Phenylephrine infusion for spinal-induced hypotension in elective cesarean delivery: Does preload make a difference?

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Abstract

Background and Aims: Patients undergoing elective cesarean delivery (CD) have a high-risk of spinal-induced hypotension (SIH). We hypothesized that a colloid preload would further reduce SIH when compared with a crystalloid preload.
Material and Methods: Eighty-two healthy parturients undergoing elective CD were included in the study. Patients were randomly assigned to two groups (41 patients in each group) to receive either Lactated Ringer's solution (1500 ml) or hydroxyethyl starch (6% in normal saline, 500 ml) 30 min prior to placement of spinal anesthesia. All patients were treated with a phenylephrine infusion (100 mcg/min), titrated during the study.
Results: There was no statistical difference between groups with regards to the incidence of hypotension (10.8% in the colloid group vs. 27.0% in the crystalloid group, $P = 0.12$). There was also no difference between groups with respect to bradycardia, APGAR scores, and nausea and vomiting. Significantly less phenylephrine (1077.5 ± 514 mcg) was used in the colloid group than the crystalloid group (1477 ± 591 mcg, $P = 0.003$).
Conclusion: The preload with 6% of hydroxyethyl starch before CD might be beneficial for the prevention of SIH.

Key words: Cesarean section, colloid, phenylephrine, preload, spinal anesthesia

Introduction

Spinal-induced hypotension (SIH) for cesarean delivery (CD) is a frequently encountered problem, with a reported incidence of approximately 80%.[1] Morbidity includes maternal nausea, vomiting, and dizziness. If hypotension is prolonged, impairment in placental blood flow[2,3] and fetal acidosis[4] may ensue. A common approach to prophylaxis includes a fluid bolus with prophylactic phenylephrine infusion; although, no single approach has been embraced as the gold standard, each prophylactic treatment comes with accompanying risks. Crystalloid preload alone has a poor efficacy in preventing hypotension, due to rapid redistribution into the extracellular space, while colloid has been more effective.[5,6] Although commonly used, synthetic colloids such as hydroxyethyl starch are more expensive than crystalloid; side effects include pruritis, anaphylactoid reactions, association with kidney injury, and coagulopathy.[5,7,8] The benefits of prophylactic phenylephrine infusion are controversial. However, it has been associated with a decreased incidence of hypotension and maternal nausea and vomiting and improved umbilical artery pH.[9-12] A combination of crystalloid cohydration and phenylephrine infusion decreased the incidence of hypotension to 1.9%.[12] Concerns surrounding the use of

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phenylephrine include maternal bradycardia, a relatively low risk of dysrhythmia,[13] and decreased cardiac output resulting in reduced placental perfusion.[14-16] However, in *ex vivo* studies, phenylephrine has been shown to improve fetal arterial perfusion more reliably than ephedrine,[15] which is known to cross the placenta,[17] resulting in increased fetal heart rate (HR), HR variability,[18] and fetal acidosis.[19]

Considering the encouraging reduction in the incidence of SIH demonstrated with the use of a crystalloid load and phenylephrine infusion,[12] as well as supporting literature that colloid is more effective than crystalloid preload in isolation,[5] we rationalized that we might further reduce the incidence of SIH by using a colloid load concomitantly with a phenylephrine infusion.

In this prospective, randomized, comparative study, we studied two groups of patients receiving prophylactic phenylephrine infusions, combined with either a colloid or crystalloid preload. We hypothesized that patients receiving prophylaxis with a phenylephrine infusion and colloid preload would show a reduced incidence of hypotension (defined as <20% below baseline) in comparison to patients receiving a phenylephrine infusion with crystalloid preload. We selected our secondary outcomes to reflect the clinical evidence of reduced cardiac output; these included the total dose of phenylephrine, incidence of bradycardia, nausea, and vomiting, as well as APGAR scores at 1 and 5 min.

Material and Methods

After approval by the Institutional Review Board for our research and protocol, 82 pregnant patients scheduled for elective CD under spinal anesthesia were recruited by the investigators from August 2008 to June 2010.

Patient selection

Inclusion criteria were: Normal singleton pregnancy, beyond 36 weeks gestation, between 18 and 35 years of age, American Society of Anesthesiologist physical Class I or II status, weight between 50 and 120 kg, and height ranging from 150-180 cm. Exclusion criteria were: Contraindications to spinal anesthesia, complications of pregnancy, pregnancy-induced hypertension, preeclampsia, known uteroplacental insufficiency, multiple gestation, fetal abnormalities, congenital heart abnormalities, known genetic abnormalities, prematurity, or clinical evidence of fetal distress, signs of onset of labor, or history of adverse reactions to hydroxyethyl starch.

Research protocol

After obtaining written informed consent, patients were randomized to be in the colloid or crystalloid infusion groups via computer-generated blocked randomization. The result of the randomization for each patient was sealed in sequentially numbered opaque envelopes and was opened by the primary anesthesia team prior to arrival in the operating room. Due to the rare, but the potentially catastrophic incidence of anaphylaxis associated with hydroxyethyl starch products, no parties were blinded to the preload used.

For all patients, an 18-gauge intravenous (IV) catheter was inserted into a forearm vein, and vein patency was maintained with Lactated Ringer's solution (LR) at a rate of 5 ml/h before administering the preload. Colloid preload was 500 ml hydroxyethyl starch in 0.9% normal saline (NS) (MW 600 kDa, molar substitution 0.75, Hespan®, Braun Medical, Irvine, CA, USA), and crystalloid preload was LR (1500 ml). The volume of crystalloid and colloid preload was chosen based on a 1:3 colloid to crystalloid ratio to achieve a similar degree of volume expansion.[20] IV administration of preload was delivered over 30 min, prior to spinal placement. After the fluid load was complete, IV patency was maintained at a rate of 5 ml/h and medications were flushed with LR.

All patients received 0.3 M sodium citrate (30 ml) orally, 30 min before arrival to the operating room. Standard monitoring for all patients consisted of noninvasive blood pressure (NIBP) measurement, electrocardiography, and pulse oximetry. Oxygen (2 l/min) was administered via nasal cannula. Appropriately sized, reusable adult NIBP cuffs (Solaris Medical Technologies®, San Francisco, CA, USA) were applied by the primary anesthesia team. In the operating room, 3 automated measurements of NIBP and HR were taken every minute until the systolic BP (SBP) measurements were consistent (no more than 10% variation), with the patient lying supine with left lateral tilt. The average SBP and accompanying HR of these 3 measurements were recorded as mean baseline values.

Spinal anesthesia was performed in the sitting position with a 25-gauge pencil point needle at the L2-L3 or L3-L4 vertebral interspace. A mixture of hyperbaric bupivacaine 0.75%, 12 mg with morphine, 200 mcg was injected intrathecally. Patients were then positioned supine with 15° left lateral tilt. BP and HR were measured and recorded at 1-min intervals starting 1-min after intrathecal injection until uterine incision. BP measurements were then taken at the discretion of the primary anesthesia team.

Phenylephrine infusion protocol

All patients were placed on a phenylephrine infusion (10 mg phenylephrine in 100 ml 0.9% NS) via an Alaris® IV infusion system (PC Unit, Cardinal Health, San Diego, CA, USA) immediately after intrathecal injection at a rate of

100 mcg/min. Phenylephrine infusion protocol was continued until the time of uterine incision. After uterine incision, further hemodynamic management was at the discretion of the attending anesthesiologist who administered IV fluids and vasopressors as appropriate to replace the surgical losses and maintain perfusion pressure. The infusion was stopped if the HR decreased below 60 beats per minute (bpm), or if the SBP increased to >20% above baseline (defined as reactive hypertension), and was restarted when the BP decreased to <20% below baseline (defined as hypotension). The total dose of phenylephrine used during the study period was recorded.

To treat hypotension despite concurrent phenylephrine infusion, an additional bolus of 100 mcg phenylephrine was administered. If bradycardia was encountered with SBP ≥100% baseline, the phenylephrine infusion was temporarily discontinued until the HR increased to >60 bpm. If the HR was <60 bpm with a SBP <100% baseline, IV glycopyrrolate (0.2-0.6 mg) was administered. If hypotension with bradycardia persisted, a bolus of 5 mg ephedrine was given, and the study was discontinued.

BP and HR were measured and recorded at 1-min intervals starting 1-min after intrathecal injection until uterine incision, and instances of hyper/hypotension were noted. BP measurements were then taken at the discretion of the primary anesthesia team.

Data collection

Patients were asked if they were nauseated at multiple points (in average every 5 min) before and after spinal insertion, and their response was recorded as a "yes" or "no." Episodes of emesis were noted. Preoperative risk factors for postoperative nausea and vomiting were not recorded. Any nausea and vomiting encountered during the course of the study in the setting of normal BP was treated with our institutional protocol for perioperative nausea and vomiting, including ondansetron (4 mg), and dexamethasone (4 mg).

Five minutes after intrathecal injection, sensory levels were checked for loss of temperature sensation with an ice cube. The following parameters were recorded: Sensory levels, times of skin incision, uterine incision, delivery, placental delivery, and oxytocin administration. APGAR scores were assessed at 1 and 5 min after delivery by the pediatric team and recorded.

Statistics

We defined hypotension as the primary outcome variable. Based on previous studies,[11,12] we assumed an effective method would reduce the incidence of hypotension to ≤5%. We calculated that a sample size of 37 patients in each group

would have an 80% of power, at 5% of significance level, to detect an incidence of hypotension of 5% or less in the colloid group.

All normally distributed data were expressed as mean ± standard deviation. Data that were not normally distributed were expressed as median (interquartile range). The data for the incidence of hypotension and occurrence of nausea and/or vomiting were compared using the Chi-squared test or Fisher's exact test as appropriate. Data for serial BP measurements and HR were analyzed using a one-way analysis of variance for repeated measures. The Student's *t*-test was used to compare the phenylephrine dose, whereas the Mann-Whitney Rank sum test was used to compare APGAR scores. A $P < 0.05$ was considered as significant.

Results

Eighty-two patients were enrolled in the study, 41 patients in each group. Eight patients were excluded from the study. Four patients in the crystalloid preload group were excluded because of the following reasons: One had excessively prolonged time to skin incision (20 min), two had high sensory levels (above T3), and one had hypotension and bradycardia refractory to treatment. Four patients in the colloid preload group were excluded: One patient experienced significant hypertension prior to starting the phenylephrine infusion, which persisted after spinal placement: One patient had a sensory level to T3, and two patients had inadequate spinal analgesia.

Patient demographic characteristics, hemodynamic data, and surgical data are presented in Table 1. Although patients in the colloid group had a lower incidence of hypotension (10.8%) when compared with the crystalloid group (27.0%) the difference was not statistically significant ($P = 0.12$). There was no significant difference in SBP changes over time within each group and between the two groups at each time point. The incidence of bradycardia was not significantly different in the colloid group (45.8%) versus the crystalloid group (35.1%) ($P = 0.4$). A significant decrease in HR from the baseline values was observed in both groups ($P < 0.001$); however, no difference was found between the two groups at individual time points.

Significantly less phenylephrine was used in the colloid group (1077 ± 514 mcg) compared to the crystalloid group (1477 ± 591 mcg) ($P = 0.003$) [Table 2]. The incidence of maternal nausea and vomiting, as well as APGAR scores at 1 and 5 min, were not significantly different within each group and between groups [Table 2]. The overall incidence of APGAR scores below 7 was 2.7% in the crystalloid

Table 1: Patient demographic data

Parameter	LR group	HES group	P, test
Age (years) (mean±SD)	29.45±4.98	28.33±5.86	0.379, *t*-test
Height (cm) (median [IQR])	168 (163-172.25)	167.5 (164-170)	0.598, Mann-Whitney rank sum test
Weight (kg) (median [IQR])	89 (75.5-104)	88.5 (75-99.5)	0.856, Mann-Whitney rank sum test
Spinal-skin incision time (min) (median [IQR])	10 (9.75-12.2)	11 (9-15)	0.812, Mann-Whitney rank sum test
Spinal-uterine incision time (min) (mean±SD)	17.98±5.18	17.75±5.42	0.858, *t*-test
EBL (mL) (median [IQR])	500 (500-762)	625 (500-800)	0.322, Mann-Whitney rank sum test
Baseline SBP (mmHg) (mean±SD)	130.93±11.35	132.91±11.22	0.461, *t*-test
Baseline HR (mean±SD)	90.42±13.75	87.85±11.4	0.396, *t*-test

EBL = Estimated blood loss, SBP = Systolic blood pressure, HR = Heart rate, LR = Lactated Ringer's solution, HES = Hydroxyethyl starch, SD = Standard deviation, IQR = Interquartile range

Table 2: Secondary outcome measures

Parameter	LR group	HES group	P, test
Total does of phenylephrine (mcg) (mean±SD)	1477±591	1077.5±514	0.003*, *t*-test
APGAR scores at 1 min (median [IQR])	8 (8-9)	8 (8-9)	1, Mann-Whitney rank sum test
APGAR scores at 5 min (median [IQR])	9 (9-9)	9 (9-9)	0.89, Mann-Whitney rank sum test
Incidence of bradycardia (%)	35.1	45.9	0.478, Chi-square test
Incidence of hypertension (%)	8.1	21.62	0.32, Chi-square test
Incidence of nausea (%)	16.2	18.9	1, Fisher's exact test
Incidence of vomiting (%)	8.1	8.1	1, Fisher's exact test

*Statistically significant, LR = Lactated Ringer's solution, HES = Hydroxyethyl starch, SD = Standard deviation, IQR = Interquartile range

group and 8.1% in the colloid group respectively, but was not significantly different ($P = 0.358$).

Rescue medications were administered to a total of eight patients [Table 3], resulting in improved hemodynamic stability. No other clinical interventions were necessary. During the study protocol, episodes of self-limited supraventricular tachycardia were documented in one patient in the crystalloid group and four patients in the colloid group.

Discussion

This study demonstrated that the use of a colloid preload required a lower dose of phenylephrine to maintain SBP within 5% of baseline, compared to the crystalloid group. This finding is consistent with previous studies suggesting a beneficial effect of colloids in maintaining SBP.[21,22] Further, while there was a lower incidence of hypotension with colloid preload (10.8%) when compared with the crystalloid group (27.0%) the difference was not statistically significant ($P = 0.12$). It is possible that a larger number of patients may have confirmed this trend. In addition, despite less need of phenylephrine in the colloid group, we did not observe a difference in the incidence of bradycardia (<60 bpm), or absolute decreases in HR over time between the two groups.

We initiated our fluid bolus of either crystalloid or colloid 30 min prior to arrival in the operation room to ensure the entire bolus would be administered prior to the uterine incision, or the end of the study period. Although crystalloid co-loading is reportedly better than preloading for preventing hypotension,[6,12,23] the response to a crystalloid co-load is a variable, depending on the rate of infusion and the amount infused.[5] In contrast, colloid co-loading seems to be as effective as preloading.[5] A recent meta-analysis, including studies without vasopressors and various prophylactic regimens, demonstrated no benefit in using co-load in comparison to preload in preventing SIH.[24]

Recently, concerns have been raised about hydroxyethyl starch administration in critically ill patients, particularly those with significant kidney dysfunction.[25] It is not clear, however, whether this applies to pregnant patients.

We chose a phenylephrine infusion at a rate of 100 mcg/min as it has been effectively shown to reduce the incidence of SIH.[12] The similar gradual decrease in HR in both groups, despite the different dose required, may be attributed to the effect of the spinal anesthetic as well as the phenylephrine infusion. Of note, although reductions in cardiac output have been correlated with HR changes,[26] bradycardia has not been shown to affect the neonatal outcome.[27] We found a higher incidence of bradycardia with the use of high-dose phenylephrine infusion than reported in previous studies.[11,12] This is likely due to our definition of bradycardia as a HR less than 60 bpm and not 50 bpm as reported in other investigations.[11,12] Since the time of the design of our study, lower phenylephrine dosing regimens (25 and 50 mcg/min) have been described to decrease SIH with similar fetal and maternal outcomes;[9] these regimens in combination with co-load

Table 3: Rescue medications delivered

Rescue medication	HES group	LR group
Phenylephrine 100 mcg bolus	1	2 (1 patient 300 mcg)
Ephedrine bolus 5 mg	0	2
Glycopyrrolate 0.6 mg	1	2

LR = Lactated Ringer's solution, HES = Hydroxyethyl starch

are an area of future investigation. Although shown to have a relatively low risk of ventricular dysrhythmias,[13] phenylephrine administration has been associated with decreased cardiac output and dysrhythmias, including ventricular tachycardia, supraventricular tachycardia, coronary artery spasm, and myocardial infarction, although these side effects seem to be reduced when compared with ephedrine.[26] In our study, four patients in the colloid group and one patient in the crystalloid group experienced episodes of supraventricular tachycardia whereas the phenylephrine infusion was running, prior to the uterine incision. Although an interesting finding, our study was not powered to determine an incidence of supraventricular tachycardia or to detect a difference between the two groups with regards to the occurrence of arrhythmias.

APGAR scores were not significantly different at 1 and 5 min between the two groups, suggesting no difference in the neonatal outcome. No fetal arterial or venous blood gases were available to demonstrate the presence or absence of fetal acidosis. However, recent evidence indicates that 5-min APGAR scores are a better predictor of neonatal outcome than the measurement of umbilical artery pH, even for newborns with severe acidemia.[28]

One of our study limitations was the measurement of cardiac output; direct or indirect measurement is not common practice in healthy pregnant parturients presenting for CD. Due to ethical concerns, we chose to use NIBP measurements taken every minute. A number of recent publications have demonstrated a good correlation between invasive and NIBP measurements in different clinical settings.[29-31]

Another limitation of our study was the absence of blinding. Ideally, a prospective trial would be double-blinded and randomized; however, the small risk of anaphylaxis with hydroxyethyl starch had to be considered. If in this scenario the primary anesthesia team was blinded to the fluid being administered, a cause for an adverse reaction may not be immediately recognized and may delay treatment.

Conclusion

A phenylephrine sparing effect associated with preloading colloids suggests a possible superiority of colloids against crystalloids in prevention and treatment of SIH.

Conflicts of interest
There are no conflicts of interest.

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