

Large-dose Hydroxyethyl Starch 130/0.4 Does Not Increase Blood Loss and Transfusion Requirements in Coronary Artery Bypass Surgery Compared with Hydroxyethyl Starch 200/0.5 at Recommended Doses

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Background: **Hydroxyethyl starch (HES) 130/0.4 may impair blood coagulation less than other HES solutions and, thus, may be used at larger doses without increasing the risk of postoperative bleeding. This study tested the hypothesis that volume replacement with 6% HES 130/0.4 at a dose of up to 50 ml/kg does not increase blood loss and transfusion requirements in elective coronary artery bypass surgery compared with 6% HES 200/0.5 at a dose of up to 33 ml/kg.**

Methods: **One hundred twenty adult patients scheduled for elective coronary artery bypass surgery were randomized to receive up to 50 ml/kg of 6% HES 130/0.4 or up to 33 ml/kg of 6% HES 200/0.5 for volume replacement during surgery and until 24 h thereafter. Volume requirements in excess of the respective maximum dose of HES were treated with gelatin. Colloid use was at the discretion of the attending physicians and not dictated by protocol. The primary outcome variable was chest tube drainage volume during the first 24 h after surgery.**

Results: **The data from 117 patients (HES 130/0.4, 59 patients; HES 200/0.5, 58 patients) who completed the study according to protocol were analyzed. The median volumes of HES administered were 49 and 33 ml/kg in the HES 130/0.4 and HES 200/0.5 groups, respectively ($P < 0.001$). Consequently, patients in the HES 130/0.4 group required less gelatin in addition to HES than those in the HES 200/0.5 group (medians: 7 ml/kg *vs.* 20 ml/kg, $P < 0.001$). The combined volumes of HES and gelatin were similar for both groups ($P = 0.21$). The 24-h chest tube drainage (medians: 660 ml *vs.* 705 ml, $P = 0.60$) did not differ significantly between the groups, nor did transfusion outcome.**

Conclusion: **Six percent HES 130/0.4 at a median dose of 49 ml/kg did not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with 6% HES 200/0.5 at a median dose of 33 ml/kg.**

EXCESSIVE bleeding after cardiopulmonary bypass (CPB) can result from incomplete surgical hemostasis or coagulopathy, the latter most often due to acquired transient platelet dysfunction.[1] Perioperative fluid management may modify the risk of postoperative bleeding due to coagulopathy.[2–3] Hydroxyethyl starch (HES) solutions are widely used for intravascular volume replacement in cardiac surgery, but they may cause coagulopathy when administered in large doses.[4–6] Therefore, it is recommended that the maximum doses of HES not exceed 20 and 33 ml/kg per day for high- and medium-molecular-weight HES solutions, respectively.

Hydroxyethyl starch 130/0.4 (mean molecular weight, 130 kd; degree of substitution, 0.4) is a relatively new medium-molecular-weight HES solution that has been licensed for medical use in Europe and is undergoing phase III clinical testing in the United States. HES 130/0.4 may impair blood coagulation less than other HES solutions[7–10] and, thus, may be used at doses larger than 33 ml/kg per day without increasing the risk of coagulopathy. This controlled, randomized trial tested the hypothesis that intravascular volume replacement with 6% HES 130/0.4 at a dose of up to 50 ml/kg (approximately 1.5 times the manufacturer's recommended maximum dose) does not increase blood loss and transfusion requirements in elective coronary artery bypass surgery compared with 6% HES 200/0.5 (mean molecular weight, 200 kd; degree of substitution, 0.5) at a dose of up to 33 ml/kg.

Materials and Methods

Patients

The study was conducted between August 2000 and April 2001 in a 1,400-bed university hospital. After obtaining approval from the Ethics Committee of the Medical Faculty of the University of Cologne (Cologne, Germany), 120 patients scheduled to undergo elective primary coronary artery bypass grafting gave written, informed consent for their participation. Patients were eligible if they were aged between 40 and 75 yr and had a body mass index between 19 and 30 kg/m^2. Exclusion criteria were left ventricular ejection fraction less than 40%, recent (< 7 days) or current medication with any drugs known to affect blood coagulation, abnormal blood coagulation test results (prothrombin time [international normalized ratio] > 1.2, activated partial thromboplastin time > 40 s, platelet count < 100 × 10^9/l), plasma creatinine concentration greater than 1.5 mg/dl, and known allergy to HES.

Procedure

Patients were randomly allocated to receive either up to 50 ml/kg of 6% HES 130/0.4 (Voluven®; Fresenius

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Received from the Department of Anesthesiology, University of Cologne, Cologne, Germany. Submitted for publication September 18, 2002. Accepted for publication February 26, 2003. Supported by a grant from Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany. Presented in part at the 22nd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, March 19–22, 2002.

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Kabi, Bad Homburg, Germany) or up to 33 ml/kg of 6% HES 200/0.5 (6% HAES-steril®; Fresenius Kabi) for intravascular volume replacement during surgery and until 24 h thereafter. Randomization was based on a computer-generated code that was prepared at a remote site and sealed in sequentially numbered, opaque envelopes. Both HES solutions were supplied in identical-looking, sequentially numbered plastic bags containing either 6% HES 130/0.4 or 6% HES 200/0.5 according to the random code. The first 33 ml/kg HES was administered in a double-blind fashion. Treatment assignment was then disclosed to the investigators to enable them to adhere to the different maximum doses allowed for HES 130/0.4 and HES 200/0.5. Patients were kept blinded throughout the study. In both groups, volume requirements in excess of the respective maximum dose of HES were treated with a 4% solution of gelatin polysuccinate (Gelafundin®; B. Braun, Melsungen, Germany). Colloid use (*i.e.*, any decision when to give colloids, and how much) was at the discretion of the attending physicians and not dictated by protocol. The principal indication for colloid administration was hypovolemia, as suggested by low cardiac filling pressures, marked fluctuation of the arterial pressure waveform, arterial hypotension, tachycardia, and low urine output.

All patients received a standard anesthetic consisting of intravenous sufentanil, propofol, and pancuronium in body weight–related doses. After intubation of the trachea, the lungs were ventilated with 50% oxygen in air using a semiopen circle system. Tidal volume and ventilatory rate were adjusted to keep the arterial carbon dioxide partial pressure between 36 and 44 mmHg, except during total CPB. Patients were anticoagulated with porcine heparin at an initial dose of 300 U/kg, injected intravenously before cannulation of the aorta. Additional heparin was administered when the celite activated clotting time was less than 600 s. CPB was accomplished with a nonocclusive roller pump and a hollow fiber membrane oxygenator (Quadrox®; Jostra, Hirrlingen, Germany). The circuit was primed with 1,000 ml HES (either 6% HES 130/0.4 or 6% HES 200/0.5, according to randomization), 1,000 ml lactated Ringer's solution, 50 mM sodium bicarbonate, and 2,000 U heparin. A standard aprotinin regimen (2×10^6 kallikrein inactivator units [KIU] into the CPB circuit, 2×10^6 KIU as an intravenous bolus injection before CPB followed by a continuous intravenous infusion of 5×10^5 KIU/h until termination of CPB) was used in all patients.[11] Pump flow was maintained at 2.4 $l \cdot min^{-1} \cdot m^{-2}$ during moderate hypothermia (urinary bladder temperature > 30°C). Cardiac arrest was induced with 20 ml/kg cold crystalloid cardioplegia (Bretschneider's solution, Custodiol®; Dr. Franz Köhler Chemie, Alsbach-Hähnlein, Germany). Lactated Ringer's solution was added to the CPB circuit to maintain filling volume when needed. Packed erythrocytes were added when the hemoglobin concentration was less than 7 g/dl. After rewarming the patient to 37°C and discontinuation of CPB, 80% of the cumulative heparin dose was neutralized by intravenous infusion of protamine hydrochloride. Heparin neutralization was regarded as adequate if the postprotamine activated clotting time value was within 10% of the preheparin value. Increments of protamine were administered if the activated clotting time did not return to within 10% of baseline after the calculated dose. The residual blood in the CPB circuit was processed through a blood salvage device (Brat2®; Cobe Cardiovascular, Inc., Arvada, CO), with the erythrocytes returned in all cases.

Postoperatively, patients were transferred to the intensive care unit, and their lungs were mechanically ventilated until they were hemodynamically stable and no major bleeding was noted. Major bleeding was defined as a chest tube drainage greater than 200 ml/h for 2 consecutive hours. Fluid therapy in the intensive care unit consisted of a basic crystalloid infusion (40–60 ml/h). Additional fluids were administered as deemed necessary by the attending physicians. Packed erythrocytes were transfused when the hemoglobin concentration was less than 9 g/dl. Fresh frozen plasma and platelet concentrates, respectively, were transfused for correction of microvascular bleeding (chest tube drainage $>$ 200 ml/h for 2 consecutive hours) in the presence of abnormal blood coagulation values (prothrombin time [international normalized ratio] > 1.5, activated partial thromboplastin time > 60 s, fibrinogen concentration < 1 g/l, platelet count $< 50 \times 10^9$/l).[12]

Chest tube drainage volume was recorded until 24 h postoperatively. Recordings were made 6, 12, 18, and 24 h after surgery by a person who was not otherwise involved in the study and who was unaware of the patients' group assignments. At 2 and 6 h postoperatively, samples of the drainage fluid were collected for measurement of the hematocrit. Blood product use was recorded until postoperative day 7. Blood samples for laboratory studies were obtained before the induction of anesthesia (baseline), on arrival in the intensive care unit, 24 h after arrival in the intensive care unit, and on postoperative day 7. Blood samples at baseline and on postoperative day 7 were obtained by venipuncture. Blood samples at the other times were drawn from a central venous catheter after flushing with normal saline and discarding the first 10 ml of aspirated blood (approximately five times the dead space of the system). Laboratory studies included hemoglobin concentration, platelet count, prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, and plasma creatinine concentration. In the last consecutive 40 patients (20 patients from each group), laboratory studies also included determinations of factor VIII activity, von Willebrand factor antigen, and ristocetin cofactor activity. Factor VIII activity was determined by one-stage assay, von Willebrand factor antigen was mea-

sured with an enzyme-linked immunosorbent assay (Asserachrom® vWF; Diagnostica Stago, Asnières-sur-Seine, France), and ristocetin cofactor activity was determined by a quantitative assay based on ristocetin-induced platelet agglutination.

Statistical Analysis

The primary outcome variable was postoperative blood loss, which was defined as the chest tube drainage during the first 24 h after surgery. Based on previous data from our institution indicating an SD for the 24-h chest tube output of approximately 350 ml, we estimated that a sample size of 82 patients (41 patients per group) was sufficient to detect, with 90% power at the 0.05 significance level, a 250-ml difference in chest tube drainage between the two groups. Assuming a hematocrit of the drainage fluid of 25%,[13–15] 250 ml chest tube drainage contains approximately 60 ml erythrocytes, or approximately one third of the erythrocyte mass (200 ml) of a typical unit of packed erythrocytes.[16] A difference less than this was considered unlikely to be clinically important. Although the estimated minimum sample size was 41 patients per group, we decided to enroll 60 patients per group to allow for possible dropouts.

Results are reported as mean ± SD and median (range) for parametric and nonparametric data, respectively. Patient characteristics and data related to the surgical procedure were compared by Student *t* test. Laboratory variables were compared by repeated-measures analysis of variance. The volumes of infused fluids, chest tube drainage volume, the hematocrit of the drainage fluid, and perioperative blood use were compared using the Mann–Whitney U test. Proportions were compared by Fisher exact test and chi-square test, as appropriate. All tests were two-sided, with $P < 0.05$ considered significant.

Results

One hundred twenty patients were enrolled in the study, and 117 patients (HES 130/0.4, 59 patients; HES 200/0.5, 58 patients) completed it according to protocol. Three patients (HES 130/0.4, one patient; HES 200/0.5, two patients) required reexploration for bleeding, which was confined to specific sites, with no observation of generalized bleeding. As these three patients all were reexamined within 24 h after surgery, the primary outcome variable (24-h chest tube output) was not available for them. Hence, they were excluded from the analysis. Demographic data and baseline laboratory variables of the remaining 117 patients did not differ significantly between the groups (tables 1 and 2).

The median dose of HES administered during surgery and until 24 h thereafter was 49 (range, 21–53) ml/kg and 33 (29–40) ml/kg in the HES 130/0.4 and HES 200/0.5 groups, respectively ($P < 0.001$). Patients in the HES 130/0.4 group required less gelatin in addition to HES than those in the HES 200/0.5 group (7 [0–60] *vs.* 20 [0–58] ml/kg, $P < 0.001$). Twenty one patients (36%) from the HES 130/0.4 group *versus* 3 patients (5%) from the HES 200/0.5 group ($P < 0.001$) did not receive any gelatin. The total volume of colloids (HES and gelatin combined) administered to patients during surgery and until 24 h thereafter did not differ significantly between the groups (table 3).

Table 1. Patients and Procedures

	HES 130/0.4 (n = 59)	HES 200/0.5 (n = 58)
Sex (M/F)	47/12	46/12
Age (yr)	63 ± 8	64 ± 7
Weight (kg)	79 ± 10	76 ± 10
No. of bypass grafts	3 ± 1	3 ± 1
Patients receiving LIMA grafts (n)	57	57
Duration of surgery (min)	189 ± 39	181 ± 37
Cardiopulmonary bypass time (min)	88 ± 23	87 ± 24
Cross clamp time (min)	50 ± 17	50 ± 14
Lowest temperature on CPB (°C)	32.8 ± 2.0	32.6 ± 1.8
Temperature on arrival in ICU (°C)	35.8 ± 0.7	35.7 ± 0.9
ACT before heparin (s)	122 ± 16	122 ± 15
ACT after protamine (s)	130 ± 14	128 ± 15
Intraoperative blood salvage (ml)	618 ± 254	592 ± 180
Hematocrit of salvaged blood (%)	51 ± 7	53 ± 7
Ventilator time, postoperative (h)	13 ± 6	13 ± 5
ICU duration of stay (days)	2 ± 1	2 ± 1
Hospital duration of stay (days)	9 ± 3	8 ± 3

Values are expressed as mean ± SD or count. There was no significant difference between the groups.

ACT = activated clotting time; CPB = cardiopulmonary bypass; HES = hydroxyethyl starch; ICU = intensive care unit; LIMA = left internal mammary artery.

Chest tube drainage during the first 24 h after surgery ranged from 380 to 1,440 ml in the HES 130/0.4 group and from 330 to 1,750 ml in the HES 200/0.5 group (difference between medians: 45 ml, $P = 0.60$; table 4). Nine patients from the HES 130/0.4 group and 10 patients from the HES 200/0.5 group ($P = 0.77$) had a 24-h chest tube output greater than 1,000 ml. The hematocrit of the drainage fluid, as measured in samples collected 2 and 6 h postoperatively, did not differ significantly between the groups (table 4).

Perioperative erythrocyte transfusion requirements were similar in both groups (table 4). Ten patients from the HES 130/0.4 group and 19 patients from the HES 200/0.5 group ($P = 0.056$) were transfused with a median number of 2 units fresh frozen plasma. The total numbers of transfused units of fresh frozen plasma were

Table 2. Laboratory Variables

Variable	Baseline	End of Surgery	24 h ICU	POD 7
Hemoglobin (g/dl)				
HES 130/0.4	14.1 ± 1.2	10.1 ± 1.0	11.1 ± 1.1	12.0 ± 1.2
HES 200/0.5	14.0 ± 1.3	9.9 ± 1.0	11.1 ± 1.1	11.9 ± 1.3
Platelet count ($\times 10^9$/l)				
HES 130/0.4	252 ± 65	139 ± 43	166 ± 44	309 ± 107
HES 200/0.5	240 ± 69	127 ± 39	162 ± 50	291 ± 89
Prothrombin time (INR)				
HES 130/0.4	1.0 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1
HES 200/0.5	1.0 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.2
aPTT (s)				
HES 130/0.4	28 ± 13	65 ± 29	40 ± 23	25 ± 4
HES 200/0.5	26 ± 4	69 ± 27	37 ± 11	26 ± 4
Fibrinogen (g/l)				
HES 130/0.4	3.6 ± 1.1	2.3 ± 0.8	4.5 ± 1.1	6.6 ± 1.3
HES 200/0.5	3.6 ± 0.9	2.2 ± 0.6	4.6 ± 1.0	6.6 ± 1.1
Creatinine (mg/dl)				
HES 130/0.4	0.9 ± 0.2	0.8 ± 0.2	1.0 ± 0.4	1.0 ± 0.3
HES 200/0.5	0.9 ± 0.2	0.8 ± 0.2	1.1 ± 0.4	1.1 ± 0.6
Factor VIII:C (%)				
HES 130/0.4	164 ± 40	97 ± 34	162 ± 46	ND
HES 200/0.5	170 ± 29	102 ± 35	166 ± 52	ND
von Willebrand factor antigen (%)				
HES 130/0.4	142 ± 66	131 ± 38	252 ± 93	ND
HES 200/0.5	171 ± 70	152 ± 78	255 ± 79	ND
Ristocetin cofactor (%)				
HES 130/0.4	162 ± 77	173 ± 53	341 ± 138	ND
HES 200/0.5	193 ± 78	188 ± 110	324 ± 96	ND

Values are expressed as mean ± SD.

Normal ranges: hemoglobin, men: 13.5–18 g/dl, women: 12–16 g/dl; platelet count: 150–400 $\times 10^9$/l; prothrombin time (international normalized ratio [INR]): ≤ 1.2; activated partial thromboplastin time (aPTT): ≤ 38 s; fibrinogen: 1.8–3.5 g/l; creatinine, men: 0.5–1.1 mg/dl, women: 0.5–0.9 mg/dl, factor VIII:C: 50–200%, von Willeband factor antigen: 50–150%, ristocetin cofactor: 50–150%.

Baseline = before induction of anesthesia; HES = hydroxyethyl starch; 24 h ICU = 24 h after arrival in the intensive care unit; ND = not done; POD 7 = postoperative day 7.

24 and 41 in the HES 130/0.4 and HES 200/0.5 groups, respectively. No patient from either group received a platelet or cryoprecipitate transfusion. The number of patients who were transfused with any blood component (except for erythrocytes from intraoperative salvage) was not significantly different between the HES 130/0.4 and HES 200/0.5 groups (33 *vs.* 37 patients, $P = 0.45$).

Blood coagulation test results and plasma creatinine concentrations did not differ significantly between the

Table 3. Perioperative Infusions

	HES 130/0.4 (n = 59)	HES 200/0.5 (n = 58)	*P* Value
HES (ml)			
Intraoperative	2,500 (1,500–3,000)	2,231 (1,500–2,970)	0.24
Postoperative (0–24 h)	1,400 (0–2,500)	100 (0–1,500)	< 0.001
Total	3,500 (2,000–4,500)	2,500 (1,850–3,250)	< 0.001
Gelatin (ml)			
Intraoperative	0 (0–500)	0 (0–900)	< 0.001
Postoperative (0–24 h)	500 (0–4,000)	1,500 (0–4,000)	< 0.001
Total	500 (0–4,000)	1,700 (0–4,000)	< 0.001
HES and gelatin combined (ml)			
Intraoperative	2,500 (1,500–3,000)	2,400 (1,500–3,200)	0.98
Postoperative (0–24 h)	2,150 (0–5,500)	2,000 (500–4,000)	0.11
Total	4,500 (2,000–7,500)	4,265 (2,300–6,500)	0.21
Crystalloids (ml)			
Intraoperative	1,500 (500–3,050)	1,500 (500–2,500)	0.88
Postoperative (0–24 h)	1,900 (672–6,000)	1,800 (600–5,250)	0.61
Total	3,700 (2,172–7,500)	3,433 (1,600–6,750)	0.53

Values are expressed as median (range).

HES = hydroxyethyl starch.

Table 4. Chest Tube Drainage and Erythrocyte Transfusion

	HES 130/0.4 (n = 59)	HES 200/0.5 (n = 58)	*P* Value
Chest tube drainage (ml)			
0–12 h postoperative	410 (210–1,100)	495 (180–1,370)	0.34
0–24 h postoperative	660 (380–1,440)	705 (330–1,750)	0.60
Hematocrit (%) of drainage fluid			
2 h postoperative	17 (6–27)	18 (3–31)	0.50
6 h postoperative	11 (4–32)	10 (1–38)	0.62
Erythrocyte transfusion (U)			
Intraoperative	0 (0–4)	0 (0–4)	0.26
Postoperative (0–24 h)	0 (0–3)	0 (0–4)	0.17
Perioperative*	1 (0–6)	1 (0–6)	0.45
Patients receiving ≥ 1 unit erythrocytes			
Intraoperative	18	23	0.34
Postoperative (0–24 h)	12	18	0.21
Perioperative*	32	32	1.0

Values are expressed as median (range) or count.

* From the start of induction of anesthesia until postoperative day 7.

HES = hydroxyethyl starch.

groups at any time (table 2). Two patients from the HES 130/0.4 group and 3 patients from the HES 200/0.5 group were treated with continuous venovenous hemofiltration over a maximum period of 4 days for the management of acute renal failure. There was one in-hospital death in each group (HES 130/0.4: cardiac failure, HES 200/0.5: septic shock). All of the observed serious adverse events and fatalities were considered to be normal complications of open-heart surgery.

Discussion

We found that intravascular volume replacement with 6% HES 130/0.4 at a median dose of 49 ml/kg did not increase postoperative blood loss and perioperative erythrocyte transfusion requirements in elective coronary artery bypass surgery compared with 6% HES 200/0.5 at the manufacturer's recommended dose of 33 ml/kg. Because of the smaller maximum dose allowed for HES 200/0.5, patients in the HES 200/0.5 group received three times as much gelatin in addition to HES as those in the HES 130/0.4 group. If this should have introduced any bias, it would have biased the results toward reduced blood loss in the HES 200/0.5 group because gelatin is considered not to impair blood coagulation (at least not unless infused in very large volumes).[6] In addition, the combination of HES with gelatin has been found to impair blood coagulation less than HES alone.[17] It is also important to note that the total volume of colloids administered did not differ significantly between the HES 130/0.4 and HES 200/0.5 groups.

One previous study of volume replacement with 6% HES 130/0.4, 31 ml/kg, *versus* 6% HES 200/0.5, 31 ml/kg, suggested that HES 130/0.4 can reduce blood loss in coronary artery bypass surgery compared with HES 200/0.5.[18] In that study, the 16-h chest tube drainage volume was 390 ml less in the HES 130/0.4 group than in the HES 200/0.5 group, but the difference (800 ± 486 *vs.* 1,192 ± 1,225 ml) was not significant. We found that chest tube output was virtually the same with HES 130/0.4 as with HES 200/0.5. Considering that in our study HES 130/0.4 was administered at a dose 1.5-fold that of HES 200/0.5, one possible conclusion is that HES 130/0.4 was associated with a smaller relative risk of bleeding than HES 200/0.5. Other possible inferences include that the effects of the two HES solutions on postoperative bleeding were similar and independent of the dose administered. Because our study did not include a non-HES control group, it is also possible that both HES solutions increased bleeding compared with other types of fluids.

In this context, it may be relevant that a recent study found no difference in chest tube drainage volume and coagulation analysis results between two groups of patients who had received approximately 40 ml/kg of either 6% HES 130/0.4 or gelatin for volume replacement during elective cardiac surgery and until 24 h thereafter.[19] The authors concluded that, with regard to coagulation, volume replacement with 6% HES 130/0.4 was as safe as volume replacement with gelatin in cardiac surgical patients.

Several study limitations must be considered in the interpretation of our results. First, this study was not completely double blind. The unblinding of the investigators that occurred when 33 ml/kg HES was infused could have biased their subsequent clinical decisions and, thus, the study outcomes. Second, in the absence of a non-HES control group, no conclusion can be drawn regarding the effects of the two HES solutions on postoperative bleeding as compared with other types of intravenous fluids. Finally, the lack of a protocol to guide the administration of colloids may be considered a shortcoming. We hoped that without a strict protocol colloid use would be representative of routine clinical practice.

Fortunately, the infused total volume of colloids did not differ significantly between the groups, suggesting that similar criteria for colloid use had been applied to all patients.

In conclusion, we found that 6% HES 130/0.4 at a median dose of 49 ml/kg did not increase postoperative blood loss and perioperative erythrocyte transfusion requirements in elective coronary artery bypass surgery compared with 6% HES 200/0.5 at the manufacturer's recommended maximum dose of 33 ml/kg. Based in part on the data collected in this study, the manufacturer recently obtained approval from European Union authorities to adjust the dose recommendation for 6% HES 130/0.4 from a maximum of 33 ml/kg per day to a maximum of 50 ml/kg per day.

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