*Original Article*

# Role of Ephedrine for Management of Hypotension During Spinal Anaesthesia for Caesarean Delivery

**Esrat Zahan[1], Md. Zakir Hossain[2], Abdur Rahman[3], Waheeda Nargirs[4]**

[1]Medical Officer, Department of Anaesthesiology, Uttara Adhunik Medical College & Hospital, [2]Senior Consultant & Admin, Head Dept. of Anaesthesiology, Uttara Adhunik Medical College & Hospital, [3]Professor and Head of Intensive Care Unit, Bangladesh Medical College & Hospital, [4]Associate Professor, Department of Biochemistry, Uttara Adhunik Medical College & Hospital

**Corresponding Author:** Dr. Esrat Zahan, Medical Officer, Dept. of Anaesthesiology, Uttara Adhunik Medical College & Hospital

**Abstract**

***Background:*** *Hypotension during spinal anaesthesia for caesarean section remains a common scenario in our clinical practice. Certain risk factors play a role in altering the incidence of hypotension. Ephedrine has been the drug of choice for more than 30 years in the treatment of spinal anesthesia induced maternal hypotension. It has a good safety record, ready availability, and familiarity to most anesthesiologists.*

***Aims:*** *To determine the efficacy and safety of prophylactic bolus dose of 0.5 mg/kg intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery.*

***Methods:*** *It was designed a randomized, double-blinded study. Patients were randomly allocated into two groups: ephedrine group (n=30) and control group (n=30). Intravenous preload of 15 mL/kg lactated Ringer's solution was given. Shortly after the spinal injection, ep-hedrine 0.5 mg/kg or saline was injected intravenous for 60 sec.*

***Results:*** *The mean of high-est and lowest heart rate in the ephedrine group was higher than those of control group (p<0.05). There were significant lower incidences of hypotension and nau-sea and vomiting in the ephedrine group compared with the control group 11(36.7%) vs. 24(80.0%); 6(20.0%) vs. 17 (56.7%), respectively) (p<0.05). The first rescue ephedrine time in the ephedrine group was significantly longer (14.9±7.1 min vs. 7.9±5.4 min) than that of the control group (p<0.05). Neonatal outcome were simi-lar between the study groups.*

***Conclusion:*** *The above findings suggest, the prophylactic bolus dose of 0.5 mg/kg intravenous ephedrine given at the time of intrathecal block after a crys-talloid fluid preload, plus rescue boluses reduce the incidence of hypotension.*

***Key Words:*** *Anesthesia, Spinal; Cesarean Section; Ephedrine; Hypotension*

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## Introduction

Spinal anesthesia, recently, has been known as an acceptable anesthesia technique, especially for cesarean section, due to advantageous on epidural anesthesia, such as rapid onset, intensity, symmetric sensory and motor block[1,2]. However, hypotension triggered by spinal anesthesia during cesarean delivery has been known as a common complication that might endanger the lives of both mother and fetus.

Spinal anesthesia provides a fast, profound, and symmetrical sensory and motor block of high quality in patients undergo-ing cesarean delivery[1,2]. The most common serious adverse effect of spinal anesthesia for cesarean delivery is hypotension, with a reported incidence greater than 80%[3].

A number of strategies for preventing hypotension have been investigated, because it may have detrimental mater-nal and neonatal effects. The

use of lateral uterine displace-ment is routine procedure to prevent hypotension[4]. Other strategies have included the use of intravenous fluid preload, gravity (Trendelenburg or leg rising), compression devices on the legs, and prophylactic vasopressors[1]. However, no meth-ods have proved satisfactory. Ephedrine is the most common-ly used drug among the vasopressors.

The prophylactic administration of ephedrine by the intra-muscular route is very controversial because its systemic ab-sorption and peak effect are difficult to predict, thus, possi-bly resulting in rebound hypertension[5]. The intravenous route may be more effective and controllable, although large doses are used; the incidence of hypotension was still high in some studies[6,7].

Intravenous ephedrine given immediately after the induc-tion of spinal anesthesia has been described[7,8]. Doses of 10-20-30 mg or 0.25 mg/kg were not effective in eliminat-ing hypotension completely[7-10]. Therefore, we designed a case controlled study to determine efficacy and safety of 0.5 mg/kg intravenous ephedrine for preventing hypotension during spinal anesthesia for cesarean delivery.

**Methods**

It was designed a randomized, double-blinded study. During the study period, 60 consecutive patients were iden-tified suitable for the study. They were women, ASA status I or II, undergoing elective cesarean section under spinal anesthesia and included in the study. Written informed consent was obtained from each subject, and the study protocol was approved by the Ethical Committee of Uttara Adhunik Medical College, Uttara, Dhaka. Patients with pre-existing or pregnancy-induced hypertension, known cardio-vascular or cerebrovascular disease, abnormal cardiotocography (CTG) tracing, or contraindications to spinal anesthesia were excluded. Randomization was based on a computer-generated code that was prepared at a remote site and sealed in opaque, sequentially numbered envelopes. The patients were randomly divided into 2 groups: ephedrine group (n=30) and control group (n=30) after spinal anesthesia.

None of patients was premeditated. On arrival in the oper-ation room, baseline measurements of systolic arterial pres-sure (SAP) and heart rate (HR) were calculated with a Criticare System 1100 monitor as the mean of three successive measurements, 1 min apart and in the modified supine position with at least 15 of left lateral tilt. 18-gauge intravenous cannula was sited in the non-dominant hand and intravenous preload of 15 mL/ kg lactated Ringer's solution was given, within 15 min, after which the intravenous infusion was slowed to the minimum rate required to maintain vein patency.

Spinal anesthesia was administered with the patient in the right lateral position. After skin infiltration with lidocaine, a 25-gauge Whitacre needle was inserted at the L2-3 or L3-4 vertebral interspace and hyperbaric 5% bupivacaine 2 mL with fentanyl 10 mg was deposited intrathecally. The patient was then immediately turned supine with left lateral tilt. Oxygen 4 L/min was given by nasal cannula until delivery.

Shortly after the spinal injection, ephedrine 0.5 mg/kg in the ephedrine group or saline in the control group was inject-ed intravenous slowly. Study medication and management of the patient in the preoperative period was done by the author which the data were collected by a second anesthesiologist who was unaware of the study. The study period started at the time of randomized group up to end of surgery. The Blood pressure and heart rate were recorded at 2-min intervals. The baseline SAP and HR, lowest and highest SAP and HR, nausea, vomiting, dizziness, and chest symp-toms were recorded up to clamping of the cord and then at 10 min interval till end of surgery. Any hypotension in the intraoperative period were treated with fluid bolus and further IV ephedrine 5 mg bolus. Upper sensory level of anes-thesia was achieved a level of $6^{th}$ thoracic vertebra and the level was ascertained T6 assessing by loss of cold sensation. After ascertained block of T6 surgery was allowed to start.

Hypotension was defined as 20% decrease in SAP from baseline. Hypertension was defined as 20% increase in SAP from baseline. Maternal bradycardia was defined as heart rate <60 beats/ min and treated immediately by using intravenous atropine 0.5 mg. Tachycardia was defined as heart rate >120 beats/min. Hypotension was treated immediately by using rescue intravenous ephedrine 5 mg IV bolus until SAP returned to values (>80 of baseline value).[29]

After delivery, Apgar scores were assessed at 1 and 5 min by the attending pediatrician. Arterial blood

samples were taken from umbilical cord for blood-gas analysis within 2 min. All patients received oxytocin 20 units/L in crystalloid after delivery.

Data were presented as mean±standard deviation, medi-an (range), or percentage, as appropriate. Statistical analyses were performed by SPSS version 22. Demographic parameters, delivery time, first rescue ephedrine time, total ephedrine requirement, umbilical arterial pH, SAP, and HR were compared with t-test. Changes over time in SAP and HR between and within the study groups, comparing values at each time point, were analyzed with repeated measures ANOVA followed by a post hoc Bonferroni test to identify significant differences. Total doses rescue requirement of ephe-drine. Hypotension, hypertension, tac-hycardia, bradycardia and nausea and vomiting of the study groups were compared with Fisher's exact test, as appro-priate. A P value of <0.05 was considered significant.

## Results

Of 60 patients randomized, two in the both group (n=30). In each study group, 30 patients completed the study protocol. There was no difference between the study groups with regard to the age, weight, height, and delivery time (p>0.05) (Table 1). All patients had adequate surgical anesthesia. The median upper sensory level 10 min after the intrathecal injection was T4 (T3-T5) for all the study groups.

**Table 1** *Comparison of Patient characteristics (n=60)*

| Variables | Ephedrine group(n=30) Mean±SD | Control group(n=30) Mean±SD | p-value |
|---|---|---|---|
| Age (yr) | 25.6±4.1 | 27.9±6.4 | 0.103 |
| Height (cm) | 156.2±5.2 | 155.6±4.9 | 0.647 |
| Weight (kg) | 61.9±7.7 | 61.8±6.9 | 0.957 |
| Spinal to delivery time (min) | 21.0±2.5 | 20.6±2.6 | 0.546 |

Values are expressed as mean±SD, p value reached from Unpaired t-test.

There was no significant difference in the SAP and HR values at baseline between the study groups (p>0.05). The mean highest and lowest HR in the ephedrine group was higher than those of control group (p<0.05). There were significant differences in mean lowest SAP between the study groups (p<0.05). The mean highest SAP in the ephedrine group was higher than that of control group, but this difference was not significant (Table-2).

**Table-II** *Comparison of systolic arterial pressure and heart rate between case and control group.*

| Variables | Ephedrine group (n=30) Mean±SD | Control group (n=30) Mean±SD | p-value |
|---|---|---|---|
| Systolic arterial pressure (mmHg) | | | |
| Baseline | 124.4±2.31 | 126.2±2.31 | 0.185$^{ns}$ |
| Lowest | 104.5±2.3 | 92.12±1.83 | 0.001* |
| Highest | 133.1±3.12 | 131.8±3.02 | 0.107$^{ns}$ |
| Heart rate (mmHg) | | | |
| Baseline | 100.2±3.68 | 98.9±2.93 | 0.136$^{ns}$ |
| Lowest | 94.6±2.1 | 85.6±1.75 | 0.001* |
| Highest | 126.3±2.39 | 112.3±2.17 | 0.001* |

Values are expressed as mean±SD, p value reached from Unpaired t-test, *significant, ns= not significant

From 2 to 8 min, the mean SAPs in the control group were significantly lower than those of the ep-hedrine group (p<0.05) (Fig. 1). From 6 to 12 min, signifi-cant decreases of the mean SAP in the control group were ob-served as compared with baseline (p<0.05) (Fig. 1). From 4 to 8 min, the mean HR in the control group was significant-ly lower than those of the ephedrine group (p<0.05) (Fig. 2).

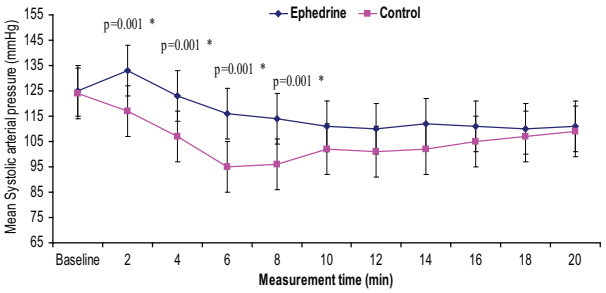


**Fig 1** *Systolic arterial pressure of the ephedrine and control groups, *significant*

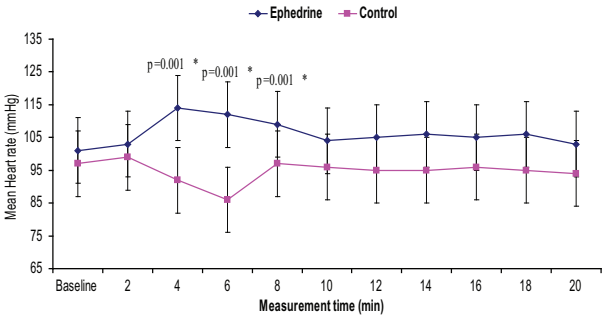


**Fig 2** *Heart rate of the ephedrine and control groups, *significant*

The occurrence of hypotension, hypertension, tachycardia, bradycardia, nausea or vomiting, the total doses rescue ephedrine, and the first rescue ephedrine time are sum-marized in Table 3. There was significant lower incidences of hypotension in the ephedrine group compared with the con-trol group 11(36.7%) vs. 24(80.0%) (p<0.05). There were significant lower incidences of nausea and vomiting in the ephedrine group compared with the control group 6(20.0%) vs. 17(56.7%) (p<0.05). There was no difference in the ratio of hypertension between the study groups (p>0.05). The ratio of bradycardia in the control group was significantly higher than that of the ephedrine group (13.3% vs. 0%; p<0.05). There were significant decrease total doses of rescue ephedrine required in the ephedrine group (p<0.05). Total doses of used ephedrine in the ephedrine group were significant higher than that of control group. The first rescue ephedrine time in the ephedrine group was significantly longer (14.9±7.1 min vs. 7.9±5.4 min) than that of the control group (P<0.05) (Table III).

**Table III** *Comparison of hemodynamic data between two groups (n=60)*

| Variables | Ephedrine group (n=30) Mean±SD | Control group (n=30) Mean±SD | p-value |
|---|---|---|---|
| Hypotension | 11 (36.7%) | 24 (80.0%) | <0.001* |
| Hypertension | 8 (26.7%) | 6 (20.0%) | 0.542 |
| Tachycardia | 16 (53.3%) | 14 (46.7%) | 0.605 |
| Bradycardia | 1 (0.0%) | 5 (13.3%) | 0.038* |
| Nausea or vomiting | 6 (20.0%) | 17(56.7%) | 0.003* |
| Total ephedrine requirement (mg) | 18.6±11.2 | 39.6±8.6 | <0.001* |
| The first rescue ephedrine time (min) | 14.9±7.1 | 7.9±5.4 | <0.001* |

Values are expressed as frequency (%) and mean±SD, p value reached from Chi-square test for qualitative variables and Unpaired t-test for quantitative variables, *significant, ns= not significant

Analysis of neonatal data showed no differences between the study groups. No Apgar scores were below 7 at 1 min or 5 min. Umbilical arterial pH were similar between the study groups (p>0.05). There was no pH <7.2 in the both groups (Table IV).

**Table IV** *Comparison of APGAR score and umbilical arterial pH between two group (n=60)*

| Variable | Ephedrine group (n=30) Mean±SD | Control group (n=30) Mean±SD | P-value |
|---|---|---|---|
| APGAR score 1 min | 7.5±0.50 | 7.4±51 | 0.800$^{ns}$ |
| APGAR score 5 min | 8.6±0.52 | 8.7±0.53 | 0.463$^{ns}$ |
| Umbilical arterial pH | 7.34±0.05 | 7.32±0.03 | 0.093$^{ns}$ |

Values are expressed as mean±SD, p value reached from Unpaired t-test, *significant, ns= not significant

## Discussion

This case randomized, double-blinded study conducted in the Department of Anaesthesia, Uttara Adhunik Medical College, Uttara, Dhaka. This is the first report to our knowledge to investigate the effect of intravenous ephedrine given according to maternal weight dose of 0.5 mg/kg after the induction of spinal anes-thesia for cesarean section to prevent hypotension related to spinal anesthesia. Our findings demonstrated that prophylac-tic intravenous ephedrine during spinal anesthesia for cesarean section can prevent hypotension without significant mater-nal tachycardia or hypertension, and also it increases the first rescue ephedrine time and decreases the ratio of nausea and vomiting. Umbilical arterial pH and Apgar scores were not influenced by hypotension or ephedrine medication.

The incidence of hypotension during spinal anesthesia for cesarean section is reported to be as high as 80%, despite fluid preload, lateral uterine displacement and use of vasopressor agents[11]. In the anesthesia practice, prevention and man-agement of hypotension related to spinal anesthesia remains a difficult problem and there was no consensus on its optimal management.

Phenylephrine, a1-adrenergic agonist whose action would be expected to counteract the decrease in systemic vascular resistance induced by spinal anesthesia[12]. Phenylephrine can be used for the prevention and treatment of maternal hy-potension[13-15] but a reduction of fetal oxygenation due to uterine vasoconstriction has been observed in animals[16]. It may cause maternal bradycardia[14,17]. Loughrey et al.[18] compared intravenous bolus of ephedrine and phenyle-

phrine combination with ephedrine alone. They found the combination of ephedrine and phenylephrine given as an in-travenous bolus was not superior regarding to the incidence of hypotension, maternal side effects, or umbilical blood gases when administered as a prophylactic bolus followed by res-cue boluses and compared to ephedrine alone.

Ephedrine, an indirectly acting sympathomimetic amine, is probably the vasopressor of choice in obstetric anesthesia. Although ephedrine has mixed a- and Q-adrenoreceptor activ-ity, it maintains arterial pressure mainly by increases in car-diac output (CO) and heart rate as a result of its predominant activity on Q1-adrenoreceptors[19]. Variable intravenous infu-sions of ephedrine appear to be successfu1[14,20-22]. Kee et al.[10] investigated the efficacy and optimum dose of intra-venous ephedrine for prevention of hypotension during spinal anesthesia for cesarean delivery. They compared the effect of ephedrine 10, 20, or 30 mg intravenous for the prevention of hypotension. They found that a bolus dose of 30 mg intra-venous ephedrine was required to reduce the incidence of hy-potension during spinal anesthesia for cesarean delivery. They concluded that although the incidence of hypotension was reduced to 35% in the patients who received ephedrine 30 mg compared with the control rate of 95%, this was at the expense of an increased incidence of hypertension, which oc-curred in 45% of the patients. They suggested that 30-mg intravenous ephedrine may not be suitable in some patients such as those with cardiovascular or cerebrovascular disease. Compared with the study of Kee et al.[10], the incidence of reactive hypertension is lower in our study (45% vs. 28.6%). Duration of ephedrine administration in the study of Kee et al. was 30 sec, however, in our study; it was 60 sec.

Decreased ratio of reactive hypertension in the ephedrine group in our study may result from the longer duration of ephedrine ad-ministration. Particularly if sympathetic block level is low,

reactive hypertension may be a problem. In the ephedrine and control groups, upper sensory level was T4 (T3-T5), howev-er, it was T4 (C2-T7) in the study of Kee et al.[10], and the range of sensorial block was wide compared to our study. In-creased sympathetic activity might be related to compensato-ry stimulation of thoracic sympathetic nerves, including the fibers supplying the heart (T1-T4) in the patients undergo-ing spinal anesthesia[23]. Such event also was reported in low spinal anesthesia and epidural blocks in which sympathetic block does not reach the T4 level[24]. The ratio of reactive hypertension was similar the patients given intravenous ep-hedrine and saline (28.6% vs. 19%). In the control group, cause of reactive hypertension may result from the adminis-tration of higher doses of rescue ephedrine.

Lee et al.[9] reviewed available studies to determine the dose-response characteristics of prophylactic intravenous ep-hedrine for the prevention of hypotension during spinal anes-thesia for cesarean delivery. They reported that, significant dose-response relationships were found for hypotension, hy-pertension and umbilical arterial pH. They suggested that, the use of larger doses of ephedrine (>14 mg) does not com-pletely eliminate hypotension but causes reactive hyperten-sion and a minor decrease in umbilical arterial pH. They fo-und no evidence of a dose-response relationship for nausea or vomiting, fetal acidosis, or Apgar scores. Both ratio of hypo-tension and nausea and vomiting decreased with ephedrine dose used in this study.

Some studies found significantly higher umbilical arterial pH when using prophylactic ephedrine[7]. Thus, it seems that ephedrine must be used during cesarean section to avoid spinal hypotension, which remains a major determinant of fetal acidemia[10,25]. Ephedrine has been shown to cross the placenta and to affect the fetal and neonatal heart rate[26] due to Q-adrenoreceptor activity. A greater proportion of low umbilical artery pH has been observed with ephedrine than phenylephrine[12]. Previous studies have shown that the use of ephedrine to prevent or treat hypotension associated with spinal and epidural anesthesia for cesarean delivery may not correct fetal acidosis and may even increase it, especially if hypotension still occurs[5,22,27]. Kee et al.[10] found that umbilical blood pH values were lower in patients who had hypotension compared with patients who did not, whereas hypertension was not associated with adverse effects. Alth-ough they

did not measure uteroplacental flow, their results suggest that, within the range of doses used in their study (10, 20, or 30 mg), the potential vasoconstrictive effects of ephedrine may have a less detrimental effect on uteroplacen-tal blood flow than the effects of hypotension. Eisler et al.[28] demonstrated that fetal catecholamine stimulation before de-livery might be beneficial. They suggested that when a Q-adrenergic agonist was administered before elective cesarean section, lower respiratory morbidity, and better lung func-tion and reduced risk of hypoglycaemia in the newborn infant were found. In our study, lowest SAP was maintained better in patients who received intravenous ephedrine compared with the control groups. We found no significant difference in neither Apgar scores nor umbilical arterial blood gases data between the study groups, despite a difference in the inci-dence of hypotension, probably reflecting the early recogni-tion and restoration of hypotension with rescue ephedrine.

Although mean highest HR in the ephedrine group was higher, we found no difference in ratio of tachycardia between the study groups. This could be explained by both the effect of "rescue" ephedrine and baroreceptor-mediated reflex inc-reases in heart rate in patients who became hypotensive. In addition, atropine was applied for bradycardia in the control group.

**Conclusion**

The above findings suggest, the prophylactic bolus dose of 0.5 mg/kg intravenous ephedrine given at the time of intrathe-cal block after a crystalloid fluid preload, plus rescue boluses reduce the incidence of hypotension. It has not been shown to eliminate the need to treat maternal hypotension during spinal anesthesia for elective cesarean delivery compared to intravenous rescue boluses alone.

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