A Comparative Study between Ephedrine and Phenylephrine in the Control of, Hypotension Due to Spinal Anaesthesia, in Elective LSCS

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ABSTRACT

BACKGROUND

Various techniques of anaesthesia are practiced in the management of obstetric patients, like general anaesthesia and various types of central neuraxial block including spinal anaesthesia, epidural anaesthesia, and combined spinal epidural anaesthesia. We wanted to study the effectiveness of ephedrine (3 mg / mL / min) and phenylephrine (100 mcg / mL / min) infusion in the control of intraoperative hypotension.

METHODS

The present clinical study was conducted among sixty female patients, 18 – 40 years of age, of ASA I and II, who underwent elective lower segment caesarean section. The study population was randomly divided into 2 groups with 30 patients in each group.

RESULTS

Ephedrine in the form of 3 mg / mL infusion effectively maintains maternal blood pressure after spinal anaesthesia in majority of patients. Its use is associated with a stable or slight increase in heart rate with good neonatal outcome. Phenylephrine in a dose of 100 microgram / mL raises the blood pressure in majority of patients. Its use is associated with a stable or reduced heart rate, with good neonatal outcome. Incidence of vomiting and nausea is more with ephedrine than phenylephrine.

CONCLUSIONS

Both ephedrine 3 mg infusion, and phenylephrine 100 microgram / mL intravenous infusion, can safely be employed to control hypotension in patients undergoing elective lower segment caesarean section under spinal anaesthesia. Neonatal outcome is also good with both the drugs.

KEYWORDS

Ephedrine, Phenylephrine, Spinal Anaesthesia

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BACKGROUND

Obstetric anaesthesia requires special attention for the fact that it involves caring of two lives. Poor outcome due to anaesthetic mishaps are poorly tolerated. Hence there is a little margin for error in practice of obstetric anaesthesia. Various techniques of anaesthesia are practiced in the management of obstetric patients, like general anaesthesia and various types of central neuraxial block, which includes spinal anaesthesia, epidural anaesthesia and combined spinal epidural anaesthesia. Irrespective of anaesthetic technique employed, the goals for safe conduct of anaesthesia.

General anaesthesia is complicated in obstetric patients due to multitude of physiological changes induced by pregnancy. Airway of pregnant woman becomes difficult due to congestion and oedema of pharyngeal and laryngeal structures, large breasts. Progesterone induced CNS depression decreases the requirement of anaesthetic agents, there by throwing caution regarding the drug dosage.

Epidural anaesthesia, although safe is not preferred due to its delayed hemodynamic effect technically difficult and time consuming in a pregnant lady because of lumbar lordosis. Also there are increased chances of intravascular placement of catheter and accidental injection of local anaesthetics due to engorged epidural veins. Hence spinal anaesthesia automatically becomes the choice of anaesthetic technique in an elective uncomplicated caesarean section because of its technical simplicity, rapid onset and minimal drug use. However, it is not devoid of side effects. Hypotension is frequently associated with sub arachnoid block which is further complicated by aortocaval compression. The hemodynamic alterations following regional anaesthesia vary with differing levels of regional blocks. Hypotension if left untreated can lead to hypoperfusion of maternal vital organs. It can also produce significant decrease in uteroplacental blood flow thus jeopardizing the life of foetus.[1]

Various modalities have been tried to correct this spinal anaesthesia induced hypotension. Nonpharmacological methods include patient positioning (left uterine displacement and Trendelenburg position) and use of compressive bandage for lower limbs. Left uterine displacement is to prevent aortocaval compression. However, this cannot decrease the effect of spinal induced hypotension. Leg wrapping and use of compression devices may be beneficial in reducing the incidence of hypotension, but these are labour intensive and not widely practiced. Of the pharmacological methods used crystalloid preloading is a popular technique. Numerous studies using both crystalloid prehydration and uterine displacement have failed to completely eliminate hypotension as a consequence of spinal anaesthesia for caesarean section.[2] The increase in central venous pressure is probably transient due to a relatively short intravascular half-life of crystalloid with rapid extravascular equilibration. Usage of colloids like 6% hydroxyethyl starch also was not beneficial in prevention of maternal hypotension and its effects on neonatal outcome. Colloid coloading is also being tried in several studies but was not effective in preventing maternal hypotension after spinal anaesthesia in elective caesarean sections.[3]

Vasopressors are most promising of pharmacological methods used to combat hypotension due to spinal anaesthesia. Vasopressors have been administered either for prophylaxis by intramuscular and intravascular routes or as treatment modality by intravenous infusion or bolus. Intramuscular administration is associated with erratic absorption and unpredictable effect.[4] combating hypotension by vasopressor boluses is not preferable because incidence of post neuraxial hypotension is very high (65-85%) moreover many studies have shown in to be inadequate, hence prophylactic infusion is being chosen in many recent studies therefore in the present study also prophylactic infusion.

Phenylephrine, an agonist increases blood pressure primarily by peripheral vasoconstrictor effect (increased venous tone leading to increased preload and cardiac output). Phenylephrine has been safely used for the treatment of maternal hypotension due to spinal anaesthesia for caesarean section. Studies have shown increased uterine and placental arcuate artery blood flow velocity waveform indices and decreased vascular resistance in foetal renal arteries. Comparisons have been made between ephedrine and phenylephrine as vasopressor for managing spinal hypotension during caesarean section.

METHODS

The present clinical study was performed among sixty female patients who underwent elective lower segment caesarean section during the period March 2019 – November 2019. Institutional ethical committee approval has been taken. Written informed consent has been taken from every patient before surgery. The cases were selected between the age of 18 to 40 yrs. of ASA I and II. The study population was randomly divided into 2 groups with 30 patients in each group. Group E – Ephedrine group (number-30), Group P – Phenylephrine (number- 30).

Inclusion Criteria

Pregnant ladies belonging to ASA grade I and II, having uncomplicated singleton pregnancy beyond 36 weeks, scheduled to have elective caesarean section under spinal anaesthesia aged between 18 to 35 yrs., Weight between 40 and 70 kg and Height between 140 and 170 cms.

Exclusion Criteria

Patients with any contraindications for subarachnoid block like coagulation disorders, cardiovascular abnormalities, patient's refusal, spinal abnormalities, Patients with pregnancy induced hypertension, hypertension, renal disease, DM, placenta previa, abruption placenta and Patients posted for caesarean section for foetal abnormalities.

Pre anaesthetic assessment of each patient including detailed medical history such as diabetes mellitus,

hypertension, and pulmonary tuberculosis, allergy to drugs, bronchial asthma, epilepsy and bleeding disorders were taken. History of pregnancy induced hypertension, Gestational diabetes were also elicited. Symptoms and signs suggestive of antepartum haemorrhage like placenta previa and abruption placenta were ruled out.

Clinical examination included general physical examination and recording of vital data as well as systemic examination of cardiovascular system, respiratory system, gastrointestinal tract, central nervous system and also airway and spine assessment. All basic Investigations were done. All the patients were advised overnight fasting. Patients were premedicated with injection Ondansetron 4mg and inj. Ranitidine 50 mg IV 1 hr before surgery. Both the groups (E and P) were preloaded with RL 10 mL/kg over 20 minutes before anaesthetic procedure.

Technique

Patients pulse rate, Blood pressure were recorded on the operative table.

Position

Patients were positioned in left lateral position with the flexion of thigh and legs, hip and knees and flexion at the head. The operating table was kept flat. Under strict aseptic precautions, lumbar puncture was performed at L_{3-4} using midline approach with 26G sterile Quickie needle. After the clear and free flow of CSF Bupivacaine 0.5% heavy, 2 mL was injected into L_{3-4} subarachnoid space over 10 - 15 sec. Then patient was turned to supine posture using a wedge under the right buttock for a tilt of 15^0.

Immediately after the patient is given spinal drug and turned supine, the vasopressor infusion was started which was done with the help of an infusion pump. Group 'E' received infusion of a solution containing 3 mg / mL of ephedrine in normal saline at a rate of 60 mL / hour. Group 'P' received infusion of a solution containing 100 mcg/mL of phenylephrine in normal saline at a rate of 60 mL/hour.

The infusion was stopped in both the groups immediately after baby delivery (umbilical cord clamping). Any patient who attained sensory level greater than T_4 or lesser than T_6 are excluded from the study. Non-invasive blood pressure, pulse rate, respiratory rate and oxygen saturation were monitored every 2 minutes till baby delivery. If there was hypotension 1 mL of the test drug ephedrine (3 mg / mL) or phenylephrine (100 microgram / mL) with normal saline was given. The anaesthesiologist monitoring the patient and administering the drug were blinded about the drug in the syringe. The effectiveness of maintenance of blood pressure and any side effects if present by the administration of test drug were noted.

Heart rate was monitored and any bradycardia (HR less than 60 bpm) was treated with atropine 0.6 mg IV. Any tachycardia (HR >30% above the basal HR) was noted. Intra operative nausea and vomiting was recorded. Neonatal wellbeing was assessed at 1 minute and 5 minutes using APGAR score by the attending neonatologist. Postoperatively the patient was monitored in the postoperative ward for 24 hrs., for any adverse events. All data was entered into an excel sheet and analysed statistically with software SPSS 20 version.

RESULTS

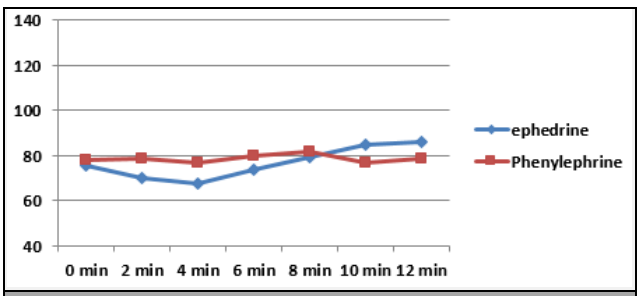

Figure 1. Comparison of Mean Heart Rates at 2-Minute Intervals

The mean heart rates at 2 minutes interval in ephedrine group increased transiently but later reached to the base line values. In phenylephrine group it was maintained around baseline throughout the procedure

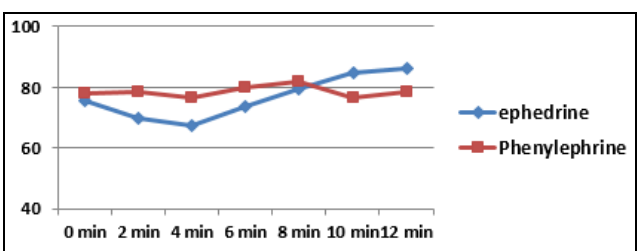

Figure 2. Comparison of Mean Systolic Blood Pressures at 2-Minute Intervals

The mean systolic blood pressures at 2 minutes interval in ephedrine group decreased initially but later reached to the base line values, in phenylephrine group it was maintained around baseline throughout the procedure

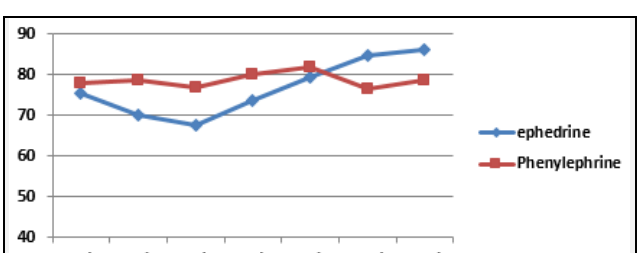

Figure 3. Comparison of Mean Diastolic Blood Pressures at 2 Minute Intervals

The mean diastolic blood pressures at 2 minutes interval in ephedrine group decreased initially but later reached to the base line values, in phenylephrine group it was maintained around baseline throughout the procedure. The mean values for age, height and weight in both ephedrine and phenylephrine group are comparable. The mean arterial blood pressures at 2 minutes interval in ephedrine group decreased initially but later reached to the base line values, in phenylephrine group it was maintained around baseline

throughout the procedure. The mean values of Apgar scores in both the groups are similar at 1 min and 5 min.

Parameter	Ephedrine	Phenylephrine
Age (yr)	23.43	23.70
Height (cm)	152.57	151.90
Weight (kg)	56.20	56.97

Table 1. Comparison of Demographic Details in Both Ephedrine and Phenylephrine Groups

Map at time in Minutes	Ephedrine	Phenylephrine	'P' Value
0 (basal)	89.81 ± 7.83	92.56 ± 6.15	0.626
2	83.74 ± 7.64	93.72 ± 6.99	0.747
4	80.81 ± 9.76	91.80 ± 9.36	0.682
6	88.32 ± 9.83	95.21 ± 9.62	0.038
8	94.51 ± 9.16	98.41 ± 10.71	0.360
10	101.19 ± 4.64	93.66 ± 8.70	0.132
12	101.00	91.66 ± 2.35	-

Table 2. Change in Mean Arterial Blood Pressure in Both the Groups at 2 Minute Intervals

Apgar Score	At 1 min	At 5 min
Ephedrine	>8	10
Phenylephrine	>8	10

Table 3. Mean Values of Apgar Scores

	Ephedrine	Phenylephrine	'P' Value
Nausea	4	1	0.161
Vomiting	2	1	0.554
Hypotension	2	1	0.554

Table 4. Incidence of Side Effects in Both the Groups

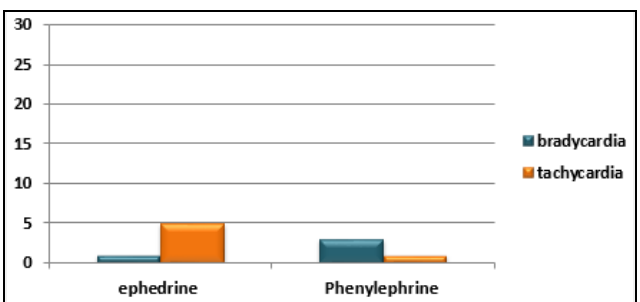

Figure 4. Comparison of Incidence of Bradycardia and Tachycardia in Both the Groups

The incidence of both nausea and vomiting are higher in ephedrine group than phenylephrine group. The incidence of hypotension is less both the groups, but it is much lesser in phenylephrine group than ephedrine. Tachycardia is more common in ephedrine group while bradycardia is more common in phenylephrine group.

DISCUSSION

Spinal anaesthesia is a popular anaesthetic technique employed in lower segment caesarean section because of its advantages like technical simplicity, usage of small dose of drug, minimal disturbance of physiological milieu interior, early postoperative ambulation and minimal post-operative pulmonary complications. Many enquiries into maternal deaths reported that of the maternal deaths attributed to anaesthesia, most of them were associated with difficulties during general anaesthesia. Although a number of regional anaesthesia techniques are available, spinal anaesthesia is particularly popular because it is fast, easy to perform and provides excellent post-operative analgesia.[5]

Although spinal anaesthesia has all the benefits, its administration is invariably associated with hypotension. Apart from affecting the mother, it can also have deleterious effects on foetus. On the maternal side, it causes hypoperfusion of the vital organs leading to hypoxia. By decreasing the uteroplacental blood flow it can induce hypoxia in foetus also. Various methods have been employed in the management of hypotension including foot end elevation, use of leg compression, prophylactic preloading with crystalloids[1]. However none of them have shown to produce consistent results.

Various studies have repeatedly established the efficacy of the ephedrine as vasopressor of choice in obstetric practice which increases the blood pressure by increasing the cardiac output and also has favourable effect on uteroplacental circulation. But few studies pose question about its effect on neonatal Apgar scores and umbilical artery blood pH values.[6] Phenylephrine has also been reported to be efficient in management of hypotension due to spinal anaesthesia for caesarean section without having any effect on foetal outcome[1]. Hence this study was undertaken to compare the efficacy of ephedrine and phenylephrine for management of hypotension due to spinal anaesthesia in lower segment caesarean section prior to baby extraction and their effect on neonatal APGAR score.

Sixty patients were enrolled in the present study and randomly divided into two groups E & P of 30 each. Group E received ephedrine to prevent spinal hypotension whereas group P received phenylephrine. The demographic data in both the groups were comparable. The level of blockade was similar in both groups.

Dosage Selected

Various authors have studied the efficacy of ephedrine either for prophylaxis or as treatment using various routes of administration such as intramuscular, intravenous bolus or intravenous infusion. The efficacy of intramuscular administration has been inconsistent, and its use may be associated with unacceptable hypertension, especially when subarachnoid block fails. Furthermore, ephedrine has a relatively slow onset and long duration of action. These factors mean that ephedrine may be difficult to titrate, especially when given by IV infusion compared with direct acting vasopressors. Intravenous boluses seem to be less effective than infusion in terms of incidence of hypotension as well as uniformity in maintaining blood pressure over the time of surgery. Various studies were mentioning different rations of ephedrine and phenylephrine ranging from 1:11 to 1:250 respectively (like 1:30, 1:40, 1:80, 1:125). We have chosen the dose of 3 mg/min infusion for ephedrine and 100 mcg/min of phenylephrine as mentioned in majority of studies.[7]

Blood Pressure Changes

David W Cooper et al. observed that ephedrine and phenylephrine given alone or in combination, maintained SAP effectively during spinal anaesthesia.[8] Incidence of

hypotension was less with phenylephrine group (48%) compared to ephedrine group (68%). The incidence of hypotension is much lower in the present study than that mentioned by David W Cooper et al. because the concentrations of the vasopressors given in the present study are higher.

Although there is difference in the incidence of hypotension between the two groups, the 'p' value (0.554) in the present study shows that there is no statistical difference between the two groups. Anna Lee MPH et al. studied and observed that there was no difference between phenylephrine and ephedrine in the management of maternal hypotension.[9] Hence it can be said that the efficacy of ephedrine and phenylephrine is similar, and the present study is concurrent with the conclusion given by Anna Lee MPH et al.

Ngan Kee W.D. et al. studied concluded that phenylephrine is more efficient in maintaining maternal blood pressures and there is no added advantage of combining ephedrine and phenylephrine.[10] The results in the present study show that phenylephrine has lower incidence (1 case) of hypotension than ephedrine (2 cases) and is concurrent with the conclusion given by Nagan Kee WD et al.

Sabyasachi Das et al., observed that incidence of hypotension was 4 out of 29 in ephedrine group while in the phenylephrine group it is 1 out of 31 patients.[11] They concluded that Prophylactic phenylephrine infusion is superior to ephedrine infusion or combination of phenylephrine and ephedrine in the management of predelivery maternal hypotension during spinal anaesthesia for caesarean delivery. In the present study the incidence of hypotension is also 4 in ephedrine group and 1 in phenylephrine group of each 30 patients and is very much similar to those mentioned by Sabyasachi Das et al.

Bradycardia is common accompanying manifestation apart from hypotension in a subarachnoid block. Bradycardia in lower segment caesarean section is more frequent than in other surgeries. Higher spread of local anaesthetics in pregnancy due to engorgement of epidural veins (leading to cardioaccelerator nerve fibre paralysis), increased neuronal sensitivity for local anaesthetics due to progesterone effect, exaggerated activation of Bain bridge reflex due to aortocaval compression and peritoneal traction have been implicated as the causes of bradycardia. Treatment of bradycardia is important as it can significantly affect the cardiac output there by affecting mother and foetus.

Ephedrine due to its intrinsic sympathomimetic effects through beta receptors increases the heart rate during spinal anaesthesia. Phenylephrine is said to produce significant bradycardia. Thomas DG et al postulated that this bradycardia could be caused by cardiac sympathetic denervation or secondary baroreflex response to phenylephrine induced hypertension.[12]

In the present study, there was an increase in heart rate in 5 patients (15.66%) of the ephedrine group and only 1 (3.33%) patient went into bradycardia that had to be given atropine 0.6 mg intravenously to correct. In the phenylephrine group 3(10%) patients had bradycardia for a short duration of time which got corrected spontaneously but in 1 patient atropine had to be given to correct bradycardia reflecting the probable baroreceptor reflex. This effect was transient lasting for 2 to 5 min, but in 1 (3.33%) heart rate persistently decreased to bradycardic levels, this promptly responded to intravenous atropine 0.6 mg. However, in studies of Thomas DG et al the incidence of bradycardia was higher with 11 out of 19 patients developing heart rate less than 60/min requiring atropine for treatment. This may probably due to higher level block achieved in their study (T2-T4). Wardwick D e al also have noted the decrease in heart rate in all the patients receiving prophylactic phenylephrine infusion given to prevent hypotension during spinal anaesthesia.[13] Only 2 patients developed bradycardia in their study which responded to atropine. The incidence of decrease in heart rate and bradycardia observed in the present study associated with administration of phenylephrine concurs with studies of Thomas DG et al and Warwick et al.[12,13]

APGAR Score done for Neonatal well-being has been assessed using various techniques ranging from simple APGAR score to sophisticated techniques such as umbilical cord blood gas assessment and pH measurement. Umbilical cord blood flow which has direct impact on foetal wellbeing has also been evaluated using Doppler flow velocimetry to ensure foetal well-being.

Several authors have noted lower umbilical cord pH with use of ephedrine.[5] Umbilical artery pH was 7.21 with the use of 10 mg ephedrine and 7.20 with 20 mg ephedrine. Saravanan et al. postulated that one possible mechanism of foetal academia is not associated to the uteroplacental or foetoplacental circulation, but to the ephedrine induced foetal beta adrenergic stimulation, as it crosses the placenta and increases foetal catecholamine levels and heart rate.[14] Though there was a decrease in umbilical artery pH in all these studies, clinical neonatal outcome as assessed by APGAR score remained above threshold levels both at 1 & 5 min as evidenced by APGAR scores of 9 and 10 at 1 and 5 min. In studies of Warwick et al. and David Cooper et al. also noted that though pH ranged from 7.23 to 7.31 with administration of ephedrine, it is not clinically significant, APGAR scores were 9 & 10 at 1 & 5 min. In the present study also APGAR scores are used as yard stick to assess foetal well-being as umbilical cord blood gas & pH is not done routinely for all the babies. In our study, APGAR score in all neonates in the ephedrine group was >7 at 1 min and 10 at 5 min. This concurs well with the results of David Cooper et al. and Ayorinide BT et al who also noted APGAR scores >7 and >8 at 1 and 5 min respectively.[15]

Phenylephrine is also associated with maintenance of umbilical artery pH was maintained between 7.29 & 7.33 with APGAR scores being 9 at 1st and 5th min with administration of phenylephrine to mother.[6] Ayorinide BT observed that APGAR scores were 9 and 10 at 1 & 5 min with administration of phenylephrine as prophylaxis for hypotension.[15] In our study also, we observed that APGAR scores of all neonates were >7 and 10 in phenylephrine

group. The 5-minute score concurs with the results of David Cooper et al and Ayorinide BT et al., but at 1 min it is 9 in 15 patients as in the reference study. The score is >8 in 14 babies except one. An APGAR score of 8 has no difference in predicting the neonatal wellbeing when compared to 9 as mentioned by Ayorinide BT et al. so can be presumed to be similar. Thomas DG et al. noted that umbilical artery pH was significantly higher in phenylephrine and also a small reduction in the heart rate in phenylephrine group.[12] However, in their study, there was no clinical effect in neonatal outcome as suggested by absence of APGAR score<7 in any of the neonates of either groups.

Ando Y et al. studied the effect of ephedrine and phenylephrine on neonatal umbilical artery pH values and APGAR scores and concluded that there is no significant difference between the two groups although phenylephrine group has a very little higher values.[16] Though the umbilical arterial blood pH were not measured in the present study, neonatal APGAR scores were similar in both the groups and are concurrent with the conclusion given by Ando Y et al.

Nausea and Vomiting

Maternal nausea & vomiting is an important problem in obstetric anaesthesia, and majority of the times it heralds the onset of hypotension well before the change in numerical values of blood pressure. Maintenance of effective blood pressure is associated with similar incidence of nausea and vomiting in both the groups, thus suggesting that ephedrine and phenylephrine have the same emetic potential.[14]

In the present study 2 (6.67%) patients had both nausea and vomiting while another 2 (6.67%) patients had only nausea. Only 1 (3.33%) patient had both nausea and vomiting in phenylephrine group. Saravanan et al noted that incidence of vomiting was higher in ephedrine group compared to phenylephrine group (1 v/s 9 patients).[14] David Cooper et al. also noted increased incidence of nausea and vomiting in ephedrine group compared to phenylephrine group.[8] In their study 17 patients had nausea without vomiting in phenylephrine group compared to 30 patients in ephedrine group, and concurs with the studies of Saravanan et al. and David Cooper et al.[8,14]

The possible explanation for this difference cited by Cooper et al seems to be due to increased vagal tone following reduction of preload more likely, in the presence of beta stimulation (ephedrine stimulation), but phenylephrine is a pure alpha agonist provides better vasoconstriction reducing the decrease in the cardiac preload and diminishing the vagal reflex. This may explain the high incidence of vomiting after the ephedrine where the dose is ineffective.

CONCLUSIONS

Ephedrine in a dose of 3 mg / mL as IV infusion effectively maintains maternal blood pressure after spinal anaesthesia in majority of patients. Its use is associated with a stable or slightly increased heart rate with good neonatal outcome. Phenylephrine in the dose of 100 microgram / mL raises the blood pressure in majority of patients. Its use is associated with a stable or reduction in heart rate, with good neonatal outcome. Incidence of vomiting and nausea is more with ephedrine than phenylephrine. Hence, it can be concluded that both ephedrine and phenylephrine intravenous infusion of 3 mg and 100 microgram / mL respectively can safely be employed to control hypotension in patients undergoing elective lower segment caesarean section under spinal anaesthesia. Neonatal outcome is also good with both the drugs.

Financial or Other Competing Interests: None.

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