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Comparision of intravenous Ephedrine/Mephentermine for spinal hypotension in parturients undergoing LSCS

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Abstract
Introduction: Ephedrine and mephentermine are synthetic sympathomimetic drugs used as vasopressors. Ephedrine has direct and indirect effects on α, beta 1, and beta 2 receptors, and it also releases endogenous norepinephrine from synaptic storage sites. This leads to an elevation in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). On the other hand, mephentermine indirectly stimulates beta-adrenergic receptors and to some extent alpha-adrenergic receptors as well. Its primary effect is cardiac stimulation, which increases peripheral vascular resistance and contributes to an increase in blood pressure.
Aim: The aim of this study is to examine the efficacy of ephedrine and mephentermine in the treatment of hypotension during the Lower Segment Caesarean Section (LSCS).
Materials and Methods: This observational study was conducted in the Department of Anaesthesiology among 90 pregnant females scheduled for caesarean delivery at Narendra Modi Medical college, Ahmedabad, India. Patients who developed hypotension (SBP <90 mmHg or <20% of the baseline) after receiving spinal anaesthesia were included in the study and divided into two groups.
Group A received an intravenous bolus of 6 mg of ephedrine, and group B received an intravenous bolus of 6 mg of mephentermine.
The variables studied included age, height, weight, Mean Arterial Pressure (MAP), Heart Rate (HR), SBP, DBP, bolus doses, and any side effects that occurred. HR, SBP, and DBP were recorded at baseline and then monitored every two minutes for a total of 10 minutes, and then every five minutes until the end of surgery.
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 21.0 for Windows, and the results were represented as numbers (%) and mean ± Standard Deviation (SD).
Results: The mean age of patients in group A and group B was 24.35 years and 24.72 years, respectively. All vital parameters were comparable. The need for bolus doses after hypotension was significantly higher in group B (1.68±0.81) than in group A (mean 1.28). The statistically significant complications identified were tachycardia, nausea, and vomiting, which were more prevalent in group B with 13 and 16 patients, respectively.
Conclusion: In this study, the authors found that ephedrine was more effective than mephentermine in terms of the requirement for bolus doses and the occurrence of intraoperative side effects. The requirement for bolus doses and occurrence of significant complications were higher in the group that received mephentermine. Therefore, ephedrine bolus immediately following spinal anaesthesia would be a safe and effective technique for preventing hypotension in females scheduled for LSCS.

Keywords: Ceserean section, ephedrine, mephentermine, spinal hypotension

Introduction
Spinal anaesthesia offers numerous advantages during caesarean delivery, such as rapid onset of action, effective neural block, minimal risk of local anaesthetic toxicity, and limited drug transfer to the fetus [1, 2]. However, there are common and serious side effects associated with spinal anaesthesia, including maternal hypotension, bradycardia, dizziness, nausea, vomiting, cardiovascular collapse, fetal acidosis, and, in severe cases, fetal bradycardia [3]. The incidence of hypotension during spinal anaesthesia varies in different studies, ranging from 7.4% to 74.1% [4-6]. Choosing the most effective treatment strategy to achieve hemodynamic stability during spinal anaesthesia continues to be a challenge [7, 8]. Various measures have been used to prevent maternal hypotension and bradycardia, such as volume preloading with crystalloid or colloid, administration of vasopressors, left uterine

displacement, and frequent monitoring. Among these, intravascular volume expansion through preloading with intravenous fluids immediately before spinal anaesthesia induction and the use of vasopressors are common methods [9]. Vasopressor therapy plays a key role in managing hypotension when other measures fail. These medications primarily act on adrenergic receptors α1-, β1-, and β2-, producing distinct physiological consequences. Key considerations include the relative α and β adrenergic effects, onset and duration of action, and effects on the fetus. Ephedrine and mephentermine are two potent vasopressors commonly used to treat and prevent hypotension during spinal anaesthesia for caesarean section [10]. Ephedrine has been the drug of choice for over 30 years due to its safety record, availability, and familiarity among anaesthesiologists. It is a sympathomimetic agent that acts through both direct and indirect mechanisms [11]. Additionally, mephentermine, a sympathomimetic amine with alpha and beta adrenergic agonist actions, is commonly used by anaesthesiologists to manage hypotension induced by spinal anaesthesia [12]. Pharmacologically, mephentermine is an indirectly acting vasopressor that stimulates the release of endogenous catecholamines, and its impact on heart rate depends on vagal tone [13]. Despite the various preventive measures, the incidence of hypotension following spinal anaesthesia in caesarean section remains high [4-6]. According to a survey conducted in the United Kingdom and published in 2001, ephedrine was chosen as the sole vasoconstrictor by 95.2% of obstetric anaesthesiologists [11]. It describes the doses of ephedrine for managing hypotension in detail [14]. Several articles have used intravenous doses of ephedrine ranging from 10-20 mg for prophylaxis against hypotension [15, 16]. Different dosage regimens mentioned for treating hypotension with mephentermine include 30 mg intravenously, 30-45 mg intravenously, and 6 mg intravenous boluses [17]. Hypotension remains a significant complication of spinal anaesthesia and should be promptly and effectively treated to minimise patient discomfort, nausea, vomiting, and the risk of cardiac arrest. It is widely recognized that there is no definitive superiority of one vasopressor over the others in the literature, although arguments have been made in favor of each vasopressor at different times [15]. In patients undergoing Lower Segment Caesarean Section (LSCS), spinal anaesthesia provides a rapid, deep, and symmetrical sensory and motor blockade of superior quality. However, hypotension is the most frequently observed side effect of spinal anaesthesia during LSCS. In daily practice, sympathomimetic agents are commonly used drugs that exert their effects via adrenergic receptors, either directly or indirectly by inducing the release of norepinephrine, which further acts on these receptors. Therefore, the primary objective of this study was to compare the use of bolus ephedrine and mephentermine for managing hypotension during the caesarean section under spinal anaesthesia, with a secondary objective of comparing the intraoperative adverse effects.

Materials and Methods

A prospective observational study was conducted in the Department of Anaesthesiology involving 90 pregnant females scheduled for caesarean delivery at our center.

Sample size calculations: Considering values from a study conducted by Dokania S *et al*., and assuming a mean duration of surgery of 43.5 and 34.15 in group A (received ephedrine) and group B (received mephentermine) with a bias of 10%, the total sample size was calculated to be 90 pregnant females [18]. Therefore, considering a 99% confidence interval and 90% power, the total sample size was 90 (45 in each group).

Inclusion criteria: All female patients between the ages of 18-35 years who met the American Society of Anaesthesiologists (ASA) classification [19] (patients with mild systemic disease including normal pregnancy) were included in the study.

Exclusion criteria: Patients with contraindications for spinal anaesthesia, underlying co-morbid conditions, BMI >30, PIH, Type 2 diabetes, gestational hypertension, or a history of antepartum haemorrhage were excluded from the study.

Premedication: After overnight fasting, all patients were given premedication consisting of 50 mg of intravenous ranitidine one hour before surgery, according to institutional protocol, to prevent the risk of regurgitation and aspiration. Pregnancy is considered a “full stomach” regardless of the fasting period. Under aseptic precautions, spinal anaesthesia was administered in the sitting position using a 25-gauge Quincke needle at the L3-L4 level. A total dose of 2.0 mL was given for spinal anaesthesia, by 2 mL (10 mg) of hyperbaric Bupivacaine. The level of anaesthesia was achieved up to T4-T6, which was confirmed using the Bromage scale and pinprick method. The study drug was administered only after confirming free flow of cerebrospinal fluid. A wedge was placed to prevent hypotension, and a warmer was attached to the patient. Patients who developed hypotension after spinal anaesthesia were included in the study, while the rest were excluded. Hypotensive patients were randomly assigned to two groups using odd/ even number method:

- **Group A:** Patients received a 6 mg intravenous bolus of ephedrine.
- **Group B:** Patients received a 6 mg intravenous bolus of mephentermine. The dose of the drugs was determined through discussion in the department, and a dose of 6 mg was chosen based on a standard article [20]. All patients were preloaded with 10 mL/kg of Ringer lactate over 15 minutes. Baseline values for Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) were recorded after preloading and achieving the sensory block level. The same parameters were recorded every two minutes for the first ten minutes and then every five minutes until 30 mins & then at the end of anaesthesia fixation. Surgery was allowed when sensory level T_4 & bromage scale 3 achieve. Spinal to delivery of baby time, uterine incision delivery time & highest sensory level notified. Duration of surgery was time to spinal anaesthesia to end of skin stiches.

Whenever hypotension (a decrease in SBP <20% from baseline or SBP <90 mm Hg) occurred, the study drug was administered as an intravenous bolus [7]. The study drug was administered every two minutes until the target SBP was achieved within 20% of the baseline value. A maximum of

three bolus doses (18 mg) of the study drug were used in this study. Intraoperatively, nausea and vomiting were managed with 10 mg of intravenous metoclopramide. Additionally, 100% oxygen was given to reduce central hypoxia.

Bradycardia was decrease in Heart rate 20% of baseline or HR<60/ min. It was treated conventionally. Other adverse reactions like nausea vomiting also noticed and treated according to standard protocol.

Statistical analysis

The statistical analysis was performed using SPSS software version 21.0. Continuous variables were assessed using mean (Standard deviation) or range values when necessary and compared using Student t-test (Unpaired) with a 95% confidence interval. Dichotomous variables were presented as number/frequency and analysed using the Chi-square test. A p-value <0.05 was considered significant.

Results

Informed Written Consent was obtained from 120 female patients, out of which 90 patients who developed hypotension were included in this study. They were randomly assigned to two groups, with 45 patients in each group.

Table 1: Demographics & sensorimotor parameters

Parameters	Gr.A(n=45)	Gr.B(n=45)	*p*>value	Inference
Age (yrs)	22.8+/-5.2	24.1+/-2.6	>0.05	NS
Height (cms)	152.1+/-3.2	153.4+/-2.1	>0.05	NS
Weight (kg)	52.2+/-6.8	53.3+/-5.3	>0.05	NS
ASA gradel/ll	23/22	22/23	>0.05	NS
Duration of surgery (mins)	35.3 +/-2.4	34.2+/-3.6	>0.05	NS
Spinal to delivery time(mins)	10.5+/-2.2	10.2+/-1.9	>0.05	NS
Uterine incision delivery time (sec)	122.2+/-2.3	120.8+/-4.3	>0.05	NS
Highest sensory level	T 4-5	T 4-5	>0.05	NS

**All neonates have Apgar score >8 at 1 & 5 mins

Table 2: Hemodynamic parameters (A) SBP

Time	SBP (mm of Hg) Gr A(n=45)	SBP (mm of Hg) Gr.B (n=45)	P>value	Inference
Baseline	118.2 +/- 2.2	120.2+/-3.1	>0.05	NS
2 min	82.4 +/- 1.4	84.3. +/- 2.2	>0.05	NS
4 min	104.6 +/-1.8	98.8+/- 2.6	<0.05	S
8 min	112.8 +/-2.8	110.4+/-2.6	>0.05	NS
10 min	110.6+/-2.8	108.6+/-1.6	>0.05	NS
15 min	110.2+/-2.2	106.8+/-3.2	>0.05	NS
20 min	100.6+/-2.5	100.2+/-1.8	>0.05	NS
25 min	96.8+/-3.2	90.0+/-1.4	<0.05	S
30 min	100.8+/-2.4	103.5+/-1.4	>0.05	NS
End of surgery	116.6+/-2.2	118.2+/-2.2	>0.05	NS

Regarding SBP both groups are comparable. (*p*>0.05).Regarding intergroup Comparision at 2 mins hypotension following spinal anaesthesia occur. & Study drug given. In Group B rebound hypotension occur at 25 min. (*p*<0.05)

Table 2: (B) DBP

Time	DBP(mm of Hg) GrA(n=45)	DBP(mm of Jg) Gr B(n=45)	P value	Inference
Baseline	78.2 +/- 2.4	77.4+/-1.9	>0.05	NS
2 min	64.2+/-1.6	63.7+/-1.5	>0.05	NS
4 min	74.6+/-1.4	72.8+/-1.6	>0.05	NS
6 min	72.8+/-2.1	74.1+/-1.3	>0.05	NS
8 min	74.3+/-1.8	73.4+/-1.7	>0.05	NS
10 min	74.1+/-1.6	73.8+/-1.6	>0.05	NS
15 min	70.8+/-1.2	68.5+/-1.6	>0.05	NS
20 min	71.4+/-1.4	72.4+/-1.0	>0.05	NS
25 min	72.4+/-1.2	71.9+/-0.8	>0.05	NS
30 min	72.8+/-2.2	72.0+/-1.6	>0.05	NS
At end of surgery	72.6+/-1.8	74.2+/-1.9	>0.05	NS

Regarding DBP both groups are comparable. (*p*>0.05).Regarding intergroup Comparision at 2 mins hypotension following spinal anaesthesia occur.& Study drug given.

Table 2: (C) HR

Time	HR Gr A(n=45)	HR Gr B(n=45)	P value	Inference
Baseline	88.6+/-2.1	86.9+/-1.2	>0.05	NS
2 min	82.6+/-2.8	81.6+/-1.8	>0.05	NS
4 min	80.8+/-1.6	80.4+/-2.0	>0.05	NS
6 min	78.2+/-1.5	79.2+/-1.8	>0.05	NS
8 min	78.0+/-1.4	78.2+/-1.2	>0.05	NS
10 min	77.8+/-1.8	78.0+/-1.6	>0.05	NS

15 min	78.0+/-1.6	78.0+/-1.4	>0.05	NS
20 min	78.2+/-1.2	78.2+/-1.2	>0.05	NS
25 min	80.0+/-2.2	80+/-1.5	>0.05	NS
30 min	80.6+/-1.8	80.8+/-1.2	>0.05	NS
At end of surgery	80.0+/-1.6	81+/-1.9	>0.05	NS

Table 3: Requirement of bolus doses of study drug

Parameter	Gr A(n=45)	Gr.B(n=45)	P value	Inference
Total requirement of Bolus of study drug	1.18+/+0.52	1.76+/-0.8	<0.05	S
Requirement of second bolus(number of patients)	8	12	<0.05	S
Requirement of third bolus(number of patients	2	10	<0.001	HS

Table 4: Adverse effects

Adverse reaction	Gr A(n=45)	Gr B (n=45)	P value	Inference
Bradycardia	7	9	>0.05	NS
Tachycardia	2	10	<0.001	HS
Hypertension	3	2	>0.05	NS
Nausea vomiting	10	14	<0.001	HS

Discussions

The current study included a total of 45 patients in each group. Various demographic factors, such as age, height, and weight, were comparable. Hypotension was defined as a decrease in blood pressure (SBP) of more than 20% from the baseline value or less than 90 mmHg.

The present study suggests that ephedrine can be used safely and effectively as mephentermine for the prevention and treatment of hypotension during spinal anaesthesia. However, the results showed that ephedrine was more effective than mephentermine when comparing the statistical data with group B. The incidence of side effects, such as nausea, vomiting, and tachycardia, was lower in the ephedrine group compared to the mephentermine group. These findings are similar to the study conducted by Kol IO *et al*., which also demonstrated a lower incidence of hypotension, nausea, and vomiting in the ephedrine group compared to the control group [21].

Lauckner W *et al*., administered 30 mg of intravenous mephentermine to treat hypotension in pregnant females. The drug facts provided by Wyeth (An American pharmaceutical company) recommend intramuscular doses of 30 to 45 mg for prevention and intravenous doses of 30 to 45 mg for the treatment of post-spinal hypotension. In the study institution, the standard bolus dose used for treating post-spinal hypotension is 6 mg, repeated as needed [22]. There are a few clinical trials comparing these two vasopressors.

Sahu D *et al*., conducted a study using 6 mg bolus doses of ephedrine and mephentermine following the onset of hypotension and found similar requirements for both drugs in maintaining blood pressure during caesarean section [17]. The maximum dose of ephedrine used in their study was 18.34±2.53 mg in two patients, while 10 patients required 18 mg of mephentermine to maintain their SBP. Simon L *et al*., concluded that a single bolus of intravenous ephedrine at a dosage of either 15 or 20 mg significantly reduced the incidence of maternal hypotension compared to a single 10 mg bolus of ephedrine [23]. Peak effect of ephedrine is seen within 2-5 minutes, while mephentermine typically takes around 5 minutes to reach its peak effect [17]. Similar findings were observed in this study, where the SBP became equivalent between the two groups at 6 minutes after the bolus dose. The recorded SBP at 6 minutes was 113 mmHg in group A and 112 mmHg in group B.

Kol IO *et al*., mentioned that a prophylactic bolus dose of 0.5 mg/kg intravenous ephedrine, given at the time of intrathecal block after a crystalloid fluid preload, along with rescue bolus doses, reduces the occurrence of hypotension [21]. This may be due to the specific protocol of drug administration followed in their study, which involved continuous infusion rather than bolus doses. Kaur D *et al*., conducted a study comparing phenylephrine, ephedrine, and mephentermine bolus doses for maintaining blood pressure during spinal anaesthesia in lower abdominal surgeries [20]. Their findings indicated that ephedrine and mephentermine had a relatively gradual and stable normotensive effect with no bradycardia effect. They also observed that there was only one episode of hypotension following ephedrine bolus compared to other vasopressors [20].

A study conducted by Chandak AV *et al*. [16], compared the bolus of phenylephrine (group P), ephedrine (group E), and mephentermine (group M) for maintaining blood pressure during elective caesarean section in 120 patients divided into 40 in each group. The study concluded that there was no difference in managing hypotension between the three groups, and all three vasopressors were effective in maintaining maternal arterial pressure. The bolus doses used were 100 mcg intravenous phenylepherine, 10 mg intravenous ephedrine, and 6 mg of mephentermine in groups P, E, and M, respectively [16].

Limitations

The results are from a single tertiary care centre and may not be generalisable to other contexts. Therefore, they cannot be extrapolated to a wider population.

Future recommendations

Large scale multicentered studies may be required.

Conclusions

In conclusion, both Mephentermine & ephedrine bolus provide prevention of spinal hypotension in parturients. In comparision of Iv Mephentermine bolus, administration of an ephedrine bolus is a safe and effective pharmacological intervention to prevent spinal hypotension along with minimum adverse effects in parturients for LSCS.

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