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Comparison of the treatment effects of methoxamine and combining methoxamine with atropine infusion to maintain blood pressure during spinal anesthesia for cesarean delivery: a double blind randomized trial

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Abstract. – OBJECTIVE: Hypotension is a common complication of spinal anesthesia for cesarean delivery. Atropine is a vagus nerve blocker that can antagonize vagus excitation to mitigate the reflex bradycardia. We aimed to assess the effect of methoxamine-atropine therapy in treating spinal anesthesia hypotension for cesarean section.

PATIENTS AND METHODS: This is a double-blind randomized controlled study. Women under spinal anesthesia for elective caesarean delivery received boluses of methoxamine 2 mg alone (Group M, n = 40), or with addition of atropine 0.1 mg (Group MA1, n = 40), atropine 0.2 mg (Group MA2, n = 40) or atropine 0.3 mg (Group MA3, n = 40) upon a maternal systolic pressure ≤ 80% of baseline. The primary endpoint was systolic blood pressure and the secondary endpoints were maternal heart rates, instant neonatal heart rates, umbilical artery pH and umbilical artery base excess.

RESULTS: Changes in systolic blood pressure were similar among the four groups. The incidences of bradycardia in groups M and MA1 were significantly higher than those in group MA2 and MA3. The fetal heart rates after delivery in groups MA2 and MA3 were higher than those in group M and MA1 but within the normal range. The acid-base status had no difference in the four groups.

CONCLUSIONS: Methoxamine-atropine combination has a similar efficacy to methoxamine alone but has an increased hemodynamic stability and a less adverse effect occurrence.

Key Words:
Spinal anesthesia, Cesarean delivery, Hypotension, Methoxamine, Atropine, Hemodynamic control.

Introduction

Hypotension is a common complication of spinal anesthesia for cesarean delivery and usually causes adverse effects to both maternal and fetal health. Severe hypotension may cause maternal nausea, vomiting and even circulatory arrest. Hypotension also resulted in uteroplacental blood flow decline, leading to fetal hypoxia, acidosis, and even central nervous system damage[1]. Hypotension is generally defined as a systolic blood pressure decreased by 20%, initially because of the decline in sympathetic tone, and then may be exacerbated by vena cava compression. At present, the treatment of hypotension during spinal anesthesia for cesarean delivery mainly relies on vasopressor drugs. For years, ephedrine has been considered the preferred vasopressor drug in treatment of hypotension during spinal anesthesia for cesarean delivery[1-4]. However, some studies[5] found that ephedrine could easily pass through the placental barrier, decrease fetal pH through stimulating fetal metabolism, and even lead to the metabolic acidosis. In contrast, other studies have shown that α-receptor agonists are safe and effective in the treatment of hypotension during spinal anesthesia for cesarean delivery[6], which could reduce maternal nausea, vomiting and not cause fetal acidosis[7]. However, the reflex bradycardia caused by α-receptor agonist was one of the major obstacles to its clinical application.

Though the application of vasopressors in the treatment of hypotension during spinal anesthe-

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sia has been recognized, there is still no agreement on the way, time and whether it should be used alone or in combination. Therefore, we are continually searching for better therapeutic options to treat spinal induced hypotension during cesarean delivery.

In this study, we attempt to take advantage of the pharmacological effects of atropine antagonizing heart vagus nerve excitation through combining methoxamine with different doses of atropine in the treatment of maternal hypotension to mitigate the incidence and severity of reflex bradycardia caused by methoxamine.

Patients and Methods

This study was approved by the Ethics Committee of Renmin Hospital, Hubei University of Medicine and registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn, registration number: ChiCTR-IOR-1500617). Written consent was obtained from each patient.

Patients

A total of 198 ASAI-II women with singleton pregnancies scheduled for elective caesarean delivery under spinal anesthesia were recruited in this randomized and double-blind study. Patients were excluded if they had pre-existing or pregnancy-induced hypertension, diabetes mellitus, known cardiovascular or cerebrovascular disease, fetal abnormality, or contraindication to spinal anesthesia. The patients that did not develop hypotension (systolic blood pressure ≤80% of baseline) and did not require vasopressors were excluded from the study.

Spinal Anesthesia

During operation, standard monitoring with non-invasive arterial pressure, electrocardiography and pulse oximetry was established. Women rested undisturbed in the supine position with left uterine displacement for 5 min. After maternal quiet, the maternal blood pressure and heart rate were measured four times successively and the average values of those four successive measured blood pressure and heart rate were used as the basis value. Then, an 18-gauge intravenous cannula was sited and each patient received a 10-mL/kg i.v. infusion of hydroxyethyl starch 200/0.5 and sodium chloride injection over 30 min before spinal anesthesia. After prehydration, the fluid infusion was continued at the minimal rate to maintain vein patency, regardless of any maternal hemodynamic changes. With the patient in the left lateral position, 2 ml of 0.5% hyperbaric bupivacaine was injected intrathecally at L3-4 via a 25-gauge spinal needle. Patients were then immediately turned supine and positioned with left uterine displacement. Heart rate and blood pressure were monitored at 1-min intervals since the induction of spinal anesthesia until delivery, and recorded before anesthesia (T0), at the first hypotension after anesthesia (T1), and 1 (T2), 3 (T3), 5 (T4), 10 (T5) and 20 (T6) minutes after drug administration. Oxygen was delivered at 4 L/min via a facemask until delivery. The dermatomal level of anesthesia, assessed by loss of pin prick discrimination, was recorded 5 and 15 min after induction of spinal anesthesia. The tested sensitivity block for cold to T6 dermatome was considered adequate for surgery.

Intervention

Women were randomly assigned to receive one of four vasopressor solutions whenever maternal systolic blood pressure decreased to 80% of the baseline or less. Group M received a 2-mL bolus of methoxamine (containing methoxamine 2 mg), group MA1 received a 2-mL bolus of methoxamine + atropine (containing methoxamine 2mg and atropine 0.1 mg), group MA2 received a 2-mL bolus of methoxamine + atropine (containing methoxamine 2 mg and atropine 0.2 mg), and group MA3 received a 2-mL bolus of methoxamine + atropine (containing methoxamine 2 mg and atropine 0.3 mg). Additional boluses were administered if the systolic blood pressure remained at or below 80% of the baseline. The methoxamine and atropine doses used in this study were empirically selected based on our clinical experience. Women were randomized by computer-generated number allocation. The study drugs were prepared in identical 10-ml syringes by an anesthesiologist not involved with data collection. Atropine was administered in 0.3 mg whenever bradycardia (heart rate <60 beats/min) was associated with a systolic pressure less than the baseline or if the heart rate was < 50 beats/min irrespective of arterial pressure. The incidence of maternal bradycardia (heart rate < 50 beats/min) and reactive hypertension (an increase in systolic blood pressure above baseline by 20%) were recorded. The number of vasopressor required, requirement for atropine and its relation to vasopressor administration, were noted. The time of spinal anesthesia induction, uter-

ine incision and delivery were recorded. The incidence of maternal nausea and vomiting was recorded and the baby's heart rates after delivery were observed. Arterial blood samples were obtained from a double-clamped segment of umbilical cord and analyzed within 10 min of attainment. Apgar scores at 1, 5 and 10 min were determined by the attending pediatrician who was unaware of group assignment. Time of onset of sustained rhythmic respiration was noted. To allow for potential drop-outs, a total of 40 patients per group with systolic pressure ≤ 80% of baseline were recruited. The outcome measures included the incidence of maternal and neonatal bradycardia, tachycardia, reactive hypertension, nausea and vomiting, umbilical artery pH, and Apgar scores.

Endpoints

The primary endpoint was systolic blood pressure and the secondary endpoints were maternal heart rates, instant neonatal heart rates, umbilical artery pH and umbilical artery base excess.

Statistical Analysis

Results are expressed as means ± SD or number (%) unless stated otherwise. Differences among groups were compared using one-way analysis of variance and the Bonferroni post-test, the rates were compared using chi-square test. The power was 80% and a result was considered to be significant if the probability of a type-one error was less than 0.05.

Results

A total 198 women, were enrolled in the study; 38 did not develop hypotension (systolic blood pressure ≤80% of baseline) and did not require vasopressors. A total of 160 women who developed hypotension participated in the study (Figure 1). There were no significant differences in physical characteristics and baseline hemodynamics data. Dermatomal sensory levels are presented in Table I. The mean induction-to-delivery or uterine-to-delivery intervals in the four groups were not significantly different.

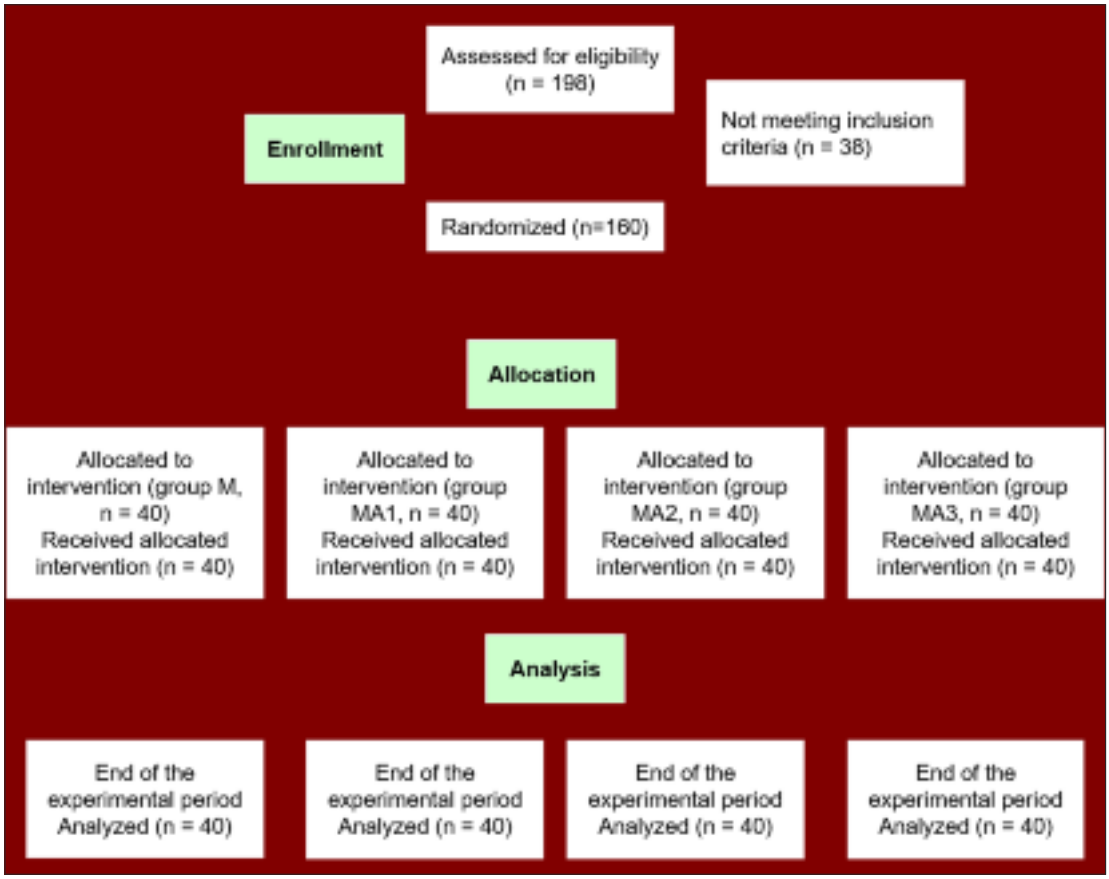

Figure 1. Flow diagram of the trial.

Table I. Patient characteristics, upper level of sensory anesthesia, and surgical times.

	Group M (n = 40)	Group MA1 (n = 40)	Group MA2 (n = 40)	Group MA3 (n = 40)
Age (year)	25.67 ± 2.77	25.45 ± 2.90	25.20 ± 2.78	25.32 ± 2.72
Weight (kg)	65 ± 4.80	64.8 ± 5.05	65.55 ± 4.27	65.15 ± 4.44
Height (cm)	159.97 ± 4.19	159.67 ± 4.34	159.45 ± 4.19	159.9 ± 4.23
Block height at 5 min (T)	5.52 ± 0.87	5.3± 0.68	5.37 ± 0.74	5.32 ± 0.69
Block height at 15 min (T)	4.37 ± 0.70	4.42 ± 0.54	4.4 ± 0.74	4.37 ± 0.66
Induction-delivery time (min)	8.27 ± 1.93	8.7 ± 1.92	8.6 ± 1.99	8.77 ± 1.81
Uterine incision-delivery time (s)	51 ± 11	52 ± 10	49 ± 9	51 ± 9

Data are expressed as mean ± SD. There were no significant differences among the four groups.

Table II. Drugs consumption, hemodynamic changes and maternal symptoms.

	Group M (n = 40)	Group MA1 (n = 40)	Group MA2 (n = 40)	Group MA3 (n = 40)
Total number of required vasopressor blouses	1.32 ± 0.52	1.30 ± 0.51	1.27 ± 0.50	1.25 ± 0.43
Maximum systolic (mmHg)	110 ± 8	111 ± 10	115 ± 11*,#	116 ± 10*,#
Minimum systolic (mmHg)	101 ± 8	102 ± 8	106 ± 10 *,#	106 ± 10*,#
Heart rate < 50 beats/min	11 (27%)	9 (22.5%)	0 (0%)*,#	0 (0%)*,#
Heart rate < 60 beats/min	19 (47.5%)	17 (42.5%)	6 (15%)*,#	4 (10%)*,#
Heart rate > 100 beats/min	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea or vomiting	4 (10%)	2 (5%)	3 (7.5%)	2 (5%)

Data are expressed as number (%) or mean ± SD. *$p < 0.05$ *vs.* group M. #$p < 0.05$ *vs.* group MA1.

Maternal hemodynamic data are summarized in Table II. The time-course changes of systolic blood pressure and heart rate are shown in Figures 2 and 3, respectively. As the time from induction to delivery varied among patients, hemodynamic changes were compared up to 20 min after drug administration, by which time all women had delivered. At T2 and T3, the systolic blood pressures in groups MA2 and MA3 were higher than in group M and MA1 and had no difference in other time points. All groups have no reactive hypertension. The extent of the

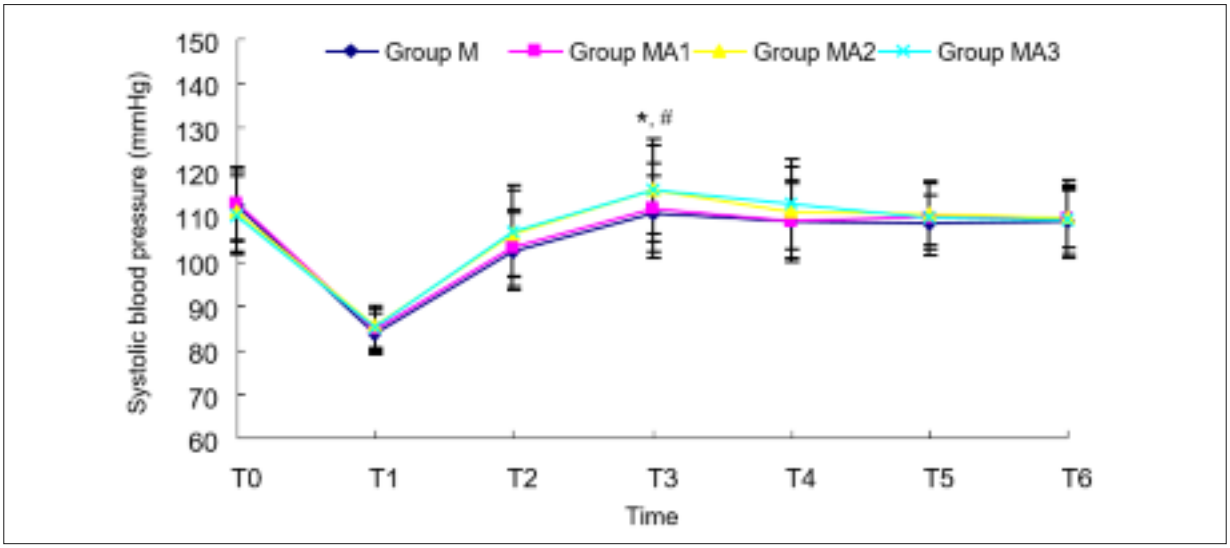

Figure 2. The systolic blood pressure. Data are shown as mean ± SD. *$p < 0.05$ *vs.* group M. #$p < 0.05$ *vs.* group MA1.

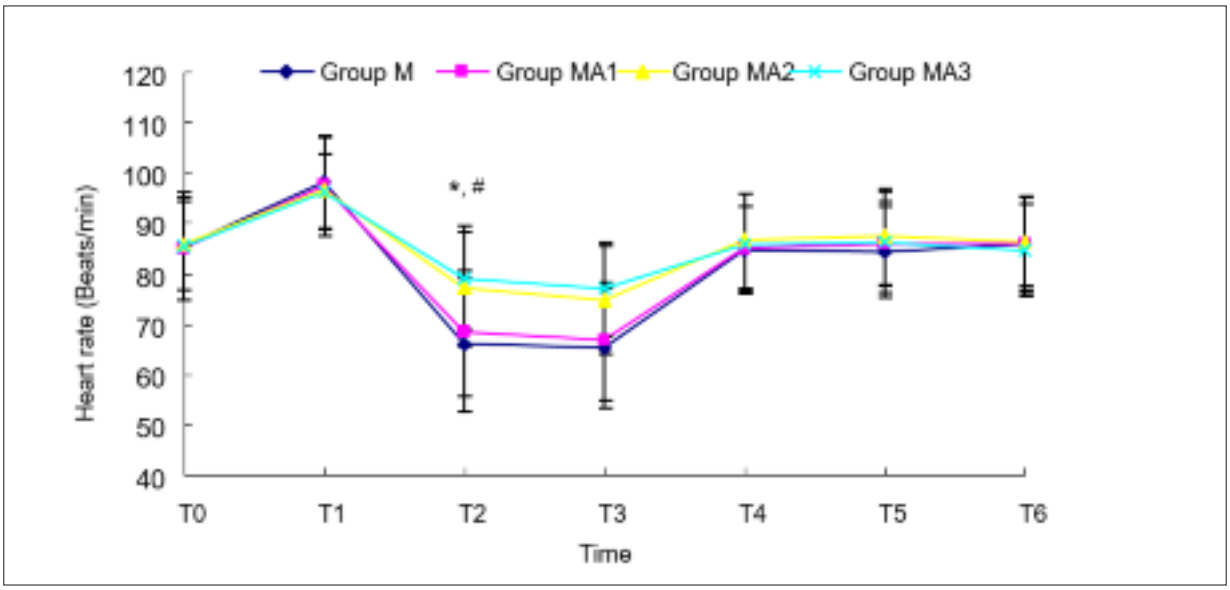

Figure 3. The heart rate. Data are shown as mean ± SD. *$p < 0.05$ vs. group M. #$p < 0.05$ vs. group MA1.

heart rate declining in group M and MA1 was significantly greater than in group MA2 and MA3 at T2 and T3 time points respectively (p <0.05), but showed no difference in other time points. Following methoxamine administration, all groups had different levels of decreased heart rates. However, the incidence of bradycardia had appeared 47.5% in group M and 42.5% in group MA1, compared with 15% in group MA2 and 10% in group MA3, respectively. Nausea and vomiting in four groups had no differences.

Neonatal data are presented in Table III. Instant neonatal heart rates after delivery in group M and MA1 were slower than in MA2 and MA3, but at 5 min after delivery there were no significant difference among the four groups

Discussion

The incidence of maternal hypotension was high and most trials reported that the incidence were over 50%[8-10]. Despite the infusion of colloid solution and the adjustment of body position that could be used to prevent hypotension during spinal anesthesia for cesarean section, there is still a considerable part of hypotension that requires vasopressor drugs. Although ephedrine almost did not affect the uteroplacental blood flow and could effectively restore hemodynamic parameters to the previous level[11], compared to α1-adrenergic receptor agonists, ephedrine could cause decreased umbilical artery blood pH value[7,12,13]. In addition, ephedrine also could cause increased cardiac load due to maternal tachycardia.

Table III. Neonatal data.

	Group M (n = 40)	Group MA1 (n = 40)	Group MA2 (n = 40)	Group MA3 (n = 40)
Heart rate after delivery	116 ± 6	118 ± 6	122 ± 7*,#	125 ± 4*,#
Heart rate at 5 min after delivery	126 ± 5	125 ± 5	125 ± 4	126 ± 5
Apgar scores at 1 min	8.25 ± 0.71	8.45 ± 0.60	8.60 ± 0.50	8.60 ± 0.50
Apgar scores at 5 min	9.90 ± 0.30	9.87 ± 0.33	9.92 ± 0.26	9.90 ± 0.30
Umbilical arterial pH	7.35 ± 0.28	7.35 ± 0.29	7.35 ± 0.26	7.35 ± 0.29
Umbilical arterial PO_2 (mmHg)	18.2 ± 0.66	18.27 ± 0.61	18.18 ± 0.56	18.18 ± 0.65
Umbilical arterial PCO_2 (mmHg)	42.54 ± 0.85	42.53 ± 0.85	42.46 ± 0.89	42.58 ± 0.88
Umbilical arterial Base excess (mEq/L)	-1.53 ± 0.07	-1.54 ± 0.07	-1.54 ± 0.07	-1.53 ± 0.07

Values are mean ± SD. *$p < 0.05$ *vs.* group M. #$p < 0.05$ *vs.* group MA1.

For a long time, due to the concern of uteroplacental vasoconstriction, α1-adrenergic receptor agonists have had limited application in obstetrics. However, a recent study[7] found that the normal dose of pure α1-adrenergic receptor agonist did not cause clinically significant reduction of placental blood flow or perfusion. After the sympathetic blockade by regional anesthesia, blood was shunted between the mesenteric vascular bed and the uteroplacental vasculature. The vasoconstriction action of α1-adrenergic receptor agonists has greater selectivity in the mesenteric vascular bed than in the uteroplacental vasculature[7]. The contraction of the mesenteric vascular bed would increase venous return, and the increased cardiac output would increase uterine perfusion pressure[14]. Comparative studies[15-19] suggested that the application of a α1-adrenergic receptor agonist was associated with better fetal acid-base status. The disadvantage of pure α1-adrenergic receptor agonists is mainly the reflex bradycardia, and that the maternal cardiac output may be reduced with the bradycardia. Although combinations of phenylephrine and ephedrine would be beneficial to a more stable heart rate, it has also seen that as the proportion of phenylephrine decreased and the proportion of ephedrine increased, hemodynamic control was reduced, the incidence of maternal nausea and vomiting was increased and fetal acid-base status was less favorable[15-20]. Thus, seeking some better methods of medication is still necessary. As one of the α1-adrenergic receptor agonists, methoxamine is similar to phenylephrine in the pharmacological effects and traits, but currently its clinical application study was rare and controversial. Mintzer et al[21] found methoxamine used *in vitro* in a human placental model had no effect on the fetal arterial perfusion pressure. However, in both animal and human obstetric anesthesia, the use of methoxamine was associated with significant, albeit transient increase in uteroplacental resistance and flow[22]. Therefore, we would need to study further the application of methoxamine in obstetrics.

In our study, the systolic blood pressure in four groups could rebound to near normal levels 1-3 minute after administration, but the heart rates dropped to lower than 60 beats/min that required atropine to correct the heart rates in the group M and MA1 were significantly higher than that in the group MA2 and MA3. This shows that combining methoxamine with certain dose of atropine had a more obvious superiority in maternal hemodynamic stability. Although the duration is short and 5 minutes after administration, the heart rate basically recovered to the normal level, the cardiac output may decrease with the significant heart rate drop. In addition, the high level of spinal anesthesia would block the cardiac sympathetic nerve and cause the heart rate to decrease and the force of contraction to disappear. Therefore, the simple increasing vasoconstriction could not effectively compensate the cardiac output. Atropine can block the vagus nerve and drive up the heart rate. Combining methoxamine with atropine in spinal anesthesia for cesarean delivery could take advantage of the effect of atropine antagonizing vagus nerve excitation to mitigate the incidence and severity of methoxamine reflex bradycardia and would be conducive to fetal well-being. Particularly, the onset time of atropine is 0.5 to 1 minutes while methoxamine is 1 to 3 minutes. Our previous study had found that the drop of the heart rate emerged prior to the significant ascend of blood pressure caused by methoxamine. If the two drugs are used simultaneously, atropine would preventively block the reflex decreasing of the heart rate, so that the hemodynamics may be more stable.

We also compared the heart rates of newborns in each group and the value of umbilical artery acid-base balance and neonatal Apgar score. The results showed that newborns' heart rates in the group M and MA1 were slower than that in the group MA2 and MA3, suggesting a certain dose of atropine could prevent the heart rates of fetal or neonatal drop caused by methoxamine. However, the neonatal umbilical arterial blood pH in the four groups showed no significant difference, suggesting that from the point of view of fetal oxygen supply, the combination of methoxamine with atropine is same as methoxamine.

Conclusions

Overall, we found that combining methoxamine with atropine and methoxamine alone in the treatment of hypotension during spinal anesthesia for cesarean delivery had a similar efficacy, but in comparison with methoxamine alone, combining methoxamine with a certain dose of atropine had more stable the maternal and neonatal hemodynamics and less adverse effects. Further study is still needed to find out a better proportion between methoxamine and atropine.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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