Norepinephrine versus Ephedrine to Maintain Arterial Blood Pressure during Spinal Anesthesia for Cesarean Delivery: A Prospective Double-blinded Trial

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Abstract

Background: Ephedrine was conventionally regarded as the first-choice drug to maintain maternal blood pressure during spinal anesthesia for cesarean delivery, due to its stimulant activity on α- and β-adrenergic receptors. Norepinephrine is a weak β-adrenergic and potent α-adrenergic receptor agonist. Therefore, it may be suitable for maintaining blood pressure with less chronotropic effects compared to ephedrine. Patients and Methods: One hundred and forty healthy patients having cesarean delivery under spinal anesthesia were randomized to Group N (n = 61) who received a prophylactic bolus of norepinephrine 5 µg intravenous (i.v.) at the time of intrathecal block or Group E (n = 61) who received a prophylactic bolus of i.v. ephedrine 10 mg. Rescue i.v. bolus interventions of norepinephrine 5 µg or ephedrine 10 mg were given as required to maintain systolic blood pressure. Maternal and fetal hemodynamic variables, Apgar score, and number of boluses of vasopressors used were recorded. Results: The numbers of maternal hypotension and hypertension episodes and the frequency of bradycardia and tachycardia were significantly lower in Group N compared with Group E (P = 0.02, 0.003, 0.0002, and 0.008, respectively). The number of boluses of vasopressors used was also lower in Group N (P = 0.005). Uterine artery pulsatility index was lower in Group N compared to Group E (P = 0.01) when measured 5 min after spinal anesthesia. Moreover, it was higher at 5 min in Group E when compared with the baseline readings in the same group (P = 0.001). Conclusions: Norepinephrine is a suitable and potent drug to counterbalance the hemodynamic effects of spinal anesthesia during cesarean delivery.

Keywords: Cesarean section, ephedrine, norepinephrine, spinal anesthesia

Introduction

Spinal anesthesia is the preferred method for elective cesarean sections due to considerable risks regarding airway management associated with physiological changes of pregnancy. Cesarean sections normally require an anesthetic block at T4 level, so hypotension is reported to occur in up to 80% of spinal anesthesia cases.

When maternal hypotension associated with spinal anesthesia for cesarean section is severe and sustained, it can lead to serious maternal complications as well as impairment of the uterine and placental blood flow with consecutive fetal hypoxia, acidosis, and neurological injury. Many approaches have been investigated to prevent spinal hypotension, e.g., fluid loading, vasopressors, or both. Intravenous fluid protocols have been investigated in many trials to prevent spinal hypotension, but the clinical results were not satisfactory.

With this in mind, investigators have turned their attention to vasopressor protocols to prevent spinal hypotension. Phenylephrine, a direct α1-agonist, is effective for preventing hypotension during cesarean deliveries with spinal anesthesia and does not exert an adverse effect on the fetus. Conventionally, ephedrine was regarded as the first-choice drug to maintain maternal blood pressure. Its sympathomimetic stimulant activity on α- and β-adrenergic receptors causes positive inotropic and chronotropic effects on the heart and maintains uterine blood flow. However, repeated...

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administration of ephedrine diminishes its vasoconstrictive effect,[9] and its slow onset of action and relatively long duration make accurate titration of blood pressure difficult.[10] Due to ephedrine’s slow onset of action, fetal tachycardia may appear rather unexpectedly. If tachycardia appears in concurrence with a preexisting oxygen deficit, it may lead to acidosis.[9,10]

Norepinephrine is a weak β-adrenergic and potent α-adrenergic receptor agonist. Therefore, it may be a more suitable option for maintaining maternal blood pressure with less negative effects on heart rate (HR) and cardiac output.[24] One of the main concerns in using α-agonists is a decrease in uteroplacental blood flow. Minzter et al.[11] reported that norepinephrine had no effect on fetal arterial perfusion pressure, and the fetoplacental microcirculation was not compromised.

There are limited informations available for the use of norepinephrine for the treatment of hypotension during spinal anesthesia in the literature and there are few reports of its use in obstetric patients.[2,8]

We hypothesized that using norepinephrine to maintain maternal blood pressure during spinal anesthesia for cesarean delivery provides better hemodynamic stability with subsequent better maternal and neonatal outcomes compared to ephedrine.

**Patients and Methods**

After ethical approval for this study protocol by the “research and ethics committee” of our institute, all patients participated in the study gave written informed consent. One hundred and forty healthy women, American Society of Anesthesiologists physical status Classes I and II, with singleton pregnancies at term scheduled for elective cesarean section under spinal anesthesia were targeted for the study. All of them were randomized to receive either norepinephrine or ephedrine to maintain their blood pressure. The exclusion criteria were emergency cesarean section, active labor, high-risk pregnancies (intrauterine growth retardation, preeclampsia), and maternal cardiovascular or pulmonary diseases. Patients allergic to any of the medications used in the study were also excluded.

Patients were fasted overnight and were given routine antacid prophylaxis. On arrival in the operating room, they were positioned on the operating table in the supine position with left lateral tilt and routine monitors were attached. The baseline hemodynamic measurements (HR, oxygen saturation, electrocardiography, and arterial blood pressure) were recorded using a patient monitoring system (Mindray PM-8000E®, Medical International Co., Ltd., China). External cardiotocography was used to monitor the fetal HR.

Following measurement of baseline hemodynamic variables and after thorough disinfection at the puncture site, the skin was infiltrated with 2 ml lidocaine 1%. Then, a 25-gauge pencil-point spinal needle (Pencan®, B. Braun Medical Inc., Germany) was inserted through an introducer needle at L3–4 or L4–5 vertebral interspace in the sitting position. After confirmation of free flow of cerebrospinal fluid, a mixture of 12.5 mg of hyperbaric bupivacaine 0.5% and 15 µg fentanyl was injected intrathecally, and the patient was returned to the tilted supine position. At the start of intrathecal injection, rapid intravenous (i.v.) cohydration of lactated Ringer’s solution was commenced through a large-bore i.v. cannula. Cohydration was continued to a maximum of 2 l after which the flow was reduced to a slow maintenance rate.[12]

For randomization and blinding, 122 slips labeled with either norepinephrine or ephedrine (61 for each group) were sealed with an adhesive and placed in a container. Norepinephrine bitartrate, 1 mg/ml (Levophed®, Hospira, Inc., Lake Forest, IL, USA) or ephedrine sulfate, 50 mg/ml (Ephedrine Sulfate®, Akorn, Inc., India), was diluted in an identical-coded 10 ml syringes to give norepinephrine 5 µg/ml and ephedrine 10 µg/ml. The study drug was prepared by a physician not involved in any other aspects of the study. This physician held the code for randomization and group allocation.

Group N (norepinephrine group) received a prophylactic bolus of norepinephrine 5 µg i.v. at the time of intrathecal block, plus rescue boluses of 5 µg norepinephrine, whenever maternal systolic blood pressure (SBP) dropped by 20% or more from the baseline value. Group E (ephedrine group) received a prophylactic bolus of ephedrine 10 mg i.v. at the time of intrathecal block, plus rescue boluses of 10 mg ephedrine, whenever SBP dropped by 20% or more from the baseline value.

The numbers of the boluses of vasopressors used were recorded and considered as the primary outcome of the study. HR (beats/min) and SBP (mmHg) were recorded every 2 min after spinal injection until delivery of the baby and then every 5 min till the end of the study period. The incidence of hypotension (defined as a reduction in SBP of >20% from baseline determined just before the administration of spinal anesthesia) was recorded. Reactive hypertension (defined as a rise of SBP >20% of baseline) was also recorded. Bradycardia (defined as HR <60 beats/min) was recorded and treated with atropine up to 3 mg i.v. Tachycardia (defined as a HR >120 beats/min) was also recorded. The highest level of sensory anesthesia assessed using ice cubes was recorded 5 min after intrathecal injection.

Surgery could commence when the attending anesthesiologist considered that the block was adequate. Supplemental oxygen will be given only when the pulse oximeter reading decreased below 95%.

Uterine artery pulsatility index (UtA-PI) and umbilical artery pulsatility index were measured before spinal anesthesia (baseline) and 5 min after spinal anesthesia. Ultrasound Doppler indices measurements were made by a researcher obstetrician (Selim MF, who was unaware of the vasopressor used) using 4 MHz convex transabdominal probe with color Doppler facility (GE Healthcare ultrasound-LOGIQ
9, 5125134-10 Rev4). Increased values of Doppler indices of vascular resistance which obtained from three similar consecutive waveforms correlate with the decreased flow.

The uterine artery blood velocity was recorded from both sides. Pulsed-wave Doppler was used where the uterine artery crosses the external iliac artery. When three similar, consecutive waveforms were obtained, the PI was measured and the mean UtA-PI was calculated.

The umbilical artery Doppler flow spectrum was recorded from a free-floating central part of the umbilical cord. The mean of three consecutive blood velocity waveforms was analyzed for PI.[13]

The incidence of nausea, vomiting, shivering, restlessness, headache, and pruritus was recorded and managed accordingly. I.v. ondansetron 4 mg was administered after delivery of the baby to treat nausea and vomiting. The times of induction to skin incision and skin incision to delivery of the baby were recorded. The frequency of hypotension episodes, hypertension episodes, bradycardia, tachycardia, and administration of boluses of norepinephrine and ephedrine were all recorded. Arterial blood samples from the umbilical cord were obtained by clamping it on both sides. A bedside blood gas analysis was performed; an arterial pH value under 7.20 was considered as fetal acidosis. Furthermore, Apgar scores at 1, 5, and 10 min after delivery were recorded by the attending pediatrician, who was unaware of the vasopressor used.

**Sample size**

The sample size calculation was based on a pilot study on 20 patients considering the primary outcome of this study as the difference in the number of boluses of vasopressors needed to maintain maternal blood pressure. Assuming that the confidence interval 95% and power of the test 80%, 49 patients per group was the minimum sample size required to demonstrate a statistically significant difference in the number of boluses of vasopressors between both groups. Considering the anticipated dropout rate, we included 140 patients, 70 in each group.

**Statistical tests**

Statistical analysis was performed using SPSS program version 19 (IBM Corp., Armonk, NY, USA) and EP16 program.

Differences between both groups were compared using Student’s *t*-test for parametric data and the Mann–Whitney test for nonparametric data. Comparison of proportions was performed using Chi-square test and Fisher’s exact test as appropriate. Data are presented as a mean ± standard deviation, median, numbers, and proportions. Statistical significance was considered at a *P* < 0.05

**RESULTS**

One hundred and twenty-two patients were consented and enrolled in the study. They were randomly allocated to two equal groups. All patients received the allocated interventions and were available for statistical analysis in both groups [Figure 1].

Patients characteristics (age, weight, and height), indication for cesarean section (previous cesarean section, breech presentation, and cephalopelvic disproportion), level of dermatological block, surgery duration, induction to skin incision time, and skin incision to fetal delivery time all were comparable, and no statistically significant differences were observed between the studied groups [Table 1].

The numbers of hypotension and hypertension episodes were significantly lower in Group N compared with Group E, *P* = 0.02 and 0.003, respectively. Further, the frequency of bradycardia and tachycardia was significantly lower in Group N compared with Group E, *P* = 0.0002 and 0.008, respectively. Furthermore, the number of boluses of vasopressors used during spinal anesthesia was also significantly lower in Group N compared with Group E, *P* = 0.005 [Table 2].

The average baseline values of UtA-PI did not differ in the studied groups; however, it was significantly lower in Group N compared to Group E (*P* = 0.01) when measured 5 min after spinal anesthesia. Furthermore, on comparing the average values of UtA-PI 5 min after anesthesia with the baseline readings in the same group, there was no significant difference in Group N while in Group E significantly increased (*P* = 0.001). Umbilical artery Doppler pulsatility indices showed nonsignificant changes in both studied groups.

### Table 1: Patients characteristics, indications for cesarean section, dermatomal block, and surgical data

|                      | Norepinephrine group (n=61) | Ephedrine group (n=61) | *P* |
|----------------------|-----------------------------|------------------------|-----|
| **Patients characteristics** |                             |                        |     |
| Age (years)          | 27.04±4.5                   | 27.48±7.2              | 0.3 |
| Weight (kg)          | 81.2±9.2                    | 77.8±11.6              | 0.1 |
| Height (cm)          | 162.2±9.7                   | 161.3±9.7              | 0.3 |
| **Indications for cesarean section** |                             |                        |     |
| Previous cesarean section | 42                          | 35                     | 0.4 |
| Breech presentation  | 10                          | 14                     |     |
| Cephalopelvic disproportion | 8                           | 11                     |     |
| **Dermatoma block**  | T5 (T1-T6)                  | T4 (T2-T6)             | 0.2 |
| Surgical times       | 50.1±6.25                   | 52.9±7.19              | 0.07|
| Induction to skin incision | 13.76±3.3                   | 15.2±3.37              | 0.1 |
| Skin incision to fetal delivery | 12.9±3.33                   | 14.04±3.81             | 0.4 |

Values are mean±SD, n, median (range). Data were analyzed using Student’s *t*-test, *Chi-square test, and Mann-Whitney U-test as appropriate. SD=Standard deviation.
when compared before and 5 min after spinal anesthesia [Figure 2].

The fetal characteristics (fetal HRs, birth weight, umbilical cord pH, and Apgar scores at 1, 5, and 10 min postdelivery) all were comparable, and no statistically significant differences were detected in studied groups [Table 3].

The incidence of maternal complications during the operation (nausea, vomiting, shivering, headache, restlessness, and pruritus) was comparable, and no statistically significant differences were detected between the studied groups [Table 4].

**Discussion**

In this study, we compared the administration of intermittent i.v. boluses of norepinephrine and ephedrine to counterbalance the hypotensive effect of spinal anesthesia during cesarean delivery.

The results of the study showed that compared with ephedrine, norepinephrine maintained maternal blood pressure and uterine artery blood flow. Further, it was associated with lower numbers of hypotension and hypertension episodes and less frequency of bradycardia and tachycardia during cesarean delivery. Furthermore, the numbers of boluses of vasopressors used during spinal anesthesia were lower in norepinephrine compared with the use of ephedrine.

Spinal hypotension is primarily driven by a decrease in sympathetic tone in the arterial system and not by the reduction in central venous pressure due to increased venous capacitance. There are marked reduction in systemic vascular resistance and a modest increase in cardiac output, HR, and stroke volume after induction of spinal anesthesia.\(^{[14,15]}\)

Because uteroplacental blood flow is not autoregulated but directly coupled to maternal blood pressure, maternal hypotension must be treated immediately to avoid the risk of fetal acidosis.\(^{[2]}\)

Vaspressors are effective in preventing and treating hypotension of spinal anesthesia, but the choice of vasopressor has been debated. Phenylephrine and ephedrine are the vasopressors of choice. Ephedrine has been the gold standard vasopressor because of its safety, ready availability, and familiarity to most anesthesiologists. Ephedrine is a sympathomimetic that has both a direct (α-and β-receptor agonist) and an indirect mechanism of action (release of norepinephrine) causing an increase in myocardial contractility and HR and hence cardiac output; it also causes peripheral vasoconstriction and raises the blood pressure.

Phenylephrine is a short-acting, potent vasoconstrictor that causes an increase in both SBP and diastolic blood pressure.

**Table 2: Maternal hemodynamic variables**

|                | Norepinephrine group (n=61) | Ephedrine group (n=61) | P     |
|----------------|-----------------------------|------------------------|-------|
| Number of hypotension episodes | 1 (0-3)                    | 3 (1-5)                | 0.02* |
| Number of hypertension episodes | 1 (0-2)                    | 2 (1-3)                | 0.003*|
| Frequency of bradycardia | 1 (0-2)                    | 0                      | 0.0002*|
| Frequency of tachycardia | 0 (0-1)                    | 1 (0-3)                | 0.008*|
| Number of boluses of vasopressors used | 2 (1-3)                | 3 (2-4)                | 0.005*|

Values are median (range). Data were analyzed using Mann-Whitney U-test. *P<0.05 - significant difference

**Table 3: Fetal variables**

|                | Norepinephrine group (n=61) | Ephedrine group (n=61) | P     |
|----------------|-----------------------------|------------------------|-------|
| Baseline fetal heart rate (beats/min) | 146.7±14.1 | 143±15.8 | 0.5   |
| Birth weight (kg) | 3.29±0.32                | 3.27±0.37             | 0.8   |
| Umbilical cord pH | 7.25±0.06                | 7.28±0.04             | 0.3   |
| Umbilical cord pH <7.2* (%) | 3 (4.9) | 5 (8.1) | 0.7   |
| Apgar <7 at 1 min** (%) | 8 (13.1) | 10 (16.3) | 0.6   |
| Apgar <7 at 5 min** (%) | 5 (8.1) | 7 (11.4) | 0.5   |
| Apgar <7 at 10 min* (%) | 3 (4.9) | 4 (6.5) | 0.6   |

Values are mean (SD) and n (proportion). Data were analyzed using Student’s t-test, *Fisher’s exact test and **Chi-square test as appropriate. SD=Standard deviation

**Table 4: Maternal complications during the operation**

|                | Norepinephrine group (n=61), n (%) | Ephedrine group (n=61), n (%) | P     |
|----------------|-----------------------------------|--------------------------------|-------|
| Nausea* | 11 (18)                           | 18 (29.5)                      | 0.1   |
| Vomiting | 3 (4.9)                           | 2 (3.2)                        | 0.6   |
| Shivering* | 7 (11.4)                      | 5 (8.1)                        | 0.5   |
| Headache | 3 (4.9)                           | 8 (13.1)                       | 0.1   |
| Restlessness | 4 (6.5)                       | 6 (9.8)                        | 0.7   |
| Pruritus* | 8 (13.1)                          | 6 (9.8)                        | 0.5   |

Values are n (proportions). Data were analyzed using Fisher’s exact test and *Chi-square test as appropriate
Conventionally, phenylephrine was used as a second-line vasoconstrictor in obstetrics because of concerns that it caused vasoconstriction in the uteroplacental circulation.[16-18] In contrast to β-mimetic ephedrine, no acidosis was observed with phenylephrine. However, in larger doses, it decreases uteroplacental perfusion.[19,20] Compared with ephedrine, phenylephrine is associated with less neonatal acidosis. However, phenylephrine has clinically significant bradycardia with a consequent decrease in cardiac output.[14,15,21]

Recent studies showed that norepinephrine was also effective for maintaining blood pressure in obstetric patients. It has weak β-adrenergic receptor agonist activity in addition to its α-adrenergic receptor activity and therefore may be a more suitable option for maintaining maternal blood pressure with less negative effects on HR and cardiac output.[2,8]

In the current study, we used norepinephrine which binds to adrenergic α1- and β1-receptors. Hence, it increases SBP by increasing both peripheral vascular resistance and cardiac output with immediate antagonize consequence of the sympathetic block of spinal anesthesia.

Ngan Kee et al.[8] compared norepinephrine to phenylephrine in patients having cesarean delivery under spinal anesthesia to maintain SBP with a computer-controlled closed-loop feedback system. They found that maternal cardiac output and HR were greater in women treated with norepinephrine compared with that treated with phenylephrine. In our study, we administered the vasopressors by intermittent i.v. boluses when SBP drops 20% below the baseline. We found that uterine UtA-PI was lower in women treated with norepinephrine compared with those treated with ephedrine. This was attributed to the greater cardiac output that improved uterine blood flow in norepinephrine group although there were no significant differences between both groups regarding the fetal outcome. This was in agreement with the results obtained in the study of Ngan Kee et al.[8]

Vallejo et al.[22] randomized 85 parturients having cesarean delivery under spinal anesthesia to receive either phenylephrine 0.1 µg/kg/min or norepinephrine 0.05 µg/kg/min using a fixed-rate infusion. They found that norepinephrine fixed-rate infusion has efficacy for preventing maternal hypotension. These results support the concept that obtained in our study although we administered the vasopressors using intermittent i.v. boluses not by a fixed rate infusion.

Onwochei et al.[23] studied the effect of different intermittent i.v. boluses of norepinephrine to prevent maternal hypotension during spinal anesthesia for cesarean delivery. The results obtained were feasible and were not associated with significant maternal or fetal adverse effects. These results are coinciding with the results of our study.

Ngan Kee et al.[24] compared the prophylactic continuous i.v. norepinephrine infusion (2.5 µg/min) with a bolus of 1 ml norepinephrine 5 µg/ml (5 µg) given whenever SBP decreased to <80% of the baseline value. This study had been conducted in patients having spinal anesthesia for elective cesarean delivery. The results revealed the superiority of continuous norepinephrine infusion over the intermittent i.v. boluses. In our study, we compared two different vasopressors and we chose the regimen of intermittent i.v. boluses because of its familiarity to most of the anesthesiologists.

El Shafei et al.[25] compared norepinephrine with ephedrine to prevent spinal anesthesia-induced hypotension in coronary artery disease patients undergoing knee arthroscopy. One hundred patients were randomly allocated to two equal groups to receive either 5 mg of ephedrine or 5 µg of norepinephrine when hypotension occurs. They found that norepinephrine is more effective compared with ephedrine in the maintenance of SBP with reduction in HR, which is useful in coronary artery disease patients. These results are in agreement with the results obtained in our study although we conducted our study on a different category of patients. However, they found no difference between the two groups regarding the incidence of hypotension, hypertension, and bradycardia, and this is not coincident with the results of our study as we found lower numbers of hypotension and hypertension episodes and less frequency of bradycardia and tachycardia in the patients treated with norepinephrine.

Limitation of the present study includes that it was extended only until the end of surgery; further studies are required for long-term follow-up in the postoperative period till discharge of the patients to home.

Conclusions

Norepinephrine can be used as an alternative vasopressor to maintain maternal blood pressure during spinal anesthesia for cesarean delivery, with no adverse effect on neonatal outcome.

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Conflicts of interest

There are no conflicts of interest.

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