# RAPID FLUID ADMINISTRATION AND THE INCIDENCE OF HYPOTENSION INDUCED BY SPINAL ANESTHESIA AND EPHEDRINE REQUIREMENT: THE EFFECT OF CRYSTALLOID VERSUS COLLOID COLOADING

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**Purpose:** Spinal anesthesia for caesarean delivery is often associated with hypotension. This study was conducted to evaluate the effects of rapid crystalloid (Lactated Ringer's solution; LRS) or colloid (hydroxyethyl starch; HES) cohydration with a second intravenous access line on the incidence of hypotension and ephedrine requirement during spinal anesthesia for cesarean section.

**Methods:** We studied 90 women with uncomplicated pregnancies undergoing elective cesarean section under spinal anesthesia. ***Intravenous access was established*** in all patients with ***two peripheral intravenous*** lines, the first being used for the baseline volume infusion. Immediately after induction of spinal anesthesia, LRS (Group L) or HES (Group C) infusions were started at the maximal possible rate via the second line in groups L and C respectively. In the third group (Group E) , patients received lactated Ringer's solution at a 'keep vein open' rate to maintain the double-blind nature. The incidence of hypotension, ephedrine requirements, total amount of volume and side effects were recorded.

**Results:** The incidence of hypotension was significantly greater in group E than in groups L and C, and greater in group L than in group C ($p<0.03$ and $p<0.01$ respectively ). The total dose of ephedrine used to treat hypotension was significantly less in groups L and C than in group E ($p<0.001$ and $p<0.001$ respectively). Groups L and C received similar infusion volumes and doses of ephedrine.

**Conclusions:** Giving either LR or HES coloading via a second IV line caused less hypotension and required less use of ephedrine compared to no coloading. There were no maternal or neonatal side effects.

**Keywords:** Anesthetic techniques-subarachnoid, Pharmacology-agonists adrenergic, Fluid Therapy, Fluids iv.

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## Introduction

Spinal anesthesia for cesarean delivery often causes hypotension, which requires rapid and aggressive treatment to prevent maternal and neonatal side effects[1]. Lateral uterine displacement, the use of IV fluid preload or coload, vasopressors, and compression devices on the legs, have all been used to restore venous return and arterial blood pressure during spinal anesthesia. Phenylephrine and ephedrine are used to treat and prevent hypotension induced by spinal anesthesia; a prophylactic phenylephrine infusion together with fluid cohydration can effectively eliminate hypotension[1], but maternal reactive hypertension and bradycardia, may be a problem, even at slow infusion rates[2,3]. Unlike phenylephrine, ephedrine can cause fetal acidosis, and large doses are associated with maternal nausea and vomiting. Rapid fluid administration on initiation of spinal anesthesia offers an alternative technique[4,5], but it can cause hypervolemia, risking pulmonary edema, decreased oxygen-carrying capacity and poor wound healing[6,7]. Thus far, no method has proved entirely satisfactory.

In this study, we aimed to evaluate the effects of rapid crystalloid (Lactated Ringer's solution; LR) or colloid (hydroxyethyl starch; HES) cohydration via the second intravenous access line during spinal anesthesia for cesarean section. The hypothesis was that cohydration with LR or HES, beginning at the time of spinal injection, will reduce hypotension and ephedrine use.

## Method

Faculty Ethics Committee approval and informed parturient consent was obtained. This trial was registered al Clinical Trials. gov with trial registration number: NCT01741610.

90 ASA physical status I or II, with a singleton uncomplicated pregnancy at full-term gestation, undergoing elective cesarean section under spinal anesthesia were included in this prospective, randomized, controlled study. Exclusion criteria included significant coexisting disease such as pre-eclampsia and hepato-renal disease, pregnancy preinduced hypertension, being in active labor or requiring emergency cesarean section, and any contraindication to regional anesthesia such as local infection or bleeding disorders.

Parturient were instructed preoperatively on the use of the verbal rating scale (VRS) for pain assessment. All were fasted for 6 hours pre-operatively and no premedication was given. Intraoperative monitoring included lead II electrocardiogram (ECG), pulse oximetry and automated blood pressure cuff. Systolic blood pressure (SBP), heart rate (HR), and oxygen saturation ($SpO_2$) were monitored before spinal anesthesia and throughout the operation. ***Intravenous access was established*** with ***two peripheral intravenous*** lines (20 Gauge). The first was used for the baseline volume infusion; all parturient received iv 10 ml/kg/h of lactated Ringer's solution while the block was being performed.

Using a computer generated sequence patients were randomly allocated to one of three groups of 30 patients each. Group L received 1000 mL of lactated Ringer's solution via the second peripheral intravenous line with the flow-control clamp fully open. The Colloid group (Group C), similarly received 1000 mL of ***6*** % hydroxyethyl starch (HES) (***Voluven***®). Group E received ***lactated Ringer's solution*** at a **'*keep vein open*'** rate as control group. All study solutions were covered by a non-transparent plastic bag to maintain the double-blind nature of the study.

The spinal blocks were performed by experienced, qualified anesthetists using a standard spinal anesthetic technique. A 26 gauge Pencil Point spinal needle was inserted at the $L_{3-4}$ or $L_{4-5}$ intervertebral level via a midline approach. Following skin preparation and local infiltration with 1% lidocaine, the subarachnoid space was then punctured with the parturient in the sitting position. After return of clear cerebrospinal fluid a standard spinal anesthetic consisting of 0.5 % heavy bupivacaine 10 mg combined with 25 mcg fentanyl was given. After intrathecal injection, the parturient were placed supine with a 15°-20° left uterine tilt for the prevention of aortocaval compression. Immediately after induction of spinal anesthesia, lactated Ringer's or colloid infusions were launched at the maximal possible rate in groups L and C. It was planned that if this 1000

mL coloading was complete before the end of surgery, lactated Ringer's solution would be launched at a 'keep vein open' rate in groups L and C. Oxygen 2–4 L/min was delivered routinely via nasal cannula until delivery. No additional analgesic was administered unless requested by the patients.

A $T_5$ sensory dermatome level was obtained before surgical incision in all parturient. After delivery, umbilical artery blood gas samples (pH, $PO_2$, $PCO_2$ and $HCO_3$) were taken and neonatal Apgar scores were recorded at 1 and 5 min by an attending pediatrician. Demographic data (age, height, weight, parity and gravity) and duration of surgery were noted by an observer blinded to the treatment group. Systolic and diastolic blood pressures (SBP, DBP), heart rate (HR) and peripheral oxygen saturation ($SpO_2$) were recorded by an anesthetist blinded to the patient group, preoperatively and at 1, 3, 5 10, 15, 20, 30, 45 and 60 min after the IT injection and at 5, 15, 30 min and 1, 2, 6, 12, 24 hours postoperatively.

Sensory and motor block levels were assessed and recorded at 1, 5 15, 30 and 60 min after IT injection. Sensory block was assessed by pinprick test. Motor block was assessed by modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; 3, inability to flex the ankle). The duration of total sensory block (defined as the time for regression of two segments from the maximum block height evaluated by pinprick) and of spinal anesthesia (defined as the period from spinal injection to the

*Fig. 1*
*Flowchart of the patients*

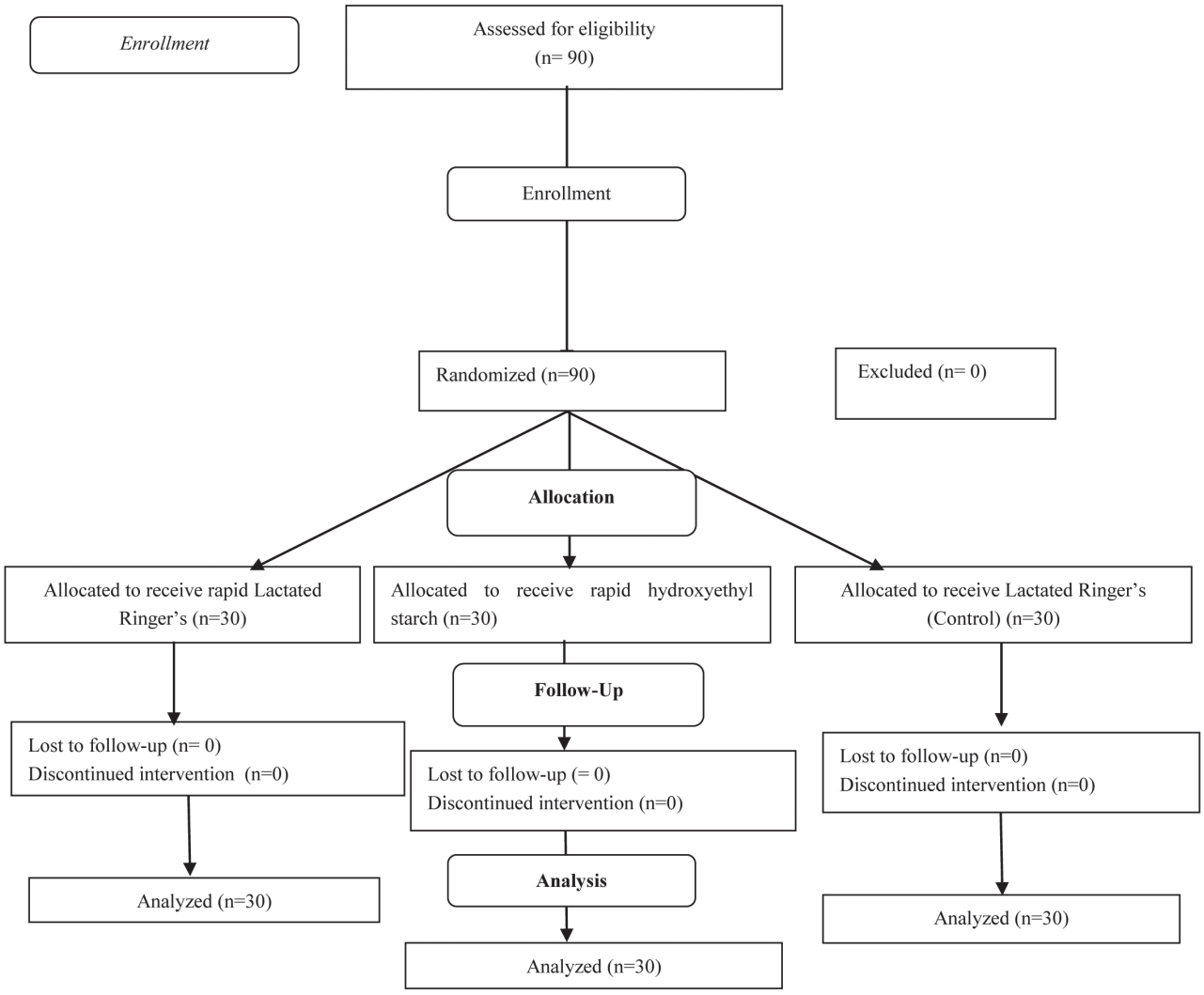


*Fig. 2*
*Perioperative Systolic Blood Pressure variables in groups*

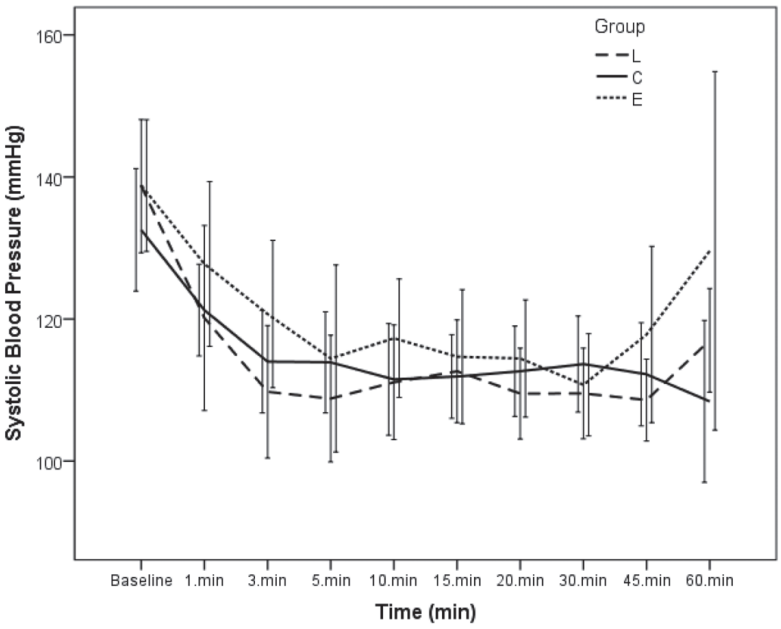
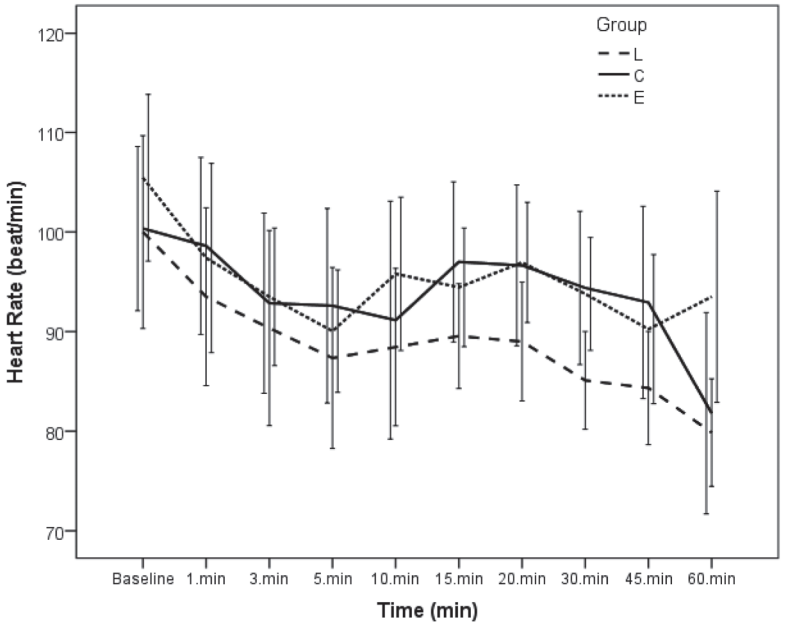



*Fig. 3*
*Perioperative Heart Rate variables in groups*




first occasion when the patient complained of pain in the postoperative period) were also recorded after IT injection.

Hypotension, defined as systolic blood pressure less than 80% of baseline (prenatal) or <90 mm Hg, was treated with IV ephedrine 10 mg. If HR was less than 50 beats/min, 0.5 mg of atropine sulphate was given intravenously. Total fluid volumes, ephedrine requirements, the occurrence of hypotension (defined as the administration of at least one dose of ephedrine), bradycardia (heart rate <50 beats/min), hypoxemia ($SpO_2$ <95 %), excessive sedation, pruritus, dizziness, nausea and vomiting were recorded. Discharge criteria for the ward were resolved motor block, stable vital signs, and absence of nausea, vomiting and pain.

## *Data Analysis*

The primary study endpoint was the ephedrine requirement (incidence of hypotension). We calculated that 90 women, 30 for each group would be required to

*Table 1*

*Demographic data, patient characteristics, duration of surgery, sensory and spinal block in groups*

| | Group L (n=30) | Group C (n=30) | Group E (n=30) | P-value |
|---|---|---|---|---|
| **Age (year)** | 30.8 ±5.8 | 31.8±5.2 | 29.8±4.2 | 0.3 |
| **Height (cm)** | 162.7±5 | 163.7±5.5 | 161±5.8 | 0.2 |
| **Weight (kg)** | 84.5±11.4 | 85.7±14.4 | 79.5±10 | 0.1 |
| **Parity** | 2.6±1.4 | 2.5±1.1 | 2.7±1.5 | 0.8 |
| **Gravidity** | 2.9±1.7 | 2.8±1.1 | 3.1±1.6 | 0,7 |
| **Duration of surgery (min); median(range)** | 52 (30-120) | 47 (25-120) | 46 (25-105) | 0,1 |
| **Duration of sensory block (min); median (range)** | 58 (25-120) | 63 (24-120) | 57 (28-120) | 0.1 |
| **Duration of spinal block (min); median (range)** | 124(45-180) | 134(50-200) | 133(45-220) | 0.6 |

Data are presented as mean ± SD or median (range).

*Table 2*

*Neonatal Apgar scores and umbilical artery gas values*

| | Group L (n=30) | Group C (n=30) | Group E (n=30) | P-value |
|---|---|---|---|---|
| **Apgar score 1. min median (range)** | 8 (4-9) | 8 (3-9) | 8 (5-9) | 0,4 |
| **Apgar score 5. min median(range)** | 9 (7-10) | 9 (7-10) | 9 (8-10) | 0,5 |
| **Umbilical artery blood gases** | | | | |
| **pH** | 7.32±0 | 7.32±0 | 7.34±0 | 0.5 |
| **$pO_2$ (mmHg)** | 23.5±9 | 23.1±9.1 | 26.9±16 | 0.4 |
| **$pCO_2$ (mmHg)** | 44.3±9 | 46.5±9.4 | 43±8.2 | 0.3 |
| **$HCO_3$** | 22.1±2.8 | 23.1±4.8 | 22.5±2 | 0.5 |

Data are presented as mean±SD or median (range).

*Table 3*

*Sensory and motor blockade levels*

| | Group L (n=30) | Group C (n=30) | Group E (n=30) | P K-Wallis test |
|---|---|---|---|---|
| **Sensory block level** | | | | |
| **1 min** | T6 (T3 T12) | T6 (T3 T12) | T6 (T3 T10) | 0.3 |
| **5 min** | T4 (T2 T6) | T4 (T3 T10) | T4 (T2 T8) | 0.4 |
| **15 min** | T4 (T2 T6) | T3 (T3 T10) | T4 (T3 T8) | 0.4 |
| **30 min** | T4 (T2 T6) | T4 (T3 T8) | T4 (T2 T8) | 0.1 |
| **60 min** | T4 (T2 T10) | T4 (T3 T6) | T5 (T3 T6) | 0.8 |
| | | | | |
| **Motor block level (Bomage)** | | | | |
| **1 min** | | | | |
| **5 min** | 2 (0 3) | 2 (1 3) | 3 (0 3) | 0.2 |
| **15 min** | 3 (1 3) | 3 (3 3) | 3 (2 3) | 0.2 |
| **30 min** | 3 (3 3) | 3 (3 3) | 3 (3 3) | 0.3 |
| **60 min** | 3 (2 3) | 3 (3 3) | 3 (2 3) | 0.1 |
| | 3 (2 3) | 3 (3 3) | 3 (1 3) | 0.3 |

Data are presented as median (range).

*Table 4*
*Incidence of hypotension and nausea, total amount of volume infused and vasopressor requirements*

| | Group L (n=30) | Group C (n=30) | Group E (n=30) | P-value |
|---|---|---|---|---|
| Total volume infused (mL) | 2552±572* | 2233±479* | 1617±297 | 0.001 |
| First IV Line | 1478±490 | 1336±341 | 1541±296 | 0.1 |
| Second IV Line | 1074±290* | 930±185* | 86±40 | 0.001 |
| Total ephedrine dose (mg) | 8±14* | 3.6±9.2*† | 15.3±17.4 | 0.003 |
| | 8 (2.6 13.3) | 3.6(0.2 7.1) | 15.3 (8.7 22) | |
| Incidence of hypotension; n (%) | 13/30(43%)* | 6/30(20%)*† | 20/30 (66%) | 0.001 |
| Incidence of nausea; n (%) | 10 (33%)* | 7 (23%)* | 17 (56%) | 0.03 |

Data are presented as mean±SD, mean (95 % CI) or n (%).

* p<0.05 compared with group E.

† p<0.05 compared with group L.

demonstrate a 40 % difference in ephedrine requirement between groups (beta = 0.1, alpha = 0.05). Normality was checked for each continuous variable, and normally distributed values were expressed as mean (SD) or (95% CI), number (%), others as median (range) where appropriate. Demographic (gestational age, maternal age, height and weight) data were analyzed using one way ANOVA. Clinical data were analyzed using the Kruskal-Wallis test. If there were significant differences among the three groups, the analysis was continued with posthoc comparisons of differences between pairs of groups by using Mann-Whitney's U-test. The incidence of hypotension in the groups was compared by Chi-square test. If there were significant differences between groups, a multiple comparison were applied with Bonferroni's correction (p<0,05/n; where n= number of comparisons) and p<0.017 considered statistically significant. Hemodynamic data were analyzed by repeated measure analyses. The incidence of intra- and postoperative adverse events were analyzed using Chi-square tests. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the statistical package SPSS v 19.0 (Inc, Chicago, USA).

## Results

Ninety patients were enrolled and completed the study. A flowchart of the patients was shown in Figure 1. There were no significant differences between groups in demographic data, patient characteristics and the duration of surgery (Table 1). Neonatal Apgar scores after 1 and 5 min and umbilical artery gas samples were also similar (Table 2). Maternal $SpO_2$ values remained within the normal range throughout the perioperative and postoperative study period. Sensory blockade achieved T5 and above within 10 min in all parturient, with no significant differences in the level of sensory or motor blockade between groups (Table 3). Perioperative SBP and HR variables are shown in Figure 2-3. There were no significant differences in perioperative and postoperative hemodynamic variables (SBP and HR) between groups.

Transient hypotension occurred in each group despite volume coloading. The incidence of hypotension after spinal anesthesia was 43% (13/30) in Group L and 20% (6/30) in group C. It was 66% (20/30) in Group E and significantly greater than in groups L and C (p<0.03, p<0.01, respectively). There was less hypotension in Group C than in group L (p<0.05), (Table 4).

The total amount of volume infused was significantly greater in groups L and C than in group E (p<0.001, p<0.001). Significantly less ephedrine was used in the coloading groups than in group E (p<0.001). Groups L and group C received similar total fluid volumes and ephedrine doses (Table 4).

Nausea was experienced by 10 patients (33%) in group L, by 7 patients in group C (23%) and by seventeen patients in group E (56%); which was successfully treated by correcting hypotension. There was more nausea in group E than in groups L and C (p<0.01, p<0.03) (Table 4). No major side effects or

complications related with spinal anesthesia were recorded.

## Discussion

Depending on the definition used, the incidence of hypotension caused by spinal block in pregnant females has been reported as 90%[8,9]. Current strategy for avoiding hypotension following spinal anesthesia would appear to be fluid therapy combined with the appropriate vasopressor, dependent on patient status[10]. However, there is no reliable way to determine how much volume or vasopressor is required to compensate for the decrease in systemic vascular resistance caused by sympathetic blockade. In routine clinical practice, generally single peripheral intravenous line (18-20 Gauge) is used to treat hypotension during cesarean section surgery and this frequently cannot compensate for the decrease in systemic vascular resistance caused by sympathetic blockade (at T4), even at the flow-control clamp fully open rate. Therefore, giving rapid fluid coloading via second IV line can be an alternative approach to increase stroke volume while decreasing vasopressor need. In the present study, regardless of the fluid used, rapid coloading via second IV line caused less hypotension and required less use of ephedrine compared to no coloading.

Rapid and generous fluid administration may expand the intravascular space and lead to activation of atrial natriuretic peptide, thereby counteracting the desired volume-expanding effects[11,12]. However, debate has been going on not only as to the optimal fluid volume and type (crystalloid versus colloid), and timing of fluid administration but also as to type and dose of vasopressors used (phenylephrine versus ephedrine)[1,2].

In a recent Cochrane analysis, Cyna et al[13] investigated 75 trials to assess the effect of prophylactic interventions for hypotension following spinal anesthesia for cesarean section and found that no single or combined prophylactic intervention avoids the need to treat a proportion of women for hypotension following spinal anesthesia for cesarean section. However, no conclusion has been drawn from the above analysis with respect to the optimum volume and the infusion rate of fluids needed to restore hemodynamic function during spinal anesthesia. In the present study, fluid infusion was given more rapidly with the use of two peripheral intravenous lines to achieve optimum and acute peak expansion of intravascular volume.

Block height determines the extent of sympathetic blockade and thus the degree of volume expansion to be replaced after spinal anesthesia. Sensory block levels were similar between groups, but the incidence of hypotension and ephedrine requirements were significantly greater in group E. The fluid coloading in groups L and C was probably adequate to compensate for the decrease in systemic vascular resistance caused by sympathetic block.

Most studies have attempted to restore venous return using crystalloids, but colloids remain within the intravascular space for longer and less is needed to restore hemodynamic function[14]. Thus, our parturient receiving 6% HES experienced less hypotension than those receiving crystalloid or only ephedrine. It may not be possible to infuse crystalloids fast enough to maintain intravascular volume and avoid hypotension during spinal anesthesia because of the short intravascular half-life[15]. Sharma et al[16] reported that patients given 500 mL of hetastarch had a 21% incidence of hypotension after spinal anesthesia compared to a 55% incidence in patients given 1000 mL of LR. Zorko et al[17] found that hydroxyethyl starch increased cardiac output during development of sympathetic block after spinal anesthesia.

Volume kinetic studies suggest that giving fluids as a coload at the time of onset of spinal anesthesia might be better than using a preload[8]. In the present study, fluid coloading from the second iv access was started immediately after induction of spinal anesthesia rather than before. Rapid administration of crystalloid preload before spinal anesthesia does not decrease the incidence or severity of hypotension after spinal anesthesia[15]. Dyer et al reported that rapid crystalloid administration after, rather than before the induction of spinal anesthesia for elective cesarean section, provides better maternal hemodynamic control and lower ephedrine requirement prior to delivery[4]. Kamenik et al[18]. found that cardiac output remained elevated above baseline in patients given coload (11.3%) 30 min after induction of anesthesia, whereas it returned to baseline

30 min after spinal anesthesia in those given preload (20%).

Many clinicians recommend the avoidance or severe limitation of the use of vasopressors in parturient, because of their untoward side effects, but treat the hypotension aggressively after spinal anesthesia[19]. A recent review article states that hemodynamic stability after spinal anesthesia may be best restored by a low-dose phenylephrine infusion[1]. This was confirmed in the last European survey and phenylephrine administration has been recommended as the fastest and most effective way of restoring mean arterial pressure[20]. Although use of a prophylactic phenylephrine infusion concurrently with a fluid coload can virtually eliminate hypotension associated with spinal anesthesia, maternal reactive hypertension and bradycardia still occur[2,3]. Ephedrine has a long history of use in obstetrics, and is still used[21]. It may be that obstetric anesthetists may feel more comfortable with it than with phenylephrine[1]. We found the incidence of hypotension and total dose of ephedrine used to treat hypotension after spinal anesthesia were greater in group E than in groups L and C.

Spinal hypotension often causes nausea and vomiting, which can be largely avoided by maintainance of maternal blood pressure.Kee et al found that maintaining maternal systolic blood pressure at 100% of baseline was the best way to avoid nausea and vomiting[22]. However, we found an incidence of hypotension after spinal anesthesia of 43% (13/30) in Group L, 20% (6/30) in Group C, and 66% (13/30) in Group E. The incidence of nausea was 33% (10/30) in group L, 23% (7 /30) in group C and 56% (17/30) in group E. There was a positive correlation between hypotension and nausea. Most nausea episodes coincided with episodes of hypotension and were successfully treated by correcting this.

The main limitation of this study is that a non-invasive hemodynamic monitoring (ie. echocardiography) has not been used to document cardiac output during the fluid therapy. Non-invasive cardiac output monitoring in patients undergoing cesarean section with spinal anesthesia might provide more accurate determination of fluid responsiveness.

Our study supports the idea that maintaining homeostasis by infusing rapid volume coloading and minimizing the use of vasopressors in pregnant patients is an acceptable strategy because of the possible adverse consequences of vasoconstrictors. Thereby, fluid coloading via a second IV line might be an alternative approach to compensate for the decrease in systemic vascular resistance caused by sympathetic blockade while avoiding untoward side effects of vasopressors and indicated in parturients for whom ephedrine or phenylephrine are contraindicated.

In conclusion we found that parturient given either LR or HES coloading via second IV line experienced a lower incidence of hypotension and required smaller doses of ephedrine, without causing maternal or neonatal side effects compared to parturient given no coloading. 6% HES was associated with a lower incidence of hypotension after spinal anesthesia than crystalloid, although the volumes given were similar in the two groups.

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