Original Article

Prevention of post-spinal hypotension using crystalloid, colloid and ephedrine with three different combinations: A double blind randomized study

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Abstract

Background: The benefit of prophylactic combination therapy using crystalloid and colloid preload with ephedrine has not been cleared to prevent maternal hypotension after spinal anesthesia at cesarean delivery. This study evaluated the efficacy of three combinational methods to prevent hypotension following spinal anesthesia.

Materials and Methods: In this prospective double blind trial, 150 candidates of elective cesarean delivery under spinal anesthesia were randomly allocated to three treatment groups; 1---Ringer's Lactate (RL) solution (15 ml/kg) plus Hemaxel (7 ml/kg) preload, 2---RL solution (15 ml/kg) preload plus ephedrine (15 mg, IV, bolus), 3---Hemaxel (7 ml/kg) preload plus ephedrine (15 mg, IV, bolus). Maternal hemodynamic changes during 60 min after spinal injection, nausea/vomiting, and neonatal condition were compared among the groups.

Results: The cumulative incidence of hypotension was 44%, 40%, and 46% in groups 1 to 3, respectively. There were not significant differences in supplementary ephedrine requirement among groups which received or among groups which did not receive prophylactic ephedrine. Groups were not different in the incidence of hypertension and nausea or vomiting. There were no significant differences among groups in Apgar scores at 1 or 5 min and umbilical artery PH.

Conclusion: Combination of preventive methods decreased the occurrence of hypotension following spinal anesthesia to an acceptable level. Overall, the most effective method was a combination of crystalloid preload with ephedrine.

Key words: Cesarean delivery, hypotension, spinal anesthesia

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INTRODUCTION

Hypotension during spinal anesthesia for cesarean section is the most common complication.[1,2] In severe cases, it can have detrimental effects on both mother and neonate.[3,4] Various preventive methods are currently used to prevent or minimize hypotension including left uterine displacement, prophylactic

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ephedrine, crystalloids or colloid preloading, and utilizing compression stocking onto the lower extremities.[4,5] According to another meta-analysis by Lee *et al.*,[6] the efficacy of prophylactic ephedrine for the prevention of hypotension is poor at smaller doses. Mercier *et al.*[7] found that the association of vasopressor(s) with a rapid crystalloid loading at the time of spinal injection represents the interesting strategy.

Gunusen *et al.*[8] showed the hypothesis that ephedrine infusion with crystalloid loading at spinal anesthesia would reduce hypotension and alter neonatal outcome compared with fluid preloading. The frequency of moderate or severe hypotension was lower in the ephedrine group than in the crystalloid or colloid preload group.

Systematic reviews recommended future researches to be directed toward assessing a combination of the beneficial interventions, but few reports are available on the efficacy of combinational methods[9-13] and more studies are needed in this regard.

In previous study, the authors co-administered vasopressor(s) as infusions with crystalloid or colloid, but in the present study we administered ephedrine as a single bolus dose. So, our study was performed to compare the efficacy of three different combinational methods using crystalloid, colloid, and ephedrine on prevention of hypotension following spinal anesthesia in parturients undergoing elective cesarean delivery.

MATERIALS AND METHODS

This randomized double blind clinical trial was conducted in two university hospitals from summer 2005 to spring 2009 (Project No. 83036, IRCT number: IRCT201107062405N7). After obtaining approval from the Ethics Committee of Isfahan University of Medical Sciences, we recruited singleton parturients with ASA physical status I or II who were scheduled for elective cesarean delivery under spinal anesthesia. Written informed consent was obtained from all parturients after full explanations of the goals and procedures of the study. Parturients without pre-existing systemic disease or pregnancy-induced hypertension, preterm labor or signs of onset of labor, known fetal abnormalities, or without contraindications to spinal anesthesia were included in the study. Exclusion criteria were any significant history of maternal medical or obstetric illness and any fetal compromise within the current pregnancy. The patient and all staff involved in the study were blind to the protocol used. Power analysis showed that a sample size of 50 parturients per group would have 80% power at the 5% significance level to detect a difference of 30% in the incidence of hypotension among the groups. The sampling method was consecutive and eligible parturients were randomized into the following three groups using computer-generated table of random numbers:

Group 1: Prior to spinal injection, Ringer's Lactate (RL) solution (15 ml/kg) plus colloid solution (Hemaxel) (7 ml/kg) was infused in 30 min.

Group 2: RL solution (15 ml/kg) was infused in 30 min before spinal injection and ephedrine (15 mg, IV, bolus)[1,6,7] was infused immediately after spinal injection.

Group 3: Colloid solution (Hemaxel) (7 ml/kg) was infused in 30 min prior to spinal injection, and ephedrine (15 mg, IV, bolus)[1,6,7] was infused immediately after spinal injection.

Spinal anesthesia was performed in all cases in sitting position in L3-L4 space. The anesthesia was done with plain Marcaine (0.5%, 2.7 ml) and dextrose solution (50%, 0.3 ml) using a 25-gauge spinal needle (pencil point, Pajunk, Germany). Then, the parturient was set to the left lateral position and applied 5 l/min O_2 through face mask. After establishment of T4 block with a pin prick test and confirmation of anesthesia, cesarean section was done. Oxytocin (20 IU in 1000 ml RL solution) was infused during 1 h after delivery in order to retain the normal uteral tone.

From entering into the operating room to discharging from the recovery room, all cases were monitored by non-invasive blood pressure monitoring, pulse oximetry, electrocardiography, and bleeding and urine volumes. If hypotension occurred, as defined by systolic blood pressure (SBP) fell to below 90 mmHg or greater than 20% below baseline,[2] rescue boluses of ephedrine (5 mg) were given by an anesthesiologist who was blinded to the study each 5 min until hypotension resolves. The severity of nausea, as reported by parturient, was assessed by anesthetist nurse who was unaware of the study on operation bed and also in recovery room by 100 mm Visual Analog Scale (VAS) and defined as severe if exceeded 40 mm. In case of vomiting or severe nausea, during operation atropine (0.5 mg, IV) and in recovery room metoclopramide (10 mg, IV) were administered. SBP, diastolic blood pressure (DBP), and heart rate (HR) of parturients were recorded at the admission to operating room (baseline), immediately after anesthesia (displayed as time 0), and 3, 5, 15, 20, 25, 30, 35, and 60 min after spinal injection. Time interval between the spinal injection and the occurrence of hypotension, prolongation of hypotension, and the amount of rescue ephedrine administered were recorded. Also, the time interval from the intrathecal injection, skin and

uterine incision to the delivery and maternal blood loss were recorded. Following the delivery, Apgar scores at min 1 and 5 and umbilical artery PH after delivery were determined.

The primary outcome of the study was defined as the incidence of hypotension. Secondary outcomes included changes in blood pressure and HR, the incidence of bradycardia (HR < 50 bpm), hypertension (SBP > 140 mm Hg or > 20% baseline), spinal injection to hypotension interval, amount of rescue ephedrine administered, nausea, vomiting, Apgar scores at 1 and 5 min. The incidence of hypotension was analyzed using Kaplan-Meier survival analysis and a comparison between groups was performed with the log-rank test. Survival time was defined as the time from spinal injection to the first episode of hypotension. General linear measurement (GLM) repeated measures with Tukey procedure for *post hoc* pairwise comparisons was used to test sequential measurements of SBP and HR. ANOVA, with Tukey for *post hoc* pairwise comparisons, was used for comparing quantitative variables and chi-square and Kruskal-Wallis tests were used for comparing qualitative and ordinal variables among the groups. Data were analyzed using SPSS software for windows (version 16) and values of $P < 0.05$ were considered statistically significant.

RESULTS

All parturients completed the study [Figure 1]. The three groups of the study were similar in age, weight, gravity, and SBP but not DBP prior to the intervention [Table 1]. Also, the time interval from the intrathecal injection, skin, and uterine incision to the delivery and maternal blood loss are shown in Table 1.

Changes in SBP and HR during 60 min after the spinal injection are shown in Figures 2 and 3, respectively. Analysis showed that changes in SBP were significantly influenced by time ($P < 0.001$) and the combined effect of time and the intervention type (time × group; $P = 0.043$). *Post hoc* tests showed that SBP was significantly greater over time in group 2 compared with other groups, but there were no differences among other groups. In regard to HR, analysis showed that changes in HR were significantly influenced by time ($P < 0.001$) and the combined effect of time and intervention type (time × group; $P < 0.001$). *Post hoc* tests showed that there were no significant differences among three groups considering HR changes.

Primary and secondary maternal outcome variables are summarized in Table 2. There was a slight

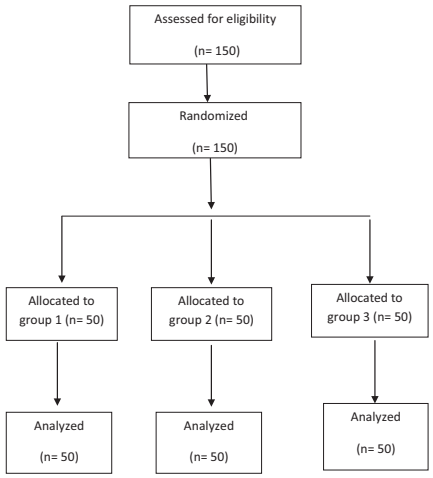

Figure 1: Flow diagram of endrolled study patients

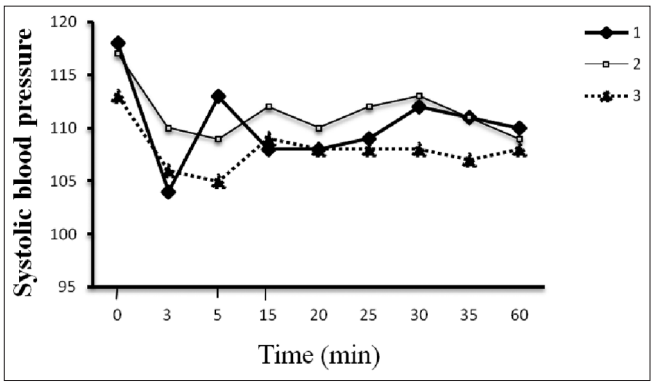

Figure 2: Blood Pressure changes during 60 min after spinal injection. Group 1: crystalloid + colloid. Group 2: crystalloid + ephedrine. Group 3: colloid + ephedrine. P < 0.001

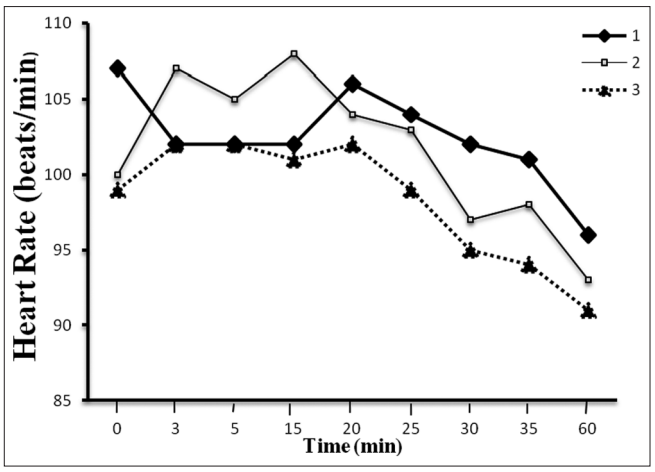

Figure 3: Heart rate changes during 60 minutes after spinal injection. Group 1: crystalloid + colloid. Group 2: crystalloid + ephedrine. Group 3: colloid + ephedrine. P < 0.05

significant difference among groups in cumulative incidence of hypotension ($P = 0.065$). There were not significant differences among groups in the incidence of hypertension. The SBP was greater in group 2

Table 1: Baseline and surgical characteristics among the three groups

	Crystalloid + Colloid	Crystalloid + Ephedrine	Colloid + Ephedrine	*P* value
Age (yr)	26.5 ± 5.1	26.0 ± 4.2	27.0 ± 6.0	0.836*
Weight (kg)	74.2 ±12.9)	76.4 ± 10.1	74.5 ± 10.9	0.163*
Gravity	1 (1-5)	2 (1-7)	2 (1-9)	0.224**
SBP (mmHg)	116.6 ± 8.4	119.1±11.2	119.4 ± 10.0	0.163*
DBP (mmHg)	78.7 ± 4.0	78.2 ± 10.0	79.1 ± 7.3	0.15*
Pulse rate (bpm)	100.0 ± 8.2	98.9 ± 10.0	99.3 ± 11.1	0.198*
Upper sensory level	T3 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)	>0.05**
Surgery time (min)	43	45	44	>0.05*
Time from spinal till delivery (min)	9	8. 5	9	> 0.05*
Skin incision to delivery (min)	6	5. 5	6	>0.05*
Uterine incision to delivery (second)	33	35	32	> 0.05*
Duration of pregnancy (week)	36. 5	37	37. 5	>0.05*
Blood loss (ml)	800	780	790	>0.05*
Total fluid (ml) during anesthesia	720	705	710	>0.05*

SBP, systolic blood pressure; DBP, diastolic blood pressure, Data are shown as mean (SD) or median (range) * ANOVA ** Kruskal-Wallis test

Table 2: Comparison of primary and secondary maternal outcome and apgar scores variables among the three groups

	Crystalloid + Colloid	Crystalloid + Ephedrine	Colloid + Ephedrine	*P* value
Incidence of hypotension	22 (44%)	20 (40%)	23 (46%)	0.15*
Incidence of hypertension	3 (6%)	6 (12%)	3 (6%)	0.43*
Bradycardia	0	0	0	0.00*
Interval between anesthesia and hypotension occurrence (min)	7.5 ± 6.2	17.5 ± 18.8	14.4 ± 18.4	0.01**
Supplementary ephedrine requirement (mg)	6.7 ± 2.4	2.5 ± 4.2	2.9 ± 4.4	0.02***
Severity of nausea (VAS)	6.4 (1.8)	6.2 (1.6)	6.0 (2.1)	0.48***
Frequency of nausea	15 (30%)	17 (34%)	20 (40%)	0.26*
Frequency of vomiting	0	2 (4%)	1 (2%)	0.51*
# 1 min Apgar score	8.6 (4-10)	8.7 (7-10)	8.6 (1-10)	0.32*
# 5 min Apgar score	9.9 (9-10)	9.8 (9-10)	9.9 (9-10)	0.15*
Umbilical artery PH	7.36 ± 0.039	7.36 ± 0.04	7.34 ± 0.043	0.09***

Data are shown as mean (SD) or n (percent) # Data are shown as mean (SD) or median (range) * Chi-square test ** Kruskal-Wallis test *** ANOVA

compared with other groups. There were no significant differences among other groups. The interval between spinal injection and the occurrence of hypotension was different among groups ($P = 0.009$). The interval was longer in group 2 compared with other groups, but the differences among other groups were not statistically significant. Regarding supplementary ephedrine requirement, groups 2 and 3 demonstrated lower requirements compared with group 1 ($P < 0.001$). However, there were not significant differences in supplementary ephedrine requirement among groups which received prophylactic ephedrine. Considering the mean severity of nausea and also the frequency of nausea and vomiting, there were no significant differences among the study groups.

Analysis of neonatal data showed that there were no significant differences among groups in Apgar scores at 1 or 5 min and umbilical artery PH.

DISCUSSION

Considering the results of the present study, all three groups experienced some degrees of hypotension following spinal anesthesia. The highest degree of hypotension was observed in groups 1 and 3, 3 min after spinal anesthesia. Also, regarding the decrease in blood pressure 5 and 60 min after anesthesia, the least and the most decrease in blood pressure were observed in group 1 (Crystalloid+Colloid) and group 3 (Colloid+ephedrine), respectively. Generally, the highest decrease in blood pressure was in group 1 [Figure 2]. The interval between administration of anesthesia and the occurrence of hypotension was significantly different between the groups.

Of all parturients, 43% experienced hypotension following spinal anesthesia, of which the lowest cumulative incidence was of group 2 (40%) and the highest prevalence was of group 3 (46%). Although it was not statistically significant, prophylactic treatment of hypotension in all groups lead to reduced prevalence of hypotension occurrence, compared with results reported from other studies. In addition, it was demonstrated that the hypotension recorded in the study occurred 3 min after spinal anesthesia. Three minutes after anesthesia, 23% of all parturients experienced hypotension. Comparing this finding

with results of other studies (44% to 55%) indicates that combination prophylactic treatment was more effective than single treatments.[12,14-19]

However, limited studies were carried out to evaluate the effectiveness of combinational treatments. A study indicated that the prevalence of hypotension after spinal anesthesia was 45% in parturients received Hetastarch solution and Ringer's solution, compared with the 85% of control group which received RL solution.[11] Mercier *et al*.[7] found that crystalloid preload alone is ineffective. Colloid preload is effective but might be better used as a second line treatment. Ephedrine has been the vasopressor of choice for long, but has a weak prophylactic efficacy. Crystalloid loading at the time of spinal injection ("co-/post-loading") enhances the hemodynamic control provided by vasopressors. They concluded that hypotension during spinal anesthesia for caesarean section must be systematically detected, prevented and treated without delay. The association of vasopressor(s) (phenylephrine with or without ephedrine) with a rapid crystalloid loading at the time of spinal injection represents the most interesting strategy nowadays.[7] Gunusen *et al*.[8] tested the hypothesis that ephedrine infusion with crystalloid loading at spinal anesthesia would reduce hypotension and alter neonatal outcome compared with fluid preloading. One hundred and twenty women undergoing elective caesarean delivery were randomly allocated to one of three groups to receive rapid infusion of lactated Ringer's solution (20 ml.kg^{-1}, n=40) or 4% succinylated gelatin solution (500 ml, n=40) before spinal anesthesia or an ephedrine infusion (1.25 mg. minute^{-1} plus lactated Ringer's solution (1000 ml, n=40) after spinal anesthesia. The incidence of hypotension (moderate and severe) and the ephedrine dose used to treat hypotension were compared. Neonatal outcome was assessed using Apgar scores and umbilical venous and arterial blood gas analysis. The frequency of moderate or severe hypotension was lower in the ephedrine group than in the crystalloid or colloid preload group (10% vs 51% and 38%; 5% vs 21 % and 23% respectively, P <0.05). The incidence of nausea was significantly different between the crystalloid preload and ephedrine group. Umbilical blood gas analysis and Apgar scores were similar in all groups. A combination of an ephedrine infusion at 1.25 mg.minute^{-1} with a crystalloid co-load was more effective than fluid preloading with crystalloid or colloid in the prevention of moderate and severe hypotension.[8] Another study demonstrated that adding albumin to RL solution significantly reduced the frequency and severity of hypotension.[10] Moreover, rapid infusion of crystalloid solution plus Phenylephrine (100 μg/min) proved to be more effective in reducing the frequency of hypotension that their slow infusion.[20] Results of another study demonstrated that prophylactic IV administration of ephedrine in combination with Hetastarch and RL solution compared with the combination treatment which used placebo instead of ephedrine in mentioned regimen, decreased the occurrence rate of hypotension from 58% to 25%. Moreover, only 8% of the parturients who received ephedrine experienced severe hypotension (SBP < 90 mmHg), while 42% of the control group experienced severe hypotension.[12]

The frequency of hypotension occurrence in the groups received IV colloid solution or ephedrine plus RL solution was lower than the previous study in which parturients were pre-hydrated with crystalloid solution (RL) (44% and 40% versus 55%[21] and 85%,[22] respectively).

Results of this study showed that combination of intravenous ephedrine and Hemaxel decreased the frequency of hypotension occurrence to 46%, while the prevalence was 66% in the study conducted by Dahlgren *et al*. which used only colloid solution. Moderate blood pressure decrease (decrease in SBP > 20%) occurred in more than 65% of cases. So, combination of ephedrine and colloid reduced the frequency of hypotension occurrence, compared with each single treatment.

Pulse rate changes were different in this study and decrease in pulse rate was low. The highest decrease occurred in group 1 immediately after spinal anesthesia. This indicates the groups received ephedrine, experienced lower decrease in pulse rate or even experienced increase in pulse rate.

Also, this can be justified by the stimulatory effect of prophylactic ephedrine on cardiac beta receptors indirectly, which lead to sinus node stimulation and consequently preventing a decrease in HR following spinal anesthesia. In some cases, this led to an increase in HR.[23] Prophylactic IV administration of ephedrine to prevent bradycardia was approved in previous studies, as well.[21]

The present study indicated that the highest decrease in SBP in all groups occurred 3 min after spinal anesthesia. This can be due to the sensitivity of the autonomous nervous system and sympathetic paralysis below the blockage site before sensory and motor paralysis. Moreover, in pregnant women, the hypotension can also be result of aortic and inferior vena cava compression in supine position after spinal anesthesia.[24]

Another study indicated that prophylactic administration of ephedrine (37.5 mg/IM) decreased the incidence of hypotension occurrence after spinal

anesthesia.[25] Also, administration of higher doses of prophylactic ephedrine reduced the incidence of post-anesthesia hypotension more.[22]

In the present study, the groups were not significantly different, considering the relative frequency of nausea, vomiting, severity of nausea, and the frequency of IV administration of atropine or metoclopramide. This was in agreement with results of previous studies.[21] Relative frequency of post-operation nausea and vomiting was 30% to 46%, which was higher than other studies.[1]

Newborns of the three groups were not different, considering the 1- and 5-min Apgar scores and umbilical artery PH as well.

Our study had several limitations. The lack of a control group precluded determination of an absolute reduction in the incidence of hypotension. For ethical reasons, we could not include a group without prehydration.

In conclusion, employing all mentioned combination treatments reduced the rate of hypotension occurrence following spinal anesthesia in parturients undergoing cesarean delivery lower than the accepted rate in the literatures. The most effective method was administration of crystalloid preload plus ephedrine. The groups were not clinically different, concerning the effect of treatment on newborn health and maternal post-operational nausea and vomiting.

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