Different preloading protocols with constant ephedrine infusion in the prevention of hypotension for elective cesarean section under spinal anesthesia

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Abstract: Ninety ASA I or II parturients were randomly allocated to three groups: group 10RL, 15RL and 20RL to receive 10, 15 and 20 mL/kg of Ringer’s lactate (RL) respectively within 15 minutes (min) before the spinal block. Spinal anesthesia was performed with hyperbaric bupivacaine 12 mg, morphine 100 µg and fentanyl 10 µg. The operating table was tilted to the left and an IV infusion of ephedrine of 3 mg/min was immediately started and continued until umbilical cord clamping in all groups. Hypotension was defined as a drop in mean arterial pressure (MAP) of more than 20% from baseline. This was treated with 10 mg ephedrine IV. The incidence of hypotension was 60%, 36.7% and 13.4% in group 10RL, 15RL and 20RL, respectively (p < 0.05). Additional ephedrine dose was the lowest in group 20RL compared to the other groups (p < 0.05). The total amount of ephedrine was 49.9 ± 13.5, 46.4 ± 13.4 and 38.4 ± 8.5 mg in group 10RL, 15RL and 20RL, respectively (p < 0.05). The incidence of nausea and vomiting in group 20RL was significantly less than in group 10RL (p = 0.02). It was concluded that preloading with 20 ml/kg of RL prior to spinal anesthesia followed by constant ephedrine infusion 3 mg/min after spinal block reduced the incidence of hypotension and of nausea and vomiting and decreased the total amount of ephedrine.

Key words: Anesthesia: obstetric; anesthetic technique: spinal; surgery: cesarean section; complication: hypotension; pharmacology: fluid therapy, ephedrine.

Various methods have been employed to reduce the incidence of hypotension during C/S under spinal anesthesia (1). Different preloading and coloading protocols with crystalloids or colloids and/or prophylactic IM or IV boluses or infusion of vasopressor (ephedrine and phenylephrine) have been recently investigated (2-4). In the earlier studies, the smallest effective dose of ephedrine to reduce the incidence of hypotension during C/S was 30 mg in parturients prehydrated with RL 20 ml/kg (5). On the other hand, it has been reported that a single IV bolus dose of 5 mg ephedrine decreased the incidence and the severity of hypotension in prehydrated parturients who received low dose spinal anesthesia (6.6 mg bupivacaine + 3.3 µg sufentanil) (6). Desalu and Kushimo (7) administered ephedrine by infusion at a rate of 50 mL/min (1.5 mg/min) in 1 liter of 0.9% saline after completion of spinal block. They observed less hypotension in the parturients who received ephedrine infusion in 1 liter of 0.9% saline compared to the parturients prehydrated only with saline (7). However, none of these maneuvers completely eliminated the spinal anesthesia induced hypotension. To date there are no studies examining the optimal preloading volume with a fixed ephedrine infusion rate during C/S under spinal anesthesia. Therefore, we investigated different preloading protocols (10, 15 and 20 mL/kg) of RL solution administered before spinal block with constant ephedrine infusion 3 mg/min after spinal block in order to prevent hypotension during spinal anesthesia and to reduce the ephedrine requirement during elective C/S.

Materials and Methods

After approval of IRB (Gazi University Faculty of Medicine) and obtaining written informed consent, 90 ASA I or II parturients scheduled for C/S under spinal anesthesia were enrolled. All parturients were fasted overnight and received aspiration of stomach and received low dose spinal anesthesia (6.6 mg bupivacaine + 3.3 µg sufentanil) (6). Desalu and Kushimo (7) administered ephedrine by infusion at a rate of 50 mL/min (1.5 mg/min) in 1 liter of 0.9% saline after completion of spinal block. They observed less hypotension in the parturients who received ephedrine infusion in 1 liter of 0.9% saline compared to the parturients prehydrated only with saline (7). However, none of these maneuvers completely eliminated the spinal anesthesia induced hypotension. To date there are no studies examining the optimal preloading volume with a fixed ephedrine infusion rate during C/S under spinal anesthesia. Therefore, we investigated different preloading protocols (10, 15 and 20 mL/kg) of RL solution administered before spinal block with constant ephedrine infusion 3 mg/min after spinal block in order to prevent hypotension during spinal anesthesia and to reduce the ephedrine requirement during elective C/S.

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prophylaxis. They were randomly allocated to three groups according to computer generated numbers written for groups and enclosed system. Parturients in group 10, 15 and 20 RL received respectively 10, 15 and 20 mL/kg of RL solution IV through a 16 G catheter within a 15 min period before spinal block. Heart rate (HR), ECG, mean arterial pressure (MAP) and peripheral oxygen saturation (SpO₂) were monitored. Spinal anesthesia was performed with a 25G pencil point spinal needle in the sitting position by midline approach using 12 mg hyperbaric bupivacaine, 100 µg of morphine and 10 µg of fentanyl. The operating table was tilted 15º to the left to avoid aortocaval compression and an IV infusion of ephedrine (50 mg diluted in 20 mL) at a rate of 3 mg/min was immediately started by an infusion pump (Colleague Volumetric Infusion Pump, Baxter Health Care, Abbott, USA) and continued until clamping of the umbilical cord.

Sensory block was evaluated by absence of sensation to cold using an alcoholic swab and loss of pin prick using a short beveled end of a needle with a blunt tip at mid-clavicular level bilaterally. Motor block was assessed using Bromage scale (0 = no paralysis, 1 = unable to raise extended leg, 2 = unable to flex knee, 3 = complete paralysis).

Sensory and motor block, HR, MAP and SpO₂ were recorded every 2 min initially and then, every 5 min until umbilical cord clamping. Hypotension was defined as a decrease in MAP of more than 20% which was treated with a bolus of 10 mg ephedrine IV. Nausea and vomiting was scored between 0 to 3 (0 = no nausea and vomiting, 1 = mild nausea without retching, 2 = nausea with retching, 3 = vomiting).

After delivery of the newborn, blood gas analysis of the umbilical artery (UA) and vein (UV) was performed. The amount of ephedrine (infusion, additional bolus, and total (= infusion + additional bolus), Apgar scores at 1 and 5 min, the incidence of hypotension and the nausea and vomiting scores were recorded.

Time interval from spinal block to skin incision, from skin incision to uterus incision and to umbilical cord clamping, were recorded, as well as the duration of ephedrine infusion. The ephedrine infusion was stopped after clamping the umbilical cord.

**Statistical Analysis**

A power analysis suggested that 30 subjects per group would be needed to detect a 30% decrease in the dose of ephedrine needed to keep the MAP 80% of baseline based on our previously published study (8). Results were expressed as mean ± standard deviation (mean ± SD), n or % where appropriate. Data were analyzed with One way ANOVA followed by post hoc correction among the groups and T-test for comparison between independent and within dependent groups. A p value less than 0.05 was considered statistically significant.

**Results**

Demographics and time intervals related to surgery and delivery were comparable between the groups (Table 1).

Significant differences were observed for HR and MAP. HR increased significantly 6 and 8 minutes after spinal block in group 15RL compared to group 10RL (Fig. 1). There were significant differences in the MAP both within and among the groups. The MAP measurements at 4, 6 and 8 minutes after spinal block in group 15RL and 20RL showed significant reductions compared to baseline, whereas significant MAP reductions in group 10RL started 2 minutes after spinal block compared to control. The MAP in group 20RL was significantly higher 6 minutes after spinal block compared to both the other groups. Eight minutes after spinal block, MAP was significantly higher in group 20RL than group 10RL (Fig. 2). Peripheral oxygen saturation was similar between groups.

The dose of ephedrine and RL solution administered to the parturients and the incidence of hypotension were presented in Table 2. The dose of additional boluses IV ephedrine in group 20 RL was significantly less than in group 10 RL and the total dose of ephedrine in group 20 RL was significantly lower than both groups (p < 0.05). The incidence of hypotension was 60%, 36.7% and 13.4% in the groups 10RL, 15RL and 20RL, respectively. The lowest incidence was observed in Group 20RL compared to the other two groups (p < 0.05) (Table 2).

Umbilical cord blood gas analysis, weight of the newborn and Apgar scores at 1 and 5 min are presented in Table 3. The mean UVpCO₂ tension in group 20 RL was significantly lower than the group 10 RL (p < 0.05). The median Apgar score at 1 min in group 20 RL was significantly higher than in group 10 RL (p < 0.05). The median Apgar scores at 5 min and pH in the UA and UV were comparable between the groups.
The median (range) nausea-vomiting scores were 1 (0-3), 0 (0-3) and 0 (0-3) in group 10RL, 15RL and 20RL, respectively. The nausea-vomiting score was significantly lower in group 20RL than in group 10RL (p = 0.02).

Sensory and motor block characteristics until the umbilical cord clamping were comparable between groups. Sensory block at T4 dermatome and complete motor block were achieved in all groups. Maximum highest or upper level of sensory block in groups 10RL, 15RL and 20RL were T4 (T4-T2), T4 (T5-T2) and T4 (T5-T2), respectively.

**DISCUSSION**

We demonstrated that 20 mL/kg of RL preloading prior to spinal block and of a constant ephedrine infusion of 3 mg/min started immediately after spinal block is effective in preventing hypotension associated with spinal anesthesia and in reducing the ephedrine requirements in parturients scheduled to undergo elective C/S.

Although the efficacy of intravenous preloading before neuraxial block to prevent hypotension has been questioned, prophylactic and/or therapeu-
tic approaches are usually necessary since the incidence of hypotension can be as high as 80% if these measures are not used (1). The lowest hypotension incidence was reported as 8% in trials using low dose spinal anesthesia (9). Doses of intrathecal bupivacaine between 5 and 7 mg were sufficient to provide effective anesthesia. However, complete motor block was seldom achieved and adequate anesthesia was limited in time. Therefore, low-dose spinal anesthesia is considered a valuable method in improving maternal and fetal outcome during anesthesia for C/S when used as part of a combined spinal-epidural technique. The dose of a single shot spinal anesthesia for C/S needs to be higher to guarantee adequate anesthetic conditions. Since sensory block at T4 dermatome with complete motor block was achieved in all groups, none of the parturients suffered from inadequate anesthesia. We have documented a 13.4% incidence of hypotension which was higher than the previously reported rate of 8%, but is the lowest rate reported with intrathecal hyperbaric bupivacaine 12 mg combined with opioids.

It has been reported that the incidence of maternal hypotension was 35% within the 1st 12 minutes after the spinal injection when parturients received 30 mg of IV ephedrine prophylaxis.
1 min after intrathecal injection in addition to preloading 20 mL/kg of RL solution (5). We administered ephedrine by infusion immediately after the spinal block instead of bolus injection 1 min after spinal block. Additionally, we have been the first to present ephedrine infusion at a constant rate of 3 mg/min during the time interval from spinal block to delivery. Although the present infusion rate might seem high compared to the previously reported infusion regimens, additional ephedrine was still required to keep the MAP within 80% of the baseline. In comparison with the previously used ephedrine infusion rates, the rate we administered was the highest but most effective in reducing the rate of hypotension when applied with preload of 20 mL/kg RL. The average amount of ephedrine administered by infusion was around 36-39 mg in the present study. So the doses of ephedrine administered by infusion or and the total amount may be considered to be reasonable. Median nausea and vomiting scores which were lower in group 20Rl than in group 10Rl are also consistent with decreased incidence of hypotension.

According to a dose response meta-analysis of prophylactic IV bolus ephedrine for the prevention of spinal anesthesia associated hypotension during elective C/S, larger doses of ephedrine did not eliminate hypotension but caused reactive hypertension and a minor decrease in umbilical arterial pH (10). On the contrary to that meta-analysis, we did not observe any reactive hypertension or change in umbilical blood gas analysis and pH. The possible explanation for the difference in our study is that the meta-analysis mentioned above lacks studies including prophylactic ephedrine infusion regimens. However, we observed a considerable decrease in the hypotension rate. Significant reductions in the blood pressure from the baseline developed at 4 min in both group 15RL and group 20RL, but appeared at 2 minutes in group 10RL. This may be explained by the choice of the prehydration volume.

The MAP in group 20RL at 6 min after the spinal block was significantly higher compared to the two other groups, whereas 8 min after spinal block it was significantly higher when compared to group 10RL only. Despite the significant changes in MAP, umbilical pH in both UA and UV blood samples were not only within clinically normal limits i.e. higher than 7.2 but also were comparable among the groups. Since the umbilical pH, which was not statistically different among the groups, shows the fetal condition better and is more objective than Apgar score, it is of interest in the neonatal assessment. Although the Apgar score at 1 min in the group 20RL was significantly higher than the group 10RL, Apgar scores were comparable after 5 min among all groups.

The incidence of spinal anesthesia induced hypotension might vary according to the prophylactic strategy selected for ephedrine administration. It has been demonstrated that 30 mg IV bolus ephedrine and 30 mg ephedrine in 1 liter saline solution infused at 50 mL/min caused a hypotension incidence of 35% and 13.3%, respectively (5, 7). In the present study hypotension rates in groups receiving preload of 10, 15 or 20 mL/kg RL were 60%, 36.7% and 13.4%, respectively. Presence of a higher incidence of hypotension in group 10RL and a moderate effect in reducing this incidence in the

| Table 3 Blood gas analysis in umbilical cord, newborn demographics and Apgar scores |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                | Group 10RL (n = 30) | Group 15RL (n = 30) | Group 20RL (n = 30) |
| UA pH                          | 7.34 ± 0.07       | 7.35 ± 0.05       | 7.36 ± 0.03       |
| UA PO2 (mmHg)                  | 28.9 ± 9.7        | 25.2 ± 6.3        | 26.6 ± 6.5        |
| UA PCO2 (mmHg)                 | 48.5 ± 10.5       | 45.5 ± 8.3        | 45.5 ± 5.8        |
| UV pH                          | 7.38 ± 0.07       | 7.39 ± 0.05       | 7.40 ± 0.03       |
| UV PO2 (mmHg)                  | 35.3 ± 9.5        | 36.3 ± 7.8        | 37.8 ± 6.7        |
| UV PCO2 (mmHg)                 | 42.3 ± 8.5        | 38.7 ± 6.2        | 37.7 ± 5.8*       |
| Apgar score 1 min              | 9 (7-9)           | 9 (8-10)          | 9 (9-9)*          |
| Apgar score 5 min              | 10 (9-10)         | 10 (9-10)         | 10 (10-10)        |
| Birthweight (g)                | 3343.3 ± 483.9    | 3231 ± 401.1      | 3397 ± 462.0      |

Demographics and blood gas analysis data are presented as mean ± SD and range, while Apgar scores are presented as median and range.

*p < 0.05 vs Group 10RL.
group 15 mL/kg led us to conclude that a proportional relationship exists between the preloading protocol and the incidence of hypotension when co-administering a 3 mg/min ephedrine infusion. The incidence of hypotension was almost identical in the study of Desalu and Kushimo’s (7).

Some limitations of our study might be noted due to the evidences supporting phenylephrine as the best vasopressor in obstetrics while ephedrine is not the preferred choice for elective C/S in healthy non-laboring women (4, 11, 12). Since we haven’t observed any undesired effects including reactive hypertension or fetal acidosis due to ephedrine infusion, the present 3 mg/min infusion rate + pre-load of 20 mL/kg RL might be an option when phenylephrine is contraindicated or not available.

In conclusion, fluid preloading with 20 mL/kg of RL within 15 minutes prior to spinal anesthesia and ephedrine infusion of 3 mg/min started after the spinal block resulted in a significantly lower incidence of hypotension and nausea and vomiting, required less ephedrine and provided better Apgar scores at 1 min without changing the umbilical cord pH during elective cesarean section. Therefore we might recommend prehydration with 20 mL/kg RL and an ephedrine infusion of 3 mg/min as a valuable strategy for the prevention of spinal anesthesia induced hypotension during elective cesarean section.

References


