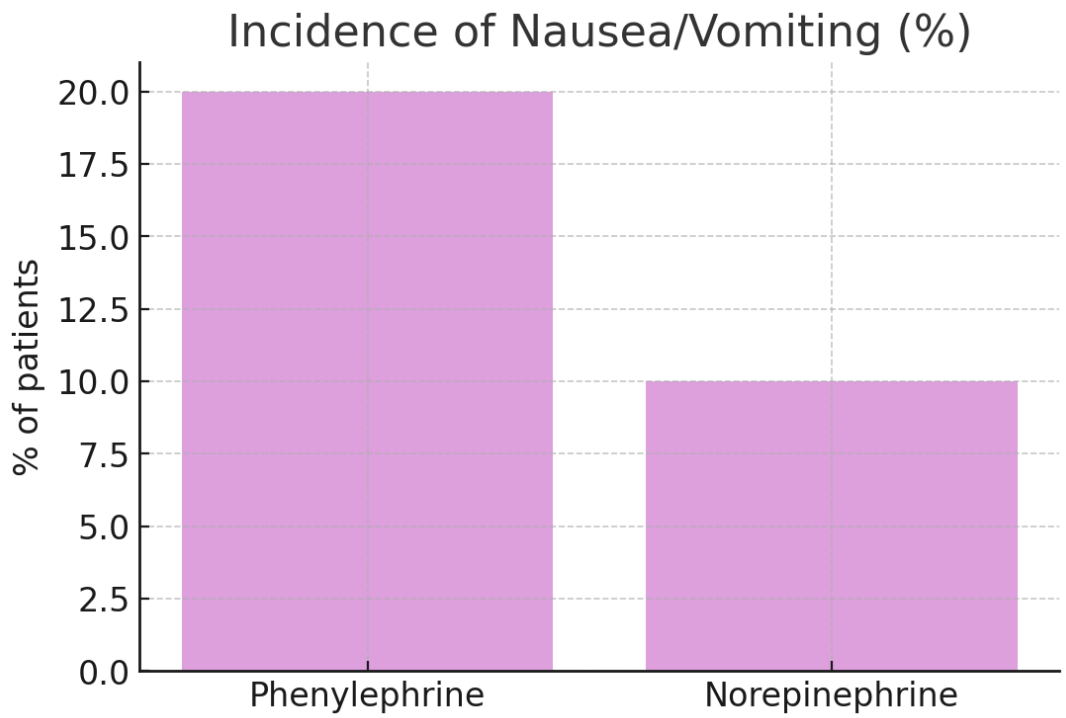


Figure 4.4 Incidence of Nausea Vomiting

Most of the patients were stable with regard to blood pressure post-surgery with systolic blood pressure a range of 110 to 119 mmHg (45.7%), and diastolic blood pressure between 70 and 79 mmHg (47.1%). 30-minute adverse symptoms included headache (42.1%), dizziness (31.6%), and nausea (21.1%). The high patient-satisfaction rate of 70.7 percent (out of 10) 18.6 percent (out of 10) and 10.7 percent (out of 10) showed that overall, positive postoperative outcomes and satisfaction were achieved.

Table 4.5 Postoperative Observations of Mothers (n =280)

Variable	**Category**	**Frequency (n)**	**Percentage (%)**
Postoperative Systolic BP at 30 min (mmHg)	100–109	62	22.1
	110–119	128	45.7
	120–129	68	24.3
	≥130	22	7.9
Postoperative Diastolic BP at 30 min (mmHg)	60–69	94	33.6

	70–79	132	47.1
	80–89	54	19.3
Adverse Effects Reported	Yes	38	13.6
	No	242	86.4
Type of Adverse Effect *(n = 38)*	Headache	16	42.1
	Dizziness	12	31.6
	Nausea	8	21.1
	Others	2	5.2
Patient Satisfaction Score (0–10)	6–7	30	10.7
	8	52	18.6
	9	98	35.0
	10	100	35.7

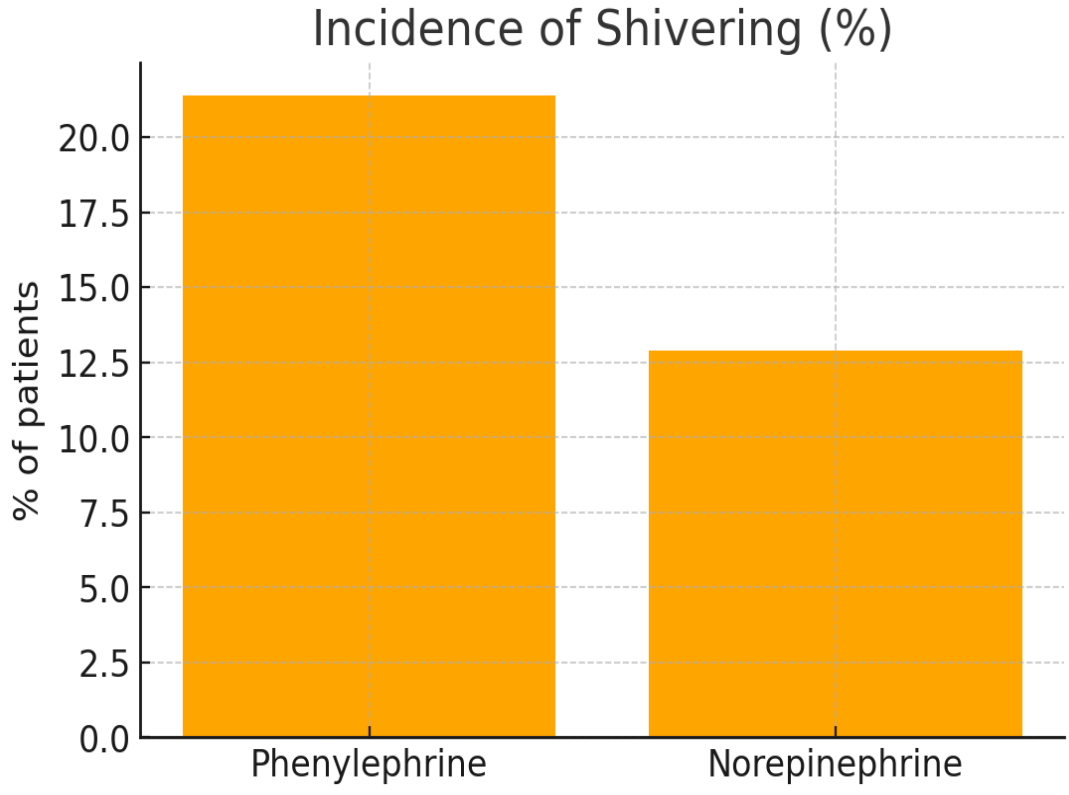


Figure 4.5 Incidence of Shivering

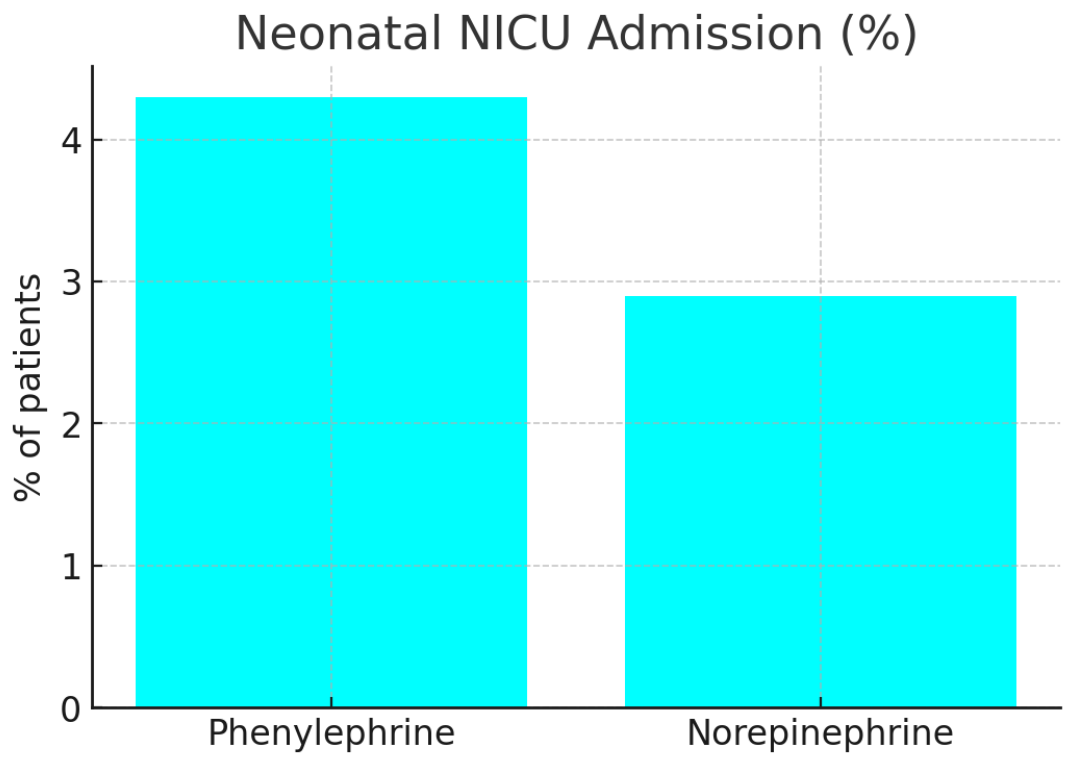


Figure 4.6 Neonatal NICU Admission

There was no significant difference in baseline hemodynamics, as SBP, DBP, MAP and HR ($p > 0.05$), indicating that there was a similar pre-spinal cardiovascular status in the prophylactic phenylephrine and norepinephrine groups. The lowest intraoperative SBP (90 +- 9 vs. 85 +- 10 mmHg, $p = 0.001$), and DBP (58 +- 6 vs. 55 +- 7 mmHg, $p = 0.003$) were significantly higher with the use of norepinephrine, and there were also fewer hypotensive episodes (1.1 +- 0.4 vs. 1.5 +- 0.7, $p = 0.002$), which is The blood pressure of the groups post operation after 30 minutes and time to delivery was similar ($p > 0.05$). Statistically significant yet clinically nonsignificant differences in favor of norepinephrine in terms of hemodynamic stability were statistically significant, though marginally, higher in the norepinephrine than the alternative group (9.5 +- 0.8 vs. 9.2 +- 1.0, $p = 0.02$) with an overall positive rating of care in both conditions.

Table 4.6 Comparison of Hemodynamic Effect of Prophylactic Phenylephrine and Norepinephrine and the patient satisfaction in Cesarean section under spinal anesthesia.

Variable	Phenylephrine (n=140) Mean ± SD	Norepinephrine (n=140) Mean ± SD	p-value
Baseline SBP (mmHg)	118 ± 10	117 ± 9	0.38
Baseline DBP (mmHg)	74 ± 8	73 ± 7	0.25
Baseline MAP (mmHg)	88 ± 9	87 ± 8	0.40
Baseline HR (bpm)	82 ± 10	81 ± 11	0.52
Lowest SBP (mmHg)	85 ± 10	90 ± 9	0.001*
Lowest DBP (mmHg)	55 ± 7	58 ± 6	0.003*
Number of Hypotensive Episodes	1.5 ± 0.7	1.1 ± 0.4	0.002*
Time to Delivery (min)	12.0 ± 3.2	11.8 ± 3.1	0.60
Postoperative SBP at 30 min (mmHg)	118 ± 11	120 ± 10	0.09
Postoperative DBP at 30 min (mmHg)	74 ± 7	76 ± 6	0.06
Patient Satisfaction (0–10)	9.2 ± 1.0	9.5 ± 0.8	0.02*

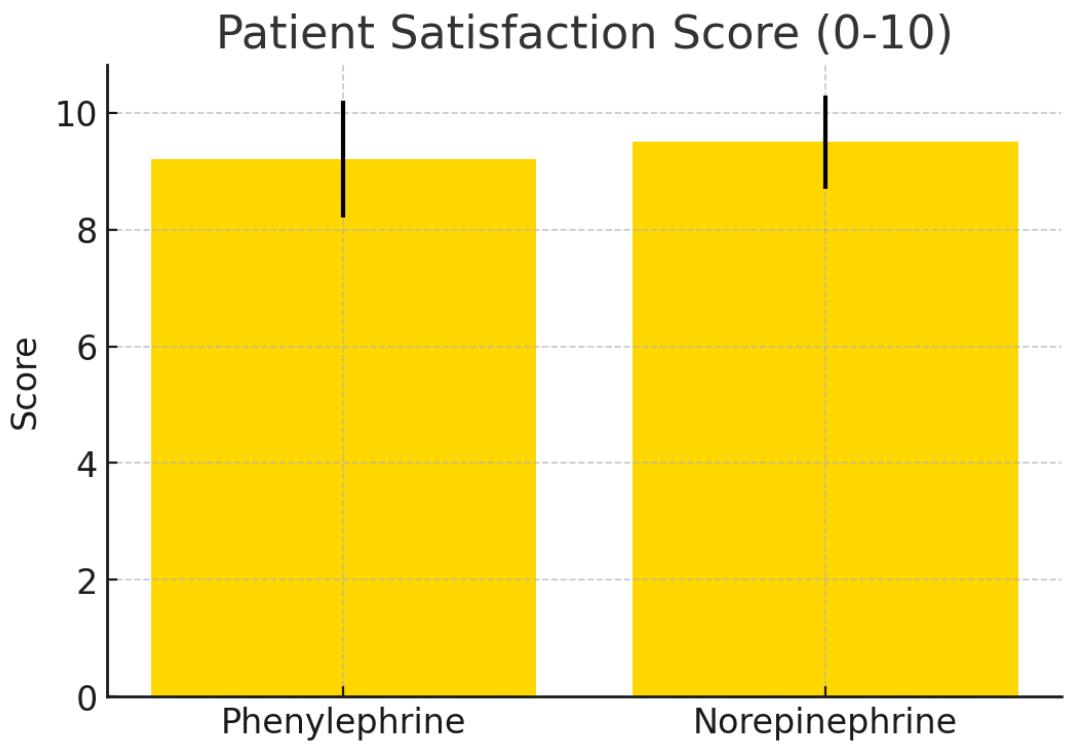


Figure 4.7 Patient Satisfaction

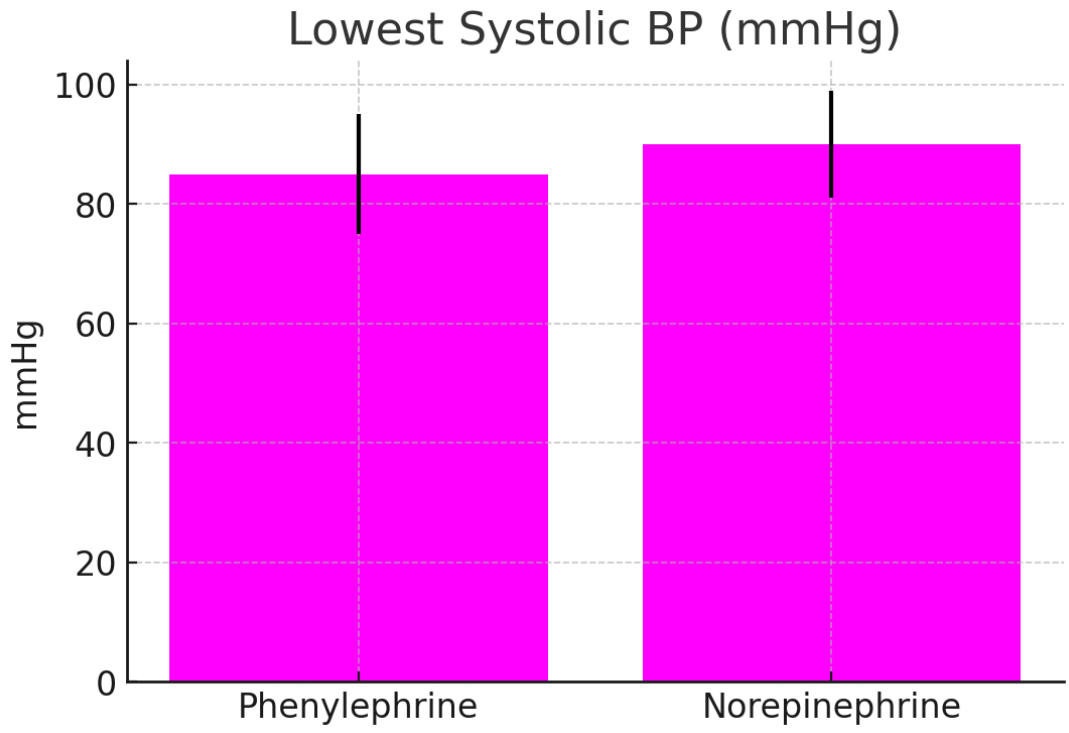


Figure 4.8 Lowest Systolic Blood pressure

When compared to norepinephrine, it was established that the phenylephrine group had much higher rates of bradycardia (15.7 vs. 2.9, p = 0.001), and hypotension

(37.1 vs. 22.9, p = 0.012) in the case of maternal and neonatal outcomes respectively. The phenylephrine group had much higher incidences of nausea and vomiting (20.0% vs. 10.0% p = 0.031) and higher incidences of rescue vasopressors (27.1% vs. 14.3, p = 0.012). Higher shivering was found with phenylephrine (21.4% vs. 12.9%), although the difference was not significant (p = 0.063). An immediate neonatal outcomes effect could not be identified because the low and similar neonatal NICU admissions rates between the groups showed insignificance (4.3 vs. 2.9, p = 0.51). Overall, norepinephrine was associated with fewer negative outcomes and hemodynamic deviations among mothers.

Table 4.7 Major Intraoperative and Neonatal Outcomes by Drug, Cross tabulated (n= 280).

Outcome	**Phenylephrine (n=140)**	**Norepinephrine (n=140)**	**p-value**
Hypotension	52 (37.1%)	32 (22.9%)	0.012*
Bradycardia (HR <50 bpm)	22 (15.7%)	4 (2.9%)	<0.001*
Rescue Vasopressor Required	38 (27.1%)	20 (14.3%)	0.012*
Nausea/Vomiting	28 (20.0%)	14 (10.0%)	0.031*
Shivering	30 (21.4%)	18 (12.9%)	0.063
Neonatal NICU Admission	6 (4.3%)	4 (2.9%)	0.51

Multivariate analysis of logistic regression analysis showed that the type of prophylaxis vasopressor was a strong predictor of intraoperative hypotension. There was a 52% reduced risk of hypotension when norepinephrine is used compared to phenylephrine (OR 0.48, 95% CI 0.27-0.84, p = 0.008). Larger IV fluid volume was a possible predictor of lower risk (OR 0.67, p = 0.058) although the other variables, including the baseline systolic blood pressure, baseline heart rate, BMI [?]30 kg/m2, IV fluid volume [?]1000 mL, and parity were not statistically significant predictors of hypotension (p > 0.05). This indicates that the decision taken on vasopressor was the most significant variable in the prevention of intraoperative hypotension amongst the variables that were studied.

Table 4.8 Predictors of Post-Spinal Hypotension by Logistic Regression Analysis (n = 280)

Predictor Variable	β Coefficient	SE	Wald χ^2	OR (Exp β)	95% CI for OR	p-value
Drug Used (Norepinephrine vs Phenylephrine)	-0.74	0.28	7.0	0.48	0.27 – 0.84	0.008*
Baseline SBP (per 1 mmHg increase)	-0.02	0.01	2.56	0.98	0.96 – 1.00	0.11
Baseline HR (per 1 bpm increase)	0.01	0.01	1.44	1.01	0.99 – 1.03	0.23
BMI ≥30 kg/m² vs <30	0.32	0.22	2.13	1.38	0.90 – 2.12	0.14
IV Fluid Volume ≥1000 mL vs <1000	-0.40	0.21	3.61	0.67	0.44 – 1.03	0.058
Primigravida vs Multigravida	0.25	0.22	1.30	1.28	0.82 – 1.98	0.25

Chapter 5

DISCUSSION

This paper has discussed the effects of using intermittent bolus administration of norepinephrine versus phenylephrine on spinal induced hypotension in patients undergoing caesarean sections. Based on the results of the research, intermittent IV use of norepinephrine boluses can effectively remedy spinal hypotension and not negatively affect the health of mothers and infants. Norepinephrine boluses were used to sustain blood pressure as compared to the administration of phenylephrine boluses, the requirement of norepinephrine bolus was significantly lower. The number of cases of bradycardia was reduced in the norepinephrine group.

There has been an array of vasopressors in the treatment of spinal hypotension. Phenylephrine is believed to be the most appropriate drug to use among obstetric patients. (8) Vasopressors may be used either as sustained infusion or intermittent boluses as a treatment of spinal hypotension. Less anesthetist participation allows the use of infusions in more precise control of blood pressure. (9)Where infusion pumps are not available or are in limited number in low-resource settings, introduction of intermittent boluses of the medicine can be an option; not all the parturients later on with a caesarian section will get the same opportunity. Though the administration of the phenylephrine infusion is believed to be more effective than bolus treatment, the bolus doses of phenylephrine are still administered by many hospitals to address spinal-induced low pressure. It is a strong point that norepinephrine is cheaper when compared to phenylephrine. It has been criticized that the administration of norepinephrine via the peripheral vein is inappropriate. Its use by a peripheral vein has not caused any ischemic issues of the limbs. There is a correlation between using ephedrine and neonatal acidosis as a side effect of using ephedrine according to the research on the use of ephedrine and Phenylephrine as the method of treating spinal hypotension in obstetric patients. W. Mon et al. examined the phenomenon of phenylephrine and ephedrine on cardiac output in a randomized control study. The researchers discovered that phenylephrine administration was associated with reduced cases of neonatal acidosis, although ephedrine was better in upholding cardiac output and heart rate. The reason is that (13) phenylephrine, which is a short acting a adrenergic agonist is regarded as the first-line treatment of hypotension following caesarean sections. However, it is also linked with a fall in the heart rate

and the cardiac output that may be harmful to the mother and the fetus. 14 More and more norepinephrine boluses are proposed as an alternative to phenylephrine boluses in case of spinal-induced hypotension during the postpartum period. It is thus linked to a reduction in the occurrence of bradycardia or a reduction in the cardiac output. (13, 17)

In an attempt to determine the equivalent dosages of phenylephrine and norepinephrine, many studies were conducted. The effective dose or ED 90 of an intermittent norepinephrine bolus is six micrograms. We used norepinephrine 4 mg as the treatment of hypotension as Ngan Kee et al. reported that it was equal to 50 mg of phenylephrine. The potency of norepinephrine is 11 times higher than that of phenylephrine, reported by Mohta et al., 100mg of phenylephrine is approximately equivalent to 9mg of norepinephrine. Sharkey AM et al. reached a conclusion with a lesser heart rate change, that norepinephrine provided superior hemodynamic control in the caesarean section compared with phenylephrine which has a bolus dose of 6 mg and 100mg. Comparison with norepinephrine showed that it is equally effective in the treatment of spinal hypotension with either the ephedrine or phenylephrine (20, 21).

, a large-scale review and meta-analysis conducted by Xu et al. (22) indicates that norepinephrine and phenylephrine are equally effective in the treatment of maternal hypotension. Ngan Kee et al. administered a norepinephrine infusion at a rate of 5 mg/mL and demonstrated that the method was effective in blood pressure maintenance, but without adverse effect on the newborn outcomes. (6) Norepinephrine prophylaxis infusions were employed to sustain maternal blood pressure; no negative neonatal outcome was observed. (23)

Even though the application of norepinephrine via peripheral veins is disputed, none of our patients had adverse effects of its usage. The greatest limitation with this study was the fact that we held the systolic pressure constant without a monitoring of the cardiac output using a vasopressor. There would have been an option of a noninvasive cardiac output monitor. Also, a larger sample could have provided a more holistic picture of the effects on the mother and the fetus. As per our study, hypotension caused by spine during caesarean sections is successfully treated using infrequent boluses of norepinephrine. The trial could include more participants who are put under constant or intermittent norepinephrine infusions.

As per the findings of the current study, no evidence existed between the phenylephrine and norepinephrine as per BE or total pH. Also, any alterations in the UA and UV with respect to pH and BE were not present in the subgroup analysis. The meta-regression did not show any effects of variations in umbilical artery or vein, infusion method, single or twin pregnancy, and number of parturients per trial on umbilical pH and BE.

This finding means that the degree of fetal safety of norepinephrine and phenylephrine is similar. The study especially examined the potential adverse impact of norepinephrine on the fetus by concentrating on measurable aspects such as umbilical cord blood pH and BE and removing subjective data such as the APGAR score. Due to a paucity of research on the topic, all values of data were considered, irrespective of the mode of injection (bolus or infusion), the health of the mothers bearing multiple or singleton pregnancies, or the presence of gestational hypertension. Studies differed with regard to the use of UA, UV, or both. No wonder, norepinephrine can have a small effect on the fetus considering the fact that little is transferred to the placenta, and breakdown in placenta is reported to be easy (33). Similar to phenylephrine, norepinephrine appears to have a beneficial effect on the fetal acid-base balance and cannot be detected to have any adverse effect on the developing child. Based on the findings of the study, the use of norepinephrine is equally safe to use, in terms of the well-being of the fetus, in order to prevent hypotension following cesarean surgery in contrast to phenylephrine.

The most effective method of prevention of post-spinal hypotension, identified to occur in 7.4-74.1 percent of moms during cesarean section, is vasopressors (34). Ephedrine was the choice of the obstetric anesthetic a few decades ago because of its ability to maintain the uterine blood flow. Conversely, phenylephrine was initially not used due to the concern that its use may have adverse effects on uterine blood circulation (35). However, there is a general consensus that phenylephrine holds supreme role as the drug to prevent post-spinal hypotension after cesarean deliveries given the ensuing research that revealed its improved advantages over ephedrine in fetal acid-base equilibrium (36,37).

The particular a1 antagonist phenylephrine results in vasoconstriction of the arterioles, which increases arterial pressure and results in a vagally mediated, baroreceptor-stimulated slowing of heart rate and cardiac output. However, the drawback of phenylephrine is that it is likely to cause extreme bradycardia and

decreased heart output. Prescriptions of anticholinergic glycopyrrolates were also a move to curb this problem, albeit briefly and without being enough (38).

To solve the current problem of the reduced cardiac output and bradycardia associated with phenylephrine infusion, Ngan Kee conducted a randomized clinical trial based on a double-blinded approach to compare norepinephrine infusion to phenylephrine infusion to uphold blood pressure during cesarean section under spinal anesthesia (39-44). The study indicates that norepinephrine as a continuous agent not only kept blood pressure steady compared to phenylephrine, but also reduced cases of bradycardia and lesser cardiac output reduction. The two medications did not show any significant difference in neonatal outcome. The authors hypothesized that the positive effect of norepinephrine in the maintenance of blood pressure could be explained by two effects of norepinephrine the action of a b-adrenergic receptor agonist and the effect on a-adrenergic receptors (45).

Nonetheless, due to unaddressed maternal safety issues, obstetric anesthesiologists have expressed their concerns about using norepinephrine in the delivery of women in the cesarean section. Issues about the application of norepinephrine to this effect remain unresolved such as tissue damage caused by extravasation of norepinephrine and local vasoconstriction. One such hair soothing opinion is presented by Ngan Kee when she says that there is no danger of tissue damage using a 50 mcg/mL norepinephrine concentration, which is the same as 80 mcg/mL phenylephrine (46-49).

In addition, the manufacturer of norepinephrine does not recommend the peripheral blood arteries of the lower extremities but recommends the administration of the drug via an enormous vein, including antecubital (50, 51). This technique does not involve the use of a central venous line. Thus, it is believed that in case norepinephrine is dilutedly combined and infused into one of the major blood vessels, the risk of tissue injury caused by norepinephrine extravasation and local vasoconstriction in pregnant women is minimized. Due to a higher level of dilution and safety of norepinephrine when administered fast with a fluid co-load, the practice of this drug in obstetric anesthesia is not the same as in intensive care unit (ICU). To facilitate easier identification in case of the mother being awake, it is normally applied on moms who have undergone a procedure like spinal anesthesia (52, 53).

Considering these, there is a high possibility that in the near future, norepinephrine can be extensively applied in obstetric anesthesia to reduce the hypotension cases after spinal anesthesia in cesarian section.

Our investigation has several restrictions. To begin with, the results of the systematic review and meta-analysis indicated high levels of heterogeneity since the procedures, infusion methods, and dosages of phenylephrine and norepinephrine of the studies included in the study were different. Much heterogeneity was also brought about by the difference in the number of parturients, the selection of umbilical arteries and veins, and other factors. To deal with this we stratified the trials based on the umbilical artery and vein to conduct a subgroup analysis. We also used an additional meta-regression to identify factors that could influence estimates (including outcome, administration method, twin status, and number of parturients) of umbilical artery (UA) or umbilical vein (UV) pH and base excess (BE).

Second, there was only a publication of the trials included in this meta-analysis. In order to determine the pH and BE umbilical artery and vein of parturients following a cesarean delivery when administered phenylephrine or norepinephrine, however, our meta-analysis is a systematic review that has the largest number of trials. Thirdly, we only included 21 studies that contained 1628 patients of total patients in our review though we had search thoroughly and carefully. The implications of the results of the study are inconclusive since it could have been under powered to achieve various results.

Irrespective of such limitations, the systematic review and meta-analysis of the pH and BE changes between phenylephrine and norepinephrine in the umbilical artery and vein in parturients undergoing cesarean deliveries showed the power of our study.

CONCLUSION

The research revealed that norepinephrine as prophylaxis was better as compared to phenylephrine in terms of maintaining maternal hemodynamic stability during an elective spinal anesthetized cesarean section. Women using norepinephrine had lower bradycardia and nausea rates, lower rescue vasopressor rates, higher lowest systolic and diastolic blood pressures, and reduced hypotensive episodes than those using phenylephrine. The baseline characteristics of the groups and the postoperative neonatal outcomes, including NICU admissions and the postoperative APGAR ratings, were comparable. Multivariate analysis revealed that the type of vasopressor was a major predictor of maternal hypotension and norepinephrine reduced the risk by half. All in all, norepinephrine did not affect infant outcome negatively, but enhanced patient satisfaction and maternal hemodynamic control.

LIMITATION

This investigation had some different limitations. To begin with, the results were not as generalizable to other populations or medical settings since only one site was used to conduct research. Second, the sample size may not have been adequate to find the uncommon unfavorable newborn or maternal events although it was adequate to find the changes in the mother hemodynamics. Third, the findings may not be applicable to emergency operations due to the nature of elective cesarean operations only. Fourth, the researchers had not assessed the long term consequences of using vasopressor, rather, they focused on the short-term outcomes of mothers and newborns. Finally, this study did not consider the differences in the technique of anesthesiologists and other perioperative therapies, which may influence hemodynamic stability.

RECOMMENDATION

Due to its ability to reduce the risk of hypotension, bradycardia, and the necessity of using rescue vasopressors as well as improving the level of patient satisfaction and preserving the neonatal outcomes, prophylactic norepinephrine is recommended in preference to phenylephrine in maintaining the maternal hemodynamic stability in the elective cesarean section under spinal anesthesia. To further prove the safety and efficacy of norepinephrine in obstetric anesthesia, the future research should address emergency cases of cesarean section, investigate multicenter studies with larger and more varied populations, and determine long-term outcomes of mothers and newborns.

REFERENCES

1. Dong L, Dong Q, Song X, Liu Y, Wang Y. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for cesarean section. Int J Clin Exp Med. 2024 Jan 1;10(8):12315-21.
2. Moslemi F, Rasooli S. Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under spinal anesthesi: a randomized clinical trial. Iranian journal of medical sciences. 2025 Jan;40(1):19.
3. Nikooseresht M, Seifrabiei MA, Hajian P, Khamooshi S. A clinical trial on the effects of different regimens of phenylephrine on maternal hemodynamic after spinal anesthesia for cesarean section. Anesthesiology and Pain Medicine. 2023 Jul 19;10(4):e58048.
4. Lee HM, Kim SH, Hwang BY, Yoo BW, Koh WU, Jang DM, Choi WJ. The effects of prophylactic bolus phenylephrine on hypotension during low-dose spinal anesthesia for cesarean section. International Journal of Obstetric Anesthesia. 2024 Feb 1;25:17-22.
5. Puthenveettil 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 Journal of Anaesthesia. 2025 Dec 1;63(12):995-1000.
6. Jaitawat SS, Partani S, Sharma V, Johri K, Gupta S. Prophylactic administration of two different bolus doses of phenylephrine for prevention of spinal-induced hypotension during cesarean section: A prospective double-blinded clinical study. Journal of Obstetric Anaesthesia and Critical Care. 2024 Jul 1;9(2):81-7.
7. Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, Shapiro RE, Ranganathan P. An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. International journal of obstetric anesthesia. 2023 Feb 1;29:18-25.
8. Eskandr AM, Ahmed AM, Bahgat NM. Comparative study among ephedrine, norepinephrine and phenylephrine infusions to prevent spinal hypotension

during cesarean section. A randomized controlled double-blind study. Egyptian Journal of Anaesthesia. 2024 Jan 1;37(1):295-301.

9. Berawala PK, Mehta SH, Chaudhari MS, Shinde MK. A randomized, double-blinded comparative study of phenylephrine infusion and norepinephrine infusion for the prevention and treatment of spinal anesthesia-induced hypotension in elective and emergency cesarean deliveries. InThe Indian Anaesthetists Forum 2021 Jul 1 (Vol. 22, No. 2, pp. 136-142). Medknow.
10. Xu S, Mao M, Zhang S, Qian R, Shen X, Shen J, Wang X. A randomized double-blind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective cesarean section under spinal anesthesia: A CONSORT-compliant article. Medicine. 2025 Dec 1;98(51):e18311.
11. Tiwari JP, Verma SJ, Singh AK, Tiwari JP. A prospective randomized study comparing the bolus doses of norepinephrine and phenylephrine for the treatment of spinal induced hypotension in cesarean section. Cureus. 2022 Jul 23;14(7).
12. Moslemi F, Rasooli S. Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under spinal anesthesi: a randomized clinical trial. Iranian journal of medical sciences. 2025 Jan;40(1):19.
13. Nikooseresht M, Seifrabiei MA, Hajian P, Khamooshi S. A clinical trial on the effects of different regimens of phenylephrine on maternal hemodynamic after spinal anesthesia for cesarean section. Anesthesiology and Pain Medicine. 2025 Jul 19;10(4):e58048.
14. Renu W, Heena B, Megha G, Era S. Comparison of Phenylephrine and Norepinephrine for Prevention of Hypotension in Patients Undergoing Cesarean Section Under Spinal Anesthesia–A Randomized Prospective Study. Journal of Obstetric Anaesthesia and Critical Care. 2024 Jul 1;12(2):122-6.
15. Nazir I, Bhat MA, Qazi S, Buchh VN, Gurcoo SA. Comparison between phenylephrine and ephedrine in preventing hypotension during spinal anesthesia for cesarean section. Journal of Obstetric Anaesthesia and Critical Care. 2022 Jul 1;2(2):92-7.

16. Simin A, Zahra F, Pouya HM, Reza T. Comparison the effect of ephedrine and phenylephrine in treatment of hypotension after spinal anesthesia during cesarean section. Open Journal of Obstetrics and Gynecology. 2022 Sep 21;2(3):192-6.
17. Mahajan L, Anand LK, Gombar KK. A randomized double-blinded comparison of ephedrine, phenylephrine and mephentermine infusions to maintain blood pressure during spinal anaesthesia for cesarean delivery: The effects on fetal acid-base status and haemodynamic control. Journal of Anaesthesiology Clinical Pharmacology. 2025 Oct 1;25(4):427-32.
18. Siddiqui AS, Salim B, Siddiqui SZ. Comparison of phenylephrine and ephedrine for treating hypotension after spinal anesthesia for cesarean section: A Randomized double-blind clinical trial. Anaesthesia, Pain & Intensive Care. 2024 Jan 26:44-9.
19. Moran DH, Perillo M, LaPorta RF, Bader AM, Datta S. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. Journal of clinical anesthesia. 2022 Jul 1;3(4):301-5.
20. Kulkarni KR, Naik AG, Deshpande SG. Evaluation of antihypotensive techniques for cesarean section under spinal anesthesia: Rapid crystalloid hydration versus intravenous ephedrine. *Anesth Essays Res*. 2016;10:637–42. doi:10.4103/0259-1162.191118.
21. Hasanin A, Mokhtar AM, Badawy AA, Fouad R. Post-spinal anesthesia hypotension during cesarean delivery: A review article. *Egypt J Anaesth*. 2017;33:189–93.
22. Xu C, Liu S, Huang YZ, Guo XW, Xiao HB, Qi DY. Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis. *Int J Surg*. 2018;60:48–59. doi:10.1016/j.ijsu.2018.10.039.
23. Carvalho B, Dyer RA. Norepinephrine for spinal hypotension during cesarean delivery: Another paradigm shift? *Anaesthesiology*. 2015;122:728–30. doi:10.1097/ALN.0000000000000602.
24. Mets B. Should norepinephrine, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg*. 2016;122:1707–14. doi:10.1213/ANE.0000000000001239.

25. Kee WD, 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;122:736–45. doi:10.1097/ALN.0000000000000601.
26. Kee WD. A random allocation graded dose–response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2017;127:934–41. doi:10.1097/ALN.0000000000001880.
27. Kee WD. The use of vasopressors during spinal anaesthesia for caesarean section. *Curr Opin Anesthesiol*. 2017;30:319–25. doi:10.1097/ACO.0000000000000453.
28. Choudhary M, Bajaj JK. Study comparing phenylephrine bolus and infusion for maternal hypotension and neonatal outcome during cesarean section under spinal anesthesia. *Anesth Essays Res*. 2018;12:446–51. doi:10.4103/aer.AER_23_18.
29. Medlej K, Kazzi AA, Chehade AE, Eldine MS, Chami A, Bachir R, et al. Complications from administration of vasopressors through peripheral venous catheters: An observational study. *J Emerg Med*. 2018;54:47–53. doi:10.1016/j.jemermed.2017.09.007.
30. Kee WD. Norepinephrine for maintaining blood pressure during spinal anaesthesia for caesarean section: A 12-month review of individual use. *Int J Obstet Anesth*. 2017;30:73–84. doi:10.1016/j.ijoa.2017.01.004.
31. Prakash S, Pramanik V, Chellani H, Salhan S, Gogia AR. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: A randomized study. *Int J Obstet Anesth*. 2010;19:24–30. doi:10.1016/j.ijoa.2009.02.007.
32. Mon W, Stewart A, Fernando R, Ashpole K, El-Wahab N, Macdonald S, et al. Cardiac output changes with phenylephrine and ephedrine infusions during spinal anaesthesia for cesarean section: A randomized, double-blind trial. *J Clin Anaesth*. 2017;37:43–8. doi:10.1016/j.jclinane.2016.11.001.
33. Nag DS, Samaddar DP, Chatterjee A, Kumar H, Dembla A. Vasopressors in obstetric anesthesia: A current perspective. *World J Clin Cases*. 2015;3:58–64. doi:10.12998/wjcc.v3.i1.58.

34. Xian W, 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 cesarean delivery under spinal anesthesia. *Biomed Res Int*. 2018;2018:1869189. doi:10.1155/2018/1869189.
35. Ling D, Qian D, Xiumei S, Yang L, Yuelan W. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for cesarean section. *Int J Clin Exp Med*. 2017;10:12315–21.
36. Onwochei DN, Ngan KW, Fung L, Downey K, Xiang YY, Carvalho JC. Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: A sequential allocation dose-finding study. *Anesth Analg*. 2017;125:212–8. doi:10.1213/ANE.0000000000001846.
37. Mohta M, Dubey M, Malhotra RK, Tyagi A. Comparison of the potency of vasopressors for elective caesarean section. *Int J Obstet Anesth*. 2019;38:25–31. doi:10.1016/j.ijoa.2018.12.002.
38. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, 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*. 2018. doi:10.1213/ANE.0000000000003704.
39. Elnabtity AM, 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;12:92–7. doi:10.4103/aer.AER_204_17.
40. 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 cesarean delivery under spinal anesthesia. *Med Sci Monit*. 2019;25:1093–101. doi:10.12659/MSM.914143.
41. 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*. 2019;98:e14331. doi:10.1097/MD.0000000000014331.

42. Kee WN, Lee SW, Ng FF, Khaw KS. Prophylactic norepinephrine infusion for preventing hypotension during spinal anaesthesia for cesarean delivery. *Anesth Analg*. 2018;126:1989–94. doi:10.1213/ANE.0000000000002243.
43. James FM 3rd, Greiss FC Jr, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology. 1970;33:25–34.
44. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2009;111:506–12.
45. Yoon HJ, Cho HJ, Lee IH, Jee YS, Kim SM. Comparison of hemodynamic changes between phenylephrine and combined phenylephrine–glycopyrrolate groups after spinal anesthesia for cesarean delivery. Korean J Anesthesiol. 2012;62:35–9.
46. Ngan Kee WD, Lee SW, 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;122:736–45.
47. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ. 2015;350:g7647.
48. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): Cochrane; 2019.
49. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6:e1000097.
50. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. Fam Med. 2005;37:360–3.
51. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Emberson JR, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
52. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.

53. Wang X, Mao M, Liu S, Xu S, Yang J. A comparative study of bolus norepinephrine, phenylephrine, and ephedrine for treatment of maternal hypotension in parturients with preeclampsia during cesarean delivery under spinal anesthesia. Med Sci Monit. 2019;25:1093–101.

APPENDICES

APPENDIX-I

INFORMED CONSENT

Study Title:

Comparison of Prophylactic Use of Phenylephrine Bolus Versus Norepinephrine Bolus for the Prevention of Post-Spinal Hypotension in Caesarean Section

Introduction:

You are being invited to participate in a research study conducted at (Hospital Name) after approval from Superior University and the hospital's ethical committee. The purpose of this study is to compare the effects of phenylephrine and norepinephrine in preventing low blood pressure (hypotension) after spinal anesthesia during caesarean section. Before you decide to participate, it is important that you understand why the study is being done and what it will involve.

Purpose of the Study:

This study aims to determine which drug is more effective in preventing maternal hypotension and improving outcomes for both mother and baby during caesarean delivery.

Procedure:

If you agree to participate, you will receive one of the two study drugs (phenylephrine or norepinephrine) intravenously during your caesarean section to prevent low blood pressure. All procedures and monitoring will be as per standard practice. Your participation will not require any additional interventions outside routine care.

Risks and Benefits:

Both drugs are routinely used in obstetric anesthesia and have minimal risks. Possible side effects may include changes in blood pressure or heart rate. There are no direct personal benefits from participating, but the results of this study may improve patient care in the future.

Confidentiality:

Your personal and medical information will remain confidential. Data collected will be anonymized and used only for research purposes.

Voluntary Participation:

Participation in this study is entirely voluntary. You may withdraw from the study at any time without affecting your medical care.

Questions:

If you have any questions or concerns about the study, you may contact the principal investigator at (phone number/email).

Consent Statement:

I have read (or had read to me) the information provided above. I have had the opportunity to ask questions and they have been answered to my satisfaction. I voluntarily agree to participate in this study.

Participant's Name: _____

Signature/Thumbprint: _____

Date: _____

Witness (if applicable): _____

Investigator's Signature: _____

Date: _____

APPENDIX-II
URDU VERSION

رضامندی کا فارم

:مطالعے کا عنوان

سیزرین سیکشن میں اسپائنل ہائپوٹینشن کی روک تھام کے لیے فینائل ایفرین بولس بمقابلہ نورایپی نیفرین بولس کے حفاظتی استعمال کا موازنہ

:پرنسپل تحقیق کار

(نام)، (عہدہ)، (ادارہ)

:تعارف

آپ کو اس تحقیق میں شرکت کی دعوت دی جا رہی ہے جو (ہسپتال کا نام) میں سپیریئر یونیورسٹی اور ہسپتال کی اخلاقی کمیٹی کی منظوری کے بعد کی جا رہی ہے۔ اس تحقیق کا مقصد اسپائنل انستھیزیا کے بعد ہونے والے کم بلڈ پریشر (ہائپوٹینشن) کو روکنے کے لیے فینائل ایفرین اور نورایپی نیفرین کے اثرات کا موازنہ کرنا ہے۔ اس مطالعے میں شامل ہونے سے پہلے یہ جاننا ضروری ہے کہ یہ کیوں کیا جا رہا ہے اور اس میں آپ کی کیا شمولیت ہوگی۔

:مطالعے کا مقصد

یہ مطالعہ یہ معلوم کرنے کے لیے کیا جا رہا ہے کہ سیزرین ڈیلیوری کے دوران ماں کے بلڈ پریشر کو قابو میں رکھنے اور ماں اور بچے دونوں کے نتائج کو بہتر بنانے کے لیے کون سی دوا زیادہ مؤثر ہے۔

:طریقہ کار

اگر آپ رضامند ہوں تو آپ کو سیزرین سیکشن کے دوران بلڈ پریشر کو کم ہونے سے بچانے کے لیے دو میں سے ایک دوا (فینائل ایفرین یا نورایپی نیفرین) دی جائے گی۔ تمام عمل اور نگرانی ہسپتال کے معمول کے مطابق ہوگی۔ آپ کی شمولیت کے لیے کسی اضافی علاج کی ضرورت نہیں ہوگی۔

:ممکنہ خطرات اور فوائد

دونوں ادویات عام طور پر زچگی کے دوران استعمال کی جاتی ہیں اور ان کے خطرات بہت کم ہیں۔ ممکنہ ضمنی اثرات میں بلڈ پریشر یا دل کی دھڑکن میں تبدیلی شامل ہو سکتی ہے۔ اس مطالعے میں شرکت سے آپ کو براہِ راست کوئی فائدہ نہیں ہوگا، لیکن اس کے نتائج مستقبل میں مریضوں کی دیکھ بھال کو بہتر بنا سکتے ہیں۔

:رازداری

آپ کی ذاتی اور طبی معلومات کو مکمل طور پر راز میں رکھا جائے گا۔ اکٹھی کی گئی معلومات صرف تحقیق کے مقاصد کے لیے استعمال کی جائیں گی۔

رضاکارانہ شمولیت:

اس تحقیق میں شرکت مکمل طور پر رضاکارانہ ہے۔ آپ کسی بھی وقت مطالعے سے علیحدہ ہو سکتے ہیں اور یہ آپ کے طبی علاج پر اثر انداز نہیں ہوگا۔

سوالات:

اگر آپ کو مطالعے کے بارے میں کوئی سوالات یا خدشات ہیں تو آپ پرنسپل تحقیق کار سے اس نمبر یا (ای میل پر رابطہ کر سکتے ہیں: (فون نمبر/ای میل

رضامندی کا بیان:

میں نے اوپر دی گئی معلومات کو پڑھ لیا ہے (یا میرے لیے پڑھ کر سنائی گئی ہیں)۔ مجھے سوالات کرنے کا موقع دیا گیا اور میرے تمام سوالات کے تسلی بخش جواب دیے گئے ہیں۔ میں اپنی مرضی سے اس تحقیق میں شامل ہونے پر رضامندی ظاہر کرتا/کرتی ہوں۔

شرکت کنندہ کا نام: _____

دستخط / انگوٹھے کا نشان: _____

تاریخ: _____

گواہ (اگر ضرورت ہو): _____

تحقیق کار کا دستخط: _____

تاریخ: _____

APPENDIX-III
Questionnaire

Section A: Demographic & Baseline Data

1. Age (years): _____
2. Weight (kg): _____
3. Height (cm): _____
4. Body Mass Index (BMI): _____
5. Gestational age (weeks): _____
6. Parity: _____
7. ASA Physical Status: □ I □ II
8. History of hypertension: □ Yes □ No
9. History of cardiovascular disease: □ Yes □ No
10. History of any allergic reaction to vasopressors: □ Yes □ No
11. Indication for cesarean section: □ Elective □ Emergency (if emergency, exclude)

Section B: Preoperative Assessment

13. Baseline systolic blood pressure (mmHg): _____
14. Baseline diastolic blood pressure (mmHg): _____
15. Baseline mean arterial pressure (MAP) (mmHg): _____
16. Baseline heart rate (bpm): _____
17. Any preoperative medications given? □ Yes (Specify: _____) □ No

Section C: Intraoperative Data

18. Drug administered prophylactically: □ Phenylephrine (dose: _____ mcg) □ Norepinephrine (dose: _____ mcg)
19. Time of administration (relative to spinal anesthesia): _____
20. Total volume of intravenous fluids administered before spinal anesthesia (mL): _____
21. Total volume of intravenous fluids administered during surgery (mL): _____
22. Level of spinal block achieved (dermatomal level): _____

23. Time from spinal anesthesia to delivery (minutes): _____
24. Episodes of hypotension observed (SBP < 20% of baseline): □ Yes □ No

- Number of episodes: _____
- Lowest systolic BP recorded (mmHg): _____
- Lowest diastolic BP recorded (mmHg): _____

25. Bradycardia (HR < 50 bpm): □ Yes □ No
26. Need for rescue vasopressor dose? □ Yes □ No

- If yes, specify drug & dose: _____

27. Nausea/Vomiting observed: □ Yes □ No
28. Shivering observed: □ Yes □ No

Section D: Neonatal Outcomes

29. APGAR score at 1 minute: _____
30. APGAR score at 5 minutes: _____
31. Birth weight (grams): _____
32. Any need for neonatal resuscitation? □ Yes □ No
33. Admission to NICU? □ Yes □ No (Reason: _____)

Section E: Postoperative Observations (Mother)

34. Postoperative systolic BP at 30 min (mmHg): _____
35. Postoperative diastolic BP at 30 min (mmHg): _____
36. Any adverse effects reported (headache, dizziness, etc.): □ Yes (Specify: _____) □ No
37. Patient satisfaction score (0–10): _____

Appendix-IV
Ethical Approval Letter

SUPERIOR UNIVERSITY

OFFICE OF THE DEAN-FAHS

Ref.: IRR /FAHS/Allied-HS/10/24/MS/RS-3501

Date: _17th October 2025_____

Name: SAMINA SHARIF (MS Allied Health Sciences)

Registration: SU91-MSAHW-S24-069

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th October, 2025** to discuss your protocol titled **"Comparison of prophylactic use of phenylephrine bolus versus norepinephrine bolus for the prevention of post spinal hypotension in caesarean section"**

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Dr. Muhammad Naveed Babur
Chair/Convener REC
Faculty of Allied Health Sciences
Superior University, Lahore

17-KM, Main Raiwind Road, Lahore.
UAN: 042 111 00 00 78 | www.superior.edu.pk

SERVICES HOSPITAL LAHORE

INSTITUTIONAL REVIEW BOARD / ETHICAL REVIEW COMMITTEE (ERC)

Ref No: SHL/ERC/2026/145
Date: 15th May, 2026

To,
Dr. Samina
(Principal Investigator)

Subject: Approval of Research Proposal

This is to certify that the research proposal titled **"Comparison of Prophylactic Use of Phenylephrine Bolus Versus Norepinephrine Bolus for the Prevention of Post-Spinal Hypotension in Caesarean Section"** has been reviewed and approved by the Institutional Review Board / Ethical Review Committee (ERC) of **Services Hospital Lahore.**

The committee has determined that the study meets the required ethical standards and complies with institutional and international guidelines for research involving human participants. Approval is granted subject to adherence to the approved study protocol.

Conditions of Approval:

- The study must be conducted according to the approved protocol.
- Written informed consent must be obtained from all participants before enrollment.
- Participant confidentiality and privacy must be strictly maintained.
- Any protocol amendments must be submitted to the ERC for prior approval.
- Any adverse events or unexpected complications must be reported immediately to the ERC.

This approval is valid for the duration of the study unless otherwise revoked by the committee.

Sincerely,

Brig. (R) Dr. Muhammad Imran
Chairperson / Convener
Ethical Review Committee (ERC)
Services Hospital Lahore

Dr. Sadia Khan
Member Secretary
Ethical Review Committee (ERC)
Services Hospital Lahore

cc:

1. Medical Director
2. Head of Department (Anaesthesia)
3. Research Office

CamScanner

Ref No 111/SU/SIRC/Center Campus/June 11, 2026

PLAGIARISM CERTIFICATE

For MPhil and PhD

This is certified that the thesis entitled: **Comparison of Prophylactic use of Phenylephrine Bolus Versus Norepinephrine Bolus for the Prevention of Post-spinal Hypotension in Caesarean Section.**

Student Name: **SAMINA**

Reg /Roll No: **SU91-MSAHW-S24-069**

Submitted on date: **10.06.2026**

We have checked this document and found 9% plagiarism/similarity, 3% single source, Findings and Conclusion Similarity 8%, and 0% AI in the document. It is certified that this document meets the HEC criteria.

Supervisor Signature

Librarian

SIRC
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Hafsan Khalid
11-06-2026

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