Original Article

Comparing slow and rapid bolus of ephedrine in pregnant patients undergoing planned cesarean section under spinal anesthesia

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Abstract

Background and Aims: While ephedrine was the preferred drug for treating spinal-induced hypotension in pregnancy, its use has declined because of resultant fetal acidosis. The objective of this randomized control trial was to compare the effects of a slow and rapid bolus of ephedrine on fetal acidosis, maternal blood pressure, and heart rate (HR) during cesarean section performed under spinal anesthesia.

Material and Methods: Eighty full-term parturients scheduled for cesarean section under spinal anesthesia were randomly allocated into two groups. While both groups received 6 mg of ephedrine to treat hypotension, Group R (n = 40) received it as a rapid intravenous bolus and Group S (n = 40) received it slowly over 20 s with an infusion pump. The maternal vital parameters were recorded until delivery of the baby using a video camera. Umbilical cord blood was obtained using the three clamp method. Hemodynamic parameters, fetal acidosis, total number of ephedrine bolus used, peak HR after the ephedrine bolus, and occurrence of postoperative nausea and vomiting (PONV) were compared between the groups.

Results: Mean increase in HR and blood pressure were significantly higher in Group R than the Group S after the first ephedrine bolus. Umbilical artery pH was significantly lower in Group R than in Group S (7.2 [6.8-7.3] vs. 7.3 [7.3-7.4], $P < 0.01$). A total number of ephedrine boluses were comparable in the two groups. 35% of the patients had PONV in Group R, whereas none had it in Group S ($P < 0.01$).

Conclusion: Slow bolus of ephedrine is better than rapid bolus to treat spinal-induced hypotension during cesarean section in view of less fetal acidosis.

Key words: Cesarean section, ephedrine, vasoconstrictor agents

Introduction

Hypotension succeeding a neuraxial blockade during cesarean section is the foremost concern for an anesthesiologist.[1,2] Severe and sustained hypotension can impair the uterine and intervillous blood flow and in due course result in fetal acidosis and neonatal depression.[2,3] Regardless of several preventive measures such as fluid preload and left lateral tilt, a pharmacological agent is almost always required for treating hypotension.[4-6] Among the available agents, ephedrine increases the uterine blood flow attributable to β_2 receptor stimulation.[7,8] However, several studies had observed that it causes fetal acidosis by increasing fetal heart rate (HR) and metabolic activity.[9,10] We hypothesized that the fetal acidosis could be minimized by reducing the maternal blood ephedrine concentration. We expected an optimal effect on maternal blood pressure and HR and less fetal acidosis with a slow

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bolus of ephedrine. Hence, we designed this randomized double-blinded controlled trial to compare the slow and rapid bolus of ephedrine on fetal acidosis, maternal blood pressure, and HR during cesarean section under spinal anesthesia.

Material and Methods

This study was conducted in a tertiary care referral hospital after obtaining ethical clearance from the Institute Ethics Committee. A 110 term pregnant women belonging to American Society of Anaesthesiologists Physical Status I scheduled for planned cesarean section under spinal anesthesia were recruited into the study after obtaining written informed consent. Parturients with systemic diseases, allergy to local anesthetics, short stature (<145 cm), fetus with a congenital anomaly, active labor or fetal distress and those not willing for spinal anesthesia were excluded from the study.

Participants were randomly allocated to one of the two groups (Group R or Group S) by computer-generated random number list. Sequentially numbered opaque sealed envelope technique was used for concealment of random allocation. One 20 ml and one 5 ml syringe were labeled as study drug, and the 20 ml syringe was connected to a syringe infusion pump (Model SP102, L&T). These two "study drug" syringes were a part of double dummy technique to facilitate blinding. In Group R, 20 ml syringe contained saline, and 5 ml syringe contained ephedrine (6 mg/ml). In Group S, 20 ml syringe contained ephedrine (1 mg/ml), and 5 ml syringe contained saline. In the event of hypotension, both the groups received 6 ml bolus from 20 ml syringe over 20 s, and 1 ml of bolus rapidly from 5 ml syringe simultaneously to expedite blinding. An anesthesiologist, who was not part of the study, prepared the drug and labeled these syringes.

After preanesthetic assessment, all patients received aspiration prophylaxis. Routine monitoring such as the electrocardiogram, noninvasive blood pressure, and pulse oximetry were established in the operating room and baseline parameters noted. A stand-alone video camera on a tripod stand was positioned appropriately to record the monitor. After preloading with 500 ml of Ringer's lactate over 10 min, the patient was positioned for spinal anesthesia. Spinal anesthesia was performed with aseptic precautions using 25G Quincke spinal needle at L3-L4 interspace in left lateral position and 1.8 ml of hyperbaric bupivacaine 0.5% was administered intrathecally. The patient was immediately turned supine and wedge was placed under right hip to achieve 30° lateral tilt. HR and blood pressure (systolic, diastolic and mean) were noted at every minute until delivery of the baby. Administration of bolus ephedrine with simultaneous fluid resuscitation was instituted if mean blood pressure reduced by more than 20% of baseline or if systolic blood pressure decreased to <100 mmHg. The blood pressure was measured again after 1 min of the first ephedrine bolus. If needed, another ephedrine bolus was administered. Even after two ephedrine boluses, if the blood pressure targets were not met, the hypotension was treated by the anesthesiologist in charge. After the delivery of the baby, umbilical arterial blood sample was collected by the pediatrician. The study period was over with the delivery of the baby.

The total number of ephedrine bolus and the maximum HR after the ephedrine bolus were observed from the recorded video. The percentage change in the HR and blood pressure were calculated assuming the prebolus values as baseline. The patients who did not have hypotension following spinal anesthesia were excluded from the study. Time from subarachnoid block to skin incision, skin incision to uterine incision, and uterine incision to delivery were noted. Apgar score of new-born at 1 and 5 min, total amount of intravenous fluid infused, highest sensory level, bradycardia, and occurrence of postoperative nausea and vomiting (PONV) were also noted. The patient was treated with ondansetron (4 mg) in the case of nausea or vomiting even after correction of hypotension.

Statistical analysis

As no preliminary data for slow and rapid bolus were available, the sample size was calculated based on the potential difference in umbilical artery pH. While assuming standard deviation (SD) of 0.04 and anticipated difference of 0.03, it needed a sample size of 38 patients per group to have 90% power and a two-sided α value of 0.05.[11,12] However considering 30% participant may not have a fall in blood pressure after spinal anesthesia, we calculated a sample size of 110. Data were presented as mean ± SD, or median (interquartile range). Data were analyzed using SPSS Version 16.0. (Released 2007. SPSS for Windows, Chicago, SPSS Inc.). Intention to treat analysis was conducted. Parametric variables were analyzed using unpaired *t*-test and nonparametric variables using Mann-Whitney U-test. A $P < 0.05$ was taken as statistically significant.

Results

One hundred and ten patients were recruited in the study between May 2012 and June 2013. None of the patients had a partial spinal block which required supplemental sedation or general anesthesia. Thirty patients were excluded as there was

no decline in blood pressure until delivery and eighty patients were included for statistical analysis. The blood pressure did not meet the target value in two patients in Group R and five patients in Group S [Figure 1].

The demographics, various surgical time intervals, sensory level, total number of ephedrine boluses and total fluids given were comparable in the two groups [Table 1]. PONV were observed in significantly more patients with Group R (35%) than in Group S (0%, $P < 0.01$). None of the patients in our study had bradycardia. 5% patients in Group R and 12.5% patients in Group S did not respond to two doses of ephedrine. This proportion was not significantly different in the two groups ($P = 0.4$).

The systolic blood pressures were comparable between the two groups at all-time intervals except at 5 min when it was significantly higher in Group R compared to Group S (111.6 ± 15.3 vs. 104.2 ± 13.4 mmHg, $P = 0.008$). The mean arterial blood pressure (MAP) was significantly higher in Group R compared with Group S at the 5th min (80.3 ± 11.5 vs. 74.7 ± 11.4 mmHg, $P = 0.04$).

The increase in HR after the first bolus was significantly more in Group R when compared with Group S. Increase in MAP after the first bolus in Group R was significantly higher than in Group S. Increase in HR and MAP after the second bolus was comparable in the groups [Table 2]. The mean umbilical artery pH was significantly lower in Group R compared to Group S. Six neonates in Group R had a pH <7.2, whereas none in Group S had abnormal values ($P = 0.01$). Base excess was also significantly low in Group R than in Group S [Table 2].

The umbilical arteries PO_2, PCO_2, HCO_3 and neonatal Apgar score were comparable between the groups. In Group R, two neonates had Apgar score of 7 and 8 at 1 and 5 min respectively. The other neonates in Group R and Group S had Apgar of 8 and 9 at 1 and 5 min, respectively.

Table 1: Demographic and perioperative patient parameters

Variables	Group R (n = 40)	Group S (n = 40)	*P*
Age (years)	24.6±2.3	25.3±2.1	0.1
Weight (kg)	63±9.5	65±10.1	0.8
SAB_SI (min)	2 (1-5)	1 (1-5)	0.2
SI_UT (min)	5 (2-11)	4 (2-8)	0.1
UT_DT (min)	1 (1-2)	1 (1-1)	0.3
Total fluids (ml)	1462±84	1492±78.4	0.1
Upper sensory level	T4 (4-6)	T4 (4-6)	1

Values are in mean ± SD and median (interquartile range). SAB_SI = Subarachnoid block to skin incision time, SI_UT = Skin incision to uterine incision time, UT_DT = Uterine incision to delivery time, SD = Standard deviation

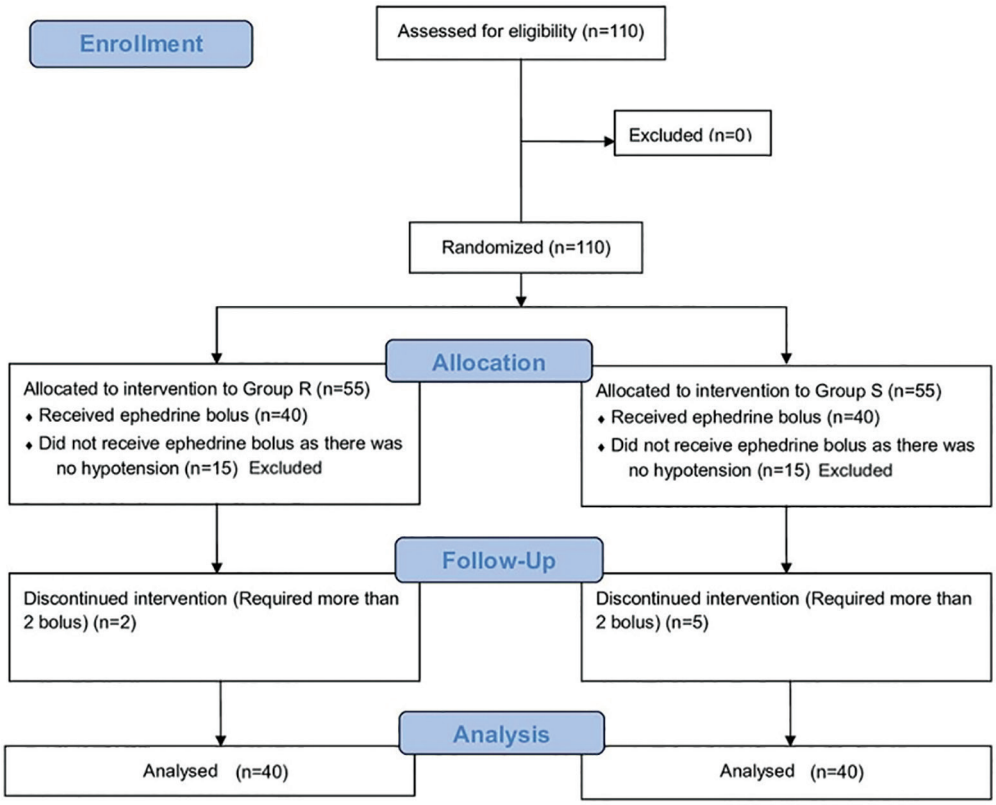

Figure 1: Consort flow diagram

Table 2: Outcome parameters

Variables	Group R (n = 40)	Group S (n = 40)	P
Increase in HR after first bolus (in %)	7.7 (0-44.6)	1.2 (0.0-40.3)	0.01
Increase in HR after second bolus (in %)	2.5 (0-33.3)	6.8 (0.0-31.7)	0.56
Increase in MAP after first bolus (in %)	23.5 (1.4-68.6)	20.7 (2.7-35.5)	0.04
Increase in MAP after second bolus (in %)	18.4 (1.4-46.7)	17.3 (0.0-69.1)	0.66
Apgar 1 min	8 (7-8)	8 (8-8)	0.17
Apgar 5 min	9 (8-9)	9 (9-9)	0.17
Umbilical artery pH	7.2 (6.8-7.4)	7.3 (7.3-7.4)	0.01
BE	−2.3 (−10.1-3.3)	1.7 (−2.8-4.0)	0.008
PONV	14/38	0/35	0.01
Total ephedrine bolus per patient (in mg)	12 (6-16.5)	12 (6-12)	0.07
Non responders after two ephedrine bolus (%)	2 (5)	5 (12.5)	0.4

Values are in median (interquartile range). HR = Heart rate, MAP = Mean arterial blood pressure, PONV = Postoperative nausea and vomiting, BE = Base excess

Discussion

In our study, we witnessed that the slow bolus of ephedrine was associated with less fetal acidosis. Both the groups were comparable with respect to efficacy in maintaining hemodynamics. However, the degree of change in MAP and HR was significantly higher in Group R.[7] The increase in HR after the first bolus was significantly less in Group S. The incidence of PONV was more in Group R compared to the Group S.

We considered a pH of <7.2 as fetal acidosis. In our study, 15.8% patients in Group R had fetal acidosis, whereas none had it in the Group S. Cooper *et al.* compared the effect of phenylephrine and ephedrine (3 mg) and concluded that the fetal acidosis was more in ephedrine group.[7] Ngan Kee *et al.* studied the placental transfer and fetal metabolic effects of ephedrine and phenylephrine.[9] They found that the umbilical arterial and umbilical venous pH and base excess were lower in ephedrine group. A similar finding was observed in Group R also. The significant fetal acidosis found in Group R could probably be explained by the fact that rapid bolus crosses the placenta to a greater extent.[9] Eventually, it undergoes less early metabolism in the fetus and increases the metabolic effects secondary to stimulation of fetal β adrenergic receptors.[7,10] It supports the hypothesis that the reduction in fetal pH and increased base excess is related to metabolic effects.[13]

Varying dose of ephedrine (3-15 mg) has been used for treating the hypotension in pregnant patients after subarachnoid block. However, we used a dose 6 mg ephedrine based on our previous clinical experience in our institution. Robson *et al.* suggested that the relatively high dose of ephedrine when administrated in an attempt to maintain blood pressure near baseline resulted in the increased incidence of acidosis.[14] It was supported by Cooper *et al.* who observed that 3 mg of ephedrine resulted in fetal acidosis more frequently than 1.5 mg of ephedrine.[7]

Kol *et al.* administered 0.5 mg/kg ephedrine over 60 s to prevent hypotension.[15] There was a risk of increased acidosis with increasing duration of hypotension.[16] We selected 20 s duration arbitrarily in the Group S and found the results of our study with respect to fetal acidosis and Apgar scores to be similar to their study. This could be probably due to the slow injection of ephedrine.

In our study, 35% patients developed PONV in Group R whereas none in Group S. Varying incidence of PONV with ephedrine (35-66%) had been reported.[7,9] A possible explanation might be an increase in vagal tone following reduction of preload, which is more likely to occur in the presence of beta stimulation.[7] The alternate mechanism could be a side effect of the drug or its lipid solubility, thereby exerting a central effect.[17]

The mean increase in HR after the first bolus was significantly lower in Group S. Probably this could be attributed to less placental transfer and less redistribution of ephedrine in fetus.[9] The reduced adverse effects, both maternal and fetal, when giving ephedrine as a slow infusion could be due to concentration achieved in the blood.[18,19] This leads to less amount of ephedrine transferred to the fetus and reduced fetal metabolic effects. However, the increase in both MAP and HR was not statistically significant between the groups after the second bolus dose of ephedrine. This could be probably due to tachyphylaxis, the repeated administration of a constant dose within a short time which leads to a rapid decline of response due to the gradual decrease in the amount of norepinephrine at the stores.[20]

Five patients in Group S and two patients in Group R blood pressure did not respond even after two boluses of ephedrine. Further management of hypotension in these 7 patients was left to the concerned anesthesiologists. The anesthesiologists gave a slow bolus of study drug (either manually or via infusion

pump) to these patients. We had observed that the systolic blood pressure improved in all seven patients after the third bolus of ephedrine. All the neonates of these patients had an Apgar of 8 and 9 in 1 and 5 min respectively with pH more than 7.2. The total numbers of bolus received in both groups during the study period were comparable. Thus, there was no difference between slow and rapid bolus of ephedrine in their efficacy in maintaining the blood pressure.

Another possible application of slow bolus of ephedrine is when the patient's HR is on the lower side. As the bolus of phenylephrine is known to cause bradycardia, slow ephedrine bolus may be preferred. The limitation of this study is that the plasma concentration of ephedrine and postdelivery monitoring of fetal HR was not done.[21] Increased placental transfer would have been evident in these parameters. Metabolic products such as lactate, epinephrine, and norepinephrine levels and cardiac output were also not measured in our study.[9] Maternal arterial blood sampling to rule out the possible cause of fetal acidosis was not done in our study because of ethical consideration.[21] Hemodynamic changes due to ephedrine after delivery were not determined in our study as our aim was to assess the effect of ephedrine on maternal blood pressure and HR in relation to fetal acidosis.

Conclusion

We have observed that the slow bolus of ephedrine is as effective as a rapid bolus of ephedrine in maintaining maternal blood pressure and HR. We have also found that the slow bolus of ephedrine had no fetal acidosis, and less tachycardia, and PONV when compared to a rapid bolus of ephedrine. Hence, we conclude that the slow bolus of ephedrine is better than rapid bolus to treat the hypotension during planned cesarean section under spinal anesthesia.

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Conflicts of interest
There are no conflicts of interest.

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