

Comparison of Ephedrine, Mephentermine and Phenylephrine for the Management of Hypotension during Spinal Anesthesia for Caesarian Section

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Abstract

Introduction: Numerous pressor agents have been tried to counteract the hypotensive effect of subarachnoid block, usually by vasoconstriction and also by increasing the cardiac output. In practice, the most commonly used drugs are the sympathomimetic agents which exert their effects through the adrenergic receptors, either acting directly or indirectly by inducing the release of noradrenaline which further acts on these receptors. Aim and objectives: To compare the efficacy of IV bolus phenylephrine, ephedrine and mephentermine for the maintenance of hemodynamic status and its effect on fetal outcome during spinal anesthesia in cesarean section.

Methodology: This prospective double blind randomized controlled study was conducted in the Department of Anesthesiology and Critical Care in Alfalah institute of medical sciences, Faridabad, from July 2021 to July 2022. After a proper approval of Institute ethical committee and a written informed consent, 100 ASA grade I patients undergoing elective cesarean section under spinal anesthesia with a normal singleton pregnancy beyond 36 weeks gestation were recruited.

Result: There is no significant variation of systolic BP among all the 3 drugs, and there is no significant difference among the three groups with p value- 0.23, 0.076, 0.66 and 0.16, for diastolic Bp also there is no significant variation of diastolic BP among all the 3 drugs, and there is no significant difference among the three groups with p value- 0.23, 0.21, 0.15 and 0.08, There is also no significant difference among three group of drugs for heart rate and MAP.

Conclusions: On the basis of our study we concluded that all three drugs, i.e ephedrine, phenylephrine and mephentermine can be used to treat hypotension during spinal anaesthesia for caesarean section, however, phenylephrine has more fluctuation in vitals during spinal anesthesia,

Keywords: Vasopressors, phenylephrine, mephentermine, ephedrine, spinal anesthesia

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Introduction

Spinal anaesthesia is commonly used for elective caesarean section as it is easier and

quicker than epidural anaesthesia and it exposes the fetus to fewer drugs than general

anaesthesia, while the mother can be awake when her baby is delivered. Spinal anaesthesia has gained immense popularity among the anaesthesiologists owing to the ease of administration with lesser doses, less stress response and early patient recovery [1].

However, spinal anaesthesia despite its benefits has its limitations too. The common complications of spinal anaesthesia include hypotension, bradycardia, limited duration of anaesthesia and lesser control of level of blockade. The incidence of hypotension following spinal anaesthesia can reach as high as 70-80% if pharmacological prophylaxis is not used. This continues to be one of the dreaded side effects of spinal anaesthesia despite several attempts to minimise the same. Hypotension following spinal anaesthesia for caesarean delivery may compromise placental perfusion and resulting in fetal complications like hypoxia, acidosis and neurological injury. Hypotension following spinal anaesthesia can lead to dizziness, loss of consciousness, vomiting or even sudden cardiac arrest in the mother [2].

Because hypotension may be associated with both maternal and neonatal morbidity, many different methods have been investigated alone and in combination for both its prevention and treatment. Left uterine displacement is known to decrease the effects of aortocaval compression. Leg elevation alone has not been shown to reduce the incidence of hypotension. Prehydration or preloading is commonly administered but it has controversial results, acting both directly and also indirectly [3].

Numerous pressor agents have been tried to counteract the hypotensive effect of subarachnoid block, usually by vasoconstriction and also by increasing the cardiac output. In practice, the most commonly used drugs are the sympathomimetic agents which exert their effects through the adrenergic receptors,

either acting directly or indirectly by inducing the release of noradrenaline which further acts on these receptors. Phenylephrine is a direct-acting, potent alpha-1 agonist with no beta activity. It, therefore, causes a rapid increase in systemic vascular resistance and blood pressure. Mephentermine acts by indirect stimulation of beta-adrenergic receptors causing release of norepinephrine from its storage sites. It has positive inotropic effect on the myocardium. Ephedrine is a potent alpha and beta agonist acting both directly and indirectly [4].

Aims and Objectives

To compare the efficacy of IV bolus phenylephrine, ephedrine and mephentermine for the maintenance of hemodynamic status and its effect on fetal outcome during spinal anaesthesia in cesarean section

To compare the incidence of nausea, vomiting and other effects of these drugs.

Materials and Method

This prospective double blind randomized controlled study was conducted in the Department of Anesthesiology and Critical Care in Alfalah institute of medical sciences, Faridabad, from July 2021 to July 2022. After a proper approval of Institute ethical committee and a written informed consent, 100 ASA grade I patients undergoing elective cesarean section under spinal anaesthesia with a normal singleton pregnancy beyond 36 weeks gestation were recruited. Patients with pregnancy-induced hypertension, history of diabetes, cardiovascular and cerebrovascular disease, fetal abnormalities, and contraindication to spinal anaesthesia were excluded from the study.

Patients were randomized into 3 groups of 30 each using sealed envelope technique.

Group A – received Phenylephrine 100 microgram (1 ml) as iv bolus.

Group B – received Ephedrine 6 mg (1 ml) as iv bolus

Group C – received Mephentermine 6 mg (1 ml) as iv bolus

Drug was prepared by Anesthetic Assistant or Anesthesia Resident who were not involved in the study. All patients underwent pre-anesthetic evaluation, kept nil per oral for 6 hours and received oral premedication with Ranitidine 150 mg and Metoclopramide 10 mg the night before and the early morning of surgery. In preparation room Ringer's Lactate (10 ml/Kg) was infused intravenously and baseline vital parameters like Heart rate, Systolic BP and Diastolic BP were recorded. Patients were then shifted to OT. ECG, BP, SpO₂ were attached and monitored.

On arrival in the operation theatre heart rate (ECG), blood pressure (NIBP), respiratory rate, and arterial O₂ saturation (SaO₂) were monitored. Patients were placed in lateral or sitting position according to their convenience. Lumbar puncture was performed with 25 gauge Quincke's needle in L3-L4 intervertebral space. Once free flow of cerebrospinal fluid was obtained, 2.5 ml of 0.5% bupivacaine was administered over 10–15 seconds. Time of injection of drug was noted and patient was placed in supine position immediately with a left lateral tilt of 15–20 degrees. Inspired air was supplemented with oxygen at 5 l/min until clamping of umbilical cord. Immediately after induction of spinal anesthesia, systolic blood pressure, diastolic blood pressure, and heart rate were recorded. One minute after intrathecal injection, patients were given either phenylephrine 100 µg IV bolus or

ephedrine 10 mg IV bolus or mephentermine 6mg IV bolus. Hemodynamic variables like blood pressure and heart rate was recorded every 2 minutes up to delivery of baby and then after every 5 minutes. Whenever systolic blood pressure decreased to less than 90 mmHg, vasopressor was administered, either 5 mg of ephedrine or 50 µg of phenylephrine or 3mg of mephentermine. On each occasion when maternal heart rate decreased to below 60 beats per minute (bpm), atropine 0.3 mg IV was administered.

After delivery of baby, cord was clamped, 5 units oxytocin was given as iv bolus followed by 10 units of injection oxytocin in Ringer's lactate as slow iv infusion. Neonatal outcomes were assessed using APGAR scores at 1 and 5 minutes after delivery. neonatal umbilical cord blood pH values were also assessed. At delivery umbilical cord was clamped and 1 ml of blood sample collected in heparinized syringe for acid base analysis. Umbilical artery pH value less than 7.2 indicates asphyxia.

Total amount of IV fluid given (maintenance and bolus), amount of vasopressor and atropine required during intraoperative period was recorded. Any untoward effects like nausea / vomiting, shivering, restlessness during intra-operative period was noted and treated.

Statistical analysis was performed using Statistical Package for SPSS version 20.0. Student's unpaired t-test and Mann Whitney U-test were used to compare demographic and other characteristics in the two groups. The data for these characteristics are presented as mean (SD) or median (range).

Result

Table 1: Comparison of heart rate at different time interval of the three drugs

| Drug group | | heartrate0 hr | heartrate2 hr | heartrate4hr | heartrate6hr |
|---------------|---------|---------------|---------------|--------------|--------------|
| Ephedrine | Mean | 73.30±9.44 | 71.60±24.81 | 75.00±7.47 | 74.80±9.21 |
| Mephenterine | Mean | 78.53±9.68 | 69.90±10.02 | 72.70±8.35 | 72.77±9.87 |
| Phenylephrine | Mean | 69.33±7.95 | 63.13±7.94 | 72.20±5.52 | 74.40±7.89 |
| | P value | 0.098 | 0.17 | 0.28 | 0.65 |

Table 1 shows Comparison of heart rate at different time interval of the three drugs, On comparing the three drugs, we found that in study subjects who are given ephedrine, heart rate at the different time interval was 73.30 ± 9.44 , 71.60 ± 24.81 , 75.00 ± 7.47 and 74.80 ± 9.21 , for mephenterine it was 68.53 ± 9.68 , 65.90 ± 10.02 , 72.70 ± 8.35 and 72.77 ± 9.87 . and for phenylephrine it was 69.33 ± 7.95 , 63.13 ± 7.94 , 72.20 ± 5.52 and 74.40 ± 7.89 . however there is no significant variation of heart rate among all the 3 drugs, slight bradycardia was found for the study subjects of phenylephrine group.

Table 2: Comparison of systolic BP at different time interval of the three drugs

| Drug group | | sysbp0hr | sysbp2hr | sysbp4hr | sysbp6hr |
|---------------|------|--------------------|--------------------|--------------------|--------------------|
| Ephedrine | Mean | 129.13 ± 17.97 | 117.97 ± 10.38 | 121.73 ± 14.89 | 122.37 ± 11.64 |
| Mephenterine | Mean | 122.97 ± 10.89 | 122.13 ± 11.39 | 123.10 ± 12.07 | 127.97 ± 11.23 |
| Phenylephrine | Mean | 125.23 ± 12.16 | 124.83 ± 12.93 | 125.03 ± 14.71 | 126.20 ± 11.51 |
| | | 0.23 | 0.076 | 0.66 | 0.16 |

Table 2 shows Comparison of Systolic BP at different time interval of the three drugs, On comparing the three drugs, we found that in study subjects who are given ephedrine, SYS BP at the different time interval was 129.13 ± 17.97 , 117.97 ± 10.38 , 121.73 ± 14.89 and 122.37 ± 11.64 , for mephenterine it was 122.97 ± 10.89 , 122.13 ± 11.39 , 123.10 ± 12.07 and 127.97 ± 11.23 . and for phenylephrine it was 125.23 ± 12.16 , 124.83 ± 12.93 , 125.03 ± 14.71 and 126.20 ± 11.51 . however, there is no significant variation of systolic BP among all the 3 drugs, and there is no significant difference among the three groups with p value- 0.23, 0.076, 0.66 and 0.16.

Table 3: Comparison of diastolic BP at different time interval of the three drugs

| Drug group | | diasbp0hr | diasbp2hr | diasbp4hr | diasbp6hr |
|---------------|---------|-------------------|------------------|------------------|-------------------|
| Ephedrine | Mean | 77.07 ± 10.16 | 81.73 ± 5.42 | 81.50 ± 6.62 | 80.87 ± 10.35 |
| Mephenterine | Mean | 76.77 ± 11.32 | 81.30 ± 5.39 | 77.17 ± 9.56 | 82.43 ± 6.81 |
| Phenylephrine | Mean | 81.40 ± 13.31 | 83.53 ± 4.78 | 79.80 ± 9.24 | 85.20 ± 3.61 |
| | P value | 0.23 | 0.21 | 0.15 | 0.08 |

Table 3 shows Comparison of Diastolic BP at different time interval of the three drugs, On comparing the three drugs, we found that in study subjects who are given ephedrine, Diastolic BP at the different time interval was 77.07 ± 10.16 , 81.73 ± 5.42 , 81.50 ± 6.62 and 80.87 ± 10.35 , for mephenterine it was 76.77 ± 11.32 , 81.30 ± 5.39 , 77.17 ± 9.56 and 82.43 ± 6.81 . and for phenylephrine it was 81.40 ± 13.31 , 83.53 ± 4.78 , 79.80 ± 9.24 and 85.20 ± 3.61 . however there is no significant variation of diastolic BP among all the 3 drugs, and there is no significant difference among the three groups with p value- 0.23, 0.21, 0.15 and 0.08.

Table 4: Comparison of MAP at different time interval of the three drugs

| Drug group | | MAP0HR | MAP2HR | MAP4HR | MAP6HR |
|---------------|---------|-------------------|------------------|------------------|------------------|
| Ephedrine | Mean | 96.83 ± 10.29 | 84.90 ± 9.12 | 79.27 ± 8.36 | 80.47 ± 6.72 |
| Mephenterine | Mean | 94.43 ± 7.16 | 82.27 ± 6.77 | 79.47 ± 6.21 | 82.83 ± 6.25 |
| Phenylephrine | Mean | 95.43 ± 6.98 | 82.47 ± 6.97 | 80.33 ± 6.41 | 83.23 ± 6.51 |
| | P value | 0.53 | 0.34 | 0.82 | 0.21 |

Table 4 shows Comparison of MAP at different time interval of the three drugs, On comparing the three drugs, we found that in

study subjects who are given ephedrine, MAP at the different time interval was 96.83 ± 10.29 , 84.90 ± 9.12 , 79.27 ± 8.36 and

80.47±6.72, for mephenterine it was 94.43±7.16, 82.27±6.77, 79.47±6.21 and 82.83±6.25. and for phenylephrine it was 95.43±6.98, 82.47±6.97, 80.33±6.41 and 83.23±6.51. however there is no significant variation of MAP among all the 3 drugs, and there is no significant difference among the three groups with p value- 0.53, 0.34, 0.82 and 0.21

In our present study most common complications was bradycardia, hypotension and headache, there is no significant difference among the three groups as far as complications are concerned. However, bradycardia was more common in phenylephrine group as compared to other groups.

Discussion

Preloading with I.V. crystalloid or colloid solution is a standard practice for prevention of hypotension after spinal anaesthesia, but, this practice has been found to be ineffective when used alone, without concomitant use of vasopressor drugs. Sympathetic blockage resulting in vasodilatation is the primary cause of fall in arterial blood pressure, so use of vasopressor agents in conjugation with fluid preloading appears to be more logical approach to correct it.

Inadequately treated hypotension occurring during caesarean section can cause undue effects on both mother and fetus. Ephedrine and mephentermine, both are mixed sympathomimetic amines that act both directly and indirectly on α and β adrenergic receptors, whereas phenylephrine is a pure α agonist which stimulates α_1 -adrenergic receptors by a direct effect. There have been several attempts to find the optimal therapy for spinal anaesthesia induced hypotension during C section. Thomas DG and colleagues [5], in their similar randomized trial study of bolus phenylephrine (100 mcg) versus ephedrine (5mg), reported that both drugs are equally effective in restoring cardiac output and maternal systolic blood pressures above

100 mm Hg. Kansal A, et al.[6] found that mephentermine can be used as safely and effectively as ephedrine for the management of hypotension during spinal anaesthesia in patients undergoing elective Caesarean section. Neonatal APGAR scores acid base profiles were also comparable in both groups.

Bhardwaj and colleagues [7] compared phenylephrine, metaraminol and ephedrine and found all the three vasopressors were equally effective in maintaining maternal blood pressure as well as umbilical pH without any detrimental effects on fetal and maternal outcome. Recent studies by Simin, et al. [8], Muñoz E, et al. [9] and Nazir, et al. [10] also concluded ephedrine and phenylephrine are both effective vasopressors for treatment of hypotension (no significant difference) associated to spinal block during caesarean section without adverse effects on infants/neonates.

Ramanathan, et al. [11] and Adigun TA [12], reported that bolus ephedrine (5 mg) is equipotent to iv bolus phenylephrine (100 mcg) for the maintenance of maternal arterial blood pressure. In a similar comparative study of bolus phenylephrine 100 mcg and mephentermine 6 mg study, Sneha dhokania et al, [13] showed that there was rise in mean SBP and DBP was significantly higher in phenylephrine group ($p < 0.05$), at all the time intervals compared to mephentermine group In our study, all the three vasopressors effectively maintained mean blood pressure and mean arterial pressure within normal range of baseline value.

However different results were found in the study conducted by Lakshmi Mahajan, et al. [14] where maternal blood pressure was higher in group P, compared with group E and M which was statistically significant in phenylephrine group till 6 mins of bolus dose as compared with ephedrine and mephentermine groups. In this study, heart rate significantly dropped after bolus dose of phenylephrine at 4 mins ($p < 0.001$) as

compared to mephentermine and ephedrine. The incidence of bradycardia in the phenylephrine group may be explained due to its lack of action on beta receptors.

Conclusions

On the basis of our study we concluded that all three drugs, i.e ephedrine, phenylephrine and mephentermine can be used to treat hypotension during spinal anaesthesia for caesarean section, however, phenylephrine has more fluctuation in vitals during spinal anaesthesia, Considering the limitations of the study further studies on management of hypotension during spinal anaesthesia for caesarean delivery in varied population is needed.

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