Vasopressor choice for hypotension in elective Cesarean section: ephedrine or phenylephrine?

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Abstract

Introduction: Hypotensive episodes are a common complication of spinal anesthesia during Cesarean section. The purpose of this study was to compare the effectiveness and the side effects of vasopressors, ephedrine and phenylephrine, administered for hypotension during elective Cesarean section under spinal anesthesia.

Material and methods: The study consisted of 100 selected ASA I/II females scheduled for elective Cesarean section under spinal anesthesia. Each patient was randomly assigned to one of the two double-blind study groups. Group E received 1 ml ephedrine (5 mg/ml) with normal saline if hypotension was present (n = 50). Group P received 1 ml phenylephrine (100 µg/ml) with normal saline if hypotension developed (n = 50). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were compared within and between groups to basal levels at time increments of 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, and 60 min from start of surgery. Incidence of side effects and neonatal outcomes were studied between groups.

Results: All patients required vasopressor therapy for hypotension. Administration of phenylephrine was associated with significant drop in HR. Changes in SBP, DBP, and MAP were similar in both groups for most observed times. The incidences of nausea/vomiting and tachycardia were significantly higher in the ephedrine group.

Conclusions: Phenylephrine and ephedrine are acceptable choices to combat maternal hypotension related to spinal anesthesia in elective Cesarean section. Complications of intra-operative nausea and vomiting, tachycardia and bradycardia should be considered when choosing a vasopressor, suggesting phenylephrine may be more appropriate when considering maternal well-being.

Key words: ephedrine, phenylephrine, spinal anesthesia, Cesarean section.

Introduction

Cesarean section is one of the most commonly performed operations. Many countries have seen increases in their rates due to factors such as widespread use of fetal monitoring, high private insurance rates, restrictive insurance policies, advancing maternal age and high medical malpractice costs [1-4]. With the large number of women undergoing this procedure, it is necessary to consider the inherent risks involved for both mother and child. General anesthesia has generally fallen out of favor in the international community for elective Cesarean sections. Increased risk to

the fetus from the anesthetic drugs, maternal airway management and post-operative effects are well documented, though it is still used for emergency surgery [5-8]. Avoidance of the risks inherent in general anesthesia is crucial for improved maternal and fetal outcome [6, 9].

Regional anesthesia in Cesarean section offers significant benefit over general anesthesia. Epidural anesthesia provides the opportunity to extend surgical anesthesia to post-surgical analgesia via catheter and control of the level of anesthesia. Spinal anesthesia is inexpensive and yields symmetric block rapidly. Combined spinal-epidural anesthesia offers the benefit of both epidural and spinal techniques with less medication, better reliability and less incidence of hypotension [10, 11]. However, regional anesthesia in Cesarean section is not without complication. Supine hypotension syndrome due to aortocaval compression could deteriorate the hemodynamic effect of spinal anesthesia [12, 13]. The risk to the mother includes symptoms of dizziness, nausea and vomiting due the rapid decline in blood pressure, while fetal acidosis may be among the fetal consequences of prolonged maternal hypotension [11, 14]. To prevent injury to mother or fetus caused by hypotension, it is customary to treat supine hypotension syndrome quickly and efficiently.

Routinely, vasopressors such as ephedrine, metaraminol, and phenylephrine have been given prophylactically and preoperatively to combat maternal hypotension [15-18]. Until recently, ephedrine has been the vasopressor used most often in North America as it reliably prevents maternal hypotension, while mephentermine is used commonly in many Asian countries including India [11, 19]. Conversely, ephedrine has been implicated in lower umbilical pH levels, especially when used in dosages high enough to stem nausea and vomiting related to hypotension [20, 21]. Recent studies have indicated a decrease in side effects related to vasopressors, such as nausea and vomiting, and increased uteroplacental blood flow with the use of phenylephrine [17, 22]. Phenylephrine, an α-agonist, has been found to be detrimental to the well-being of the fetus based on numerous animal models [16, 23, 24]. However, studies have begun to question the application of the results of animal models to human clinical practice due to physiological species differences [16, 22, 25, 26]. The purpose of this study was to investigate the effectiveness and the side effects of intravenous phenylephrine and ephedrine in combating maternal hypotension resulting from spinal anesthesia in patients undergoing elective Cesarean section.

Material and methods

This study was performed at K.R. Hospital, Government Medical College, Rajiv Gandhi University of Health Sciences (Karnataka state, India), during 2007-2008, after institutional approval was granted from the hospital's ethical and scientific committees. Informed consent was obtained from 100 female patients, ASA I/II status, scheduled for elective Cesarean section under spinal anesthesia.

Study design

Each patient was randomly assigned to one of the two double-blind study groups. The Group E received 1 ml ephedrine, 50 mg diluted to 10 ml (5 mg/ml), with normal saline if hypotension was present. The Group P was given 1 ml phenylephrine, 1 mg diluted to 10 ml (100 µg/ml), with normal saline if hypotension was present. Blood pressure, oxygen saturation, pulse rate, and respiratory rate were monitored every 2 min for the first 10 min, every 5 min from 10 to 30 min and every 15 min from 30 to 60 min. Times of baby extraction, vasopressor administration and duration of surgery were recorded. Neonatal monitoring was performed by attending neonatologist at 1 and 5 min using APGAR scoring rubric [27].

Pre-surgical protocol

Prior to surgery each patient was examined and a thorough medical history taken with emphasis on respiratory and cardiovascular systems. Potential participants with diabetes mellitus, hypertension, pulmonary tuberculosis, drug allergies, bronchial asthma, epilepsy and bleeding disorders were excluded from the study. A history of pregnancy-induced hypertension and gestational diabetes, symptoms and signs of antepartum hemorrhage by placenta previa and abruption placenta were considered exclusion criteria. All patients received 10 ml/kg of ringer lactate for pre loading. Intra-operatively around 1000-1500 ml of normal saline was infused to the patients. In ephedrine group, 92% of patients received a total dose of 5 mg of ephedrine (single bolus) and 8% of patients received a total dose of 10 mg of ephedrine (2 boluses). In phenylephrine group, 94% of patients received a total dose of 100 µg of phenylephrine (single bolus) and 6% of patients received a total dose of 200 µg of phenylephrine (2 boluses).

Surgical protocol

On the day of surgery, patients were pre-medicated with a single injection of metoclopramide 10 mg and a single injection of ranitidine 50 mg IV one hour prior to surgery. Both groups were pre-loaded with RL 10 ml/kg 20 min before spinal anesthetic procedure. Patients were positioned in the right lateral position with flexion of thigh and legs, hip and knees and flexion at the

head. The operating table was kept flat. Using aseptic precautions, lumbar puncture was performed at L_{3-4} using midline approach with 23G sterile Quinke's needle. After visualization of clear and free flow of cerebrospinal fluid (CSF), bupivacaine 0.5% heavy, 1.6 ml bolus was injected into L_{3-4} subarachnoid space. Patients were turned to supine position with a wedge under the right buttock. After recording preoperative (basal) heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and SPO_2 patients were monitored according to the protocol as indicated in the study design section. If hypotension occurred, defined as a fall of systolic blood pressure ≤ 90 mm Hg and/or 30% less than the basal SBP, patients were given either phenylephrine or ephedrine by anesthesiologist who was blinded about the drug in the syringe. Time of vasopressor administration, duration of surgery, and time of neonate extraction were recorded as minutes after start of surgery. All incidences of bradycardia (HR < 60 bpm) were treated with atropine 0.5 mg IV; any tachycardia (HR > 30% above the basal HR) was noted. Intra-operative nausea and vomiting were recorded. After baby extraction, all patients received 20 units oxytocin by infusion through a separate line. Neonatal well-being was assessed by attending neonatologist. Patients were monitored postoperatively for 24 h for adverse effects.

Statistical analysis

Summary statistics of age, weight, height for both "P" group and "E" group were reported as means ± standard deviation. Intra- and inter-group analysis for HR, SBP, DBP, and MAP were statistically evaluated using one-way ANOVA and paired *t*-tests using both StatPlus™ v2, and Minitab™, where $p < 0.05$ was considered significant and $p < 0.001$ highly significant. Complications of nausea, vomiting, tachycardia and bradycardia were evaluated with the Fisher's exact test, where $p < 0.05$ was considered significant and $p < 0.001$ highly significant.

Results

Overall, the demographic characteristics of both groups were similar. There were no statistical differences between the groups with respect to age, weight, or height (Table I). All patients required vasopressor therapy for hypotension. In our study, top-off doses of vasopressor for repeat hypotension were comparable between groups (6% in group P, 8% in group E). Decline from the basal heart rate was observed in phenylephrine (P) group but was not significant across all measured times (Figure 1). An increase in heart rate from basal levels was seen in ephedrine (E) group across all times and this was significant at each time. The mean maximum heart rate recorded after vasopressor administration was

Table I. Demographic characteristics and operation data between groups

	Ephedrine group means (SD)	Phenylephrine group means (SD)	*P*-value
Age [years]	24.08 (3.74)	23.38 (3.54)	0.169
Weight [kg]	54.84 (6.28)	56.42 (4.70)	0.086
Height [cm]	150.74 (4.49)	151.1 (3.55)	0.344
Duration of surgery [min]	47.4 (3.81)	45.3 (3.70)	< 0.001
Time of baby extraction [min]	6.24 (2.06)	6.28 (2.94)	0.45

Data expressed as mean (SD)

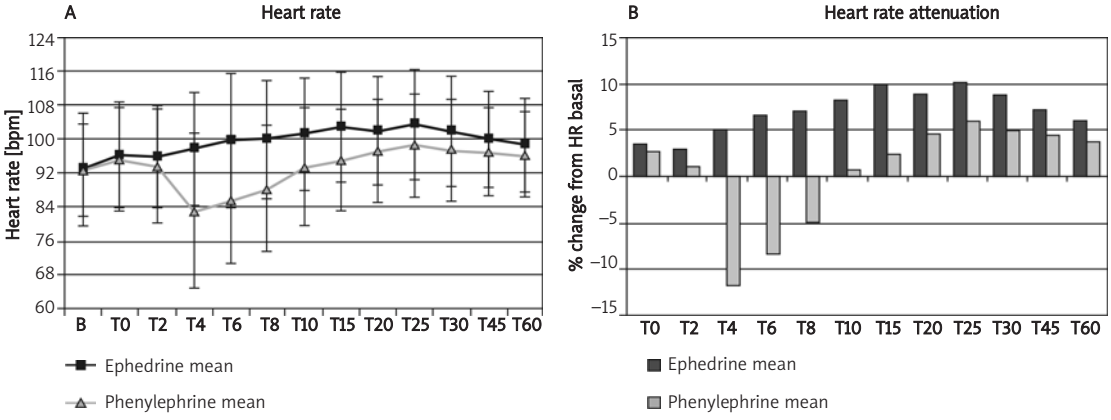

Figure 1. A – Mean heart rate (HR) values for ephedrine and phenylephrine mean ± SD, and **B** – percent difference between measured HR levels and basal values

Table II. Time of vasopressor administration and the following hemodynamic values between groups

	Ephedrine group means (SD)	Phenylephrine group means (SD)	*P*-value
Time of vasopressor administration [min]	4.52 (4.25)	3.48 (3.72)	< 0.05
Maximum HR after vasopressor administration [beats/min]	110.84 (12.89)	103.06 (11.51)	< 0.05
Minimum HR after vasopressor administration [beats/min]	90.48 (12.87)	73.46 (11.29)	< 0.001
Maximum SBP after vasopressor administration [mm Hg]	124.96 (8.18)	126.52 (8.21)	0.18
Minimum SBP after vasopressor administration [mm Hg]	99.72 (20.74)	104.16 (7.50)	0.09

Data expressed as mean (SD), HR – heart rate, SBP – systolic blood pressure

Table III. Mean heart rate values

Time [min]	Ephedrine group means (SD) [beats/min]	Phenylephrine group means (SD) [beats/min]	*P*-value
Basal	92.86 (13.22)	92.62 (10.79)	0.47
0	96.14 (12.42)	95.22 (12.12)	0.36
2	95.68 (11.88)	93.56 (13.20)	0.22
4	97.62 (13.38)	82.86 (18.23)	< 0.001
6	99.50 (15.88)	85.50 (14.91)	< 0.001
8	99.84 (13.98)	88.30 (14.69)	< 0.001
10	101.20 (13.34)	93.32 (13.75)	< 0.005
15	102.86 (12.96)	94.98 (11.76)	< 0.005
20	101.90 (12.90)	97.14 (12.23)	< 0.05
25	103.00 (12.90)	98.54 (12.10)	< 0.05
30	101.70 (13.02)	97.36 (11.92)	0.06
45	100.00 (11.42)	96.88 (10.37)	0.10
60	98.76 (11.05)	96.18 (10.03)	0.12

Data are expressed as mean value (SD)

significantly higher in group E than in group P (t = 3.06, p < 0.05) (Table II). Furthermore, administration of phenylephrine was associated with a highly significant drop in heart rate (t = 6.68, $p \leq 0.001$) (Table III). Six patients in the P group required atropine for the treatment of bradycardia and responded favorably. The maximum and minimum systolic blood pressures after vasopressor bolus were higher in group P, though the differences were not statistically significant. No significant difference in SBP between the groups was recorded at all measured points except at T = 4 min (Figure 2), when SBP of patients in group E was significantly lower than SBP of patients in group P (t = –2.85, p < 0.05). Diastolic blood pressure was comparable between the ephedrine and phenylephrine groups for all measured times except at T = 2 min, when P group DBP was significantly lower than E group DBP (t = 2.53, p < 0.05) (Figure 2). Beginning at T = 4 min, MAP values between the groups was similar and not significant (p > 0.05). Overall, phenylephrine was

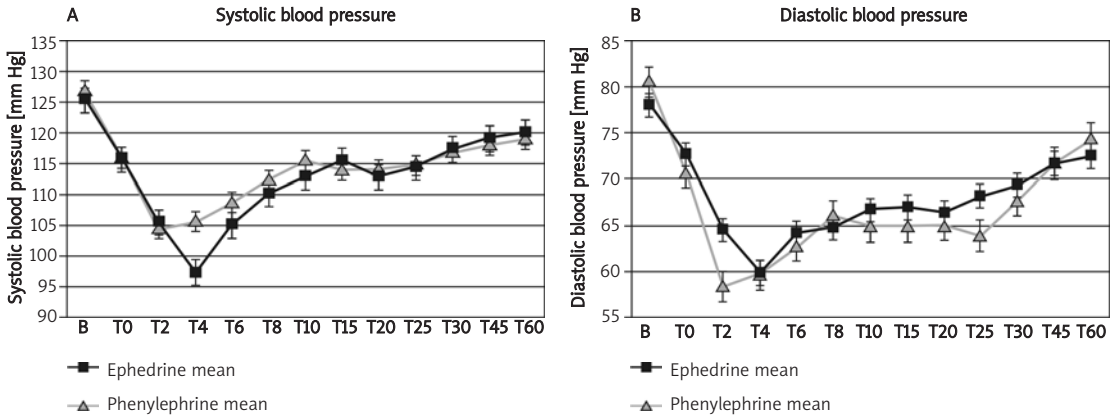

Figure 2. A – Mean systolic blood pressure values for ephedrine and phenylephrine mean ± SD and **B** – mean diastolic blood pressure values for ephedrine and phenylephrine mean ± SD

associated with a significantly higher increase in systolic blood pressure ($t = 1.89$, $p < 0.05$) and mean arterial pressure ($t = 1.92$, $p < 0.05$). In our study, 38 patients in ephedrine group and 36 patients in phenylephrine group had an upper level of sensory analgesia of T_{4-5}. Twelve patients in ephedrine group and 14 patients in phenylephrine group had upper level of sensory analgesia of T_{6-7}. The sensory level attained in both groups was therefore comparable and not significant ($p > 0.08$).

Complications

While 9 patients (18%) in the ephedrine group exhibited nausea, only 4 patients (8%) in the phenylephrine group experienced nausea (Table IV). In the ephedrine group, 7 patients (14%) vomited, while none (0%) exhibited this symptom in the phenylephrine group. The incidence of vomiting between groups is statistically significant ($p < 0.05$). The number of patients with bradycardia was higher in the phenylephrine group, however all patients with bradycardia responded well to atropine. The administration of phenylephrine caused bradycardia in 12% of patients which was not significant ($p > 0.05$), while ephedrine was seen to cause tachycardia in 16% of patients which was significant ($p < 0.05$) (Table IV). In ephedrine group only one patient had bradycardia and this patient had an upper sensory level of T_3. In Phenylephrine group six patients had bradycardia and these patients had level of T_{5-6}.

APGAR scores

APGAR scores of all neonates were satisfactory at birth. All babies in "E" group had APGAR scores between 8-9 at 1 min and 10 at 5 min. All babies in group "P" had APGAR scores between 8-9 at 1 min and 10 at 5 min. The results were comparable for both groups.

Discussion

This study demonstrated that phenylephrine and ephedrine are comparable vasopressors when used to treat hypotension during an elective Cesarean section. The significant difference in heart rate between groups can primarily be attributed to the decline in heart rate associated with phenylephrine and the increase in heart rate associated with ephedrine. Despite the significant decline in heart rate observed with phenylephrine, it provided better attenuation of heart rate than ephedrine for all measured time points except $T = 4$ min and $T = 6$ min. Bradycardia is usually seen with phenylephrine usage because of its well known α-agonist properties [28]. The incidence of tachycardia was significantly higher in the ephedrine group, possibly due to difficulty in accurate titration of ephedrine because of its initial slow response and longer duration of action. Our results are in agreement with a number of other studies where significant tachycardia was observed with ephedrine usage [15, 28]. However, Loughery's *et al*. [29] found no cases of rebound hypertension with ephedrine, while Magalhaes *et al*. [30] reported comparable numbers of both bradycardia and reactive hypertension with ephedrine and phenylephrine. Furthermore, incidence of fetal tachycardia with ephedrine was reported significant in another study [11]. Though fetal heart rate was not measured in this study, the incidence of maternal tachycardia with ephedrine was significant.

Spinal anesthesia was associated with hypotension in all patients in both groups. However, nausea and/or vomiting occurred in only 8% of patients in the phenylephrine group compared to 18% of patients in the ephedrine group. Our results are in concurrence with a number of recent studies indicating a significantly higher incidence of nausea/vomiting with ephedrine usage [19, 22, 29]. Nevertheless, Magalhaes *et al*. [30] reported a higher prevalence of nausea/vomiting in patients who received phenylephrine compared to those who received ephedrine. In all cases, administration of a second dose of vasopressor resulted in occurrence of nausea and/or vomiting. Furthermore, the maximum drop in systolic blood pressure was higher in the phenylephrine group than the ephedrine group, yet fewer incidences of nausea/vomiting occurred. We calculated the maximum drop from one time interval to the next measured time interval for each patient, then grouped them by whether or not they had nausea/vomiting. This suggests that the vasopressor choice may be more significant than the level of hypotension in predicting side effects. In addition, only one patient had bradycardia in ephedrine group, this patient had an upper sensory level of T_3, compared six patients in phenylephrine group; these patients had upper sensory level of T_{5-6}. Thus the bradycardia observed in ephedrine group may be due to activation of Bain Bridge reflex and involvement of cardio acceleratory fibers. In phenylephrine group, the bradycardia may be due

Table IV. Number of complications between groups

	Ephedrine group, *n* (%)	Phenylephrine group, *n* (%)	*P*-value
Nausea	9 (18%)	4 (8%)	0.08
Vomiting	7 (14%)	0 (0%)	< 0.05
Bradycardia	1 (2%)	6 (12%)	0.05
Tachycardia	8 (16%)	0 (0%)	< 0.05
5 min Apgar < 7	0 (0%)	0 (0%)	1.0

Data expressed as number of patients (n) (%)

to combination of Bain Bridge reflex and reflex bradycardia due to administration of phenylephrine.

Many studies have attempted to determine the best vasopressor during spinal anesthesia in elective and non-elective Cesarean section using both animal and human subjects [15, 18-20, 24, 28, 30-33]. Ephedrine has been used as a primary vasopressor in obstetric patients for years based on its efficacy in returning maternal systolic blood pressure to a normal reading during spinal anesthesia during Cesarean section. Ephedrine indirectly raises blood pressure by increasing the release of norepinephrine [11]. Since the 1960s, several studies on chronically instrumented sheep have suggested that ephedrine is a better choice as a vasopressor than phenylephrine, mephentermine, methoxamine or metaraminol [16, 24, 31, 34]. In pregnant ewes, ephedrine has not been shown to decrease blood flow to the uterus. Additionally, use of ephedrine returned fetal cardiovascular hemodynamics to baseline after maternal hypotension in a sheep model [16] and may prevent fetal late decelerations [11]. However, a number of studies have identified a decrease in fetal umbilical pH after administration of ephedrine [20, 30]. This again corroborates the conclusions drawn from extensive review article by Lee *et al*. [28] that fetal umbilical pH was lower in parturients who received ephedrine than in those who received phenylephrine. Furthermore, phenylephrine has been used for quite some time as an alternative agent for the treatment of hypotension after spinal anesthesia in Cesarean sections or in cases where ephedrine was ineffective [21, 33]. Animal models with compromised fetuses suggest that phenylephrine does not increase fetal lactate concentrations [16]. Extrapolation from animal studies must be carefully considered due to physiological species differences and pharmacological requirements. Human studies with uncompromised fetuses have not indicated a negative fetal or maternal outcome with phenylephrine use, as demonstrated by the comparable Apgar scores of the neonates. Vasopressor choice in non-elective Cesarean sections is still debatable. Phenylephrine was shown to be as effective as ephedrine in non-elective cases in one human study [26]. This differs from studies with sheep indicating compromised fetuses better tolerate ephedrine than phenylephrine [16, 24].

In conclusion, both ephedrine and phenylephrine in the bolus dose of 5 mg and 100 µg respectively can safely be employed to combat hypotension in patients undergoing elective lower segment Cesarean section under spinal anesthesia. Further studies should be considered to evaluate the incidence of fetal acidosis and comparative fetal hemodynamics as a result of treating maternal hypotension. In addition, though both vasopressors reliably raised maternal blood pressure, the clinical significance of tachycardia, bradycardia and intraoperative nausea and vomiting should not be overlooked.

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