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Comparison of single dose phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anesthesia in caesarean section

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Abstract
Introduction: *Anesthesia to a parturient is not only unique but also requires highest degree of care because the anesthesiologist has to look after two individuals, the mother and foetus. Hypotension during spinal anesthesia for caesarean delivery can have detrimental effects on both mother and neonate. In this study we compare the efficacy of Ephedrine, Mephentermine and Phenylephrine in treating the hypotension for caesarean section and their effects.*
Materials and Methods: *The primary objective of the study was to compare the single doses of intravenous Phenylephrine, Ephedrine, and Mephentermine for maintenance of arterial pressure during spinal anesthesia in caesarean section. A prospective Observational study was conducted on 90 patients undergoing caesarean section under spinal anesthesia who are allocated to one of the 3 groups (30 in each group) based on the vasopressor given (ie, ephedrine, mephentermine and phenylephrine). The sampling technique involved consecutive sampling and the data obtained were recorded in to a structured proforma. Statistical analysis was performed using statistical software package SPSS version, 20.0.*
Results: *All the three vasopressors effectively maintained arterial pressure within 20% limit of baseline value though phenylephrine maintained better in first 8 minutes of bolus dose as compared to ephedrine and mephentermine. In phenylephrine group, post study drug values of heart rate were decreased significantly from the values at onset of the hypotension till the end of the surgery when compared to other two groups.*
Conclusion: *Phenylephrine, ephedrine and mephentermine are effective in IV bolus form in maintenance of arterial pressure within 20% limit of baseline though phenylephrine has quicker peak effect of comparison to ephedrine & mephentermine and it causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable.*
Keywords: *Phenylephrine, Ephedrine, Mephentermine, Arterial pressure, Spinal anesthesia, Caesarean section.*

Introduction

Anaesthesia to a parturient is unique and also requires highest degree of care because the anesthesiologist has to take care of two individuals, the mother and fetus. In elective caesarean section under spinal anesthesia hypotension was reported in about 85% of patients[(1)]. Hypotension during spinal anesthesia for caesarean delivery can have detrimental effects on both mother and fetus. These effects include decreased utero placental blood flow, impaired fetal oxygenation with asphyxial stress and fetal acidosis and maternal symptoms of low cardiac output such as dizziness, nausea, vomiting and decreased consciousness. Therefore, there has been much attention in the literature to methods of treating and preventing hypotension in obstetric anesthesia. Careful positioning with left uterine displacement and volume preloading with colloids or crystalloids has been used to prevent it, but these are not complete measures and vasopressors may be required to correct hypotension quickly[(2,3)]. Vasopressors like Ephedrine, Mephentermine, Phenylephrine, Metaraminol and Methoxamine are used for treating hypotension. In this study we compare the efficacy of Ephedrine, Mephentermine and Phenylephrine in treating the hypotension for caesarean section and their effects.

Neuraxial anaesthesia remains the preferred choice for Caesarean deliveries across the globe. Hypotension is the physiologic consequence of spinal anesthesia and can have a potentially deleterious maternal and foetal effect. Vasopressors, which lead to an increase in systemic vascular resistance and increase in mean arterial pressures, have been traditionally used for the prevention and management of hypotension after neuraxial anaesthesia. However, the understanding of hypotension after neuraxial anaesthesia in obstetrics, and the use of vasopressors to prevent it, continues to evolve over the years. This study briefly explores the present understanding of mechanism causing hypotension and the current use of the various vasopressors in obstetric anaesthesia.

Methods and Materials

This is a prospective observational study conducted in patients aged between 20 – 35 years and ASA class I and II undergoing elective/ emergency lower segment caesarean section under spinal anesthesia with baseline systolic blood pressure between 100-140 mmHg and diastolic blood pressure between 70-89 mmHg; and developed hypotension during the operation (fall in systolic pressure >20% from the baseline value or a value less than 90 mmHg), in the Department of Anesthesiology, Government Medical College, Trivandrum from 2018 to 2019. Patients with medical complications like diabetes mellitus, cardiovascular diseases, severe anemia, cerebrovascular diseases and with obstetrical complications like antepartum hemorrhage, pregnancy induced hypertension, cord complications (nuchal cord or cord prolapse), foetal malformations or malpresentations were excluded from the study. This study was conducted after obtaining approval of Institutional ethical committee. Written informed consent were also obtained from the patients. Minimum sample size for the study was calculated to be 30 per group.Prior to surgery each patient was examined and a thorough medical history was taken with emphasis on respiratory and cardiovascular systems. Ranitidine 50 mg and Metaclopramide 10 mg was given by qualified anaesthesiologist intravenously as a routine practice before surgery.Hyperbaric bupivacaine 0.5% was used for establishing spinal anaethesia. After preloading, pulse rate, systolic and diastolic arterial pressure was recorded thrice when middle value was taken as base line values. The same parameters were recorded after subarachnoid block, then at every 2 min for 20 min and thereafter every 5 min till the end of surgery. Whenever hypotension occurs the study drug was given IV by qualified anaesthesiologist and we observed hemodynamic parameters. The number

of boluses and time taken to recover from hypotension was noted. The bradycardia i.e. a pulse rate of 60 /min or less was treated with Atropine 0.3 mg iv.We studied consecutive number of patients and the vasopressor used and hemodynamic responses till we got the desired sample size in each group[ie,30 patients to whom Phenylephrine 100 microgram (0.1 mg) in 1 ml as IV bolus was given, 30 patients to whom Ephedrine 6 mg in 1 ml as IV bolus was given and 30 patients to whom Mephentermine 6 mg in 1 ml as IV bolus was given.

Statistical Analysis

Categorical and quantitative variables was expressed as frequency (percentage) and mean ± SD respectively.Inferential statistics, one way ANOVA test and Scheffe Multiple Comparisons (post hoc test) was used to compare SBP, DBP and Pulse rate between groups given respective drugs. For all statistical interpretations, $p<0.05$ value was accepted as being significant. Statistical analyses were performed with statistical software package SPSS, version 17.0.

Results and Analysis

Over a period of one year,a sample of 90 patients undergoing lower segment caesarean section under spinal anesthesia were studied. Relevant findings noted from study are as follows. The mean and standard deviation [SD] of age, height and weight of ephedrine group, mephentermine group and phenyl ephrine group are given as follows:

Table 1. Mean and standard deviation [SD] of age, height and weight of vasopressor groups

	Ephedrine		Mephentermine		Phenylephrine	
	Mean	SD	Mean	SD	Mean	SD
Age	27.2	3.7	26.7	3.6	25.8	3.2
Height	158.3	6.9	155.8	6.5	159.7	6.7
weight	62.5	1.4	62.8	1.1	62.6	1.3

All the patients were ASA PS 2 since pregnancy is considered as ASA PS 2 and patients didn't have any comorbidities. None of the study population had comorbidities like diabetes, hypertension, heart diseases, cerebrovascular accidents or anemia as these co morbidities were part of the exclusion criteria. A minimum of one and maximum of three boluses of vasopressors were required to maintain blood pressure. In ephedrine group,17 (56.7%) patients required only one bolus and 8 (26.7%) patients required two boluses and 5(16.7%) patients required three boluses. In mephentermine group,14 patients(46.7%) required one bolus,13 patients(43.3%)required two boluses and 3 patients(10%) required three boluses.In phenylephrine group,24 patients[80%] required only one bolus,5 patients(16.7%) required two boluses and 1 patient (3.3%) required three boluses.

The systolic arterial pressure was decreased at the onset of hypotension and increased after bolus dose of drug in all the three groups. On intergroup comparison, rise of systolic blood pressure at 2-minute, 4-minute, 6 minute and 8minutes after administration of drugs were significantly less in ephedrine group and mephentermine group as compared to phenylephrine group and the rise of diastolic blood pressure at 2-minute, 4-minute, 6minute and 8 minutes after administration of drugs were significantly less in ephedrine group and mephentermine group as compared to phenylephrine group. The diastolic arterial pressure was decreased at the onset of hypotension and increased after bolus dose of drug in all the three groups. Heart rate raised in all three groups during hypotension. In phenylephrine group, post study drug values of heart rate were decreased significantly from the values at onset of the hypotension till the end of the surgery when compared to other two groups. No significant differences were observed between heart rate changes in ephedrine and mephentermine group.

Figure 1 Comparison of increase in SBP at different time interval from Intraop hypotension

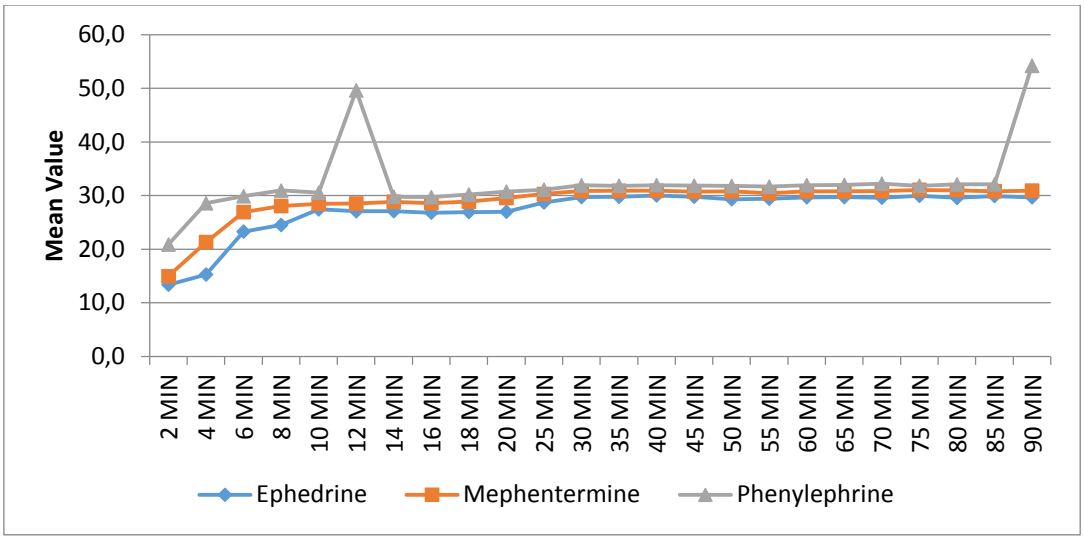


Figure 2. Comparison of SBP at different time interval based on vasopressor used

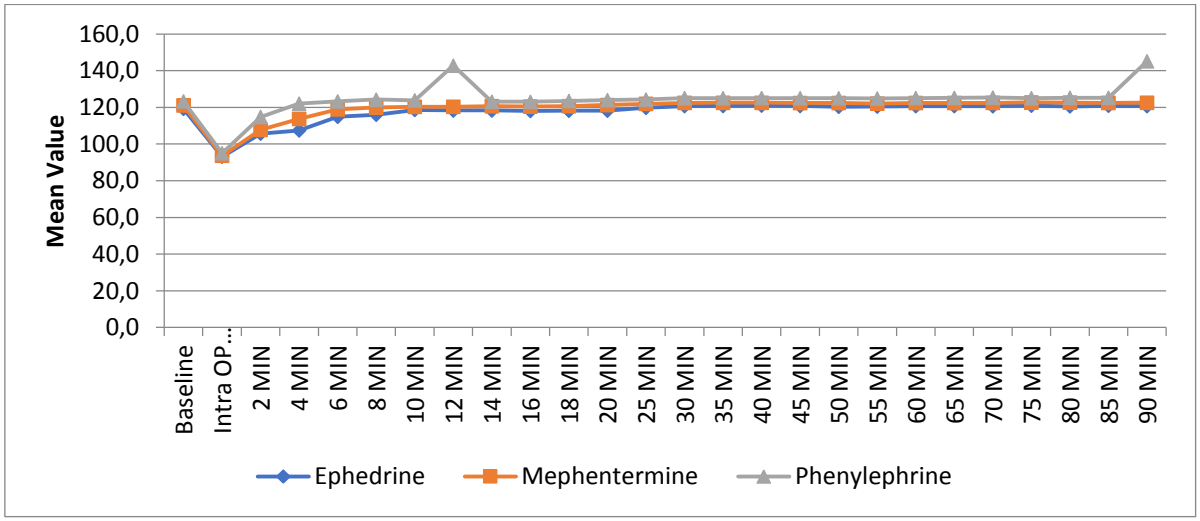


Figure 3. Comparison of increase in DBP at different time interval from Intraop hypotension

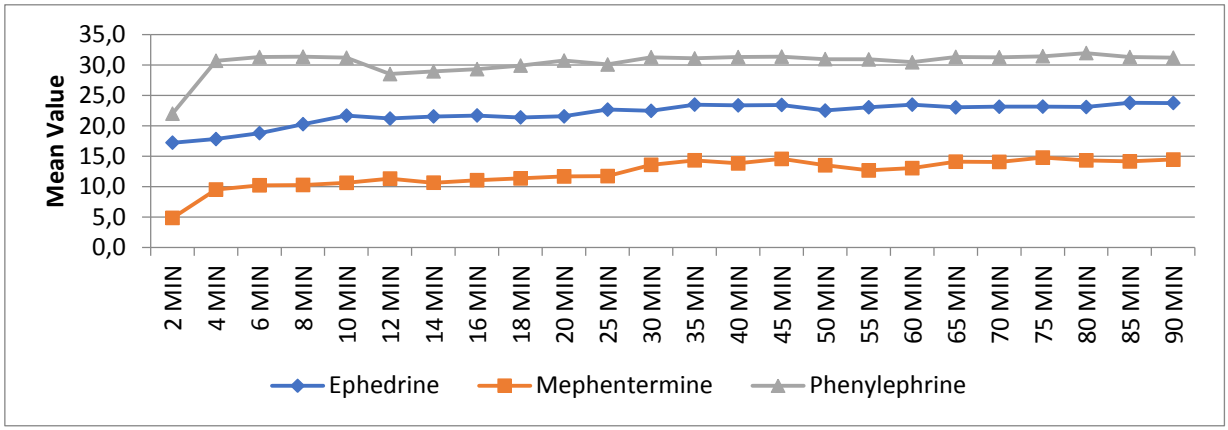


Figure 4. Comparison of DBP at different time interval based on vasopressor used

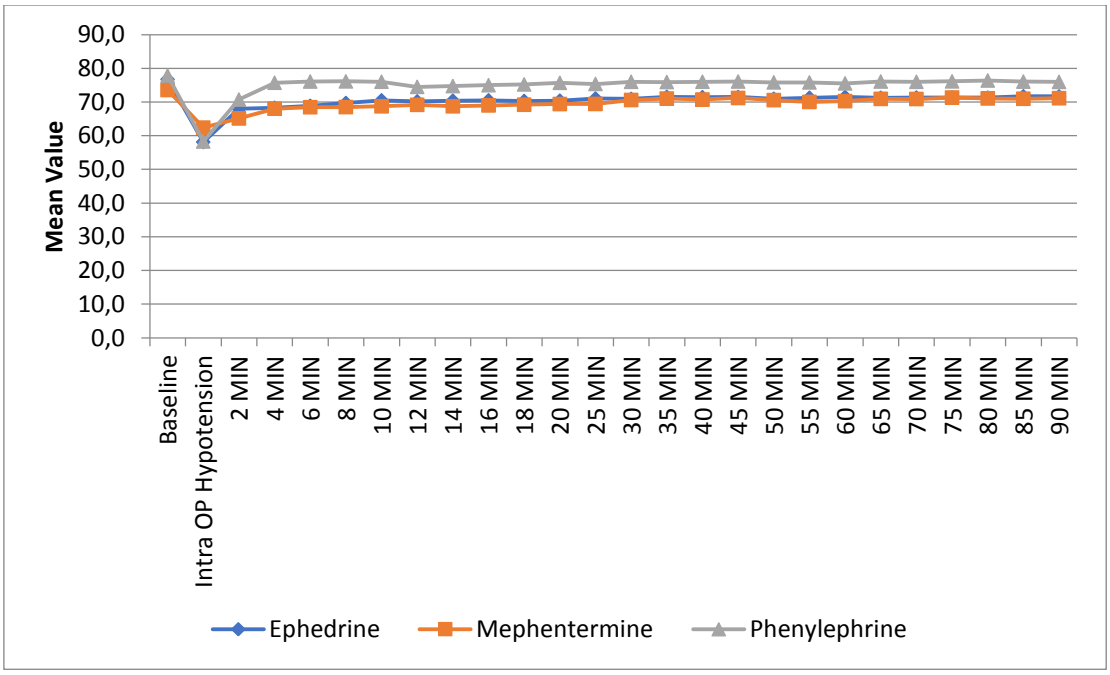
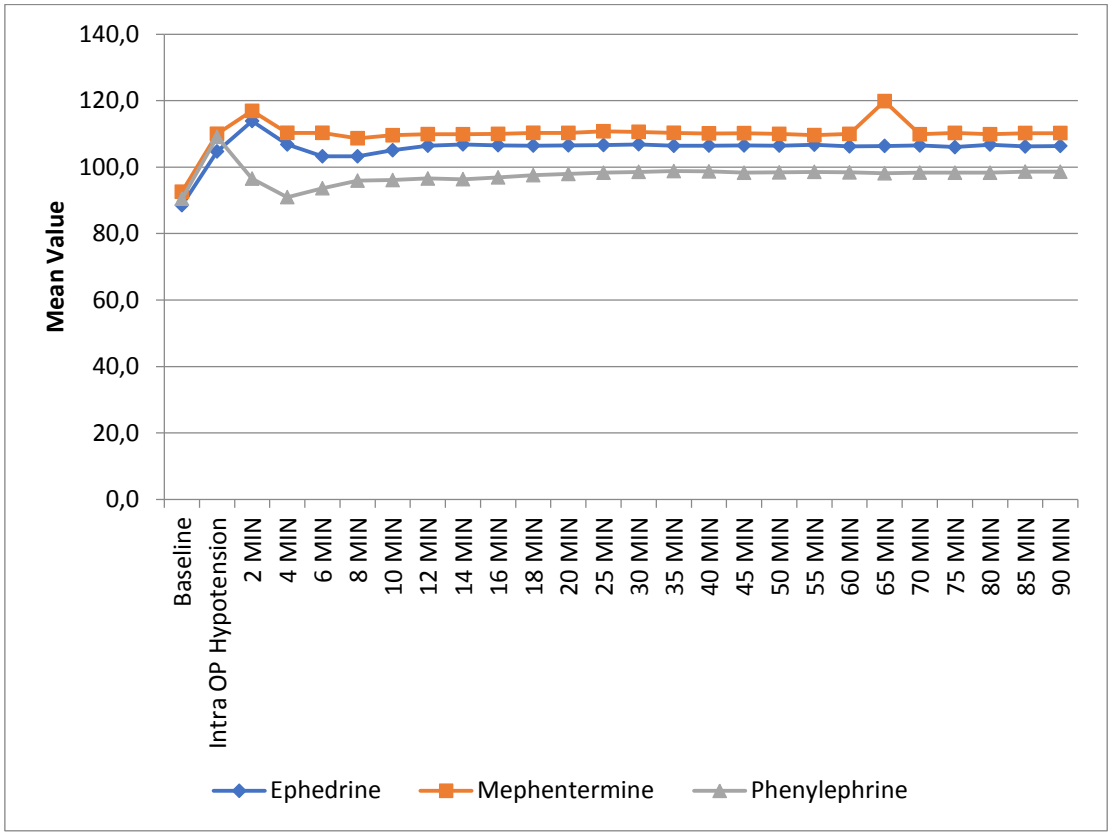


Figure 5. Comparison of HR at different time interval based on vasopressor used.



Discussion

Caesarean section is one of the oldest operations in recorded history, but anesthesia for Caesarean section is merely a century old and is not free of controversies. Over time, regional anesthesia especially spinal anesthesia proved to be the most preferred technique for Caesarean section. The reason being, the unique potential of spinal technique to provide anesthesia along with low degree of physiologic changes and with high degrees of sensory denervation and muscle relaxation. Thus, the safety of spinal anesthesia is

of both pharmacological as well as physiological. However, one main problem with this technique is the incidence of hypotension especially in gravid parturients. Hypotension is the commonest serious problem for both the mother and the child. Dinesh Sahu et al[4] found that maternal hypotension during spinal anesthesia for Caesarean delivery was a persistent problem in approximately 85% of cases. This high incidence and severity of maternal hypotension following spinal anesthesia could be attributed to various factors like the amount of local anesthetic injected, sympathetic blockade, uterus impairing venous return from extremities in supine position and several other factors.

In this study we evaluated three drugs. Each having different pharmacological properties. Phenylephrine being a synthetic noncatecholamine primarily stimulating alpha 1–adrenergic receptors by a direct action. Ephedrine being an indirectly acting synthetic non-catecholamine stimulates alpha- and beta-adrenergic receptors. Mephentermine is an indirect acting synthetic non-catecholamine and stimulates alpha- and beta-adrenergic receptors.

All the three vasopressors effectively maintained arterial pressure within 20% limit of baseline value, though phenylephrine maintained better in first 8 minutes of bolus dose as compared to ephedrine and mephentermine. This may be due to that, phenylephrine has peak effect within one minute, whereas ephedrine has 2-5 minutes and mephentermine has 5 minutes. After this time all three drugs were comparable in their control of blood pressure.

Thomas et al[5] reported that bolus phenylephrine is as effective as ephedrine in restoring maternal arterial pressure above 100 mmHg. Similarly, Moran et al[6] reached the same conclusion and further concluded that the drug appears to have no adverse neonatal effects.

In my study cardiovascular stability was better with phenylephrine. It caused significant reduction in heart rate after the bolus dose, which is a consistent effect in phenylephrine treated women in other studies also. In ephedrine and mephentermine group the heart rate increased compared to pre-operative values. This was alike to an earlier study by Dinesh Sahu et al[4]. This may be because of beta adrenergic effect of ephedrine and mephentermine which the phenylephrine lacks.

Thomas D.G. et al[5] reported a high (58%) incidence of bradycardia (heart rate less than 60 beats /min) when phenylephrine was given as IV bolus after induction of spinal anesthesia, but in our study the incidence for such extreme hypotension was not observed. Selection of patients and different criteria of treating hypotension could have caused the difference. No extreme hypertension and headache were noticed.

Moran DH et al[7] compared Ephedrine and Phenylephrine in the prevention of maternal hypotension following spinal anesthesia for caesarean section. They concluded that Phenylephrine is as effective as ephedrine in treatment of maternal hypotension, and when used in small increments did not have any adverse neonatal effects in healthy non-laboring parturients.

Anna Lee et al[8] in their quantitative systematic review, they compared the efficacy and safety of Ephedrine with Phenylephrine for the prevention and treatment of hypotension during spinal anesthesia for cesarean delivery. This review does not support the traditional idea that Ephedrine is the preferred choice for the management of maternal hypotension during spinal anesthesia for cesarean delivery in healthy non laboring parturients.

Cyna AM et al[9] studied the randomized controlled trials comparing the interventions to prevent hypotension with placebo or alternative treatment in women having spinal anesthesia for cesarean section. They finally concluded that interventions like colloids, Ephedrine, Phenylephrine or lower leg compression can reduce the incidence of hypotension; none have been shown to eliminate the need to treat maternal

hypotension during spinal anesthesia for cesarean delivery.

Conclusion

This study was to compare three drugs - ephedrine, mephentermine and phenylephrine in maintaining blood pressure during hypotension in spinal anesthesia in caesarean section. It was found that all three vasopressors maintained blood pressure within 20% limit of baseline. It was also observed that phenylephrine has quicker peak effect in comparison to ephedrine and mephentermine. Phenylephrine also causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable.

In my study population, the number of boluses required to maintain blood pressure was minimum one and maximum three boluses. In ephedrine group,17 patients [56.7%] required only one bolus,8 patients [26.7%] required two boluses and 5 patients [16.7%] required three boluses. In mephentermine group,14 patients [46.7%] required one bolus,13 patients [43.3%] required two boluses and 3 patients [10%] required three boluses. In phenylephrine group, 24 patients [80%] required only one bolus,5 patients [16.7%] required two boluses and 1 patient [3.3%] required three boluses. It was found that no significant changes were observed between ephedrine and mephentermine group. Both of them maintained blood pressure after intraop hypotension. Both ephedrine and mephentermine caused an increase in heart rate after their administration as compared to phenylephrine, which caused a decrease in heart rate. This may be undesirable for a patient with cardiac disease or a patient in whom tachycardia is undesirable.

To conclude, we have found that the phenylephrine, ephedrine and mephentermine are effective in IV bolus form in maintenance of arterial pressure within 20% limit of baseline though phenylephrine has quicker peak effect of comparison to ephedrine & mephentermine and it causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable.

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- **Disclosure of potential conflicts of interests:** The authors declare that they have no conflicts of interest.
- **Research involving human participants and/or animals:**
  a. Statements of human rights: All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

b. Statement on the welfare of animals: This chapter does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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