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Effects of hydroxyethyl starch 6 % (130/0.4) on blood loss during cesarean delivery: a propensity–matched analysis

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Abstract

Background—Hydroxyethyl starch is commonly used in the obstetric patient population to prevent hypotension during cesarean delivery. Evidence suggests hetastarch is associated with a dysfunction in coagulation cascade. We hypothesized that hetastarch use to prevent spinal hypotension during cesarean delivery would be associated with an increase in blood loss when compared to crystalloid use.

Methods—We performed a retrospective review of patients who underwent elective cesarean delivery under spinal anesthesia at the University of Virginia between 2011 and 2014. Data from 819 patients was used. Blood loss was the primary outcome. Propensity score-matching was used to match patients who received hetastarch (treatment group) with those who did not receive hetastarch (control group).

Results—Genetic matching resulted in 196 patients in the hetastarch group and 182 patients in the control group. There was no difference in estimated blood loss ($p = 0.068$), calculated blood loss ($p = 0.720$), total intra-operative fluid intake ($p = 0.289$), urine output ($p = 0.421$), Apgar 1 min ($p = 0.830$), Apgar 5 min ($p = 0.138$), phenylephrine consumption ($p = 0.742$), postoperative day 1 (POD1) hematocrit ($p = 0.070$) and POD1 platelets ($p = 0.233$). However, there was a statistically significant difference (but clinically irrelevant) in hematocrit difference between the day of admission and POD1 (mean difference 0.47, $p = 0.024$), and ephedrine consumption (mean difference 2 mg, $p = 0.017$) in favor of the control group.

Conclusions—Our study did not find an association between increased perioperative blood loss and hetastarch use in patients presenting for elective cesarean delivery.

Keywords

Hydroxyethyl starch; Cesarean delivery; Blood loss

Introduction

Options for intravascular volume loading to prevent subarachnoid anesthesia-induced hypotension at the time of cesarean delivery fall into two broad categories—crystalloids and colloids. When given as a preload to prevent hypotension, hetastarch (HES) generates osmotic pressure and has the advantage of greater volume expansion per unit infused, minimizes iatrogenic fluid overload and reduces the incidence of hypotension compared to crystalloids. Several studies and reports published in the past decade have determined that fluid preloading with HES alone or in combination with crystalloids is a better choice over crystalloids in mitigating the effects of sympathectomy due to subarachnoid anesthesia at the time of cesarean delivery, hence its common use in obstetrics [1–3].

Recently, however, HES has been at the center of scrutiny from medical agencies. The Medicine and Healthcare Products Regulatory Agency (MHRA) withdrew HES products from the United Kingdom [4], while the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) restricted its use by issuing a box warning [5, 6]. These restrictions mostly pertain to the risk of acute kidney injury and excessive bleeding in patients undergoing open-heart surgery. However, neither the FDA nor the EMA suspended HES use altogether, allowing for continuous use in a limited setting, such as cesarean delivery. However, these restrictions do not address the risk of bleeding during cesarean delivery despite the possibility of post-partum hemorrhage.

Although the causes of HES-induced excessive bleeding are not completely elucidated, some evidence suggests HES may interfere with fibrinogen polymerization [7–10]. Fibrinogen is vital for the development of a firm clot and achieving hemostasis. Furthermore, in healthy term patients, functional coagulation profiles measured with thromboelastography and thromboelastometry showed changes in various viscoelastic parameters with infusion of HES at the time of cesarean delivery [11–13]. However, it is not known whether HES administration to patients undergoing cesarean delivery increases the risk of clinical bleeding.

In this retrospective analysis, we aimed to define an association between perioperative use of HES and increased intraoperative bleeding at the time of elective cesarean delivery. We hypothesized that a co-load or a preload with HES to prevent spinal hypotension would be associated with an increase in blood loss when compared to crystalloids.

Methods

Following approval of this retrospective case–control study by the institutional review board at the University of Virginia, the electronic medical records of patients scheduled for elective cesarean delivery between January 2011 and October 2014 were selected and systematically reviewed. Patients were excluded if they were aged <18 years or >40 years, if they had a

known pre-existing coagulopathy, had undergone an emergency or an urgent cesarean delivery, or had a diagnosis of pre-eclampsia or HELLP syndrome. The control group comprised solely of patients who had received crystalloids as a preload or a co-load to prevent spinal-induced hypotension and as maintenance fluid throughout the procedure. The treatment group received HES and also received maintenance crystalloid fluids during the procedure. Crystalloids commonly used at our institution are lactated Ringer's and Multiple Electrolyte (Plasma-Lyte®) injection. For colloids, patients received 6 % (130/0.4) HES in 0.9 % sodium chloride. Notably, at our institution the use of HES versus crystalloid as a preload/co-load rests on the attending anesthesiologist's preference. HES (500 mL) was given as a preload in the preoperative area followed by an additional 500 mL, up to a total of 1,000 mL, if needed intraoperatively.

Both direct estimation and calculated blood loss were used to assess our primary outcome. Direct estimation of blood loss is determined by the amount of blood collected in a metered suction canister and agreed upon by the obstetrician and the anesthesiologist, and documented in the patient's medical record. Calculated blood loss was derived using a previously published method [14]. In brief, blood loss was calculated using the patient's estimated blood volume, admission hematocrit, postoperative day 1 (POD1) hematocrit and body surface area (Box 1). A ten percent decrease between admission and day 1 hematocrit was also used as a surrogate of blood loss. Additional relevant outcomes investigated were proxies for intraoperative hypotension which included total intravenous fluids, urine output, amount of vasopressor use, antiemetic use, and Apgar scores. Blood pressure measurements after spinal anesthesia were not extracted from patient's electronic chart because of inconsistencies in recorded time intervals between patients.

Box 1

Formula for blood calculation[14]

- Total blood loss (ml) = Total RBC loss/0.35.
- Total RBC loss (ml) = uncompensated RBC loss (ml) + compensated RBC loss (ml)
- Uncompensated RBC loss (ml) = Initial RBC - Final RBC
- Compensated RBC loss (ml) = sum of RBC received from various source of transfusion
- Initial RBC= [Estimated blood volume (ml)] x [initial HCT level (%) at day -1]
- Final RBC (ml) = [Estimated blood volume (ml) x [final HCT level (%) day +1]
- Estimated Blood volume: [BSA (m²) x 2430]
- Body surface area (BSA) = 0.0235 x [height (cm)] 0.42246 x [weight (kg)] 0.51456

RBC: red blood cells; HCT: hematocrit

Other data extracted from patient charts included demographic information, gravidity, parity, number of fetuses, infant weight, gestational age, number of prior cesarean deliveries, surgery time, intraoperative use of uterotonics and blood transfusions.

Statistical methods

Our sample size calculation was based on institutional data on blood loss following cesarean delivery. A sample of 141 elective cesarean deliveries was selected between June 2013 and December 2013 and was considered to be representative of mean intraoperative blood loss at our institution. The mean estimated blood loss was 773 ± 287 mL. We assumed that half of the standard deviation (143 mL) would be considered a clinically significant difference in blood loss between the HES group and the crystalloid group as previously described elsewhere [15]. Furthermore, 143 mL is approximately 20 % blood reduction, which is a clinically meaningful.

Using the Wilcoxon–Mann–Whitney test, with two-tails, an alpha error of 0.05 and power of 90 %, a sample size of 180 patients was calculated (90 patients per group). To account for missing data and possible poor reporting, we added 30 % more patients; thus, 240 patients were required (120 patients in each group).

Risk factors for postpartum hemorrhage were identified and considered confounders. A total of 10 potential confounding variables were extracted and used for the propensity score-matching between the two groups. These confounding factors included age, gravida, para, number of fetuses, gestational age, body mass index [BMI], number of previous cesarean deliveries, infant weight, surgery time, amount of oxytocin used, whether additional uterotonic (methergine and hemabate) were used, amount of bupivacaine [16] and ondansetron [17] used, admission hematocrit, and admission platelet counts.

Propensity score-matching was performed using genetic matching with the ‘Matchit’ package in R in which a genetic search algorithm was used to optimize the balance of the covariates between the control and treatment groups [18, 19]. Genetic matching uses an automated search algorithm to optimize covariate balance between matched samples by combining multivariate matching on the covariates and propensity score-matching. Matched pairs are selected using a generalized Mahalanobis distance metric, with a vector of weights included for each covariate used in the matching. Compared with propensity score-matching, this method has been found to reduce bias and mean squared error [20]. One-to-one matching with replacement was used for its versatility and greater bias reduction. After matching, weighted least squares regression was performed to assess the treatment effect, in which all treatment patients have a weight of 1, and all control patients have a weight proportional to the number of treatment patients to whom they are matched [21]. All statistical analyses were performed with R version 3.1.1.

Results

A total of 819 patients (control group 602, HES group 217) who underwent elective cesarean delivery at our institution were screened for eligibility. Only 688 were included in the propensity score-matching. One hundred and thirty-one patients were excluded because relevant demographic and clinical characteristic information was missing. As such, 492 patients in the control group were matched to the 196 patients in the HES group.

Prior to matching, regression models (linear regression for continuous variables, Poisson regression for count variables) were used to assess whether the confounding variables differed between the two groups. Results showed a substantial imbalance in infant birth weight, oxytocin and bupivacaine use, and admission hematocrit between the two groups (all absolute standardized differences >0.25). Patients in the control group had significantly lower infant birth weight ($p < 0.0001$), more oxytocin use ($p < 0.0001$), less bupivacaine use ($p < 0.0001$), and higher admission hematocrit ($p = 0.001$). After matching, the absolute standardized difference (ASD) of all matched variables were well below 0.25, meaning the matched HES and control groups had $<25\%$ of a standard deviation difference in the corresponding variables. We therefore considered the two groups to be balanced on the selected covariates (Table 1).

Based on propensity score-matching, only 182 patients in the control group remained and were matched to 196 patients in the HES treatment group. Because patients in the treatment group were not all matched to patients in the control group, patients in the treatment group have weights of 1, control patients have weights proportional to the number of times they are matched to a treatment patient, and all unmatched controls have weights of 0, excluding them from the analyses. Mean HES infused was 785 mL (SD 248 mL), minimum 500 mL and maximum 1,500 mL.

Results from the regression models did not show a statistical difference in the amount of blood loss between the HES treatment and control groups, before and after adjusting for the confounding variables (age, gravida, para, number of fetuses, gestational age, BMI, number of previous cesarean deliveries, infant weight, surgery time, amount of oxytocin, whether additional uterotonics were used, amount of bupivacaine and ondansetron used, admission hematocrit, and admission platelets). The amount of estimated blood loss was also not statistically significant—mean estimated blood loss was 817.02 ± 327.69 in the HES group and 789.28 ± 298.39 in the control group ($p = 0.11$ before adjustment and $p = 0.068$ after controlling for confounding variables). Furthermore, the amount of calculated blood loss was not statistically different— 999.39 ± 310.17 in the control group and 937.38 ± 461.61 in the HES treatment group ($p = 0.83$ before adjustment and $p = 0.72$ after adjusting for covariates) (Table 2).

The use of ephedrine was higher in the HES group (9.80 ± 15.86) than in the control group (7.77 ± 14.04 ; $p = 0.025$; $p = 0.017$ after adjusting for covariates); with a mean difference of 2 mg, which is clinically irrelevant. Hematocrit on POD1 in the control group (31.12 ± 4.20) was slightly higher than in the HES group (30.22 ± 4.01 ; $p = 0.04$); however, the difference was not statistically significant after adjusting for covariates ($p = 0.07$). The difference in

hematocrit between the day of admission and POD1 was smaller in the control group (3.24 ± 3.59) than in the HES group (3.71 ± 4.82); $p = 0.08$, and the difference is statistically significant after controlling for covariates ($p = 0.024$). However, this difference is clinically irrelevant.

Discussion

The findings of our study do not support our hypothesis that intraoperative use of HES during elective cesarean delivery to prevent subarachnoid-induced hypotension is associated with an increase in blood loss. This difference was not significant with either method used to assess blood loss. Our results also did not show that HES use was associated with overall better outcomes such as total intraoperative fluid intake, urine output, phenylephrine use, and Apgar scores at 1 and 5 min when compared to crystalloids. There was a statistically significant (but not clinically meaningful) difference in ephedrine consumption and a difference between admission and POD1 hematocrit in favor of the control group.

Preloading with low-molecular-weight and rapidly degradable HES, either alone or in combination with crystalloids, has traditionally been considered a better choice than crystalloid alone to reduce the incidence of hypotension during cesarean delivery [22, 23]. However, there is paucity of data examining the association between HES and perioperative blood loss at the time of cesarean birth despite the potential for hemorrhage in the postpartum period. This is particularly important since previous studies of pregnant patients undergoing cesarean delivery receiving HES showed impairment in viscoelastic testing despite the rise in coagulation factors during pregnancy. In these patients, thromboelastometry demonstrated impairment in clot formation and clot firmness [12] and thromboelastography showed a mild hypocoagulable state [11, 13].

In our study, a propensity to clinical bleeding with HES use to prevent hypotension was not determined. Our results are similar to the recent CAESAR trial evaluating the effect of a combination of HES and lactated Ringer's solution on hypotension following spinal anesthesia [22]. This trial indicated that HES did not affect standard coagulation testing or a predisposition to bleeding based on difference between admission and day 1 hemoglobin levels. However, blood loss was a secondary outcome and the study may be underpowered for this outcome. Explanations for our findings are perhaps related to the chemical structure and the amount of HES used. In general, coagulation abnormalities seen with HES are more often associated with high-molecular-weight and slow degradable starches rather than low-molecular-weight and rapidly degradable ones such as those used in our study [24]. Additionally, the rise of coagulation factors during pregnancy could counterbalance any potential overt HES effect on blood loss as seen in patients undergoing open cardiac surgery [15].

Moreover, our results did not find a difference in the other outcomes measured. Previous studies examining the effect of HES on hypotension following spinal anesthesia found mixed results with regard to the use of vasopressors. Mercier et al. failed to find a difference in the amount of phenylephrine use among groups although a tendency towards more use in the crystalloid group was detected but not significantly different [22]. This was also

previously demonstrated in previous double blind randomized controlled trials comparing the effect of preload or co-load techniques with HES versus crystalloid for mitigating hypotension due to spinal anesthesia during cesarean delivery [25]. In contrast other studies found significantly different vasopressor use between groups [26, 27]. Explanation for these findings can be related to variability in the amount and concentration of bupivacaine used as well as in study designs and endpoint definitions.

Uteroplacental perfusion is an important determinant of fetal wellbeing and untreated hypotension due to subarachnoid blockade is detrimental [28]. Hence, the benefit of HES in decreasing the incidence of hypotension is valuable. However, it is unclear if the potential decrease in the incidence of hypotension with the use of HES compared to crystalloids results in better neonatal outcomes, as both groups have similar Apgar scores. This observation is common in many trials and meta-analyses comparing HES to crystalloids [29, 30].

There are limitations to our study. This is a retrospective review and there is potential for reporting bias such as conflict in estimation of blood loss between obstetrician and anesthesiologist. Direct estimation of blood loss as indicated in our study, although considered a good technique, carries the risk of an overall inaccurate estimation. Usually, the blood contained in suction canisters contains amniotic fluid and therefore overestimates true blood loss. Additionally, blood contained in drapes, floor and compresses was not added to the total blood loss contained in suction canisters at the end of the surgery, which may underestimate true blood loss [31]. To overcome this limitation, we computed blood loss using estimated blood volume, body surface area, and preoperative and postoperative hematocrit, which may be more reflective of overall blood loss as described elsewhere [14]. Admittedly, the blood loss calculation method used in this study was not previously validated in the obstetric patient population, which may not reflect the true blood loss. Nonetheless, this may not affect our conclusion since the calculation method applied to both groups. Additionally, we also considered the hematocrit difference between admission day and POD1 as an indicator of blood loss [32, 33]. Although a statistical significance was found regarding hematocrit difference, this observation is clinically irrelevant. Finally, we did not include data about the coagulation function before cesarean delivery since this was not available. However, we assumed these to be normal and thus were not checked preoperatively as a common practice in our institution.

Our study failed to demonstrate that HES increases blood loss when compared to crystalloids during elective cesarean delivery. Furthermore, our study did not identify any overt harmful effects in patients undergoing elective cesarean delivery, and further studies may be necessary to delineate its safe use in healthy patients undergoing elective surgery.

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Patient demographics and characteristics before and after group matching

Variables	Before matching				After matching					
	Control (N = 492)	HES (N = 196)	p value	D	ASD	Control (N = 182)	HES (N = 196)	p value	D	ASD
Age (years)	29.85 (5.57)	29.54 (5.06)	0.714	4	0.060	29.46 (4.96)	29.54 (5.06)	0.877	1	-0.016
G	3 [1–10]	3 [1–9]	0.850	1	-0.020	3 [1–10]	3 [1–9]	0.670	1	-0.053
P	1 [0–8]	1 [0–5]	0.650	3	0.039	1.5 [0–8]	1 [0–5]	0.770	3	0.032
Fetuses	1 [1–3]	1 [1, 2]	0.680	1	0.186	1 [1–3]	1 [1, 2]	0.900	1	0.067
GA (days)	11.79 (9.02)	11.42 (8.50)	0.613	21	0.043	11.69 (7.75)	11.42 (8.50)	0.743	21	0.034
BMI	33.73 (8.22)	32.60 (6.76)	0.065	17.51	0.156	33.28 (7.44)	32.60 (6.76)	0.356	4.24	0.095
CD	2 [0–10]	2 [1–5]	0.290	5	-0.141	2 [0–8]	2 [1–5]	0.770	3	-0.049
Infant weight (g)	3084.09 (880.02)	3381.25 (619.92)	<0.0001	1304.08	-0.422	3332.92 (639.89)	3381.25 (619.92)	0.457	725.18	-0.077
Surgery time (min)	72.73 (19.52)	74.97 (19.83)	0.180	13.75	-0.113	73.43 (18.94)	74.97 (19.83)	0.441	27.167	-0.079
Oxytocin (IU)	2.07 (2.33)	1.27 (2.05)	<0.0001	3	0.375	1.64 (2.11)	1.27 (2.05)	0.083	3	0.179
Uterotonic (% yes)	7.52	10.7	0.2	1	-0.107	10.4	10.7	1	1	-0.009
Bupivacaine (mg)	9.06 (1.04)	9.67 (0.94)	<0.0001	2	-0.633	9.44 (1.13)	9.67 (0.94)	0.033	6	-0.221
Admission hematocrit (%)	34.78 (4.12)	33.63 (4.30)	0.001	9.6	0.273	34.36 (3.76)	33.63 (4.30)	0.077	5	0.182
Admission platelets (k/ μ L)	213.88 (63.56)	210.74 (60.62)	0.546	99	0.051	219.67 (62.33)	210.74 (60.62)	0.160	21	0.145
Onandansetron (mg)	2.45 (2.02)	2.77 (1.89)	0.053	4	-0.164	2.73 (1.87)	2.77 (1.89)	0.836	4	-0.021

*HE*shestarch group, *D* maximum difference in the empirical quantile–quantile plot, *ASD* absolute standardized difference, *G* gravida, *P* para, *Fetuses* number of fetuses, *GA* gestational age, *BMI* body mass index, *CD* number of cesarean deliveries

Table 2

Comparison between groups regarding outcomes

Outcomes	Control (N = 182),	HES (N = 196)	Adjusted <i>p</i> value*
Estimated blood loss (mL)	789.28 (298.39)	817.02 (327.69)	0.068
Calculated blood loss (mL)	999.39 (1310.17)	937.38 (461.61)	0.720
Total fluids intake (mL)	2,013.22 (959.77)	2,028.89 (877.53)	0.289
Urine output (mL)	194.40 (146.57)	201.05 (149.78)	0.421
Phenylephrine (mcg)	846.08 (684.48)	829.08 (707.78)	0.742
Ephedrine (mg)	7.77 (14.04)	9.80 (15.86)	0.017
APGAR 1 min	7.81 (1.76)	7.69 (1.97)	0.830
APGAR 5 min	8.49 (1.43)	8.53 (1.53)	0.138
POD1 hematocrit (%)	31.12 (4.20)	30.22 (4.01)	0.070
Hematocrit difference (%)	3.24 (3.59)	3.71 (4.82)	0.024
POD1 platelets (k/ μ L)	195.95 (52.70)	186.48 (53.64)	0.233
Atropine (mg)	0 (0)	0 (0.04)	0.290

Differences are shown in bold

Data are expressed as mean and standard deviation

HES hetastarch group,*
p values after adjusting for confounding variables.*p* value considered significant at alpha <0.05