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Volume Replacement Therapy during Major Orthopedic Surgery Using Voluven® (Hydroxyethyl Starch 130/0.4) or Hetastarch

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Background: **The purpose of this study was to test the equivalence of efficacy and compare the safety of the 6% hydroxyethyl starches (HES) Voluven® (HES 130/0.4; Fresenius Kabi, Bad Homburg, Germany) and hetastarch (HES 670/0.75 in saline) for intravascular volume replacement therapy during major orthopedic surgery.**

Methods: **In a prospective, controlled, randomized, double-blind, multicenter trial of patients undergoing major orthopedic surgery, 49 patients were treated with HES 130/0.4 and 51 patients were treated with hetastarch. Infusion of colloids was guided by central venous and arterial blood pressures. The primary efficacy endpoint was the volume of colloid solution infused; the primary safety endpoints were calculated total erythrocyte loss, the nadir factor VIII activity, and the nadir von Willebrand factor concentration within 2 h of completion of surgery.**

Results: **The total volume of colloid solution required for intraoperative volume replacement did not differ between HES 130/0.4 and hetastarch (1,613 ± 778 [SD] ml for HES 130/0.4 and 1,584 ± 958 ml for hetastarch). The nadir factor VIII activity within 2 h of the end of surgery was lower for hetastarch than for HES 130/0.4 ($P = 0.0499$); for those who received greater than 1,000 ml colloid, the nadir factor VIII activity and von Willebrand factor concentration within 2 h of end of surgery were lower for hetastarch than for HES 130/0.4 ($P = 0.0487$ and $P = 0.008$, respectively).**

Conclusion: **Voluven® (HES 130/0.4) and hetastarch are equally efficacious plasma volume substitutes; however, HES 130/0.4 has a lesser effect on coagulation.**

HYDROXYETHYL starch (HES) and albumin are the most frequently administered colloids for intravascular volume expansion.[1] HES is an attractive choice over albumin because of lower cost, and today it is the most commonly used artificial colloid worldwide.

Hydroxyethyl starch is a large, branched, complex carbohydrate derived by adding hydroxyethyl groups to amylopectin. Hydroxyethyl groups can be introduced at the C2, C3, and/or C6 position of glucose. Clinically available HES solutions differ not only with respect to vehicle and concentration but, more importantly, by molar substitution, substitution pattern, and mean molecular weight. HES solutions are comprised of molecules derived from corn starch with a distribution of molecular weights. HES solutions are classified as high-, medium-, or low-molecular-weight preparations, depending on the mean molecular weight.[2] Molar substitution is defined as the average number of hydroxyethyl groups per glucose subunit, and substitution pattern characterizes the location of hydroxyethylation at either the C2 or the C6 position (C2/C6 ratio).

Hydroxyethyl starch is hydrolyzed *in vivo* by serum amylase and excreted by the kidneys. The rate of enzymatic degradation depends on the molar substitution and C2/C6 ratio. Higher molar substitution and C2/C6 ratios are associated with slower degradation of the molecule, leading to plasma accumulation of HES. Therefore, the most pronounced plasma accumulation occurs with preparations characterized by high-molecular-weight and highly substituted molecules compared with medium-molecular-weight HES preparations such as pentastarch.[1–4] An HES with higher *in vivo* molecular weight has a prolonged plasma half-life that would be expected to result in more protracted adverse effects. An important adverse effect of HES solutions is impairment of coagulation as manifested by reduced factor VIII activity and von Willebrand factor (vWF) antigen concentration.[5–10] The most pronounced anticoagulant actions are found for high-molecular-weight starches with high molar substitution.[5,7,11]

Voluven® (Fresenius Kabi, Bad Homburg, Germany) is a novel HES with a mean molecular weight of 130,000 dalton, a molar substitution of 0.4 (130/0.4), and a C2/C6 ratio greater than 8. The molecular weight distribution of HES 130/0.4 is the narrowest of all available HES types. It also has an improved *in vivo* molecular weight resulting in sustained volume effect despite higher elimination.[12] Renal excretion of HES 130/0.4 is faster than that for pentastarch (HES 200/0.5) or hetastarch (HES 450/0.7).[13] HES 130/0.4 does not accu-

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mulate in plasma after multiple dosing over 10 days.[14] This pharmacologic property results in a 75% reduction of tissue storage compared with HES 200/0.5.[15] *In vitro* and *in vivo* measures of coagulation are less compromised by HES 130/0.4 than by other starch-based volume substitutes.[9,10,16–21]

Hetastarch is the most commonly used HES in the United States. It is a high-molecular-weight HES (> 670,000 dalton) preparation with high substitution (0.75) as compared with HES 130/0.4. The safety and efficacy of HES 130/0.4 *versus* HES 200/0.5 (frequently used artificial colloid in Europe) have been studied extensively, but no investigation has compared HES 130/0.4 with hetastarch in saline. The purpose of the current study was to compare HES 130/0.4 and hetastarch during major surgery with an anticipated blood loss of more than 500 ml.

Materials and Methods

This prospective, controlled, randomized, double-blind study with parallel groups was performed at six centers. After institutional review board approval (Committee on Human Research, University of California, San Francisco, California; Human Studies Subcommittee, Department of Veterans Affairs, Clement J. Zablocki VA Medical Center, Milwaukee, Wisconsin; Institutional Review Board, Portland VA Medical Center, Portland, Oregon; Institutional Review Board, Oregon Health and Science University, Portland, Oregon; Institutional Review Board [IRB-01, Biomedical], The University of Iowa, Iowa City, Iowa; Institutional Review Board 0673, The University of Texas Medical Branch of Galveston, Galveston, Texas) and informed consent were obtained, a total of 110 male or female patients undergoing major elective orthopedic surgery with an expected blood loss of 500 ml or more were randomly allocated to receive either 6% HES 130/0.4 (Voluven®) or 6% hetastarch (HES 670/0.75 in saline; Abbott, North Chicago, IL) for intraoperative intravascular volume replacement.

Randomization was performed by DATAMAP GmbH (Freiburg, Germany) by means of SAS software version 8.2 (SAS Institute, Inc., Cary, NC). The computer program used the method of randomly permuted blocks. The randomization was conducted in blocks of 4 patients, in a 1:1 ratio using sealed envelopes. No more than 50 patients were allowed at any single center. Ten of the 110 patients randomized were withdrawn from the study before surgery and did not receive study colloid. The investigation was conducted between September 2001 and July 2003.

Patients with a history of known hypersensitivity to HES, coagulation disorders, renal dysfunction (oliguria [urine output < 500 ml/day]) or anuria not related to hypovolemia), severe cardiac disease (New York Heart Association class III or IV), and unstable angina or pregnancy were excluded from enrollment. Screening history and physical examinations were performed within 14 days before surgery.

On the day of surgery, patients were premedicated with midazolam (0–50 μg/kg) and fentanyl (0–1.5 μg/kg). A catheter for monitoring of central venous pressure (CVP) was inserted in each patient either preoperatively or immediately after induction of anesthesia. Propofol (1.5–2.5 mg/kg), thiopental (3–6 mg/kg), or etomidate (0.1–0.5 mg/kg) and fentanyl (0–5 μg/kg) were used for induction of anesthesia. Anesthesia was maintained with isoflurane, sevoflurane, or desflurane (≤ 1.25 minimum alveolar concentration) in nitrous oxide (0–70%) and oxygen. Opioids and neuromuscular blocking agents were used at the discretion of the anesthesiologist.

Administration of colloid started when the "trigger" was reached after induction of anesthesia and was terminated at the end of the surgery. Administration of study colloid infusion was determined by CVP and arterial blood pressure: (1) CVP less than 10 mmHg: study colloids were infused; (2) CVP 10–15 mmHg with unacceptable blood pressure: study colloids or vasoactive agents were infused; (3) CVP greater than 15 mmHg with unacceptable blood pressure: vasoactive agents were infused. Study colloid infusion was stopped at CVP greater than 15 mmHg or at CVP 10–15 mmHg when blood pressure was acceptable for the needs of the individual patient. No study or other colloids were to be administered before induction of anesthesia or within 2 h after the end of surgery. Electrolyte solutions were infused 7 ml/kg before and during induction of anesthesia and 3 $ml \cdot kg^{-1} \cdot h^{-1}$ after induction of anesthesia until the end of surgery. Blood components were administered according to American Society of Anesthesiologists guidelines.[22] If the hemoglobin concentration was at or below the transfusion trigger, erythrocytes were first transfused to increase hemoglobin values above the trigger, and then electrolyte solutions were infused as described above.

Central venous pressure, arterial pressure, and heart rate were recorded immediately before and after induction of anesthesia, every 15 min until the end of surgery, and at 2 h after surgery. Measurements of prothrombin time, activated partial thromboplastin time, fibrinogen, factor VIII, and vWF were performed immediately after induction of anesthesia, at the end of surgery, and at 2, 24, and 48 h after surgery. Factor VIII and vWF were assessed at a central laboratory using the following US Food and Drug Administration–approved methods: an activated partial thromboplastin time–based one-stage clotting time assay with FVIII-depleted plasma for FVIII, and a latex immunoagglutination assay for vWF. Other laboratory tests included hematocrit, hemoglobin, erythrocyte, leukocyte, and platelet counts, creatinine, blood urea nitrogen, bilirubin, glucose, albumin, plasma electrolytes, aspartate aminotransferase, alanine aminotrans-

Table 1.Data Sets Analyzed

Stratification, number of patients, %	HES 130/0.4 (n = 49)		HES 670/0.75 in Saline (n = 51)	
	n	%	n	%
Intent-to-treat population	49	100	51	100
Subset 1: patients hemodynamically stable	48	98	51	100
Subset 2: patients with no massive blood loss and no other colloids than study medications	45	91.8	44	86.3
Subset 3: patients who received > 1,000 ml study medications	35	71.4	32	62.7

HES = hydroxyethyl starch.

ferase, lactate dehydrogenase, γ-glutamyl transpeptidase, amylase, and urine analysis, performed at each of the study sites. Intravenous fluid input and fluid output were recorded immediately after induction of anesthesia and every hour until the end of surgery and at 2, 24, and 48 h after surgery. Patients were evaluated through 28 days after surgery for occurrence of adverse events.

Measurements and Statistical Analysis

The primary efficacy endpoint was the total volume of colloid solution required for intraoperative volume replacement. Secondary efficacy endpoints were total fluid input, total fluid output, and use of vasoactive medications. Primary safety endpoints were calculated total perioperative erythrocyte loss (induction of anesthesia to 48 h after the end of surgery), nadir factor VIII activity, nadir vWF antigen concentration within 2 h of completion of surgery, and use of fresh frozen plasma. Secondary safety endpoints were hemodynamic stability (systolic blood pressure of not more than 30% below the value immediately before induction of anesthesia) and adverse events, including bleeding complications and abnormal laboratory indices of hemostasis, serum chemistry, and urine analysis.

A total of 50 patients per treatment group was planned. Sample size was based on the primary efficacy endpoint. The sample size of 50 per group had a statistical power of greater than 99% to demonstrate that HES 130/0.4 and hetastarch have an equivalent efficacy with an α error of 5% and SD of 650 ml. Statistical power was calculated using nQuery Adviser 3.0 software (Statistical Solutions, Saugus, MA).

Analyses were conducted for the intent-to-treat (ITT) population as well as three subsets that were defined *a priori*:

Subset 1: Patients hemodynamically stable at the end of surgery, both at end of wound closure and immediately after arrival in the postanesthesia care unit

Subset 2: Patients without major (≤ 25 ml/kg body weight) blood loss and without use of colloids other than HES 130/0.4 or hetastarch

Subset 3: Patients who received more than 1,000 ml HES 130/0.4 or hetastarch

For primary efficacy and safety endpoints, the null hypothesis was tested in a confirmatory way by calculating two-sided confidence intervals for $\mu v/\mu h$ (μv and μh are the mean values for HES 130/0.4 and hetastarch for respective parameter). The confidence intervals (according to Fieller[23]) were calculated based on either analysis of variance with treatment and center as effects, or analysis of covariance with treatment, center, and baseline as effects, as appropriate. All variables were summarized descriptively by treatment group with mean, SD, median, quartiles, minimum, and maximum, for the ITT population and different subsets.

The common methodology for estimating blood loss is subject to substantial error.[24] Consequently, we estimated perioperative blood loss by a modification of the method of Mercuriali and Inghilleri[25] using the blood volume prediction as described by Nadler *et al.*[26] Total perioperative erythrocyte loss (in liters) = predicted blood volume × (hematocrit screening − hematocrit day 2 postoperative) + transfused erythrocyte volume. Transfused erythrocyte volume was estimated as = 0.7 × infused packed erythrocytes + 0.6 × infused salvaged erythrocyte suspensions + 0.35 × infused whole blood.

Results

One hundred ten patients were enrolled; 10 were withdrawn before surgery without receiving study medication, leaving 100 patients who completed the study: 49 were randomly allocated to the HES 130/0.4 group and 51 were randomly allocated to the hetastarch group. The number of patients in the three subsets is shown in table 1. Demographic data (table 2) were comparable between groups. All patients underwent major orthopedic surgery, and in both treatment groups, the most common procedure involved surgery of the spine or hip.

The mean volumes of colloid solutions administered were equivalent for the two HES groups (HES 130/0.4: 1,613 ± 778 ml; hetastarch: 1,584 ± 958; table 3 and fig. 1). The ratio of HES 130/0.4 to hetastarch volume was 1.024, with a 95% confidence interval of 0.83–1.254. Volumes of HES infused did not differ between HES groups for any of the subsets (table 3). There was no difference in the amount of crystalloid administered intraoperatively. There were no significant differences in CVP values between the two groups.

Table 2. Demographic Data

	HES 130/0.4 (n = 49)	Hetastarch (n = 51)	*P* Value
Age, yr			0.5894
Mean	60.2	58.5	
Range	29–83	24–93	
Weight, kg			0.0464
Mean	93.7	85.7	
Range	44.3–183.5	54.0–125.0	
Height, cm			0.4725
Mean	173.4	171.9	
Range	142.0–196.0	150.0–188.5	
BMI, kg/m^2			0.0573
Mean	31.1	28.9	
Range	18.4–47.8	20.6–42.5	
Sex, n (%)			0.3821
Male	37 (75.5)	34 (66.7)	
Female	12 (24.5)	17 (33.3)	
Ethnic origin, n (%)			1.0000
White	46 (93.9)	46 (90.2)	
Hispanic	2 (4.1)	2 (3.9)	
Black	1 (2.0)	2 (3.9)	
Other	0 (0.0)	1 (2.0)	
Blood group, n (%)*			0.7767
O	23 (46.9)	20 (39.2)	
A	20 (40.8)	22 (43.1)	
AB	3 (6.1)	4 (7.8)	
B	3 (6.1)	3 (5.9)	
Type of surgical procedure, n (%)			0.4280
Hip	29 (59.2)	32 (62.7)	
Spine	14 (28.6)	15 (29.4)	
Pelvis	3 (6.1)	4 (7.8)	
Lower extremity	3 (6.1)	0 (0.0)	

* n = 49 for hetastarch.

BMI = body mass index; HES = hydroxyethyl starch.

The difference between the two groups for allogeneic blood transfusion was not statistically significant (tables 4 and 5). The difference was statistically significant when the totals for all transfused erythrocytes (salvaged blood and allogeneic blood) were compared for those requiring transfusion, in both the ITT population (8.0 ± 6.4 ml/kg for HES 130/0.4 *vs.* 13.8 ± 12.9 ml/kg for hetastarch; $P = 0.0296$; table 4) and subset 3 population (8.6 ± 7.0 ml/kg for HES *vs.* 16.5 ± 13.6 ml/kg for hetastarch; $P = 0.0345$; table 5).

The slightly higher calculated erythrocyte loss in the hetastarch group for the ITT population as well as subset 3 compared with HES 130/0.4 was not statistically significant (table 6). The clinically estimated blood loss was 1.72 ± 1.09 l for HES 130/0.4 *versus* 1.92 ± 2.11 l for hetastarch ($P = 0.65$). There were no differences between treatment groups in urine output or in vasoactive drug therapy. The most common vasoactive medications given were direct and indirect sympathomimetics (phenylephrine, ephedrine) and β-adrenergic antagonists. The primary safety endpoints are summarized in table 6.

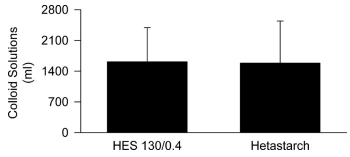

Fig. 1. Mean volume of colloid solutions administered intraoperatively. Data are mean ± SD. There was no significant difference between hydroxyethyl starch (HES) 130/0.4 and hetastarch.

The nadir factor VIII activity within 2 h of the end of surgery for the ITT population was 19% lower in the hetastarch group compared with the HES 130/0.4 group ($P = 0.0499$; table 6 and fig. 2). The factor VIII activity in those patients given more than 1,000 ml HES (subset 3) was less in those patients given hetastarch (66%) than in those given HES 130/0.4 (89%) ($P = 0.049$; table 6 and fig. 2). The nadir vWF antigen concentration within 2 h of the end of surgery for subset 3 patients was lower in the hetastarch group (72%) than in the HES 130/0.4 group (89%) ($P = 0.008$; table 6 and fig. 2). Significantly fewer patients given HES 130/0.4 than patients given hetastarch had factor VIII activity below lower limit of normal at end of surgery (5 *vs.* 13; $P = 0.031$) and 2 h after surgery (0 *vs.* 7; $P = 0.002$; fig. 3). The fraction of patients with vWF values below the lower limit of normal was significantly less 2 h after surgery in those patients given HES 130/0.4 than those given hetastarch (0 *vs.* 4; $P = 0.027$; fig. 3); the fractions did not differ at end of surgery (5 *vs.* 7; $P = 0.56$).

Only four patients in each treatment group received fresh frozen plasma. Table 7 shows coagulation parameters in the ITT population. At 24 and 48 h, values of factor VIII activity and vWF factor antigen were significantly higher for HES 130/0.4 group compared with the hetastarch group ($P < 0.0001$ for both parameters). For

Table 3. Volume of Study Colloid Solution (in Milliliters) Infused Intraoperatively

	HES 130/0.4 (n = 49)		Hetastarch (n = 51)			
	n	Mean ± SD	n	Mean ± SD	Ratio* Estimate HES 130/0.4: Estimate Hetastarch	Confidence Interval†
Intent-to-treat population	49	1,613 ± 778	51	1,584 ± 958	1.024	(0.835–1.254)
Subset 1 population	48	1,595 ± 776	51	1,584 ± 958	1.018	(0.828–1.249)
Subset 2 population	45	1,487 ± 598	44	1,340 ± 631	1.083	(0.910–1.291)
Subset 3 population	35	1,906 ± 731	32	2,063 ± 897	0.975	(0.810–1.188)

There were no significant differences between groups.

* Based on the analysis of variance model: parameter = treatment + center. † 95% confidence interval for ratio hydroxyethyl starch (HES) 130/0.4:hetastarch.

Table 4. Fluid Input, Intent-to-treat Population

	Intraoperative Fluid Input				Total Fluid Input			
	n	HES 130/0.4	n	Hetastarch	n	HES 130/0.4	n	Hetastarch
Study colloid, ml/kg	49	18.0 ± 9.4	51	19.6 ± 14.8	49	18.0 ± 9.4	51	19.6 ± 14.8
Packed erythrocytes, ml/kg	16	10.1 ± 7.4	13	14.2 ± 9.7	27	10.6 ± 8.8	28	14.1 ± 12.4
FFP, ml/kg	3	15.2 ± 8.9	3	24.0 ± 5.1	4	14.7 ± 7.5	4	26.6 ± 9.0
Salvaged blood, ml/kg	11	4.7 ± 3.0	14	10.5 ± 11.2	14	4.9 ± 2.9	15	12.2 ± 12.1
Platelets, ml/kg	0	0	3	5.4 ± 0.3	1	4.2	4	6.6 ± 1.3
Crystalloid, ml/kg	49	19.4 ± 10.0	51	19.9 ± 12.5	49	63.8 ± 26.9	51	63.4 ± 24.7
Whole blood, ml/kg	1	25.8	5	13.5 ± 11.7	2	19.4 ± 9.1	6	14.1 ± 10.1
Total volume, ml/kg	49	43.3 ± 25.2	51	49.1 ± 45.8	49	113.6 ± 46.4	51	121.6 ± 61.3
Packed erythrocytes + whole blood, ml/kg	16	7.7 ± 5.2	16	9.5 ± 7.5	28	7.7 ± 6.1	30	10.2 ± 9.1
Packed erythrocytes + whole blood + salvaged blood, ml/kg	22	7.0 ± 6.0	17	14.2 ± 11.9	32	8.0 ± 6.4*	30	13.8 ± 12.9

Data are mean ± SD.

* $P = 0.0296$, only patients who received the fluid type; $P = 0.1916$, all patients.

FFP = fresh frozen plasma; HES = hydroxyethyl starch; n = patients to whom the specified fluid was given (means are generated from the subjects who received the specific fluid; however, statistical calculations [analysis of variance] were made both from these subjects and for all).

mean activated partial thromboplastin time and mean prothrombin time values, the confidence interval showed significantly lower values for HES 130/0.4 compared with hetastarch at 24 h ($P = 0.004$ and $P < 0.0001$, respectively) and 48 h ($P = 0.0073$ and $P = 0.0033$, respectively) after surgery (table 7).

All of the patients in each treatment group experienced at least one adverse event. No patients died during the study. Five patients (10.2%) in the HES 130/0.4 group had a total of 7 serious adverse events, and 9 patients (17.6%) in the hetastarch group had a total of 11 serious adverse events. Three patients in the HES 130/0.4 group and 5 patients in the hetastarch group received more than 3 l HES. Three serious coagulopathy events occurred in the hetastarch group, and none occurred in the 130/0.4 HES group. In all three cases, a high volume (> 3,000 ml) of hetastarch had been administered. α-Amylase was higher in the hetastarch group than in the HES 130/0.4 group at 48 h (125 ± 91 *vs.* 65 ± 48 U/l; $P < 0.05$).

Discussion

The major findings of this investigation are (1) an equivalence of blood volume replacement by HES 130/0.4 and hetastarch and (2) a lesser effect on coagulation by HES 130/0.4 than by hetastarch. In addition, there were no serious coagulopathies in the HES 130/0.4 group, compared with three in the hetastarch group.

Among the different colloids, HES solutions have been used perioperatively as volume expanders for many years. The current investigation is the only study comparing HES 130/0.4 with hetastarch (HES 670/0.75) in saline. Equivalence of volume expansion by HES 130/0.4 and hetastarch was demonstrated in this study and is

Table 5. Fluid Input, Subset 3 Population

	Intraoperative Fluid Input				Total Fluid Input			
	n	HES 130/0.4	n	Hetastarch	n	HES 130/0.4	n	Hetastarch
Study colloid, ml/kg	35	21.5 ± 8.8	32	25.5 ± 15.7	35	21.6 ± 8.8	32	25.5 ± 15.7
Packed erythrocytes, ml/kg	13	11.1 ± 7.8	13	14.2 ± 9.7	22	11.4 ± 9.6	21	16.3 ± 13.5
FFP, ml/kg	3	15.2 ± 8.9	3	24.0 ± 5.1	4	14.7 ± 7.5	4	26.6 ± 9.0
Salvaged blood, ml/kg	8	5.3 ± 3.3	14	10.5 ± 11.2	10	5.3 ± 3.4	15	12.2 ± 12.1
Platelets, ml/kg	0	0	3	5.4 ± 0.3	1	4.2	4	6.6 ± 1.3
Crystalloid, ml/kg	35	18.8 ± 9.9	32	22.1 ± 14.5	35	64.8 ± 29.3	32	67.3 ± 28.1
Whole blood, ml/kg	1	25.8	5	13.5 ± 11.7	1	25.8	6	14.1 ± 10.1
Total volume, ml/kg	35	47.7 ± 27.5	32	62.8 ± 53.1	35	120.6 ± 50.6	32	135.8 ± 69.8
Packed erythrocytes + whole blood, ml/kg	13	8.4 ± 5.4	16	9.5 ± 7.5	22	8.4 ± 6.6	23	11.7 ± 9.9
Packed erythrocytes + whole blood + salvaged blood, ml/kg	17	7.9 ± 6.3	17	14.2 ± 11.9	25	8.6 ± 7.0*	23	16.5 ± 13.6

Data are mean ± SD.

* $P = 0.0345$, only patients who received the fluid type; $P = 0.1408$, all patients.

FFP = fresh frozen plasma; HES = hydroxyethyl starch; n = patients to whom the specified fluid was given (means are generated from the subjects who received the specific fluid; however, statistical calculations [analysis of variance] were made both from these subjects and for all).

Table 6. Primary Safety Parameters

	HES 130/0.4		Hetastarch		Estimate HES 130/0.4: Estimate Hetastarch* (Confidence Interval‡)	*P* Value
	n	Mean ± SD	n	Mean ± SD		
Perioperative erythrocyte loss, l†						
ITT population	44	1.17 ± 0.63	45	1.31 ± 0.84	0.910 (0.720–1.141)	0.4094
Subset 3	32	1.30 ± 0.64	29	1.63 ± 0.88	0.876 (0.668–1.142)	0.3179
Nadir factor VIII between end of surgery and 2 h later, %*						
ITT population	49	100.5 ± 55.3	50	81.4 ± 65.2	1.244 (1.000–1.563)	0.0499
Subset 3	35	88.7 ± 55.7	31	65.9 ± 39.4	1.335 (1.002–1.845)	0.0487
Nadir vWF antigen between end of surgery and 2 h later, %*						
ITT population	49	97.7 ± 39.9	50	88.7 ± 48.9	1.128 (0.991–1.285)	0.0670
Subset 3	35	89.2 ± 40.4	31	71.5 ± 36.9	1.250 (1.062–1.484)	0.0078
Overall consumption of fresh frozen plasma, ml†						
ITT population	49	72 ± 256	51	144 ± 531	0.723 (0.000–2.437)	0.5542
Subset 3	35	101 ± 299	32	229 ± 660	0.707 (0.000–4.190)	0.5940

* Statistical analysis based on analysis of covariance model: parameter = treatment + center + baseline. † Statistical analysis based on analysis of variance model: parameter = treatment + center. ‡ Two-sided 95% confidence interval for ratio hydroxyethyl starch (HES) 130/0.4:hetastarch.

ITT = intent-to-treat population; subset 3 = patients who received greater than 1,000 ml study medications; vWF = von Willebrand factor.

supported by equivalence of the total volume of fluids infused.

Hydroxyethyl starch solutions may impair coagulation at high doses.[1–10] Hydroxyethyl starches with higher *in vivo* molecular weight and greater molar substitution have more pronounced effects on coagulation than those with lower molecular weight or lesser substitution.[1–4]

In studies of patients undergoing major orthopedic surgery, HES 130/0.4 was found to be equivalent to HES 200/0.5 as a plasma expander, but with lower HES plasma levels and *in vivo* molecular weight more rapid postsurgical normalization of decreased factor VIII and vWF, less reduction of factor VIII 5 h after surgery with HES 130/0.4 *versus* HES 200/0.5, and reduced need for homologous erythrocyte transfusion in the HES 130/0.4 *versus* the HES 200/0.5 group.[17,18] In healthy volunteers, the volume expansion effect with Hextend (BioTime Inc., Berkeley, CA) is less well sustained than it is with HES 130/0.4.[27] Others have reported similar results regarding volume expansion and lesser compromised coagulation in patients treated with HES 130/0.4 than with other HES molecules.[16–18,20,21,28,29] Even at higher doses up to 70 ml/kg, HES 130/0.4 caused no coagulopathy or bleeding complications in patients with severe head injury.[30] Similar results were also observed in the study involving cardiac patients with infusions of as much as 50 ml/kg HES 130/0.4.[21] Less impairment of coagulation by HES 130/0.4 than other HES solutions

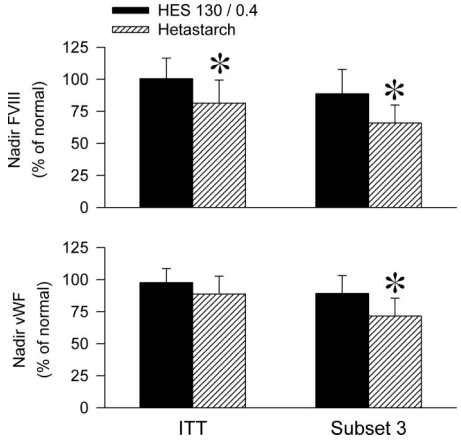

Fig. 2. Factor VIII activity (%) and von Willebrand factor (vWF) concentration (%) nadirs within 2 h of the end of surgery for intent-to-treat (ITT) population and subset 3 (patients who received > 1,000 ml hydroxyethyl starch [HES]). Data are mean ± 95% confidence interval. Nadir factor VIII activity within 2 h of the end of surgery was significantly lower in the hetastarch group compared with the HES 130/0.4 group for ITT population and subset 3 (* *P* = 0.0499 and *P* = 0.0487, respectively). Nadir vWF concentration within 2 h of the end of surgery was significantly lower in the hetastarch group compared with the HES 130/0.4 group for subset 3 (* *P* = 0.0078).

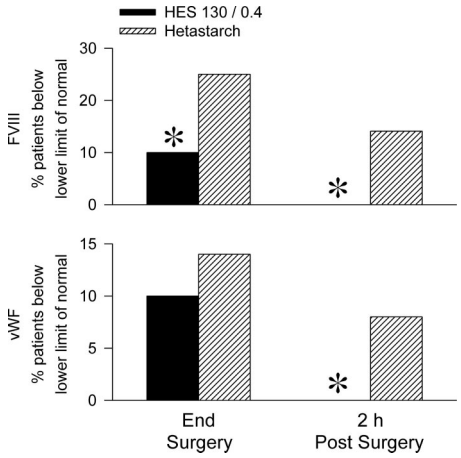

Fig. 3. Percentage of the patients with factor VIII activity and von Willebrand factor (vWF) concentration below lower limit of normal at the end of surgery and 2 h after surgery. Significantly fewer hydroxyethyl starch (HES) 130/0.4 patients had factor VIII activity below the lower limit of normal at the end of surgery (10% *vs.* 25%; * *P* = 0.031) and 2 h after surgery (0% *vs.* 14%; * *P* = 0.002). Significantly fewer HES 130/0.4 patients had vWF concentration below lower limit of normal at 2 h after surgery (0% *vs.* 8%; * *P* = 0.027).

Table 7. Absolute Values for Coagulation Parameters, Intent-to-treat Population

	HES 130/0.4		Hetastarch		HES 130/0.4 minus Hetastarch	
	n	Mean ± SD	n	Mean ± SD	Estimate†	95% CI
Factor VIII activity, %						
Immediately after induction (BL*)	49	146.3 ± 62.3	50	143.0 ± 71.0		
24 h after surgery	46	244.0 ± 92.5	46	151.1 ± 77.6	94.6	62.7 to 126.5, $P < 0.0001$
48 h after surgery	45	315.3 ± 89.1	44	228.1 ± 97.7	97.1	65.0 to 129.2, $P < 0.0001$
vWF, %						
Immediately after induction (BL*)	49	132.8 ± 55.0	50	134.6 ± 55.2		
24 h after surgery	47	220.1 ± 63.9	46	146.6 ± 63.8	78.4	59.8 to 96.9, $P < 0.0001$
48 h after surgery	45	258.9 ± 58.6	44	210.8 ± 71.0	54.0	34.8 to 73.3, $P < 0.0001$
aPTT, s						
Immediately after induction (BL*)	47	28.9 ± 5.0	45	28.1 ± 3.8		
24 h after surgery	44	29.8 ± 4.3	40	33.7 ± 7.7	−5.0	−7.7 to −2.3, $P = 0.0004$
48 h after surgery	43	30.3 ± 5.2	41	32.6 ± 5.8	−3.0	−5.1 to −0.8, $P = 0.0073$
PT, s						
Immediately after induction (BL*)	47	11.9 ± 1.3	44	12.1 ± 1.2		
24 h after surgery	45	12.8 ± 1.7	40	14.1 ± 2.6	−1.4	−2.0 to −0.8, $P < 0.0001$
48 h after surgery	43	12.5 ± 2.0	40	13.9 ± 4.1	−1.2	−2.0 to −0.4, $P = 0.0033$

* Baseline (BL) was defined as the measurement immediately after induction of anesthesia. † Measurement at time point adjusted for baseline based on the analysis of covariance model: parameter = treatment + center + BL.

aPTT = activated partial thromboplastin time; CI = confidence interval; HES = hydroxyethyl starch; PT = prothrombin time; vWF = von Willebrand factor.

have also been demonstrated *in vitro*.[19] The hemodynamic response, cardiac index, and right ventricular end-diastolic pressure during and after acute normovolemic hemodilution do not seem to differ between HES 130/0.4 and HES 200/0.5 groups.[28] Since its approval in 1999/2000, HES 130/0.4 has been used widely as a volume substitution therapy in Europe, where the currently approved daily maximum dose for HES 130/0.4 is 50 ml/kg body weight.

The results of this investigation indicated that coagulation was less affected by HES 130/0.4 than by hetastarch. In as much as assessment of perioperative hemostasis and blood loss are difficult and subject to substantial error, we used erythrocyte transfusion as a surrogate for these measures. However, only those requiring erythrocyte transfusions can be so assessed; lesser blood loss not requiring erythrocyte transfusion cannot be included in such an analysis. The lesser total transfusion of erythrocytes (allogeneic plus autologous) for those patients requiring erythrocytes suggests that the administration of HES 130/0.4 may have resulted in a lesser blood loss than did hetastarch. This is supported by the effects on coagulation and the absence of serious coagulopathies in the HES 130/0.4 group in comparison with the hetastarch group. The cases of serious coagulopathies occurred uniquely in patients who received large amounts of hetastarch. None of these cases occurred in any patient given HES 130/0.4 or lower hetastarch doses. Significantly fewer patients given HES 130/0.4 compared with hetastarch had factor VIII or vWF levels below the limit of normal, especially at 2 h after surgery—a period critical for postoperative bleeding. Previous retrospective evaluations finding increased bleeding and need for hemostatic agents or transfusion of blood components with starch with a high molar substitution in patients undergoing cardiac surgery[11,31] are now supported by our prospective, randomized, double-blind clinical trial, clearly demonstrating lesser effect on coagulation by HES 130/0.4 compared with hetastarch. Boldt *et al.* [32] evaluated measures of coagulation in patients undergoing major abdominal surgery and given either HES 130/0.4 or HES 550/0.7 (Hextend). They found higher blood loss, higher need for erythrocytes, and greater impairment of coagulations as evaluated by thrombelastography after HES 550/0.7 when compared with HES 130/0.4. This may be related to a more favorable molecular size and molecular weight distribution (*i.e.*, proportion of very large and very small molecules is reduced) as well as low molar substitution of HES 130/0.4 accounting for rapid metabolism and excretion.

Hydroxyethyl starch 130/0.4 has less effect on platelet function compared with other hydroxyethyl starches, including HES 450/0.7, HES 200/0.5, and HES 70/0.5.[33] The reduced antiplatelet effect of HES 130/0.4 may be secondary to the lower molar substitution of the HES molecule. In the current study, platelet function was not examined; nevertheless, reduced influence on platelets may be a contributing factor for absence of serious coagulopathies and reduced requirement for erythrocytes in our HES 130/0.4 group.

This first investigation comparing HES 130/0.4 with hetastarch (670/0.75 in saline) demonstrated not only equivalence of volume expansion but also lesser effects of HES 130/0.4 on coagulation. This effect on measures related to coagulation is the likely reason for the lesser transfusion of erythrocytes in the HES 130/0.4 group. In summary, the plasma volume expansion property of

Voluven® (HES 130/0.4) is equivalent to that of hetastarch; however, Voluven® has an enhanced safety profile compared with hetastarch. This may provide an important advantage in settings where higher infusion volumes are required.

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