The Effects of Crystalloid and Colloid Preload on Cardiac Output in the Parturient Undergoing Planned Cesarean Delivery Under Spinal Anesthesia: A Randomized Trial

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BACKGROUND: Hypotension after spinal anesthesia for cesarean delivery remains a major clinical problem. Fluid preloading regimens together with vasopressors have been used to reduce its incidence. Previous studies have used noninvasive arterial blood pressure measurement and vasopressor requirements to evaluate the effect of preload. We used a suprasternal Doppler flow technique to measure maternal cardiac output (CO) and corrected flow time (FTc, a measure of intravascular volume) before and after spinal anesthesia after 3 fluid preload regimens. We hypothesized that colloid solutions, compared with crystalloid, would produce the largest increase in CO and have the lowest incidence of hypotension.

METHODS: Sixty healthy term women scheduled for planned cesarean delivery under spinal anesthesia were recruited for this randomized, double-blind study. Baseline heart rate, systolic blood pressure (SBP), CO, and FTc were recorded in the left lateral tilt position. Patients were randomized to receive 1 of 3 fluid preload regimens given over 15 min: 1.5 L crystalloid (Hartman’s solution), 0.5 L of 6% w/v hydroxyethyl starch (HES) solution (HES 0.5), or 1 L of 6% w/v HES solution (HES 1.0). Further measurements were made after fluid loading every 5 min for 30 min. After 30 min, spinal anesthesia was induced with hyperbaric bupivacaine 12.5 mg with fentanyl 15 μg and recordings were continued every 5 min for 20 min or until surgery started. The primary outcome, CO, was compared among groups. The incidence of hypotension (defined as a 20% reduction in SBP from the baseline), ephedrine use, and umbilical cord blood gases were also compared.

RESULTS: Patient characteristics, heart rate, SBP, and cord gases were similar among groups. Although CO and FTc increased after preload in all groups (P < 0.005), this was only maintained with HES 1.0 after spinal anesthesia (P < 0.005). There were no differences among groups in the incidence of hypotension (70% vs 35% vs 65% for Hartman’s solution, HES 0.5, and HES 1.0, respectively; P = 0.069) or mean ephedrine dose (10.4 vs 5.7 vs 9.7 mg; P = 0.26).

CONCLUSION: Despite CO and FTc increases after fluid preload, particularly with HES 1.0 L, hypotension still occurred. The data suggest that CO increases after these preload regimens cannot compensate for reductions in arterial blood pressure after spinal anesthesia.

(Maternal hypotension is a common side effect after spinal anesthesia for cesarean delivery, with an incidence of up to 83%. Most evidence supports the use of colloid compared with crystalloid fluid loading (preload) to maintain arterial blood pressure after spinal anesthesia for cesarean delivery. The hypotension is caused by an increase in venous capacitance and a reduction in systemic vascular resistance. Because of this, arterial blood pressure measurement alone tells us little about cardiac output (CO), which has shown to be a better predictor of organ and placental perfusion than arterial blood pressure. Few studies have measured CO after spinal anesthesia in the maternal population. This is largely because of the lack of availability of accurate and reproducible noninvasive measurement techniques. Most studies...
examining the efficiency of intravascular fluid administration for preventing hypotension have continued to focus on arterial blood pressure variables, fluid, and ephedrine requirements as markers of cardiovascular status, because these are more easily measured. \(^3\) The suprasternal measurement of aortic blood flow is a simple, noninvasive method of assessing CO, described by Light in 1969. \(^9\) This is a valid technique, providing linear measures of CO (by measuring stroke distance [SD]) consistent with volumetric measures derived from thermodilution \(^10\) and has been used successfully to assess cardiac function in a range of physiological and pathological states including pregnancy. \(^11,12\) Technical issues have in the past limited the availability of this technique, but signal processing has continued to improve.

This double-blind, randomized, controlled study was designed to evaluate the effect of 3 different preloading regimens, namely, crystalloid solution, Hartman’s solution (HS) 1.5 L, hydroxyethyl starch 0.5 L (HES 0.5), and 1.0 L (HES 1.0) on changes in maternal CO and corrected flow time (FTc), a measure of intravascular volume status, using a new suprasternal ultrasound device (SupraQ\textsuperscript{®} Cardiac Function Monitor, Deltex Medical, Chichester, UK) in parturients undergoing planned cesarean delivery under combined spinal-epidural (CSE) anesthesia. We hypothesized that HES 1.0, given before spinal anesthesia, would produce the largest increase in CO.

**METHODS**

After ethics committee approval (Royal Free Hampstead NHS Trust, London, UK) and written informed consent, we recruited 60 healthy parturients scheduled for planned cesarean delivery under CSE anesthesia. Exclusion criteria included gestational age <37 wk, multiple gestation, cardiac disease, preeclampsia, obesity (weight of 70,000 Da [EloHaes 6% in 0.9% saline, Fresenius, Hamburg, Germany]) and the HES 1.0 group received 6% HES solution 1.0 L \((n = 20)\).

Baseline measures of heart rate (HR), systolic blood pressure (SBP), oxygen saturation (SpO\textsubscript{2}), (measured using a Datex monitor, Datex, Helsinki, Finland), CO, FTc, and other Doppler measurements were taken in the 15° left tilt position before a preload was given. The SBP was measured in the right arm and baseline SBP was an average of 3 readings. Each preload regimen was infused over a 15-min period through a wide-bore peripheral IV catheter with the aid of a simple pressurized infusion system. Three anesthesiologists were involved in the study. One anesthesiologist, unconnected with clinical care and data collection, performed the randomization procedure. A second anesthesiologist administered the preload with the IV setup kept out of the parturient’s field of vision. A third anesthesiologist, blinded to group allocation, performed all the Doppler measurements as well as the CSE technique after the fluid preload.

Study variables were measured immediately after the preload was administered (postfluid values) and at 5-min intervals for 30 min. At 30 min, the CSE technique was performed in the sitting position at the L3-4 interspace using a 16-gauge Tuohy needle and a 27-gauge Whitacre needle (Becton, Dickinson and Company, Franklin Lakes, NJ). The spinal injection consisted of 0.5% hyperbaric bupivacaine 12.5 mg and fentanyl 15 \(\mu\)g. All subsequent measurements of HR, SBP, SpO\textsubscript{2}, CO, FTc, and other Doppler measurements were performed in the left tilt position at 5-min intervals after spinal injection for a minimum of 20 min and continued until the surgery started. The maximum height of the block to touch sensation was assessed using ethyl chloride spray every 3 min until a block height of T5 was achieved. If sensory block to touch at the T5 dermatome was not achieved by 20 min after the intrathecal injection, 5-mL boluses of 0.5% levobupivacaine were administered through the epidural catheter to extend the block level.

Hypotension episodes, defined as reductions in SBP exceeding 20% of baseline or <90 mm Hg, were treated with boluses of ephedrine 6 mg. Ephedrine treatment was repeated if hypotension persisted or recurred. The total dose of ephedrine and the time from induction of CSE anesthesia until the administration of the first dose were noted. The presence of nausea and vomiting was measured on a 3-point scale of 1, 2, and 3 indicating no nausea and no vomiting, nausea only, and both nausea and vomiting, respectively. Assessments were done at 5-min intervals until 20 min after the spinal injection and when the parturient complained of sickness. Obstetric data collected included gestational age, time interval from spinal injection to start of surgery, uterine incision to delivery time, and neonatal outcome as assessed by Apgar scores at 1 and 5 min and umbilical arterial and venous blood gases obtained from a double-clamped segment of umbilical cord.

CO was measured using a suprasternal ultrasound device, the SupraQ\textsuperscript{®} Cardiac Function Monitor (Deltex Medical). Measurements were taken from the aortic arch and performed by a single operator trained over a 3-mo period in suprasternal ultrasound techniques. The Doppler complexes were transferred, real-time, onto a remote storage disk. The stored complexes were then played back for more detailed analysis of the velocity time profile by the anesthesiologist who was blinded to group allocation. Each CO parameter used for statistical analysis represented the mean of 3 measures...
derived from 3 consecutive complexes at each measurement time. Apart from CO and FTc, we also measured SD, minute distance, and peak velocity.

Data are presented as mean (standard deviation) and frequency. Group effects were analyzed using 1-way analysis of variance for numerical data and expanded Fisher’s exact tests for categorical data. Within- and among-group comparisons of hemodynamic variables from baseline to predefined time-points were performed using repeated-measures analysis of variance, analysis of covariance (using baseline hemodynamic variables as covariates), and Tukey-Kramer multiple comparison tests. A priori sample size analysis showed that a minimum of 15 patients in each of 3 groups would give 90% power to detect a 20% difference in CO (assuming a coefficient of variation of 15%), at an overall 2-sided $P < 0.05$ (threshold $P < 0.017$ with the Bonferroni adjustment for multiple comparisons). Analyses were performed using the following software: Excel 2000 (Microsoft, Redmond, WA) and Number Cruncher Statistical Systems 2004 (NCSS, Kaysville, UT).

**RESULTS**

Details of maternal characteristics are summarized in Table 1. These data were similar among the 3 groups with respect to age, weight, height, gestational age, and time from last fluid intake to start of surgery. Maternal CO, but not FTc, measured at baseline was lower in the HS group compared with HES 0.5 and HES 1.0 groups (Figs. 1 and 2). CO (L/min) increased significantly in all 3 groups after preloading with HS, HES 0.5, and HES 1.0, compared with baseline values (Fig. 1). The HES 1.0 and HES 0.5 groups had significantly larger increases in CO after preload than the HS group. In the HES 1.0 group, CO remained significantly higher than the baseline value at all timepoints over 20 min after the spinal injection, whereas in the HES 0.5 group, CO was only significantly more than baseline at 5 min postspinal (Fig. 1). However, CO values for the 3 groups at all timepoints after spinal injection were significantly lower than postfluid values (Fig. 1). Compared with group HES 0.5, group HES 1.0 had significantly higher CO values after spinal anesthesia at 5 and 15 min. These results did not change after controlling for baseline parameters with the analysis of covariance analysis.

FTc after fluid loading increased significantly in all the groups compared with baseline (Fig. 2). Immediately after spinal anesthesia, FTc remained significantly higher than baseline only in the HES 1.0 group. In all 3 groups, FTc remained significantly lower than

<table>
<thead>
<tr>
<th>Table 1. Maternal Characteristics</th>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Gestational age (wk)</td>
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<td>Time from last fluid intake (h)</td>
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Values are mean ± sd. There were no significant differences among groups.

HS = Hartman’s solution; HES = hydroxyethyl starch solution.
the postfluid value at all timepoints after spinal injection (Fig. 2). SD, a parameter directly measured by the suprasternal ultrasound monitor, increased significantly after fluid loading compared with baseline in all groups. After spinal anesthesia, SD remained significantly higher than baseline only in the HES 1.0 group (Table 2).

SBP remained unchanged after fluid loading in all the groups (Fig. 3). SBP in all 3 groups was significantly lower than baseline at 10 min after the spinal injection. After spinal anesthesia, hypotension was observed in 70% of the parturients in the HS group, in 35% of the HES 0.5 group, and in 65% of the HES 1.0 group (Table 3). There were no significant differences in the incidence of hypotension among the groups. The mean ephedrine dose and the time between induction of spinal anesthesia and first dose of ephedrine were similar among groups. There was no significant difference in the incidence of nausea and vomiting among the groups. Before the start of surgery, all patients achieved a bilateral sensory anesthesia level ranging from T5 to T3 with no difference among the groups. Three patients in the HS group and 2 patients in the HES 1.0 group needed supplementation with levobupivacaine 0.5% to achieve an adequate block level before surgery commenced. Apgar scores and umbilical cord blood gas values did not differ among the groups.

**DISCUSSION**

This randomized, controlled trial showed significant increases in maternal CO, FTc, and SD compared with baseline values after crystalloid and colloid preload administration, which were maintained until spinal anesthesia was given. After spinal anesthesia, the increase persisted for all 3 variables only in the HES 1.0 group, whereas only an increase in CO was maintained in the HES 0.5 group at 5 min compared with baseline values. Preloading with crystalloid solution failed to maintain any of the variables after the initiation of spinal anesthesia. Despite the significant increases in the CO, the incidence of clinically significant hypotension remained high in all groups. Robson et al. measured CO using Doppler flow combined with cross-sectional echocardiography at the aortic valve in parturients undergoing spinal or epidural anesthesia for cesarean delivery, demonstrating that CO increased after fluid preload and concluded that maximum changes in CO correlate better with utero-placental blood flow than that of SBP. In a recent study, Langesaeter et al. evaluated the effect of a low-dose phenylephrine infusion compared with placebo in reducing the incidence of hypotension in patients receiving either high-dose (bupivacaine 10 mg) or low-dose (bupivacaine 7 mg) spinal anesthesia for elective cesarean delivery. The blood pressure of the group receiving the low-dose spinal anesthesia combined with a phenylephrine infusion was the most stable. Interestingly, the authors showed that this group also had the lowest increase in CO and this was
associated with the lowest decrease in arterial blood pressure (and the highest systemic vascular resistance), resulting in the lowest umbilical artery base deficit.\textsuperscript{13} Ngan Kee et al.\textsuperscript{14} using a high-dose phenylephrine infusion in patients undergoing elective cesarean delivery under spinal anesthesia, found better umbilical artery pH values in those whose SBP was kept close to 100% of baseline compared with the lower SBP target groups. Although CO was not measured in this study, presumably higher arterial blood pressure was achieved with lower CO. It seems clear that a high CO does not necessarily lead to the best outcomes, such as a reduction in hypotension or higher umbilical artery pH, as in our study. Administration of a fluid colloid\textsuperscript{15} during spinal anesthesia has increased in popularity\textsuperscript{16} and this combined with a phenylephrine infusion may ultimately prove to be a better choice than fluid preload.\textsuperscript{17}

Despite the fact that CO was maintained above baseline values throughout the study period, we had a 35%–70% incidence of hypotension. Differences among groups in the incidence of hypotension and ephedrine use did not reach statistical significance because the study was underpowered for this outcome. The high incidence of hypotension despite the increase in CO could have been due to the relation between fluid preload and atrial natriuretic peptide. Pouta et al.\textsuperscript{18} showed that a significant increase in the release of atrial natriuretic peptide in response to intravascular volume load may decrease vascular tone and initiate diuresis, thereby attenuating the effect of volume load on arterial blood pressure during elective caesarean delivery. Limitations in our study design could account for the lack of statistical significance in the incidence of hypotension. A larger sample size (47 per group) would have been required to detect any statistical difference in the incidence of hypotension, ephedrine dose, and time to first ephedrine dose. Another limitation is the 30-min waiting period after fluid preload and before the initiation of spinal anesthesia. It is possible that within this time period most of crystalloid solution had left the intravascular compartment. Indeed, a systematic review has shown that crystalloid preload is inconsistent in preventing hypotension.\textsuperscript{19}

The incidence of nausea and vomiting was similar among the groups. Good neonatal outcome as indicated by Apgar scores and umbilical venous and arterial pH values, as shown in Table 3.

Table 3. Hypotension Incidence/Treatment and Umbilical Cord Gases

<table>
<thead>
<tr>
<th></th>
<th>HS (n = 20)</th>
<th>HES 0.5 (n = 20)</th>
<th>HES 1.0 (n = 20)</th>
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<tbody>
<tr>
<td>Hypotension incidence, n (%)</td>
<td>14 (70)</td>
<td>7 (35)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Ephedrine dose (mg)</td>
<td>12 (0–18)</td>
<td>0 (0–10)</td>
<td>6 (0–17)</td>
</tr>
<tr>
<td>Time to first ephedrine dose (min)</td>
<td>7 (0–11)</td>
<td>0 (0–9)</td>
<td>8 (0–12)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>6 (30)</td>
<td>4 (20)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Uterine incision time to delivery (s)</td>
<td>84 ± 9</td>
<td>109 ± 12</td>
<td>108 ± 13</td>
</tr>
<tr>
<td>Umbilical venous pH</td>
<td>7.35 ± 0.05</td>
<td>7.34 ± 0.04</td>
<td>7.36 ± 0.02</td>
</tr>
<tr>
<td>Umbilical venous base excess (mEq/L)</td>
<td>-2.5 ± 1.2</td>
<td>-2.7 ± 1.5</td>
<td>-2.5 ± 1.4</td>
</tr>
<tr>
<td>Umbilical arterial pH</td>
<td>7.28 ± 0.04</td>
<td>7.27 ± 0.05</td>
<td>7.28 ± 0.04</td>
</tr>
<tr>
<td>Umbilical arterial base excess (mEq/L)</td>
<td>-2.4 ± 1.7</td>
<td>-2.3 ± 2.1</td>
<td>-2.50 ± 2.0</td>
</tr>
</tbody>
</table>

Values are mean ± sd, n (%), or median (IQR). There were no significant differences among groups.

HS = Hartman’s solution; HES = hydroxyethyl starch solution; IQR = interquartile range.
arterial gases was also similar. This may suggest that if we maintain maternal arterial blood pressure after spinal anesthesia with either crystalloid or colloid, the outcome would be the same although colloid can increase the risk of an allergic reaction.19

In our study, we used a suprasternal ultrasound probe to estimate the serial changes in the maternal CO after both preload and spinal anesthesia. Other methods such as impedance cardiography have been used with some limited success in the maternal population after neuraxial anesthesia, but findings are inconsistent and measures have been shown to be poorly validated.20 We emphasize that the primary aim of our study was to compare serial measures of CO and not absolute values. This Doppler technique has been validated against the thermodilution method in critically ill nonpregnant and pregnant populations.21,22 Even though the suprasternal ultrasound probe is portable, easy to use, noninvasive, and validated against the “gold standard” method of CO monitoring, it has limitations. These include the inability to provide continuous CO monitoring, movement artifact, and operator-dependent variation. Despite these limitations of noninvasive maternal CO monitoring, a recent editorial by Dyer and James23 concluded that less-invasive CO monitors will have an important role both in the hemodynamic management of parturients with comorbidities and in research into hemodynamics of healthy and critically ill mothers.

In summary, the suprasternal ultrasound device is a noninvasive method for measuring the cardiovascular changes after preload with HS and HES and spinal anesthesia in a clinical setting. Intravascular volume preloading increased CO, Ftc, and SD in all groups, but only in the HES 1.0 group did these changes persist after the induction of spinal anesthesia. Despite the increase in CO, the incidence of hypotension and vasopressor requirements was not different among groups. Measuring CO intermittently does not seem particularly helpful for either improving clinical care or preventing adverse outcome because hypotension still occurred despite the increases in CO. Our study results support that the measurement of arterial blood pressure and HR remains the most important monitors in clinical practice.

REFERENCES