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"EFFICACY AND SAFETY OF MEPHENTERMINE, EPHEDRINE AND PHENYLEPHRINE ON POST SUBARACHNOID BLOCK INDUCED HYPOTENSION DURING LOWER SEGMENT CAESAREAN SECTION (LSCS): A RANDOMIZED, DOUBLE BLIND, PARALLEL GROUP CLINICAL TRIAL."

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SUMMARY (ABSTRACT)

Background: Lower segment caesarean section (LSCS) is commonly performed operation under subarachnoid block (SAB). Post SAB hypotension is the most common complication requiring variable doses of vasopressors to prevent detrimental consequences of hypotension to mother and fetus. **Methods:** This randomized, double blind, parallel group clinical trial included a total of 150 parturients undergoing emergency or elective LSCS. We compared the effect of mephentermine, ephedrine and phenylephrine immediately after the SAB. Parturients in the, mephentermine and ephedrine group received 10 mg intravenous bolus and 5 mg i.v. for maintenance; phenylephrine group received 100 µg i.v. bolus and 50 µg i.v. for maintenance. Maternal systolic and diastolic blood pressure, heart rate, fetal APGAR score, number of doses required were recorded for 3 hrs. Any episodes of adverse events were recorded. **Results:** We observed less changes in SBP with phenylephrine (mean diff. from baseline- MDB: 3.8 – 7.26) than mephentermine (MDB: 7.34 – 9.56) and ephedrine (MDB: 8.9 – 12.88) for initial 6 min only. We observed less changes in DBP with phenylephrine (MDB: 1.6 – 7.64) than mephentermine (MDB: 5.86 – 11.5) and ephedrine (MDB: 5.42 – 11.12) for initial 6 min only. HR decreases more significantly with phenylephrine compared to mephentermine and ephedrine ($P< 0.05$). Bradycardia, headache, nausea, reactionary hypertension (12%) were the side effects with phenylephrine. **Conclusion:** There is no clinically significant difference among mephentermine, ephedrine and phenylephrine immediately after the SAB. There was a trend for less requirement of maintenance dose with ephedrine. Phenylephrine causes fall in HR which may be advantageous in cardiac patients and in whom tachycardia is undesirable.

KEYWORDS: Subarachnoid block, mephentermine, ephedrine, phenylephrine, hypotension, LSCS.

INTRODUCTION

Subarachnoid block (SAB) is the procedure of choice for Cesarean deliveries. It's benefits include awake mother throughout the surgery, rapid onset of dense neural blockade, avoid problems associated with airway management, less blood loss and stress response of surgery and avoidance of possible neonatal depression from drugs used in general anesthesia[1-3]. Without proper prophylactic and preventive measures, the reported incidence of maternal hypotension is 50-80% after subarachnoid block [4-6].

Supine hypotension syndrome resulting from aortocaval compression can contribute to deleterious effect of hypotension following subarachnoid block[8,9]. The risk to mother includes symptoms of dizziness, fainting attacks, nausea and vomiting due to the rapid decline in blood pressure, while fetal acidosis may be among the fatal consequences of prolonged maternal hypotension[7,10]. To prevent adverse consequences to mother or fetus caused by hypotension, it is desirable to prevent the supine hypotension syndrome beforehand and quickly and efficiently treat it if develops.

There are various methods to decrease the incidence of hypotension, but till date no single method completely prevents hypotension.[11-13] There is a trend to rely more on vasopressors than either crystalloid or colloid alone.[14,15] These data forms the rational base to use prophylactic vasopressor in preventing the detrimental side effects of hypotension, as the incidence of hypotension after SAB for caesarean section can be as high as 80%.[4-6]

Routinely, vasopressors such as ephedrine, mephentermine and phenylephrine have been given prophylactically and preoperatively to prevent and treat maternal hypotension.[16-18] Mephentermine is a mixed sympathomimetic amine that acts both directly and indirectly on α and β adrenergic receptors. In India, it is widely available and is the most commonly used vasopressor, despite the availability of other vasopressors such as ephedrine and phenylephrine, for the management of SAB induced hypotension. Mephentermine has been shown to be as effective and safe as ephedrine. Use of ephedrine in obstetric patients is supported by animal studies, which showed that uteroplacental blood flow is better maintained when ephedrine was used to raise maternal blood pressure.

On the previous comparative studies of these three vasopressors were having small sample size and limited data available on prophylaxis and were open labeled.[18,19] So, we conducted the present study.

Study Methodology

Study protocol was approved by the Institutional Review Board (IRB), Govt. Medical College, Bhavnagar and was conducted in accordance with declaration of Helsinki and Good Clinical Practice guidelines. The protocol was retrospectively registered at clinical trial registry of India (CTRI/2015/10/006255). The participants were recruited from Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, India. The written informed consent in vernacular language was obtained from each parturient before enrollment.

Inclusion and exclusion criteria for parturient selection

A prospective, randomized, parallel group, interventional double blind clinical study was conducted in ASA I and II full term parturients with singleton, uncomplicated pregnancy, posted for emergency or elective lower segment caesarean section (LSCS). Parturients having systolic blood pressure (SBP) 100 to 150 mm of Hg and diastolic blood pressure (DBP) 70 to 90 mm of Hg were included in study. After thorough pre-anaesthetic evaluation, parturients with contraindications to spinal anaesthesia, pregnancy induced hypertension, pre-eclampsia, eclampsia, CVS (cardiovascular system) and CNS (central nervous system) abnormalities, diabetes mellitus, fetal and placental abnormalities and sensitivity to local anaesthetic used in study were excluded from the study.

Trial design

Parturients satisfying the inclusion and exclusion criteria were randomized through one block randomization method, where one parturient had every chance to get allocated in any group by using computer generated random numbers (Random allocation software version 1.0). The third person, independent of the study generated random allocation sequence. The sealed opaque envelops technique was used for concealment. Parturients were assigned to three groups, 50 in each.

Group I: Bolus - Mephentermine 10 mg I.V. immediately after SAB. **Maintenance –** Mephentermine 5mg I.V. if hypotension develops.

Group II: Bolus - Ephedrine 10 mg I.V. immediately after SAB. **Maintenance –** Ephedrine 5 mg I.V. if hypotension develops.

Group III: Bolus - Phenylephrine 100 µg I.V. immediately after SAB. **Maintenance –** Phenylephrine 50 µg I.V. if hypotension develops.

Preparation of study drug

Three of the vasopresors were supplied to the attending anaesthesiologist in 10ml syringe filled up to 6ml, which was prepared by the person independent of the study. All syringes were labeled with parturient's enrollment number. For group I and group II, 1ml (30 mg) of drug was taken and diluted up to 6 ml with distilled water making concentration of 5 mg/ml. For group III, 1ml (1mg) of phenylephrine was taken and diluted up to 10ml to make concentration of 100ug/ml, from which 3ml was taken in separate syringe and diluted up to 6 ml to make concentration of 50ug/ml. So for all the groups, bolus dose is 2ml and maintenance dose is 1ml. Drug was prepared by the anaesthesiologist, independent of the study and handover to attending investigator who was unaware about the content of the drug.

In pre-anaesthetic preparation room, standard monitoring for heart rate (HR), non-invasive blood pressure (NIBP) and peripheral oxygen saturation (SPO_2) was established and baseline vital parameters were recorded. An 18G i.v. cannula was secured and preloading was done with ringer's lactate at the rate of 10 ml/kg, 15 minutes before the induction of anaesthesia. Premedication consisting of glycopyrrolate 0.004 mg/kg and ondansetron 4 mg were injected 15 minutes before induction. Parturient was shifted to operation theatre. Subarachnoid block was performed with all aseptic and antiseptic precaution in left lateral position in L3-L4 intervertebral space with 23G spinal needle using 2 ml of 0.5% hyperbaric bupivacaine. Immediately after turning the parturient to supine position, bolus dose of study drug (2ml) was given as per the randomization code. After SAB, all parturients received intravenous ringer's lactate at the rate of 5ml/min. HR, NIBP, SPO_2 were recorded immediately after bolus dose of study drug, at 2min, 4min, 6min, 10min, every 5 minute till 30 min, every 10 min till 60 min, every 1 hr till 3 hrs. Maintenance doses of study drug were given if hypotension was noticed. Fall in SBP ≥20% from the baseline value or SBP <90 mm of Hg whichever is higher was considered as hypotension. APGAR score was noted at 1 min and 5 min. During study period, an investigator (attending anaesthesiologist) recorded all the observation and adverse events (AEs) in case record form (CRF). Bradycardia was defined as heart beats <60 / min and

treated with inj. atropine 0.6mg intravenously. Reactionary hypertension was defined as >20% increase in SBP from the baseline value.

Adverse events (AEs) during the course of study were noted, treated accordingly and reported to Institutional Review Board. Causality assessment for AEs was done according to WHO-UMC causality assessment.

Outcome assessment

Primary outcome measure was maternal blood pressure, secondary outcome were maternal HR, total episodes of hypotension, number of maintenance doses required, maternal hypertension and bradycardia, fetal APGAR score at 1 and 5 min after birth.

Statistical analysis

Predicting the peak effect of vasopressors on blood pressure at 6 minutes, 42 parturients per group would be required to achieve 90% power at 5% significance level. Assuming 10% total withdrawal and unfavourable outcome 50 patients were recruited in each group. Data were analyzed by per protocol analysis. Data were expressed as mean ± standard deviation. Parametric data were analysed by using Tukey Kramer's multiple comparison test and non-parametric data by Dunn's multiple comparison test. Inter-group and intragroup comparison was done by analysis of variance (ANOVA) test. Data for adverse events and doses of study drug required were expressed as percentage and analysed with Chi-square or Fisher's exact test. *P* value <0.05 was considered as statistically significant. All statistical analysis was performed through graph pad instat version 3.0 software (demo version).

RESULTS

A total of 186 parturients were screened. We excluded patients having PIH and pre-eclampsia (14), eclampsia (4), placenta previa (4), diabetes mellitus with hypertension (2) and multiple pregnancies (2) and enrolled 150 parturients. A total of 50 parturients in each group included for per-protocol analysis.

Table 1 shows demographic data and pre-operative HR, SBP, DBP, SPO_2. All parameters were comparable in all three groups at baseline. No significant (*P*> 0.05) difference was found in pre-operative data.

Primary outcome measure –Blood pressure

There was better control of SBP with phenylephrine (mean diff. from baseline 3.8 – 7.26 for first 6 min) than mephentermine (mean diff. from baseline 7.34 – 9.56 for first 6 min) and ephedrine (mean diff. from baseline 8.9 – 12.88 for first 6 min). (Table 2) Maintenance of DBP was better with phenylephrine (mean diff. from baseline 1.6 – 7.64 for first 6 min) than mephentermine (mean diff. from baseline 5.86 – 11.5 for first 6 min) and ephedrine (mean diff. from baseline 5.42 – 11.12 for first 6 min). (Table 3) After 6 min, apparently not much difference in blood pressure control among all the three vasopressors.

Secondary outcome measures

With phenylephrine HR falls immediately after bolus injection (*P*<0.05) which was not clinically significant except for 4 (8%) parturients who developed bradycardia and responded well to atropine 0.6 mg i.v.. In comparisons to mephentermine and ephedrine, there was statistically significant decrease in HR with phenylephrine after 2 minutes and it continued till the end of study period (*P*<0.05).The ephedrine and mephenteramine treated group did not show any clinically and statistically significant change in HR from baseline over a period of time (*P*>0.05). No significant difference in HR found between mephentermine and ephedrine. [Figure 2]

At all the time point during study period, SPO_2 was comparable within and between all the three groups (*P*>0.05).

To treat hypotension during study period, single maintenance dose of study drug required in 18%, 8% and 20% parturients in mephentermine, ephedrine and phenylephrine group respectively and 2 doses required in 2% parturients in each mephentermine and ephedrine group.(*P*>0.05)

No significant effect of vasopressor on fetus in terms of APGAR score at 1 and 5 minutes in all study groups. All study group showed median APGAR of 7 (IQR:7-8) at 0 min and 9 (IQR: 8-9) at 5 min.

Safety assessment

With phenylephrine (group III), a total of 6 (12%) parturients developed AEs like bradycardia (6%), bradycardia and headache (2%) and reactionary hypertension with nausea and headache (4%). Reactionary hypertension developed in 2 parturients at 4 and 6 min and reverts spontaneously to non-hypertensive value within 2 and 4 min respectively. All AEs were of mild to moderate in severity, possibly or probably related with the drugs and except bradycardia, did not require any treatment. We did not observe any AEs in mephentermine (group I) and ephedrine (group II) treated groups.

Table 1 Pre-operative data of parturients.

	Group I (mean ± SD)	Group II (mean ± SD)	Group III (mean ± SD)	*P* value
Age (years)	24.26 ± 3.85	24.64 ± 3.11	24.12 ± 3.10	0.53
Height (cms)	155.42 ± 2.32	155.36 ± 2.59	155.5 ± 2.38	0.69
Weight (kgs)	58.18 ± 4.75	58.24 ± 4.96	58.8± 4.7	0.31
HR (/ min)	104.14 ± 15.86	98.58 ± 13.9	103.66 ±12.74	0.18
SBP (mm of hg)	127.28 ± 9.88	124.34 ± 11.20	124.86 ± 8.48	0.27
DBP (mm of hg)	74.76 ± 10.44	72.34 ± 9.15	73.84 ± 10.32	0.48
SPO_2 (%)	98.58 ± 0.54	98.66 ± 0.52	98.52 ± 0.58	0.57

Table 2 Mean difference with baseline of systolic blood pressure (mm of Hg)

SBP	Mephentermine Group I	Ephedrine Group II	Phenylephrine Group III	Intergroup *P* value		
				I-II	I-III	II-III
0 min	7.34	8.9	4.76	>0.05	>0.05	>0.05
2 min	8.88	10.62	3.8	>0.05	>0.05	<0.05
4 min	9.56	12.88	4	>0.05	>0.05	<0.05
6 min	9.02	12.46	7.26	<0.05	>0.05	>0.05
10 min	9.2	11.9	9.04	>0.05	>0.05	>0.05
15 min	6.66	10.6	10.36	>0.05	<0.05	>0.05
20 min	6.84	12.28	9..42	>0.05	>0.05	>0.05
25 min	8.88	10.26	10.36	>0.05	>0.05	>0.05
30 min	7.36	10.26	10.42	<0.01	<0.05	>0.05
40 min	7.32	10.5	9.16	<0.01	>0.05	>0.05
50 min	6.8	10.76	9.28	<0.001	<0.01	>0.05
60 min	7.2	9.9	8.1	<0.001	>0.05	>0.05
2 hr	7.64	8.94	7.46	<0.05	>0.05	>0.05
3 hr	6.28	7.78	6.74	>0.05	>0.05	>0.05

Table 3 Mean difference with baseline of diastolic blood pressure (mm of Hg)

DBP	Mephentermine Group I (mean ± SD)	Ephedrine Group II (mean ± SD)	Phenylephrine Group III (mean ± SD)	Intergroup *P* value		
				I-II	I-III	II-III
0 min	5.86	5.42	1.6	>0.05	>0.05	<0.05
2 min	10.18	8.92	5.1	>0.05	>0.05	>0.05
4 min	9.88	11.12	4.64	>0.05	>0.05	<0.05
6 min	11.5	10.56	7.64	>0.05	>0.05	>0.05
10 min	12.1	13.38	9.9	>0.05	>0.05	>0.05
15 min	10.14	13.62	12.3	>0.05	>0.05	>0.05
20 min	10.76	13.2	11.98	>0.05	>0.05	>0.05
25 min	10.16	10.2	11.7	>0.05	>0.05	>0.05
30 min	10.12	9.72	11.22	>0.05	>0.05	>0.05
40 min	9.1	10.86	9.6	>0.05	>0.05	>0.05
50 min	5.84	8.84	7.46	>0.05	>0.05	>0.05
60 min	5.84	7.78	7.04	>0.05	>0.05	>0.05
2 hr	4.92	6.24	5.94	<0.01	>0.05	>0.05
3 hr	5.8	6.66	6.66	>0.05	>0.05	>0.05

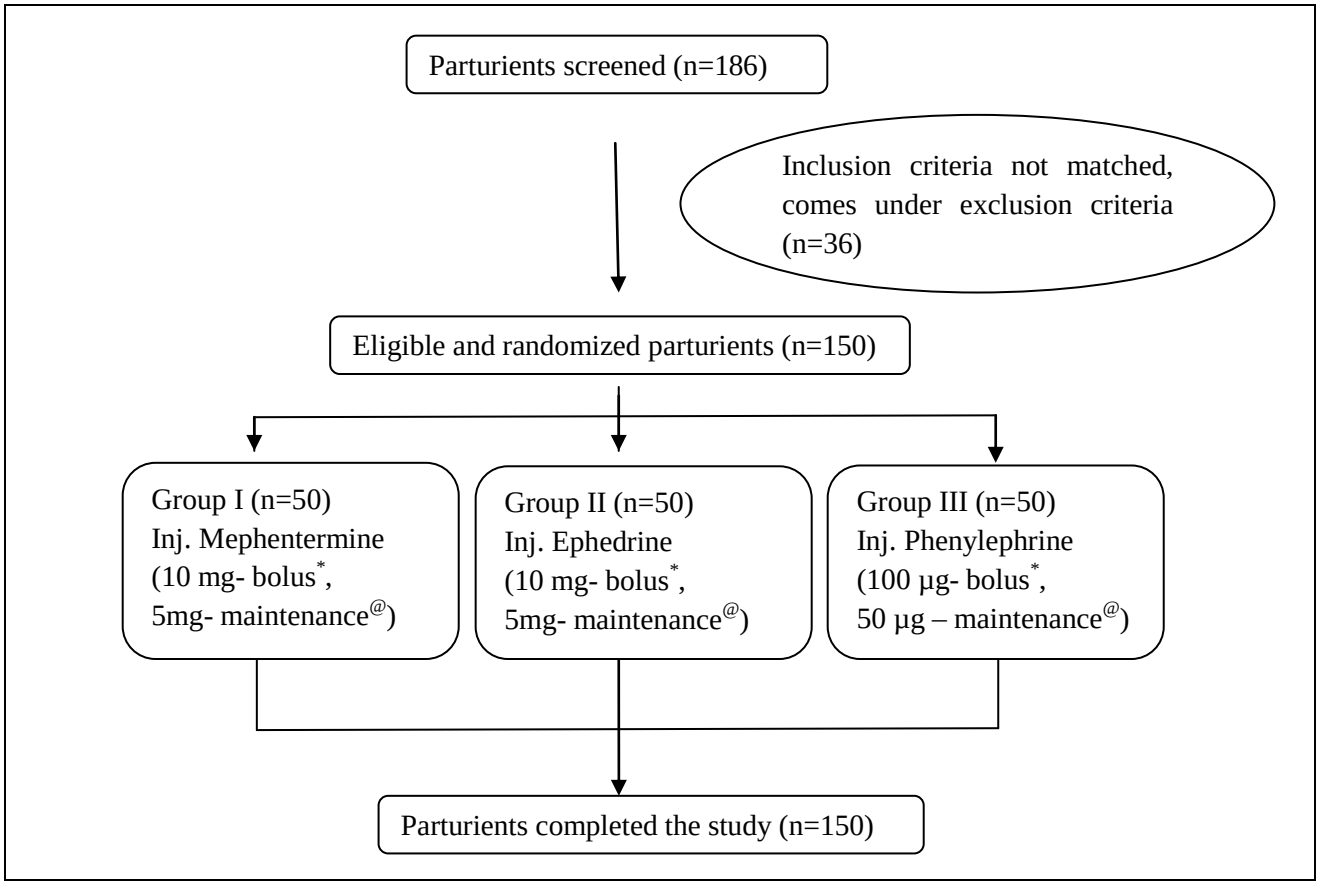

Figure 1: Study flow diagram for randomized parturients

*- Given immediately following SAB; @- Given when hypotension was noticed

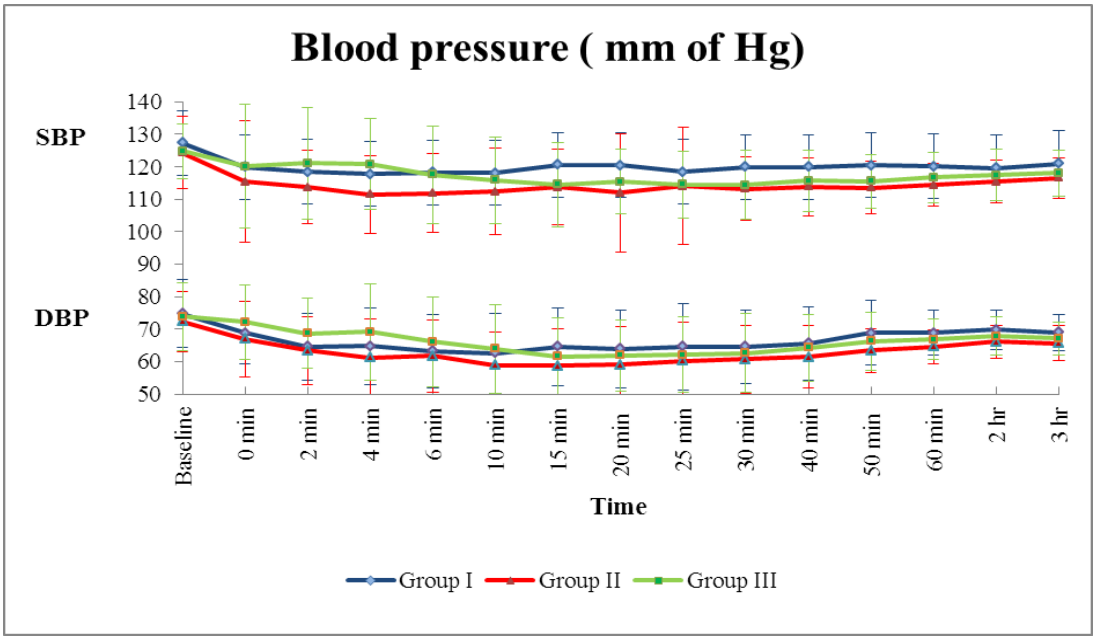

Figure 2: Blood pressure variation in three study groups (mm of Hg).

SBP – systolic blood pressure; DBP – diastolic blood pressure

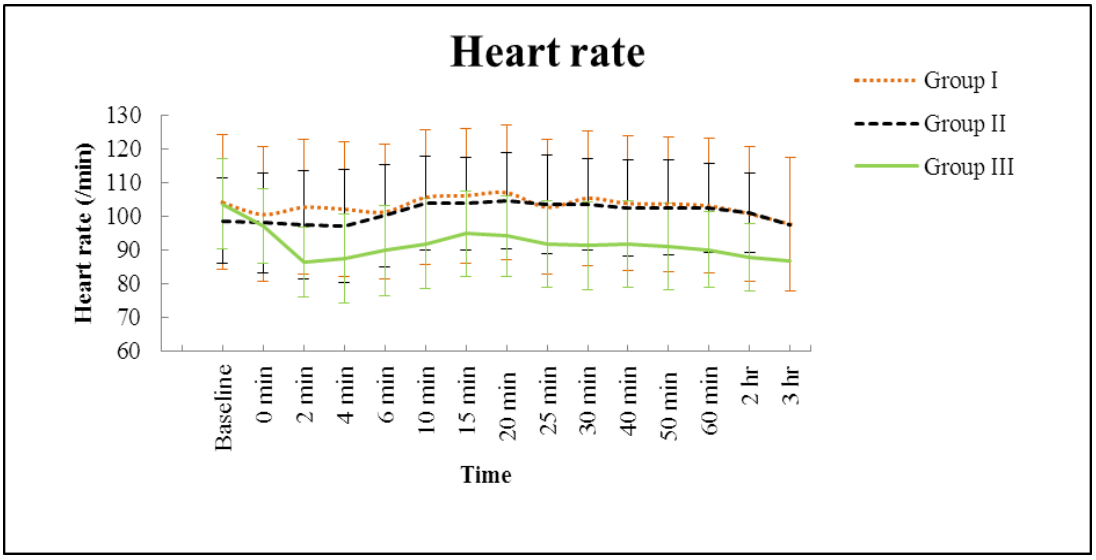

Figure 3: Heart rate variation in three study groups (beats/minute).

DISCUSSION

LSCS is one of the oldest operations but the anaesthesia for LSCS is just a century old and is not without controversies. With recent advances in scientific knowledge of physiology of pregnancy, pharmacology of local anaesthetic drugs and refinement in the technical skill led to the supremacy of regional anaesthetic techniques over general anaesthesia for LSCS.[20, 21]

Various factors are responsible for high incidence of hypotension following SAB for LSCS which includes higher sympathetic blockade as level of block required for LSCS is T6, supine hypotension syndrome of pregnancy and dose and concentration of local anaesthetic agent used. [21]

Many investigators have studied efficacy of mephentermine, ephedrine and phenylephrine for treatment of post-SAB hypotension and concluded that all the three agents are equally efficacious in maintaining SBP between baseline value and hypotensive value. [22, 23, 24] Others have studied preventive effect of these agents on post-SAB hypotension and concluded that all vasopressors are equally effective. [25, 26, 27] Results from the previous studies are similar to the present study. Phenylephrine had better control over SBP in initial period of 2 to 6 minutes (intragroup $P > 0.05$) compared to mephentermine and ephedrine group (intragroup $P < 0.05$) ($P < 0.05$) [Table 2]. No statistically significant difference found between these three groups at other time points. This can be explained by relatively early onset of peak effect of phenylephrine (2 minutes) and mephentermine (2-4 minutes) compared to ephedrine (4-6 minutes).

In present study, cardiovascular stability was better with phenylephrine than mephentermine and ephedrine. In phenylephrine group, HR decreased to statistically significant value after bolus injection, compared to its baseline, mephentermine, and ephedrine group ($P < 0.05$; Figure 2). Few parturients in phenylephrine group required injection atropine for treatment of bradycardia which is in accordance with the literature. Over the period of time, there was steady rise of HR from baseline in mephentermine and ephedrine group ($P > 0.05$). Other studies[19, 28, 29, 30] also documented the same kind of effect of these vasopressors on HR. Reason behind tachycardia from mephentermine and ephedrine can be their both α and β receptor mediated action, while phenylephrine devoid of β receptor action. [31] So, increase in blood pressure from phenylephrine, causes baroreceptor mediated reflex bradycardia. Decrease in HR with phenylephrine can be advantageous in cardiac patients and in whom tachycardia is undesirable.

There was a trend for less requirement of maintenance dose in ephedrine group (10%) compared to phenylephrine and mephenteramine groups (20% each).($P > 0.05$)

APGAR score of neonates in all the three groups was comparable at the 1 and 5 minutes APGAR score. Current evidence supports that the APGAR score is a better predictor of neonatal outcome than umbilical cord blood gas analysis. [6, 32, 33]

Two (4%) parturients in phenylephrine group developed reactionary hypertension with headache which is consistent with previous literature. [28]

Present study is not without limitation. Only healthy, ASA I/II patients were included in the study, but parturients with cardiovascular pathology, belonging to ASA III/IV are at increased risk for haemodynamic disturbances. All patients were hydrated adequately (for ethical reason) before surgery. So, our study result can't be extrapolated to parturients with suboptimal intravascular volume status. We have used single dose and could not stat the optimal dose required for prevention of hypotension. We suggest future study with

different doses in parturients with co-morbidities to further stat a clinical recommendation about efficacy and safety of these vasopressors.

In conclusion, mephentermine, ephedrine and phenylephrine are equally effective in preventing hypotension from SAB with phenylephrine being more effective in first 6 minutes during LSCS with similar neonatal outcome. There was a trend for less requirement of maintenance dose with ephedrine.

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Conflict of interest
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