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Original contribution

Minimum effective fluid volume of colloid to prevent hypotension during caesarean section under spinal anesthesia using a prophylactic phenylephrine infusion: An up-down sequential allocation study☆

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ABSTRACT

Study objective: The aim of this study was to de termine the minimum effective fluid volume (MEFV) of hydroxyethyl starch 130/0.4 (HES) infused in a preload fashion which would prevent hypotension in 50% of parturients undergoing caesarean section. A secondary objective was to measure the hemodynamic effect of fluid loading on the subjects.
Design: This is a prospective, double-blinded, dose-finding study using an up-down sequential allocation design.
Setting: In the operating room.
Patients: Thirty healthy parturients undergoing caesarean section under spinal anesthesia using a prophylactic phenylephrine infusion were included in this study.
Intervention: The initial HES volume infused in the first patient was 500 mL. A failure of treatment to HES preload was defined as a single episode of systolic hypotension below 20% of baseline value. The next patient in the sequence was given a volume of HES adjusted by either an increment or a decrement of 100 mL according to the previous subject response to fluid preload.
Measurements: Stroke volume and cardiac output were measured with a bioreactance-based non-invasive cardiac output monitor (NICOM).
Main results: The MEFV of HES was 733 mL (95% CI: 388-917 mL). Fluid loading before the administration of the spinal anesthesia resulted in an increase in stroke volume and cardiac output. The combined effect of spinal anesthesia and a phenylephrine infusion reduced the maternal heart rate and cardiac output, but not the stroke volume.
Conclusion: Our study is the first to investigate variable fluid loading volumes in this population. A HES preload of approximatively 700 mL prevented maternal hypotension in 50% of the parturients under the conditions of this study. We suggest that up-down sequential allocation design is a useful tool to compare different fluid loading regimens in this setting.

1. Introduction

Spinal anesthesia-induced hypotension, which is pronounced in term parturients undergoing elective caesarean section, may be deleterious to both the mother and the fetus. Obstetric anesthetists are increasingly opting for prophylatic phenylephrine infusions as first line therapy to prevent hypotension in pregnant women undergoing caesarean section [1]. Phenylephrine infusions significantly reduce the incidence of hypotension, nausea and vomiting and increases patient comfort while being safe for both the mother and the baby [2,3].

Some experts have questioned the usefulness of prophylactic fluid boluses for prevention of spinal anesthesia-induced maternal hypotension [4]. Several studies have shown that volumes of crystalloid up to 30mL kg^{-1}, given before the administration of spinal anesthesia (preloading) only moderately prevented hypotension [5-7]. Various fluid loading strategies including the use of fluid coloading (infusion of fluid at the time of the administration of spinal anesthesia) have

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proven superior to crystalloid preloading, although their clinical effectiveness is moderate [8-10]. Very few studies have evaluated the additional benefit of fluid loading in terms of hypotension prevention in patients already receiving a prophylactic infusion of an alpha-receptor agonist such as phenylephrine [11,12]. The studies which aimed to find an ideal fluid volume which would prevent such hypotension are limited by their design which compared fixed volumes. To our knowledge, there is no study investigating variable fluid volumes in women receiving a phenylephrine infusion to prevent spinal anesthesia-induced hypotension. The primary aim of this study was to determine the minimum effective fluid volume (MEFV) of colloid infused as a preload which would prevent hypotension in 50% of healthy term pregnant women undergoing caesarean section with spinal anesthesia used in conjunction with a phenylephrine infusion. We measured the effect of fluid loading several maternal hemodynamic parameters as a secondary objective.

2. Methods

After obtaining institutional review board approval (IRB: #11 051) and written informed consent, 30 pregnant women were enrolled in this prospective, double-blind, dose-finding study between October 2011 and September 2012 (ClinicalTrial.gov: #NCT01415284). Healthy parturients (ASA score I-II) at term gestation (37 weeks and above) with a singleton pregnancy undergoing elective caesarean section under spinal anesthesia were considered eligible for recruitment. Exclusion criteria included hypertensive disorders (chronic or gestational hypertension, pre-eclampsia and eclampsia), cardiac pathologies, a body mass index above 35at the time of delivery, abnormal placentation, known allergy to hydroxyethyl starch, refusal to participate or urgent caesarean section.

Subjects were instructed to fast from midnight on the day of the surgery and were premedicated with 30 mL of sodium citrate 0.3 mol/L on the preoperative unit before leaving for the operating theater. In the waiting area vital signs were taken every 5 minutes over 10 minutes (3 measurements) by a research nurse. All measurements were averaged to determine baseline vital signs. Abio-reactanceNon-Invasive Cardiac Output Monitor (NICOM) (Cheetah Medical, Boston, MA) was used to evaluate the ejection volume and cardiac output. The complete mechanisms underlying the use of this technology are extensively detailed by Keren etal [13] and briefly described in Appendix A. Once baseline vital signs were recorded, a total of 4 sensors were applied on the back of the patients by the research nurse in accordance with the manufacturer's instructions.

In the operating room, the subjects were placed in the left-wedged supine position and a large-bore (18G) intravenous line was inserted in the left forearm. The NICOM sensors were connected to the NICOM device and baseline ejection volume and cardiac output were determined. The studied volume of hydroxyethyl starch (HES) 130/0.4 in NaCl 0.9% (Voluven, Fresenius-Kabi, Germany) was then infused under pressure using an inflatable fluid pump as rapidly as possible while vital signs and hemodynamic parameters were recorded every minute over 10 minutes by the research nurse. The study HES volume was prepared preoperatively by the same research nurse who then covered the HES bags with an opaque plastic bag in order to ensure that both the attending anesthetist and the patient were blinded to the infusion volume. A lactated ringer infusion was administered at a rate of 100 mL h^{-1} with a Baxter infusion pump from the end of the HES infusion until the end of the study period, that is, the delivery of the baby.

After the initial 10 minute period for fluid preloading, the subjects were placed into the sitting position. A standardized «needle-through-needle» combined spinal-epidural anesthesia technique was performed by the anesthetist attending the patient's care at the L2-L3 or L3-L4 vertebral interspace level using a 17G Tuohy epidural needle and a 27G Whitacre spinal needle. The anesthetist remained in the operating room to ensure routine anesthetic care throughout the caesarean section. A dose of 10.5mg hyperbaric bupivacaine with fentanyl 15 μg and morphine 150 μg was injected in the intrathecal space after which an epidural catheter was inserted 4 to 5cm into the epidural space. At the start of the spinal injection, a phenylephrine infusion at a rate of 0.5 μg kg^{-1} min^{-1} (based on the body weight at first antenatal clinic visit) was initiated. The patient was then placed in the left-wedged supine position. Vital signs and hemodynamic parameters were recorded every minute until the delivery of the baby. The obstetricians were instructed to prepare the patient for the caesarean section in order to perform the skin incision exactly 20 minutes after the spinal injection. A loss of sensation to cold at the T4 level, measured by the attending anesthetist, at the time of skin incision was considered adequate to start surgery. This evaluation was performed at 15 minutes after the spinal injection and repeated at 20 minutes. In cases where the sensory block had not reached the T4 level at 15 minutes, a 5 mL bolus of lidocaine 2% with epinephrine 5 μg/mL was injected in the epidural space through the indwelling epidural catheter. If the sensory block was considered inadequate for surgery at 20 minutes, the patient was withdrawn from the study and left to the care of the attending anesthetist. The individual study period ended at delivery of the baby.

The up-down sequential allocation method described by Pace and Stylianou was used to determine the HES study volume [14]. In this approach, the volume injected to the next patient is determined by the clinical response of the previous patient. In our study, the initial HES volume infused to the first patient was 500 mL. This volume was arbitrarily chosen as the best estimation of the MEFV based on 2 investigations which showed that a preloading of HES of 0.5 liter reduced the incidence of hypotension between 35 and 40% [8,15]. A failure of treatment was defined as a single episode of systolic hypotension below 20% of baseline value. In such a case, the next patient was given a higher volume by an increment of 100 mL. A successful response was defined as an absence of hypotension, with, the next patient in the sequence receiving a lower volume by an decrement of 100 mL, and so on, until the last subject was enrolled. The treatment results as well as all trial data were collected on a paper case record file which was secured in a key-locked drawer within the anesthesia department. Only the research nurse involved in this trial had access to the trial CRFs and could use them in order to prepare the infused volumes of HES for each subject. Unblinding was made possible in agreement with the *International Conference for Harmonization of Good Clinical Practice E6*-based institutional protocol. For clinical safety and ethical considerations, we kept the volume infused within a range of 200 mL to 1500 mL.

When needed, vasopresors were administered by the attending anesthetist according to the study protocol. Episodes of systolic hypotension (defined as systolic blood pressure below 20% of baseline value) without bradycardia (HR >55 bpm) were treated with an intravenous bolus of phenylephrine 100 μg, whereas an episode of hypotension associated with bradycardia (HR< 55 bpm) was treated with an IV bolus of ephedrine 5 mg. An isolated episode of bradycardia with the systolic blood pressure within 20% of the baseline SBP was treated with a bolus of IV glycopyrrolate 0.2 mg. An episode of hypertension above 120% of baseline SBP was treated by reducing the phenylephrine infusion rate to 25% of its initial rate. At any time, the attending anesthetist was allowed to deviate from the study protocol if patient safety was thought to be at risk. In this instance, the patient was excluded from the trial.

The primary outcome of this study was the volume of hydroxyethyl starch infused as a preload before spinal anesthesia which would prevent an episode of systolic hypotension below 80% of baseline in 50% of the subjects (EV50). Secondary outcomes included the incidence of hypotension and of hypertension, the total dose of vasopressors administered, nausea and vomiting episodes, sensory block level, 1 and 5 minute Apgar scores as well as umbilical artery and venous cord blood gases.