



A COMPARATIVE STUDY OF EPHEDRINE, PHENYLEPHRINE AND MEPHENTERMINE FOR IMMEDIATE CONTROL OF SPINAL INDUCED HYPOTENSION IN CAESAREAN SECTION

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ABSTRACT

Introduction: Hypotension is the most common side effect of neuraxial blocks in the obstetric patients. The primary outcome measure of our study was to assess the effect of ephedrine, phenylephrine and mephentermine on maternal hemo-dynamics (hypotension and tachycardia) and the secondary outcome was to see for fetal outcome by comparing APGAR SCORE in the different groups.

Materials and method: A randomized double blinded study was conducted among 96 adult patients according to inclusion and exclusion criteria. They were randomly distributed into three groups (32 patients each). Group 1 patients received 5 mg of intravenous mephentermine, Group 2 patients received 5 mg of intravenous ephedrine Group 3 patients received 100 micrograms of intravenous phenylephrine.

Results: In the present study there were least mean number of doses needed in group 3 of 1.13 ± 0.34 and most number in group 1 of 3.69 ± 0.78 . APGAR SCORE in all the babies were found to be 9 which was clinically normal. There were no side effects like hypotension, bradycardia or tachycardia noted in any of the patients participated in the study at the end of the surgery.

Conclusion: It is concluded from our study that for immediate control of spinal induced hypotension, phenylephrine is found to be the more effective drug among the study drugs.

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INTRODUCTION

Spinal anaesthesia is often used for both elective and emergency caesarean section. Anaesthesia-related maternal mortality is decreased when general anaesthesia is avoided.¹

The proportion of women undergoing caesarean section has been increasing steadily such that in Brazil one in every three women underwent caesarean section and in the United Kingdom the overall incidence is 13%.²

Nowadays, spinal anaesthesia is the preferred technique for lower abdominal surgery.³ However hypotension is the most common side effect of neuraxial blocks in the obstetric patients. The cause of hypotension after spinal anaesthesia is the preganglionic sympathetic blockade resulting in arterial and venous vasodilatation leading to reduced cardiac preload. This in turn limits cardiac output, the main compensatory mechanism to counteract spinal vasodilatation. In the pregnant patient, compression of the inferior vena cava by the gravid uterus further impedes venous return if untreated, this process may lead to maternal hypotension and uterine hypoperfusion.⁴ Therefore regional anaesthesia for elective caesarean section is often the preferred option of caregivers when balancing risks and benefits to the mother and the fetus.

Several techniques use for preventing hypotension include intravenous fluid prehydration, sympathomimetic drugs and physical methods such as leg bindings and compression

stockings. Despite all these measures approximately 25% of patients still experience hypotension episodes.⁵

Crystalloid prehydration has poor efficacy for preventing hypotension probably because it undergoes rapid distribution.⁶ As an alternative, co-loading of crystalloids may be more physiologically appropriate because the maximum effect can be achieved during the time of block and consequent vasodilation are evolving.⁷

Recent studies have shown that any reduction in maternal blood pressure following spinal anesthesia is undesirable and the best strategy is to maximize the use of vasoconstrictors to maintain SBP at 100% of baseline.⁸

Mephentermine is the drug which is used in large scale now a days in different settings. It is a sympathomimetic drug having selective vaso-constrictive effect on the peripheral vascular bed which contributes to the increase in blood pressure, for which it is used to treat hypotension without prominent adverse effects.⁹

Ephedrine is a sympathomimetic amine. It is a potent alpha and beta agonist, and acts both by direct as well as indirect mechanism. Prophylactic ephedrine given by standard infusion set was more effective than crystalloid prehydration in the prevention of hypotension during spinal anaesthesia for elective caesarean section.¹⁰

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Whereas phenylephrine, a pure alpha adrenergic agonist drug claims better foetal acid-base status and similar efficiency in blood pressure control but its use is associated with maternal bradycardia.¹¹

Although there are various studies comparing two drugs, there are very less studies comparing three vasopressors; mephentermine, phenylephrine and ephedrine. For this reason we tried to evaluate the dose required to maintain the baseline blood pressure after spinal anaesthesia using all the three drugs in different groups.

The primary outcome measure of our study was to assess the effect of the three vasopressors on maternal hemo-dynamics (hypotension and tachycardia) and the secondary outcome was to see for fetal outcome by comparing APGAR SCORE in the different groups.

Aims and Objects

- To evaluate the vasopressor effect of phenylephrine, ephedrine and mephentermine for maintenance of arterial blood pressure during spinal anaesthesia in Caesarean section.
- To find out any unwanted side effects of the three study drugs.

MATERIALS AND METHODS

Study design: Randomised double blinded study.

Study setting: Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur.

Study duration: The study was conducted between September 2017 to August 2019 over a period of two years.

Study population: Patients of ASA II²⁹ physical status, aged 18-35 years scheduled to undergo caesarean section under spinal anaesthesia and satisfying all inclusion criteria was recruited in the study.

Inclusion criteria

1. Patients of ASA grade II.
2. Age group of 18-35 years
3. Patient scheduled to undergo caesarean section under spinal anaesthesia.

Exclusion criteria

1. Age less than 18 years and more than 35 years.
2. Patients with pregnancy induced hypertension.
3. Patients with history of cerebrovascular, neurologic, respiratory and ischemic heart disease.
4. Renal and hepatic dysfunction.
5. Patients with history of hypertension, diabetes mellitus.
6. Patients with foetal abnormality.
7. Patients with contraindication to spinal anaesthesia.

Study variables

Primary variables included was age, weight, height, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, peripheral oxygen saturation and apgar score. Sex of the patient were not compared as all the patients of our study were of female sex.

Recruitment: 96 patients were randomly allocated into three groups of 32 each using computer generated randomization method shown above. Recruitment was based on the elective

list given one day before surgery for pre-anaesthetic visit by confirming with the inclusion and exclusion criteria. After pre-anaesthetic evaluation and recruitment, patients were asked to take tablet Ranitidine 150 mg orally the night before surgery.

On the day of surgery, injection metoclopramide 10 mg was given 15 minutes prior to the induction of spinal anaesthesia.

Upon arrival of the patient at the operation theatre heart rate (HR), non-invasive arterial blood pressure (NIBP), peripheral oxygen saturation (SpO₂), continuous electrocardiogram (ECG) were recorded with the help of multichannel cardiac monitor.

The study drug was prepared by a different anaesthetist who were not conducting the study; so that neither the investigator nor the patient knew about the study drug, thus making the study double blinded.

Preloading was done with ringer lactate solution 15mg/kg body weight about 15 minutes before the intended time of intrathecal drug administration. Under adequate aseptic precautions, lumbar puncture was performed at L₃-L₄ intervertebral space using midline approach with a 25 gauge quincke spinal needle in the lateral decubitus position. When the patient developed hypotension, any one of the study drugs was given as prepared by the non-participating anaesthetist as per the randomization.

Group 1 (n = 32) patients received 5 mg of intravenous mephentermine,

Group 2 (n = 32) patients received 5 mg of intravenous ephedrine

Group 3 (n = 32) patients received 100 micrograms of intravenous phenylephrine.

The hemodynamic parameters such as HR, NIBP, SpO₂, ECG were recorded at one minute intervals till the delivery of the baby and thereafter at five minute intervals until the end of the surgery. Intravenous fluid was administered in the form of ringer lactate (RL) at the rate of 10 ml/kg body weight per hour. A decrease in systolic blood pressure of more than 20% from the baseline or less than 90 mm of Hg was treated with intravenous mephentermine 5 mg or ephedrine 5 mg or phenylephrine 100 micrograms. Number of respective drug doses required was noted.

Heart rate of less than 60 beats per minutes were treated with atropine 0.3 mg intravenously. Apgar scores of the babies were also recorded at 1 minute and 5 minutes. The effect of the drugs were followed up until the end of the surgery.

Working Definition

Hypotension was defined as a systolic blood pressure value of below 90 mm Hg or < 20% from baseline.

Bradycardia was defined as a heart rate value of below 60 beats per minute.

Statistical Analysis

The findings and observations made during the study was tabulated and statistically analysed with ANOVA test for comparison among three groups for the variables namely age, height, weight, systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation of the blood and apgar score. Student t-test was used for intergroup comparison of the variables namely systolic blood pressure, diastolic blood pressure and heart rate. All the analysis was done by using the

Statistical Package for Social Sciences (SPSS), 21version. The total number of dose of drug used for each group were also tabulated and statistically analysed using Anova test for comparing three groups and student t test for intergroup comparison. A p value of less than 0.05 was considered as statistically significant.

Ethical issues

Ethical approval was obtained from Institutional Research Review Board. Informed written consent was obtained from the respondents. Privacy of the patients was maintained by masking the personal identification. The collected data was made accessible only among the investigators and were preserved as a hard copy kept safely in a separate drawer protected by lock and key.

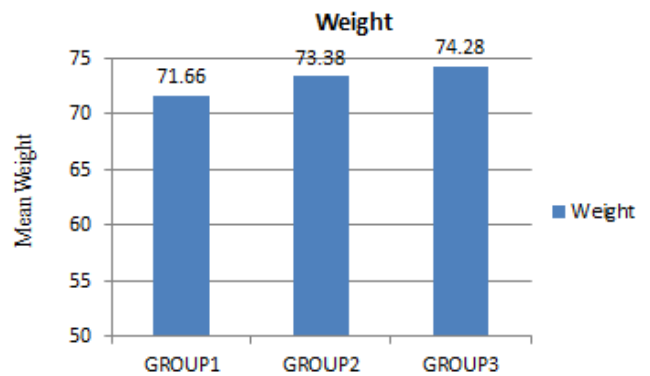
Conflicts of interest: Nil

RESULTS AND OBSERVATION

After thorough scrutiny and checking of the data, statistical analysis was performed by using the statistical package for social sciences (SPSS), 21 version. Numerical/ continuous variables are reported as Mean ± SD (standard deviation). The three group means are compared byAnova Test. The intergroup comparison was done with Student ‘t’ test. The categorical data like ASA and sex wasn’t put into account as all the patients participated in the study is of ASA II and of female sex. A p-value of < 0.05 is treated as significant.

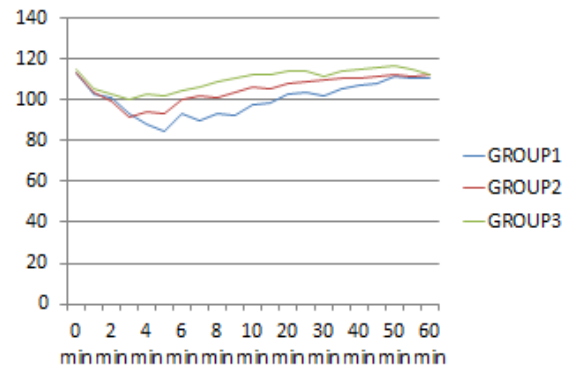
Bar and line diagrams are used to highlight more clarity of the findings.

Chart 1(b) show that patient’s height was comparable and no significant differences were observed among the three groups.



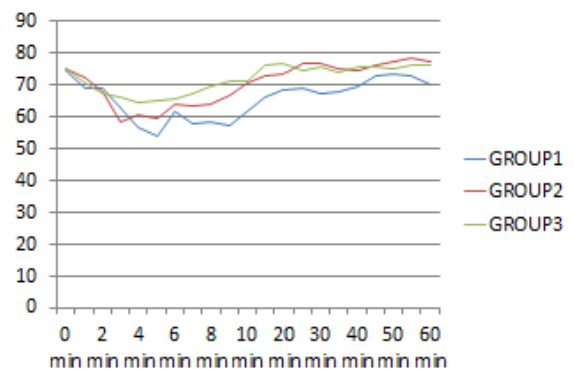
Distribution of weight among groups

Chart 1(c) showing the comparison of weight in the three groups which shows that patient’s weight was comparable and no significant differences were observed among the three groups.



Distribution of mean systolic blood pressure in different time frame among all groups

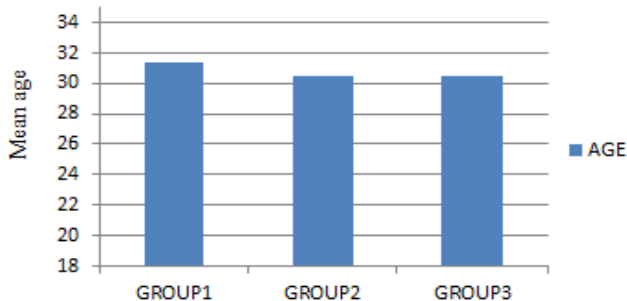
Chart 2 (a) show the distribution of systolic blood pressure at different time intervals in the three groups. The systolic blood pressure falls from its baseline value till 5 minutes in all the groups, however the fall is comparable and insignificant till the 3rd minute in all the groups.



Distribution of mean diastolic blood pressure in different time frame among all groups.

Chart 2 (b) shows the distribution of diastolic blood pressure at different time intervals in the three groups. Though there were fall of diastolic blood pressure in all the groups, till 3rd minute the fall was comparable and statistically insignificant.

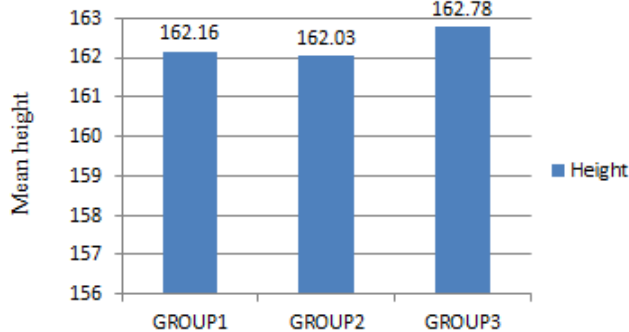
AGE



Distribution of age among groups

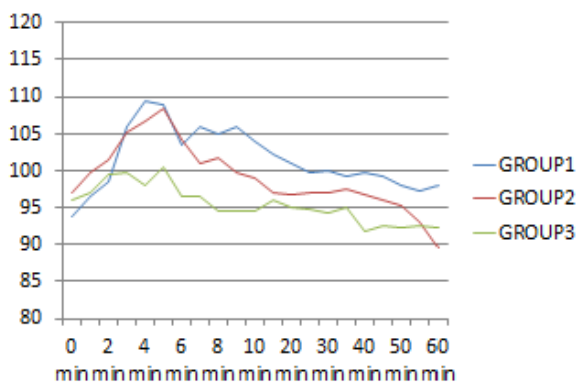
Chart 1(a) showing the comparison of age in the three groups

Height



Distribution of height among groups

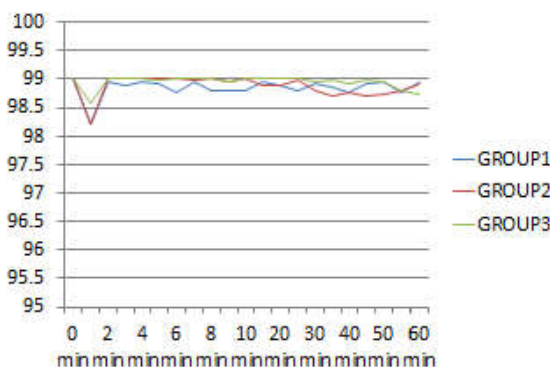
Chart 1(b) showing the comparison of age in the three groups



Distribution of mean heart rate in different time frame among all groups

Chart 2 (c) shows the distribution of heart rate at different time intervals in the three groups. The heart rate increases in all the groups, up to maximum for group 1 at 4th minute, for group 2 and group 3 at 5th minute. However group 3 approaches to the baseline value at 8th minutes whereas group 2 at 15th minutes and group 1 did not approach to baseline value till 60 minutes, up to 2 minutes the increase in heart rate was comparable and insignificant.

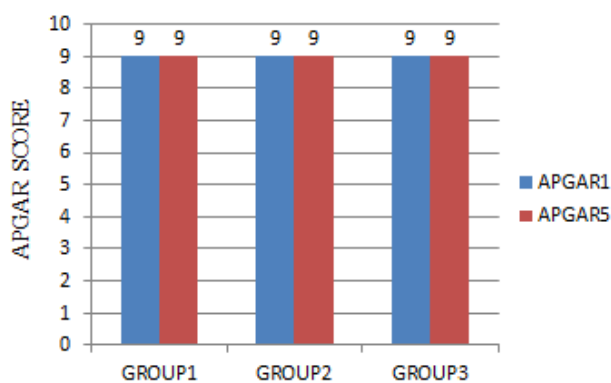
*= Statistics cannot be computed as the values are equal



Distribution of mean SPO2 in different time frame among groups

Chart 3 showing the comparison of mean SPO2 in the three groups

Chart 3 shows no significant difference in oxygen saturation among the three groups in all time points.



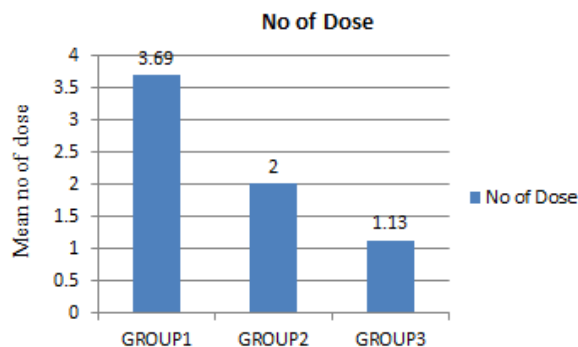
Bar diagram showing APGAR SCORE in different groups

Chart 4 showing the comparison of mean APGAR SCORE in the three groups.

As shown in chart 4, the APGAR SCORE in all the three groups were found to be 9 which is normal clinically.

Table 1 showing the distribution and comparison of number of doses of respective drugs required in the three groups

Parameter	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	Statistical Value (F)	df	p value	Inference
No of Doses	3.69±0.78	2.00±0.62	1.13±0.34	146.88	2	0.00	HS



Mean number of doses required among all groups

Chart 5 showing mean number of doses of respective drugs required among the three groups

Table 2 (a) showing the intergroup comparison of No of doses of respective drugs between GROUP1 and GROUP2

Parameter	GROUP1 (Mean ± SD)	GROUP2 (Mean ± SD)	Statistical Value (Student 't' test value)	p-value	Inference
No of Dose	3.69±0.78	2.00±0.62	9.57	0.00	HS

Table 2(b) showing the intergroup comparison of No of doses of respective drugs between GROUP2 and GROUP3

Parameter	GROUP2 (Mean ± SD)	GROUP3 (Mean ± SD)	Statistical Value (Student 't' test value)	p-value	Inference
No of Dose	2.00±0.62	1.13±0.34	7.00	0.00	HS

Table 2(c) showing the intergroup comparison of No of doses of respective drugs between GROUP1 and GROUP3

Parameter	GROUP1 (Mean ± SD)	GROUP3 (Mean ± SD)	Statistical Value (Student 't' test value)	p-value	Inference
No2of Dose	3.69±0.78	1.13±0.34	17.06	0.00	HS

Table 2 and chart 5, showing the number of doses required by the respective groups which depicts that group 3 required the least number of mean doses of 1.13 whereas group 2 required mean number of doses of 2 and group 1 required mean number of doses of 3.69. This distribution in the number of doses required is statistically highly significant with Anova test with a p-value of 0.00.

With the intergroup comparison of required drug described in table 2 (a), 2 (b) and 2 (c) we can infer that number of doses required in group 1 (3.69±0.78) <group 2 (2.00±0.62) <group 3 (1.13±0.34). Thus, drug used in group 3 (Phenylephrine) is best among the three drugs used in countering spinal induced hypotension followed by the drug used in group 2 (Ephedrine) and then group1 (Mephentermine) as the data suggest to be statistically highly significant.

The respective rescue drug was given when the systolic blood pressure fell below 20% from baseline value. Various parameters like diastolic blood pressure and heart rate were not put into account as our aim was to find out the effect of these drugs in overcoming the spinal induced hypotension only. The tables which shows heart rate and diastolic blood pressure

were put in, to find out significant effects of the drugs in those variables which were found to be in clinically normal range. APGAR SCORE in all the babies were found to be 9 which was clinically normal. ASA and sex were same for all the participants in the study of ASA II and of female sex.

There were no side effects like hypotension, bradycardia or tachycardia noted in any of the patients participated in the study at the end of the surgery. Fetal heart rate and fetal arterial blood PH was not kept as a variable in our study.

DISCUSSION

Hypotension is the most common serious adverse effect of spinal anesthesia for caesarean delivery. Various strategies for preventing hypotension have been investigated and tried as it may have detrimental maternal and neonatal effects. Many interventions such as pelvic tilt, leg elevation and wrapping, and the prophylactic administration of fluids or vasopressors have been proposed and used to reduce the incidence of maternal hypotension. Despite all these measures approximately 25% of patients still experience hypotensive episodes. Various vasopressors like mephentermine, ephedrine, phenylephrine etc, both as prophylaxis and also bolus stat dose has been in use. In our study, we used three drugs in different groups as bolus doses to find out the most effective one in augmenting spinal induced hypotension in patients undergoing cesarean section.

In our study, the insignificant variations in the weight, height and age of the parturients among the groups; charts 1(a), (b), (c) emphasize the fact that the present study was made blind on the weight, height and age of the parturients. In other words, parturients considered for our study who received Mephentermine 5 mg bolus (group1) or Ephedrine 5 mg bolus (group2) and phenylephrine 100 mc.gm bolus (group3), were comparable as regard to their age, weight and height. Sahu D *et al*⁹ also used the same doses of phenylephrine in their study. The dose of mephentermine and ephedrine of 5mg bolus each is almost comparable with them of 6 mg each, but in our study we used the bolus doses regime of Kansal A *et al*¹³.

In our study, to compare the systolic blood pressure in all the three groups, chart 2(a) suggests that there were fall in systolic blood pressure in all the groups till 5 minutes, but there were insignificant fall comparing the three groups till 3 minutes. The preloading of the patients may be the reason for the insignificance till 3 minutes.

The effectiveness of the three drugs were compared in Table 1 and intergroup comparison of effectiveness was compared in Table 2 (a), (b) and (c). These tables along with the chart 5 suggests that there were least number mean doses needed in group 3 of 1.13±0.34 and most number in group 1 of 3.69±0.78. Group 2 required mean number of doses of 2.00±0.62 with a p-value of 0.00. The aim of the study was to find out the effectiveness of the three drugs as to be used when the systolic blood pressure falls more or equal to 20% from baseline values or systolic blood pressure falls less than 90 mm of Hg to maintain the strict goal to tightly maintain the systolic blood pressure. In the present study, it can be concluded that according to our study phenylephrine is proved to be the most effective drug to maintain systolic blood pressure followed by ephedrine used in group 2 and then mephentermine used in group 1. In the study of Guneshwanavar A, Ambi US¹² the

result was comparable. Dinesh S *et al*⁹ also found that phenylephrine is better among the three drugs, though in their study they concluded that mephentermine and ephedrine boluses are having same effectiveness.

The variables like heart rate, diastolic blood pressure, SPO2 and APGAR SCORE were also compared among the groups to find out the possible effects of the drugs in the patients.

Chart 2(b) shows that there was fall in diastolic blood pressure in all the three groups, in intergroup comparison between group 1 and group 2 from 8th minute to 35th minute there were significant differences, between group 2 and group 3 the change was mostly insignificant and between group 1 and group 3 there were significant difference from 4th minute to 40th minute. Even though there were difference in the groups, at the end of the surgery all the groups had a diastolic blood pressure in normal clinical range.

Chart 2 (c) shows that there were increased in heart rate in all the groups, group 3 approached to baseline at 8th minutes, group 2 at 15th minute but group 1 never reached the baseline value. Intergroup comparison was also done. Between group 1 and group 2 there were insignificant differences in heart rate, between group 2 and group 3 there were significant difference though from 4th to 10th minute, it suggests that phenylephrine causes reflex bradycardia, but all the findings were in normal clinical range. Between group 1 and group 3, from 4th minute to 60th minute there were significant differences but all the findings were clinically normal range.

Chart 3 shows comparable and insignificant change in SPO2 in all the three groups, as there were no significant alteration of SPO2 seem in any of the groups.

Chart 4 shows that there were no significant outcome of the baby with any of the drugs as in all the baby had an APGAR SCORE of 9 in both 1 minute and 5 minute as seen in the study of Ganeshanavar A, Ambi US¹².

Limitations in the present study

1. Hypotension due to blood loss and experience of the operating surgeon in controlling bleeding might be a confounding factor.
2. Left lateral tilt by keeping a wedge done to all the parturients undergoing caesarean delivery might also be a confounding factor.
3. Block height was not equal in all the patients.
4. Fetal arterial blood gas monitoring was not done.
5. Further study is required to determine the exact dose response.

CONCLUSION

It is concluded that for immediate control of spinal induced hypotension, phenylephrine is found to be the more effective drug among the study drugs. For the subsequent dose requirement, phenylephrine group was has very less number of doses with respect to ephedrine and mephentermine respectively.

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