Rev Bras Anestesiol. 2014;64(5):299–306

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anesthesia

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Received 28 June 2013; accepted 25 July 2013
Available online 2 July 2014

KEYWORDS
Anesthesia;
Cesarean section;
Spinal anesthesia;
Hypotension;
Vasoconstrictor agents

Abstract Maternal hypotension is a common complication after spinal anesthesia for cesarean section, with deleterious effects on the fetus and mother. Among the strategies aimed at minimizing the effects of hypotension, vasopressor administration is the most efficient. The aim of this study was to compare the efficacy of phenylephrine, metaraminol, and ephedrine in the prevention and treatment of hypotension after spinal anesthesia for cesarean section. Ninety pregnant women, not in labor, undergoing cesarean section were randomized into three groups to receive a bolus followed by continuous infusion of vasopressor as follows: phenylephrine group (50 μg + 50 μg/min); metaraminol group (0.25 mg + 0.25 mg/min); ephedrine group (4 mg + 4 mg/min). Infusion dose was doubled when systolic blood pressure decreased to 80% of baseline and a bolus was given when systolic blood pressure decreased below 80%. The infusion dose was divided in half when systolic blood pressure increased to 120% and was stopped when it became higher. The incidence of hypotension, nausea and vomiting, reactive hypertension, bradycardia, tachycardia, Apgar scores, and arterial cord blood gases were assessed at the 1st and 5th minutes.

There was no difference in the incidence of hypotension, bradycardia, reactive hypertension, infusion discontinuation, atropine administration or Apgar scores. Rescue boluses were higher only in the ephedrine group compared to metaraminol group. The incidence of nausea and vomiting and fetal acidosis were greater in the ephedrine group. The three drugs were effective in preventing hypotension; however, fetal effects were more frequent in the ephedrine group, although transient.

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http://dx.doi.org/10.1016/j.bjane.2013.07.014

PALAVRAS-CHAVE
Anestesia;
Cesariana;
Raquianestesia;
Hipotensão;
Agentes vasoconstritores

Avaliação comparativa entre metaraminol, fenilefrina e efedrina na profilaxia e no tratamento da hipotensão em cesarianas sob raquianestesia

Resumo Hipotensão materna é uma complicação comum após raquianestesia em cirurgia cesariana, trazendo efeitos deletérios para o feto e a mãe. Entre as estratégias com o objetivo de minimizar os efeitos da hipotensão, a administração de vasopressores é a mais eficiente. O objetivo deste estudo foi comparar a eficácia da fenilefrina, metaraminol e efedrina na prevenção e tratamento de hipotensão após raquianestesia em cirurgia cesariana. Noventa gestantes que não estavam em trabalho de parto submetidas à cesariana eletiva foram randomizadas em três grupos para receber um *bolus*, seguido de infusão contínua de vasopressor da seguinte forma: Grupo Fenilefrina (50 μg + 50 μg/min); Grupo Metaraminol (0,25 mg + 0,25 mg/min); Grupo Efedrina (4 mg + 4 mg/min). A dose da infusão foi dobrada quando a pressão arterial sistólica (PAS) decresceu até 80% dos valores basais e um *bolus* foi dado quando a PAS decresceu para valores abaixo de 80%. A dose da infusão foi dividida ao meio quando a PAS aumentou até 120% e foi interrompida quando mais elevada. Foram analisadas as incidências de hipotensão, náuseas e vômitos, hipertensão reativa, bradicardia, taquicardia e escores de Apgar no primeiro e quinto minutos e gases de sangue arterial do cordão umbilical.

Não houve diferenças nas incidências de hipotensão, bradicardia, hipertensão reativa, interrupção da infusão, administração de atropina ou escores de Apgar. A administração de *bolus* de resgate foram superiores apenas no Grupo Efedrina em comparação com Metaraminol. A incidência de náuseas e vômitos e acidose fetal foram superiores no Grupo Efedrina. Os três fármacos foram eficazes na prevenção de hipotensão, mas repercussões fetais foram mais frequentes no Grupo Efedrina, embora transitórias.

Introduction

Maternal hypotension after spinal anesthesia for cesarean sections is a common complication and may occur in up to 80% of cases.[1] If not treated promptly, it can cause undesired effects on the mother and fetus.[2] The effects that most commonly affect mothers are nausea and vomiting, although more serious complications such as circulatory collapse and cardiac arrest may occur if treatment is not prompt and efficient. In the fetus, placental hypoperfusion may cause fetal distress, resulting in fetal acidosis, increased base excess and low Apgar values.[3]

Several strategies have been used to prevent or minimize hypotension, such as infusion of intravenous fluids, uterine displacement to the left and elastic compression of the lower limbs. However, these measures alone are generally not effective. The use of vasopressors is required.[4]

The optimal vasopressor should offset the progressive effects of ascending sympathetic blockade, which is difficult to achieve because the α- and β-adrenergic activities can vary independently during blockade installation. Still, changes in sympathetic activity may be organ-specific (inhibition of cardiac fibers), region-specific (inhibition in the lower body and increased activity in the upper body) or systemic (inhibition of catecholamine release from the adrenal medulla). The most commonly used vasopressors (phenylephrine, metaraminol, and ephedrine) have primarily systemic effects and may have undesirable effects on organs, vascular beds or fetus.[5]

Ephedrine is a non-catecholamine sympathomimetic agent that stimulates the α- and β-adrenergic receptors by direct and indirect action. It became the vasopressor of choice for treatment and prophylaxis of hypotension after a study with sheep in the 70ϒs, which showed minimal changes in uterine blood flow after administration, while drugs with predominant α-agonist effect caused a significant reduction in the flow.[6]

However, the supremacy of ephedrine as a vasopressor of choice in cesarean sections began to be questioned after its association with fetal acidosis and lower values of base excess compared to vasopressors with predominant α-agonist effect. This fact is explicable because ephedrine crosses the uteroplacental barrier, acts directly on the fetus, and increases its metabolism through β2-adrenergic receptors.[7] The administration of ephedrine for cesarean sections, besides causing fetal acidosis, also became associated with the highest incidence of maternal nausea and vomiting.[8]

The aim of this study was to compare the efficacy of phenylephrine, metaraminol and ephedrine for the prevention and treatment of maternal hypotension during cesarean section, evaluate vasopressor therapy-related adverse effects, and study fetal changes through Apgar score and umbilical cord arterial and venous blood gases.

Methodology

This study was approved by the Research Ethics Committee of the Hospital Universitário Presidente Dutra, under Opinion No 174/11. Pregnant women were included in the study only after signing the informed consent form. A randomized, controlled, double-blind clinical trial was performed involving pregnant women with gestational age between 39 weeks

and one day and 40 weeks and six days, undergoing elective cesarean delivery in a private maternity hospital of São Luís (MA).

Sample

The primary outcome was the umbilical artery pH, which served as the basis for sample calculation. With data from previous studies, it was calculated that a sample of 26 pregnant women per group would have 90% power with a significance level of 5% to detect a difference of 0.05 units in the umbilical artery pH between groups. However, in order to minimize possible losses, the inclusion was scheduled for 30 pregnant women in each group.

Inclusion, non-inclusion and exclusion criteria

Pregnant women between 39 weeks and one day and 40 weeks and six days of gestational age, undergoing elective cesarean delivery, physical status ASA I (American Society of Anesthesiologists' classification), with a single gestation and between 20 and 34 years old were included in the study, as this age group is indifferent to maternal and fetal complications.[9]

It is well documented that pregnant women over 35 years of age are more likely to have premature rupture of membranes, placenta praevia, gestational diabetes and preeclampsia, in addition to a higher chance of having chronic diseases, such as systemic hypertension[10]; and pregnant women under 20 years of age have a higher risk of fetal death.[11]

Non-inclusion criteria were pregnant women refusal, comorbidities, fetal abnormalities, contraindication for spinal anesthesia and a history of hypersensitivity to drugs used in the study.

Exclusion criteria were volume of collected umbilical cord blood insufficient to determine blood gases and anesthetic block failure.

Treatment groups

Pregnant women were randomly divided into three groups: metaraminol (Group M); phenylephrine (Group P); ephedrine (Group E). The method used was the drawing of sequential sealed envelopes containing numbers previously generated by computer. Both pregnant women and anesthesiologists who participated in the surgeries were blinded to group allocation.

Preparation of vasopressors

A second anesthetist, who did not attend the surgery, prepared the vasopressor agents. The solutions were prepared in a syringe of 20 mL as follows:

- Group P: phenylephrine 100 μg/mL;
- Group M: metaraminol 0.5 mg/mL;
- Group E: ephedrine 8 mg/mL.

Anesthetic technique

Patients were monitored with continuous electrocardiography, noninvasive blood pressure and pulse oximetry, with Infinity Delta monitor (Drägerwerk AG & Co. KGaA, 2009).

Venipuncture with an 18G Jelco was performed and then patients were placed supine, with uterine displacement to the left for a few minutes. Then, blood pressure was measured three times at 3-min intervals and the arithmetic average of the values was calculated, which was considered the basal pressure of pregnant women and recorded on the data collection form. Then, with the patient in sitting position, spinal anesthesia was performed with 27G needle (Whitacre) between the third and fourth lumbar vertebrae. Patients received 10 mg of 0.5% hyperbaric bupivacaine combined with 100 μg of morphine, at a rate of 1 mL every 15 s.[12] Immediately after the blockade, concomitant hydration of Ringer's lactate (10 mL kg^{-1}) was started.[13]

After blockade, the measurement of pregnant women systolic blood pressure (SBP) was recorded every minute on data collection form up to fetus extraction. The level of sensory block was assessed with the pinprick test every minute after the puncture, until it reached the dermatome level of the fifth thoracic nerve root (T5). The beginning of surgery was then authorized. The time from blockade to skin incision, uterine incision, and extraction of fetus were recorded.[12]

Protocol for administration of vasopressors

Immediately after blockade, the patients received a bolus of 0.5 mL of the solution, which corresponded to 50 μg of phenylephrine, 250 μg of metaraminol, and 4 mg of ephedrine, followed by subsequent doses of continuous intravenous infusion with a syringe pump (Samtronic Saúde Technologia, model 670), programmed for an infusion rate of 30 mL/h, so that all patients received the doses previously established:

- Group P: phenylephrine 50 μg/min^{-1};[14]
- Group M: Metaraminol 250 μg/min^{-1};[15]
- Group E: ephedrine 4 mg μg/min^{-1}.[16]

Although infusion with fixed rates is easier to perform, varying infusion rates were used according to the SBP values, in order to enable greater effectiveness in controlling blood pressure.[17] Thus, the rate of infusion of vasopressors was adjusted according to the protocol as shown in Table 1.

Table 1 Vasopressor infusion rates.

SBP values (%)	Approach
Above 120%	Infusion discontinuation until SBP return to <120%
100 and 120%	Reduction of infusion rate to 15 mL/h
Around 100%	Maintenance of infusion rate at 30 mL/h
80 and 100%	Increase of infusion rate to 60 mL/h
Below 80%	Solution bolus of 1 mL (rescue dose) and increased infusion to 60 mL/h

Reactive hypertension after the use of vasopressor was defined as SBP 20% greater than the baseline value and, if it occurred, it was treated with infusion discontinuation until blood pressure reached values lower than 120% of baseline, and the infusion was restarted. When patient had more than two episodes of reactive hypertension, infusion was permanently discontinued (which was recorded), and subsequent episodes of hypotension were treated with bolus infusion of the solution (1 mL). Bradycardia was considered when heart rate values were lower than 50 beats per minute and, when accompanied by hypotension, it was treated with atropine (0.5 mg). Tachycardia was considered at a heart rate greater than 100 beats per minute.[12] Values less than 100% of baseline SBP were considered hypotension.

Evaluation of pregnant woman

Maternal SBP were recorded every minute on data collection form. Episodes of hypotension, hypertension, tachycardia and bradycardia, need for rescue doses of vasopressor, infusion discontinuation, and atropine administration until birth were recorded. Episodes of nausea and vomiting were also recorded until the end of cesarean section and, if it occurred, it was treated with 4 mg intravenous ondansetron.

Newborn evaluation

Arterial blood samples were collected from the fetal umbilical cord immediately after birth, and during the clamp, the surgeon was requested to withdraw a fragment of about 10 cm long for arterial puncture. At the operating room, analysis of blood gas, lactate, and glucose was performed using a portable gas analysis device (Epoc, Epocal Inc., Ottawa, Canada). An umbilical pH less than 7.2 was considered fetal acidosis.[18]

Newborns were evaluated by an assistant pediatrician who assessed the Apgar score at the 1st and 5th minutes of birth, and a low Apgar was considered when the values assigned were less than 7.

The newborn destination was also evaluated, if he was taken to the neonatal intensive care unit, if he was under observation in the neonatal resuscitation room or taken to the apartment.

Statistical analysis

The results were statistically analyzed with the software BioEstat 5.3. Numerical variables were compared among the three groups using the Kruskal–Wallis test followed by the Mann–Whitney test. Categorical variables were compared among the three groups using the chi-square test followed by Fisher's exact test. Results were considered statistically significant when $p < 0.05$.

Results

Among the three groups, all pregnant women were over 20 and under 35 years of age, gestational age between 39 weeks and one day and 40 weeks and six days and, until birth, they received the same amount of fluids.

One of the pregnant women who received ephedrine was excluded due to insufficient volume of blood collected from the umbilical cord.

Pregnant women evaluation showed no significant difference regarding the incidence of hypotension in the three groups, as well as incidence of reactive hypertension, need for infusion discontinuation, and bradycardia. Regarding rescue dose administration, there was no statistical difference between groups M and E, although higher in Group E, which was not observed in Group P. The incidence of tachycardia, nausea and vomiting was higher in Group E (Table 2).

Clinical evaluation of newborns showed no difference in Apgar scores at the 1st or 5th minute between groups (Table 3). Only one newborn in Group E had Apgar score less than seven at the 1st minute, associated with fetal acidosis. However, he showed clinical improvement and Apgar score = 9 at the 5th minute. No infant received resuscitation maneuvers or required care in the intensive care unit.

Table 2 Hemodynamic changes related to maternal sympathetic block and side effects secondary to vasopressor therapy in pregnant women undergoing elective cesarean section under spinal anesthesia.

	Metaraminol $n = 30$	Phenylephrine $n = 30$	Ephedrine $n = 29$	p
Hypotension	5 (16.7%)	6 (20%)	10 (34.5%)	0.23
Hypertension	11 (36.7%)	7 (23.3%)	8 (27.6%)	0.51
Bradycardia	3 (10%)	3 (10%)	0 (0%)	0.24
Tachycardia	1 (3.3%)	0 (0%)	12 (41.4%)[a]	<0.0001
Rescue dose	2 (6.7%)	5 (16.7%)	10 (33.3%)[b]	0.02
Nausea	1 (3.3%)	1 (3.3%)	9 (31.0%)[c]	0.001
Vomiting	1 (3.3%)	1 (3.3%)	9 (31.0%)[d]	0.001
Discontinuation	3 (10%)	3 (10%)	5 (17.2%)	0.62
Atropine	2 (6.7%)	2 (6.7%)	0 (0%)	0.36

Results are expressed as frequency (percentage) (chi-square, Fisher).
[a] $p = 0.0004$ versus metaraminol; $p = 0.0$ versus phenylephrine.
[b] $p = 0.0102$ versus metaraminol; $p = 0.1432$ versus phenylephrine.
[c] $p = 0.0056$ versus metaraminol; $p = 0.0056$ versus phenylephrine.
[d] $p = 0.0056$ versus metaraminol; $p = 0.0056$ versus phenylephrine.

Table 3 Clinical evaluation of the newborn through the Apgar test at the 1st and 5th minutes after birth in elective cesarean sections under spinal anesthesia.

Apgar	Metaraminol	Phenylephrine	Ephedrine	*p*
1st minute	9 (7–9)	9 (8–9)	9 (6–9)	0.7413
5th minute	10 (9–10)	10 (9–10)	10 (9–10)	0.7542

Values are expressed as median and interquartile range (Kruskal–Wallis).

Regarding laboratory evaluation of newborns, the average pH was 7.31 ± 0.03 in Group M, 7.30 ± 0.03 in Group P and 7.26 ± 0.07 in Group E. In group E, three newborns (10.3%) had pH less than 7.20. However, the *p*-value was significant ($p = 0.0035$).

Considering the mean value of excess base, there was a significant difference between groups M and P in relation to E, but not between groups M and P. Lactate values also showed significant difference between groups and were higher in Group E compared to groups M and P. Parameters such as pO_2, pCO_2, HCO_3, and glucose showed no statistical differences (Table 4).

There was no statistical difference between groups regarding the time elapsed between blockade and skin incision, blockade and uterine incision, and blockade and birth (Table 5).

Discussion

The vasopressor doses administered in this study were appropriate for the prevention and treatment of maternal hypotension. Currently, it is known that the three vasopressors are considered equally effective for preventing hypotension during elective cesarean sections.[3,15,19]

When phenylephrine is administered by continuous infusion, the incidence of hypotension varies between 13% and 23%.[17] Allen et al.[14] compared fixed infusions of 25, 50, 75 and 100 μg/min of phenylephrine and reported better hemodynamic stability when doses of 25 and 50 μg/min were used. The incidence of hypotension in this study was 20% and satisfactory hemodynamic control was obtained with the variable infusion started with 50 μg/min.

In a study by Ngan Kee et al.,[15] in which metaraminol was administered as a bolus of 0.5 mg followed by continuous infusion of 0.25 mg/min, the incidence of hypotension was 35%, which is higher than that obtained in this study (16.7%). Although the initial infusion doses in both studies were similar, the difference observed probably occurred because the doses administered in this study varied according to blood pressure measurements, which promotes better hemodynamic control.[17]

Regarding ephedrine, this study observed hypotension in 34.5% of cases, whereas in the study by Carvalho et al.,[20] the incidence was 45%. Note that both the work by Ngan Kee et al.[15] and Carvalho et al. used prior administration of crystalloid, an approach proven ineffective. Because in this study fluids were concomitantly administered with the blockade, this may explain the difference in results.

On the other hand, Bhardwaj et al.[21] in a study comparing the three vasopressors used in the present study, administered bolus followed by continuous infusion and reported incidence of hypotension in Group M (14.8%) and Group P (12.5%), results closest to this study. As for ephedrine, hypotension occurred in 23% of the cases.

To avoid distortions in the results, all patients received a volume of 10 mL/kg of Ringer's solution until child delivery, as concomitant hydration (cohydration). Banerjee et al.[22] considered rational to start the rapid infusion of crystalloid, such as Ringer's solution, concurrently with the anesthetic block, as crystalloids improve systolic volume and cardiac output only transiently, and it is considered a cheaper option than colloids, with less risk of complications (anaphylaxis, coagulation disorders).[23]

In cases of reactive hypertension and vasopressor infusion discontinuation, the results match those of the literature,[19] i.e., there were no significant differences among the three groups. Regarding the incidence of bradycardia, although it was similar in the three groups, the results are opposite to the studies by Veeser et al., which reported lower risk of bradycardia in pregnant women receiving ephedrine.

Table 4 Laboratory evaluation of the newborn performed with sample collection of umbilical cord arterial blood for measurement of glucose, lactate, and blood gases during elective cesarean section under spinal anesthesia.

	Metaraminol	Phenylephrine	Ephedrine	*p*
Ph	7.31 ± 0.03	7.30 ± 0.03	7.26 ± 0.07[a]	0.0035
pO_2 (mm Hg)	17.32 ± 11.67	12.82 ± 3.76	14.21 ± 6.18	0.1139
pCO_2 (mm Hg)	49.25 ± 7.97	53.09 ± 7.19	53.98 ± 11.96	0.1681
HCO_3 (mm Hg)	24.77 ± 2.99	25.78 ± 2.37	23.80 ± 3.46	0.0745
Base excess (mEq L^{-1})	−1.71 ± 2.63	−1.22 ± 1.98	−3.44 ± 2.39[b]	0.0005
Glicemia	51.53 ± 9.72	50.60 ± 9.84	49.76 ± 11.32	0.6545
Lactate	1.46 ± 0.31	1.58 ± 0.53	2.11 ± 0.69[c]	0.0004

Values are expressed as mean and standard deviation (Kruskal–Wallis, Mann–Whitney).
[a] $p = 0.0024$ versus metaraminol; $p = 0.0177$ versus phenylephrine.
[b] $p = 0.0018$ versus metaraminol; $p = 0.0003$ versus phenylephrine.
[c] $p = 0.0002$ versus metaraminol; $p = 0.0017$ versus phenylephrine.

Table 5 Intraoperative variables.

	Metaraminol (min)	Phenylephrine (min)	Ephedrine (min)	*p*
Blockade-skin incision	7.53 ± 2.10	6.67 ± 2.55	6.97 ± 1.97	0.37
Blockade-uterine incision	13.03 ± 3.90	11.17 ± 3.79	12.52 ± 3.52	0.27
Blockade-birth	14.17 ± 3.96	12.47 ± 3.81	13.69 ± 3.53	0.34
Skin incision-birth	6.73 ± 2.49	5.73 ± 2.39	6.62 ± 2.32	0.21
Uterine incision-birth	1.17 ± 0.46	1.30 ± 0.53	1.17 ± 0.38	0.41

Values are expressed as mean and standard deviation (Kruskal–Wallis).

An interesting observation was that pregnant women treated with metaraminol had less need for rescue doses than those who received ephedrine. The same was not observed with phenylephrine. This probably occurred because metaraminol increases the systemic vascular resistance (afterload), recruits splanchnic blood, and increases the venous return (preload), besides presenting positive inotropic activity, unlike phenylephrine, which acts basically only in the afterload.[24]

The incidence of tachycardia was higher in Group E than in other groups, which was expected because when ephedrine is used to prevent hypotension during surgery under spinal anesthesia, it causes an increase of cardiac output at the expense of increased heart rate. On the other hand, it is known that α-agonist drugs, such as phenylephrine and metaraminol, may cause reflex bradycardia to the increased peripheral vascular resistance.[25] However, there were no differences between groups in the incidence of bradycardia, which may be due to the administration of adequate doses of metaraminol and phenylephrine.

In this study, despite effective blood pressure control, there was a relationship between the use of ephedrine and the incidence of nausea and vomiting. Lee et al.,[2] in a systematic review on the use of ephedrine, found that even under blood pressure control in cesarean sections there were differences between the ephedrine group and the control group (without vasopressor) regarding the occurrence of nausea and vomiting.

Ngan Kee et al.,[26] in a study comparing infusions with varying combinations of ephedrine and phenylephrine for maintenance of blood pressure during elective cesarean section, found that the higher the proportion of ephedrine and the lower the proportion of phenylephrine, the hemodynamic control was more difficult, fetal acid-base profile less favorable, and incidence of nausea and vomiting higher.

It is known that intraoperative nausea and vomiting in cesarean sections may be prevented through hypotension control and improving the use of neuraxial and intravenous opioids, which improves the anesthetic block quality, minimizes surgical stimulation, and reduces the use of uterotonic drugs. Whereas all pregnant women in this study received the same dose of opioids and uterotonic drugs, as well as adequate levels of anesthetic blockade, the increased incidence of nausea and vomiting caused by ephedrine is probably due to an effect of the drug itself, besides indicating that the etiology of nausea and vomiting is multifactorial.[27]

Some studies have reported a lower incidence of nausea, vomiting, and maternal hypotension when vasopressors are administered by continuous infusion. Therefore, in this study, the administration of bolus followed by continuous infusion was chosen.[6,17,28] However, it is known that continuous infusion of vasopressors is associated with higher doses in order to maintain blood pressure close to baseline values.[29]

The vasopressor of choice with better profile for hemodynamic control of pregnant women in cesarean sections is still largely debatable, by the observation that during the anesthetic block installation there is a reduction in systemic vascular resistance, associated with increased cardiac output, which is mediated by increased heart rate. Thus, bradycardia caused by the administration of α-agonists results in decreased maternal cardiac output, leading some anesthesiologists to base their choice on the mother's heart rate.[30]

Dyer et al., in a study evaluating pregnant women undergoing cesarean section under spinal anesthesia through minimally invasive cardiac output monitors (LiDDCO and BioZ) who received ephedrine or phenylephrine, showed that, after spinal anesthesia, the pregnant women had a marked decrease in systemic vascular resistance, with a compensatory increase in cardiac output, and concluded that low doses of phenylephrine are able to restore the systemic vascular resistance and cardiac output to baseline values.[31]

Auler et al.[32] who also assessed maternal hemodynamic changes through minimally invasive monitoring of pregnant women undergoing cesarean section under spinal anesthesia and who received metaraminol to control blood pressure, reported a decrease in systolic volume, offset by increased heart rate, but did not observe significant changes in mean arterial pressure and systemic vascular resistance, and speculated that these results occurred because of more rapid and effective correction of mean arterial pressure by the administration of metaraminol.

Although the hemodynamic control was satisfactory with the three vasopressors, a limitation of the study was that the doses administered were extracted from other studies without equipotent ratio, as there are no studies in literature comparing equipotent doses of vasopressors studied. Still, measurement of maternal pressure was used at intervals of one minute, which besides being uncomfortable for the mother may hinder blood pressure measurement, as sometimes it takes more than a minute to measure blood pressure. Cooper et al.[33] in a study evaluating the control of systolic blood pressure with continuous infusion of phenylephrine for elective cesarean sections, showed that infusion rate adjustments with measurement of maternal blood pressure at 2-min intervals are effective for controlling hypotension and nausea and vomiting incidence.

Regarding fetal prognosis, although the chosen vasopressor doses were suitable for maternal hypotension control in the three groups, the newborns of mothers who received ephedrine showed pH values and base excess lower than the other groups.

Fetal acidosis, assessed through umbilical cord blood pH and base excess, is considered a marker of neonatal prognosis. Although some studies report that only severely acidotic fetuses (pH < 7), after an acute intrapartum event, have a higher risk of mortality and morbidity (hypoxic-ischemic encephalopathy, intraventricular hemorrhage, cerebral palsy), a recent meta-analysis showed that when acidosis was defined as pH < 7.20, a four- and two-fold increase occurred in mortality and morbidity, respectively.[34]

According to Magalhães et al.[18] who used the value of 7.20 to characterize fetal acidosis in elective cesarean sections, in which patients received ephedrine or phenylephrine, there were no cases of fetal acidosis. In this work, fetal acidosis was observed in only three newborns of Group E; however, *p*-value was not significant. Despite the occurrence of fetal acidosis in the three cases mentioned above, there were no clinical consequences in any of them, as all newborn had Apgar scores >8 at the 5th minute and did not require resuscitation maneuvers or transfer to the intensive care unit.

Base excess comparison showed no differences between the M and P groups compared to Group E. The values were lower in the latter. However, despite the differences, these values are within normal limits.[35]

From fetal standpoint, no doubt that phenylephrine and metaraminol are associated with higher values of pH and base excess in umbilical cord blood that were higher than those of ephedrine,[2,15,36] which were confirmed in the present study, reason for which the use of ephedrine for hypotension management in obstetric anesthesia is being questioned as a first-choice vasopressor. Thus, one can predict that the administration of high doses of ephedrine, especially in situations of fetal compromise, should be avoided.[15,37]

Fetal changes caused by ephedrine are related to the fact that it rapidly crosses the uteroplacental barrier, stimulates fetal β-adrenergic receptors, and increases fetal metabolic demand. This can be seen by the increase in lactate, glucose, and catecholamines in umbilical cord blood. In the present study, when the mother received phenylephrine, the lactate values in umbilical cord blood were higher than when the mother received ephedrine and metaraminol. However, regarding glycemia, there were no differences between the three groups, in contrast to the results of Ngan Kee et al.[38]

Fetal metabolic response to vasopressor administered in the mother may depend on the fetal β2-adrenoceptor genotype and further complicate the understanding of the relationship between ephedrine administration and lower pH values. Fetal homozygosity for the ADRB2 gene *p.Arg*16 seems to be more resistant to ephedrine-induced acidemia.[39]

On the other hand, a recent study by Bhardwaj et al.[21] showed no differences between the M, E, and P groups regarding pH of umbilical cord blood and base excess values. This difference probably occurred due to the use of smaller doses of ephedrine.

None of the infants in this study had low Apgar score (less than 7) at the 5th minute. It is known that episodes of hypotension during elective cesarean sections are not a cause of clinically significant fetal changes when treated promptly. In a systematic review by Veeser et al.[19], which included 20 studies with a total of 1069 newborns, it was demonstrated that only one newborn had Apgar score less than 7 in the 5th minute.

In order to minimize the occurrence of fetal acidosis, in addition to the approaches already described here, it is known that the time elapsed between the skin incision and birth, and between uterine incision and birth, is directly related to fetal acidosis. This has encouraged surgeons to reduce the duration of surgeries.[40]

In this study, the duration of surgery in all study groups was lower than that reported in the literature, which may be a reasonable explanation for the favorable outcome of newborns, even in cases where fetal acidosis occurred. A study by Maayan-Metzger et al. showed that infants born to women who had an interval of more than two minutes between uterotomia and birth had a higher incidence of feeding problems and prolonged hospitalization.[41]

Currently, vasopressors with predominantly alpha-agonist effects are considered drugs of choice for preventing maternal hypotension, nausea and vomiting during spinal anesthesia for elective cesarean sections. Although its use is associated with reduced heart rate and cardiac output, it is clinically insignificant in low-risk pregnancies and elective cesarean sections.

Our results show that in elective cesarean sections under spinal anesthesia hypotension can be controlled with any of the vasopressors studied, as there were no clinically significant maternal or fetal changes, which shows that strict control of blood pressure is an important condition for maternal and fetal well-being. However, metaraminol and phenylephrine had advantages over ephedrine, especially in the incidence of nausea and vomiting. Repercussions of vasopressor therapy in emergency cesarean sections and high risk pregnancies are still a matter of much discussion.

Conflicts of interest

The authors declare no conflicts of interest.

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