Reports of Investigation

Hydroxyethylstarch 10% is superior to Ringer's solution for preloading before spinal anesthesia for Cesarean section

Sahar M. Siddik MD FRCA,
Marie T. Aouad MD,
Ghada E. Kai MD,
Maria M. Sfeir MD,
Anis S. Baraka MD FRCA

Purpose: To compare the preloading effect of 500 ml hydroxyethylstarch (HES) 10% with 1 L Lactated Ringer's solution (LR).

Methods: In 40 healthy women undergoing elective Cesarean section HES, 500 ml ($n = 20$), or LR, 1 L ($n = 20$), was administered during 10 min before spinal anesthesia. The incidence of hypotension, (systolic blood pressure $< 80\%$ of baseline and < 100 mm Hg), and the amount of ephedrine used to treat it were compared. Also, the incidence of nausea and/or vomiting were recorded. Neonatal outcome was assessed using Apgar scores and umbilical venous and arterial blood gases.

Results: The incidence of hypotension was higher in the LR than in HES group (80% vs 40%). Mean minimum systolic blood pressure was lower in the LR than in the HES group (86.1 ± 12.7 mm Hg vs 99.6 ± 9.7 mm Hg $P < 0.05$). Systolic blood pressure < 90 mmHg occurred in two of 20 patients (10%) who received HES vs 11 of 20 patients (55%) who received LR ($P < 0.05$). More doses of ephedrine were required to treat hypotension in the LR than in the HES group (35.3 ± 18.4 mg vs 10.6 ± 8.6 mg; $P < 0.05$). The incidence of nausea and/or vomiting was lower in the HES than in the crystalloid group. Neonatal outcome was good and similar in both groups.

Conclusion: Preloading patients undergoing elective Cesarean section with 500 ml HES 10%, decreases the incidence and severity of spinal-induced hypotension more than preloading with 1 L of LR solution.

Objectif : Comparer l'effet d'une précharge de 500 ml d'hydroxyéthylamidon (HEA) à 10 % avec celui de 1 L de solution de lactate de Ringer (LR).

Méthode : Pendant 10 min avant la rachianesthésie, on a administré chez 40 femmes qui devaient subir une césarienne 500 ml d'HEA ($n = 20$) ou 1 L de LR ($n = 20$). L'incidence d'hypotension (tension artérielle $< 80\%$ de la mesure de base et < 100 mmHg) et la quantité d'éphédrine utilisée pour la traiter ont été comparées. De plus, l'incidence de nausées et/ou de vomissements a été enregistrée. L'indice d'Apgar et l'analyse des gaz du sang veineux et artériel ombilical ont permis d'évaluer les nouveau-nés.

Résultats : On a noté une plus grande incidence d'hypotension avec le LR qu'avec l'HEA (80 % vs 40 %). La moyenne des mesures de tension artérielle systolique minimale était plus basse dans le groupe LR que dans le groupe HEA ($86,1 \pm 12,7$ mmHg vs $99,6 \pm 9,7$ mmHg $P < 0,05$). La tension artérielle systolique < 90 mmHg est survenue chez deux des 20 patientes (10 %) qui ont reçu de l'HEA vs 11 des 20 patientes (55 %) qui ont reçu du LR ($P < 0,05$). Le traitement de l'hypotension a nécessité plus d'éphédrine dans le groupe LR que dans le groupe HEA ($35,3 \pm 18,4$ mg vs $10,6 \pm 8,6$ mg; $P < 0,05$). L'incidence de nausées et/ou de vomissements a été plus faible avec l'HEA qu'avec le cristalloïde. L'évaluation néonatale a été satisfaisante et similaire dans les deux groupes.

Conclusion : Une précharge de 500 ml d'HEA à 10 % chez des patientes qui vont subir une césarienne diminue plus l'incidence et la sévérité de l'hypotension induite par la rachianesthésie qu'une précharge avec 1 L de solution de LR.

From the Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

Address correspondence to: Anis Baraka MD FRCA, Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.
Fax: 961-1-744464; E-mail: abaraka@aub.edu.lb

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MATERNAL hypotension is the commonest serious problem following spinal anesthesia for Cesarean section, with an incidence up to 83%.¹ Volume preloading has been recommended for prevention of spinal-induced hypotension in this situation. However, controversy regarding the different preloading regimens remains unresolved.¹⁻⁷

Recent studies have questioned the advantage of preloading with crystalloid in the prevention of spinal-induced hypotension in patients undergoing Cesarean section.²⁻⁴ Giving up to two litres of crystalloid solution may reduce but not eliminate hypotension.⁵ Mathru *et al.* has shown that hypotension is eliminated in albumin-treated parturients compared with a 30% incidence of hypotension in crystalloid-preloaded patients, and the clinical and biochemical status of the neonates improved in the colloid-treated group.⁶ When hydroxyethylstarch 6% was compared with crystalloid preloading before Cesarean section, the incidence of hypotension, although less in the colloid group, was not significantly different.⁷

Hydroxyethylstarch 10% solution (HAES-steril 10% in saline 0.9%, Fresenius) is a recently introduced hyperoncotic colloidal solution which has a volume retaining effect in excess of 100%.⁸ The present report compares, in two groups of women undergoing elective Cesarean section under spinal anesthesia, the efficacy of preloading with 500 ml hydroxyethylstarch 10% *vs* 1 L lactated Ringer's solution. Also, the incidence and severity of hypotension, the need for vasopressors, as well as the incidence of nausea and/or vomiting are compared. The neonatal outcome is assessed in both groups using Apgar scores and umbilical venous and arterial blood gases.

Methods

After institutional ethics committee approval and informed consent, 40 non-labouring ASA class I and II women scheduled for elective Cesarean section were enrolled. Exclusion criteria included obesity (weight > 115 kg), height < 152 cm, diabetes, pregnancy-induced hypertension, chronic hypertension, heart disease, multiple gestation, breech presentation, age < 18 or > 40 yr and systolic blood pressure (SBP) < 100 mmHg.

Patients were premedicated with 0.5 mg atropine *im* 30-40 min before surgery. The patients were placed comfortably in the left supine wedged position. In the operating room, baseline arterial blood pressure and heart rate were taken as the mean of three consecutive readings at three minutes intervals during which the systolic pressure did not vary by more than 10% from its average value.

Patients did not receive intravenous fluids before entering the study. Subjects were randomly assigned by drawing shuffled sealed envelopes to receive, during the ten minutes preceding the spinal block, either 1 L lactated Ringer's solution (LR) (Group LR; n=20), or 500 ml hydroxyethylstarch 10% (HES 10%) (Group HES; n=20) via a 14 G *iv* cannula. Nurses placed a brown paper bag over the *iv* solution to conceal its identity from the anesthesiologist collecting data for the study. Spinal anesthesia was performed at the L₂₋₃ or L₃₋₄ interspace, with the patient in the sitting position, and with the side-port of the needle pointing cephalad. All subjects received 13 mg bupivacaine 0.75% in dextrose 8.5% delivered through a 25-gauge Whitacre needle. Immediately after injection, the patient was positioned supine with left uterine displacement. Oxygen, 5L·min⁻¹, was administered by face mask. Blood pressure was measured with an automated blood pressure device (Hewlett Packard) every minute for 20 min and every five minutes thereafter. Hypotension was defined as SBP < 80% of the baseline blood pressure, and < 100 mm Hg. The incidence of hypotension, as well as the mean minimal SBP and the mean maximal heart rate were compared in both groups. Hypotension was treated with *iv* boluses of 5 mg ephedrine and additional rapid infusion of LR. Ephedrine treatment was repeated every two minutes if hypotension persisted or recurred.

The maximum height of the block, assessed by pinprick, was monitored in all patients. Other drugs given and their doses, and the amount of additional *iv* fluid given before delivery were recorded. Also, the incidence and timing of nausea and/or vomiting were monitored.

The interval between spinal injection and delivery, and the uterine incision-delivery interval were noted. Following delivery, neonatal outcome was assessed using Apgar scores. Also, umbilical venous and arterial blood gases were obtained from a double clamped segment of umbilical cord.

Data are expressed as mean $\pm$ SD, as absolute numbers and as percentages. The student t test was utilized in analyzing continuous variables, while the chi-square analysis was utilized to compare discrete variables. Values of $P < 0.05$ were considered significant.

TABLE I Maternal characteristics expressed as mean $\pm$ SD

	Lactated Ringer n = 20	Hetastarch 10% n = 20
Maternal Age (yr)	30 $\pm$ 4.6	29 $\pm$ 6.9
Maternal weight (kg)	78 $\pm$ 9.6	80 $\pm$ 11
Maternal Height (cm)	161 $\pm$ 5.4	162 $\pm$ 6.0
Gestation (wk)	38 $\pm$ 1.0	38 $\pm$ 1.4

Results

The two groups were similar concerning maternal age, weight, height, and gestational age (Table I). All spinal blocks extended to T₆ and above. There was no difference in the level of sensory block, or in the spinal injection-delivery or uterine incision-delivery intervals (Table II).

Both groups had similar preinduction systolic blood pressures and heart rates. However, the incidence of hypotension after spinal anesthesia was higher in the LR than in the HES group (80% *vs* 40%). The minimum SBP mean value after spinal anesthesia was lower and the maximum HR mean value was higher in group LR. Also, SBP < 90 mm Hg was noted in 11 of 20 patients pre-loaded with LR compared with two of 20 patients pre-loaded with HES 10%. Patients in group LR required more doses of ephedrine than those in group HES. However, the time to hypotension and the volume of additional *iv* fluid received before delivery were not different between the LR and the HES groups (Table II).

Nausea and/or vomiting was observed about 8-12 min after induction of spinal anesthesia, and occurred more frequently in the LR than in the HES group (10 of 20 patients *vs* 4 of 20 patients). Nausea and/or vomiting coincided with the maternal hypotension, and was successfully treated by correcting the hypotension with *iv* ephedrine and rapid fluid infusion.

Neonatal outcome was similar in both groups. In group LR, 19 of 20 of the neonates had a one minute

Apgar score > 7.0, and all newborns had a five minutes score > 7.0. In group HES, all newborns scored > 7 at one minute and at five minutes. Umbilical cord blood gases were within the normal range, and were not different between the two groups. (Table III) Also, comparing neonates pooled from mothers of both groups having SBP < 90 mm Hg *vs* > 90 mm Hg, showed no difference in umbilical cord blood gases. (Table IV)

Discussion

The present report shows, in patients undergoing elective Cesarean section under spinal anesthesia, that preloading, with 500 ml hyperoncotic colloid hydroxyethylstarch 10% resulted in a lower incidence and severity of hypotension than that following crystalloid preloading with 1L Lactated Ringer's solution. Also, the ephedrine dose requirements were lower in the hydroxyethylstarch group than in the crystalloid group.

The use of crystalloid preloading does not always prevent hypotension after spinal anesthesia for elective Cesarean section.²⁻⁴ About 75% of intravenous crystalloid solution diffuses into the interstitial space and, hence, about 2.5 to 3 times the volume of crystalloid solution is needed to achieve the same degree of blood volume expansion achieved by iso-oncotic colloid solution.⁹ Thus, colloid solutions are a more logical choice to pre-load patients undergoing surgery under spinal anesthesia since they remain in the circulation for longer depending on their physical properties. Baraka *et al.* have shown that preloading with gelatin

TABLE II Spinal injection-delivery and uterine incision-delivery intervals, anesthetic block, and hemodynamic variables

	<i>Lactated Ringer</i> <i>n</i> = 20	<i>10% Hetastarch</i> <i>n</i> = 20
Spinal injection-delivery (min)	22.7 ± 4.7	22.7 ± 4.6
Uterine incision-delivery (sec)	107 ± 46	127 ± 85
Block level at 5 min; median (range)	T8 (T4-T10)	T8 (T6-T11)
Block level at 10 min; median (range)	T4 (T2-T8)	T5 (T3-T8)
Baseline systolic blood pressure (mmHg)	123 ± 9.7	122 ± 9.8
Baseline heart rate (bpm)	93.6 ± 14.5	90.9 ± 13.1
Minimum systolic blood pressure (mmHg)	86.1 ± 12.7	99.6 ± 9.7*
Maximum heart rate (bpm)	139.4 ± 15.5	120.5 ± 9.2*
Patients with hypotension % (95% CI)	80% (63-97%)	40% (19-61%)*
Time to hypotension (min)	4.9 ± 2.8	5.9 ± 4.0
Patients with nausea and/or vomiting 5 (95% CI)	50% (28-72%)	20% (3-37%)*
Systolic blood pressure < 100 mmHg (n)	16	8*
Systolic blood pressure < 90 mmHg (n)	11	2*
Ephedrine dose (mg)	35.3 ± 18.4	10.6 ± 8.6*
Extra LR volume (ml)	647.4 ± 279.6	841 ± 492.5
Apgar score at 1 min	8.4 ± 0.9	8.2 ± 0.7
Apgar score at 5 min	9.6 ± 0.5	9.4 ± 0.5

Values are expressed as mean ± SD except where indicated

**P* < 0.05

95% CI: 95% confidence interval

TABLE III Umbilical blood gas values

	<i>Lactated Ringer</i> <i>n = 20</i>	<i>10% Hetastarch</i> <i>n = 20</i>
Umbilical Venous Blood		
PO ₂ (mmHg)	27 ± 9	29 ± 7
PCO ₂ (mmHg)	43 ± 5	42 ± 4
pH	7.34 ± 0.04	7.35 ± 0.03
BD/BE (mEq·L ⁻¹)	2.3 ± 1.65	1.3 ± 1.5
HCO ₃ ⁻ (mEq·L ⁻¹)	23.3 ± 1.5	23.8 ± 1.6
Sat (%)	48 ± 21	52 ± 18
Na ⁺ (mEq·L ⁻¹)	137 ± 4	139 ± 4
K ⁺ (mEq·L ⁻¹)	4.2 ± 0.5	4.1 ± 0.5
Umbilical Arterial Blood		
PO ₂ (mmHg)	14 ± 6	15 ± 6
PCO ₂ (mmHg)	54 ± 7	54 ± 6
pH	7.27 ± 0.05	7.29 ± 0.04
BD/BE (mEq·L ⁻¹)	2.7 ± 2.1	1.4 ± 1.8
HCO ₃ ⁻ (mEq·L ⁻¹)	24.6 ± 1.9	25.6 ± 2.4
Sat (%)	16 ± 10	19 ± 13
Na ⁺ (mEq·L ⁻¹)	138 ± 5	142 ± 6
K ⁺ (mEq·L ⁻¹)	4.1 ± 0.5	4.2 ± 0.6

TABLE IV Apgar Scores and umbilical blood gases in the mothers with SBP < 90 mm Hg *vs* mothers with SBP > 90 mmHg expressed as mean ± SD

	<i>SBP < 90 mm Hg</i> <i>n=13</i>	<i>SBP > 90 mm Hg</i> <i>n=27</i>
Apgar Score at 1 min.	8.23 ± 0.83	8.34 ± 0.83
Apgar Score at 5 min.	9.38 ± 0.5	9.60 ± 0.50
Venous Blood		
PO ₂ mmHg	26.5 ± 10.4	29.2 ± 7.5
PCO ₂ mmHg	44.1 ± 5.5	42.2 ± 3.9
pH	7.32 ± 0.4	7.36 ± 0.03
Arterial Blood		
PO ₂ mmHg	14.6 ± 6.9	14.6 ± 5.8
PCO ₂ mmHg	53.6 ± 8.2	54.1 ± 6.0
pH	7.27 ± 0.06	7.21 ± 0.03

(hemacel) solution is more effective than saline in attenuating spinal anesthesia-induced hypotension in patients undergoing elective transurethral resection of the prostate.¹⁰ Also, Sharma *et al.* observed that patients given 500 ml HES 6% had a 21% incidence of hypotension after spinal anesthesia with lidocaine for post-partum tubal ligation compared with 55% in patients given 1 L LR solution.¹¹

Recent studies have confirmed the superiority of HES 6%-crystalloid combination compared with HES 6% or crystalloid alone. Vercauteren *et al.* were able to maintain the most optimal hemodynamic stability in patients receiving high volume of HES 6%-crystalloid combination (up to 1 litre HES 6% with 1 litre LR). Hypotension (< 90 mmHg) occurred in one of 10

patients.¹² Also, Riley *et al.* reported a 45% incidence of hypotension in patients who received 500 ml HES 6% plus 1 litre LR *vs* 85% in those who received two litres of LR.⁵ The results of these two reports in patients receiving the combination of crystalloid and HES 6% solutions are comparable to those achieved in our patients receiving the hyperoncotic HES 10% only, without crystalloid supplementation.

Hydroxyethylstarch 10% has an average molecular weight of 200 000 Da. and an osmolality of 309 mosmol·L⁻¹. It is a hyperoncotic (oncotic pressure 66 mmHg) colloid, isotonic infusion solution that has a volume retaining effect in excess of 100%. It is an attractive choice because it produces a plasma volume expansion of 140%: for each ml infused, an additional 0.4 ml is recruited from the extravascular space to the intravascular compartment. The maximal volume expansion effect is reached in 10 to 15 min and lasts about 60 min.⁸ Conversely, LR distributes throughout the extracellular fluid and 1 L results in expansion of the plasma volume by only 250-300 ml. Thus, we need about 3000 ml of LR to result in an expansion of plasma volume equivalent to that achieved by the 500 ml of HES 10%. Large volumes of crystalloid fluid can decrease oxygen carrying capacity.¹³ It may also increase the risk of pulmonary edema in susceptible patients. Parturients at term may be at greater risk of pulmonary edema, with a reduced pulmonary interstitial safety margin because of a decrease in oncotic pressure and an increase in plasma volume.¹⁴

A recent report has demonstrated a lower incidence of hypotension (SBP <70% of baseline BP or <90 mm Hg) in parturients undergoing elective Cesarean section who were pre-loaded with 15 ml·kg⁻¹ pentastarch 10% in saline 0.9% (colloid oncotic pressure 40 mmHg) than in those who received an equivalent volume of Lactated Ringer solution (12.5% *vs* 47.5%).¹⁵ In our report, pre-loading with only 500 ml HES 10% (about 7.5 ml·kg⁻¹) resulted in a similar decrease in the incidence of SBP < 90 mm Hg in group HES as in group LR (10% *vs* 55%). This small volume of 500 ml HES 10% can be administered quickly, within 10 min, allowing rapid and effective pre-loading prior to spinal anesthesia for Cesarean section, which is desirable in urgent situations. The current recommendations limit the maximum dose of HES 10% to 20 ml·Kg⁻¹·day⁻¹ due to concerns of adverse hematological, immunological, renal, and reticuloendothelial function. There is concern that HES might be associated with a bleeding diathesis. Observed coagulation abnormalities include hemodilution reduction of clotting factors, decreased fibrinogen, factor VIII and von Willebrand factor levels and reduced platelet function. However,

excessive clinical bleeding was not observed in our patients who received HES 10%. Also, the allergic potential of HES is seven times lower (1/2100) than that of the gelatins¹⁶ and no adverse reactions to HES occurred in this study. HES may offer other advantages such as decreased postoperative venous thrombosis.⁸ The 10% concentration seems to be safe for the neonate as placental transfer in a sheep preparation has been found to be almost negligible.¹⁷

The present study shows that the incidence of nausea and/or vomiting is lower in patients pre-loaded with HES 10% than in patients pre-loaded with LR solution. Nausea and vomiting in patients undergoing Cesarean section under spinal anesthesia have a complex and multifactorial etiology, and can be influenced by factors such as hormonal changes, age, weight, pain, hypotension and uterine exteriorization. In our patients, most of the episodes of nausea and/or vomiting coincided with the onset of maternal hypotension, and were eliminated by treating the hypotension. Thus, the occurrence of nausea and/or vomiting in patients undergoing Cesarean section under spinal anesthesia may be secondary to hypotension, and its associated brain stem hypoxemia, which should always be anticipated and treated before administering antiemetic therapy.

Despite the decrease in the incidence and severity of hypotension in group HES than in group LR, neonatal outcome, as evidenced by the Apgar scores and the umbilical vein blood gases, was good and not different between the two groups. This reflects previous experience that transient decreases in blood pressure rapidly treated with vasopressors do not usually affect fetal acid-base status.¹⁸

In conclusion, preloading with 500 ml hyperoncotic hydroxyethylstarch 10% solution infused during the 10 min preceding the administration of spinal anesthesia for elective Cesarean section results in a lower incidence and severity of hypotension than that following crystalloid preloading with 1 L Lactated Ringer's solution. Also, the need of vasopressors for treatment of hypotension, as well as the incidence of nausea and/or vomiting, were lower in the hydroxyethylstarch than in the Lactated Ringer group. However, neonatal outcome, as assessed by Apgar scores and umbilical cord blood-gas analysis, was good and similar between the two groups, suggesting that early and prompt management of spinal-induced hypotension may be more important to the neonate than the type of fluid used for prehydration.

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