Voluven®, a Lower Substituted Novel Hydroxyethyl Starch (HES 130/0.4), Causes Fewer Effects on Coagulation in Major Orthopedic Surgery than HES 200/0.5

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Hydroxyethyl starch (HES) solutions are effective plasma volume expanders. Impairment of coagulation occurs with large HES volumes infused perioperatively. Therefore, a lower substituted novel HES (Voluven®; Fresenius Kabi, Bad Homburg, Germany) was developed to minimize hemostatic interactions, and was compared with HAES-steril® (Fresenius Kabi) (pentastarch) regarding safety and efficacy. We performed a prospective, randomized, double-blinded study in 100 major orthopedic surgery patients. Because the 95% confidence interval (-330 mL; +284 mL) for the treatment contrast Voluven®-HAES-steril® was entirely included in the predefined equivalence range (± 500 mL), comparable efficacy was established. Voluven® interfered significantly less than HAES-steril® with coagulation factor VIII levels and partial thromboplastin time postoperatively. Total amounts of red blood cells transfused were comparable between the Voluven® and HAES-steril® groups, but a significantly reduced need for homologous red blood cells was observed in the Voluven® group. We conclude that in large-blood–loss surgery, Voluven® has a comparable efficacy with HAES-steril® and may reduce coagulation impairment, possibly leading to a smaller number of allogeneic blood transfusions.

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Colloids are routinely used as plasma volume expanders for treating severe hypovolemia (1). Among the artificial colloids, hydroxyethyl starches (HES) have the fewest anaphylactoid reactions (2) and are the most commonly used colloids in Europe (3). HES are derived from waxy maize amylopectin, a branched polysaccharide closely resembling glycogen, by cleavage and hydroxyethylation. The extent of hydroxyethylation (degree of substitution), and its pattern, determine the degradation of HES by serum α-amylase, and therefore account for the pharmacological differences between various HES specifications (3). The average molecular weight plays only a minor role in determining the pharmacological profile of HES solutions (4,5). HES may interfere with coagulation and accumulate in plasma and tissues (3). The most pronounced side effects were found with large and highly substituted (i.e., ratio of hydroxyethyl groups to glucose residues) HES molecules (3,6–10), like hetastarch which has an average molecular weight of 450.000 dalton and a high degree of substitution of 0.7.

Voluven® (Fresenius Kabi, Bad Homburg, Germany) is a novel HES type. Voluven® has an average molecular weight of 130.000 dalton and a degree of substitution of 0.4 (HES 130/0.4). Its molecular weight distribution is the most narrow of all available HES types, i.e., the proportion of very large and very small molecules was significantly reduced. In the present study, Voluven® was compared with HAES-steril® (pentastarch, average molecular weight 200.000 dalton, degree of substitution 0.5; Fresenius Kabi) which is commonly used in Europe (8,11).

Voluven® does not accumulate in plasma after multiple dosing over 10 days, which is in contrast to all other HES types (12). Accordingly, renal excretion of

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Voluven® is increased (13). These pharmacological properties result in a 75% reduction in tissue storage as compared with HAES-steril® (14). *In vitro* and *in vivo* coagulation seem to be less compromised by Voluven® than by other HES specifications (15–17). Voluven® may not be associated with the typical undesired effects of higher substituted and higher molecular weight HES types, e.g., plasma accumulation, impairment of coagulation, and tissue storage. Regarding theoretical efficacy, Voluven® has a volume effect of approximately 100% (of the infused volume) and a 4- to 6-h duration (18), which is comparable with the current European standard HES, i.e., HAES-steril® (1).

The present prospective, randomized, double-blinded, multicenter study was performed in a large clinical setting during major orthopedic surgery to confirm the plasma-expanding properties of Voluven® reported in preliminary studies (12–16,18–21). The hypothesis was that perioperative administration of Voluven® in large-blood–loss surgery is comparable to the standard HAES-steril® (pentastarch) properties in restoring plasma volume. Plasma-expanding properties of Voluven® and standard HAES-steril® were assessed by comparing the colloid volumes infused in either group. Moreover, coagulation variables, estimated blood loss, and blood transfusion requirements were also compared between the two groups, as these are clearly the most relevant secondary endpoints in a fluid replacement study.

Methods

We performed a prospective, randomized, double-blinded, multicenter, clinical phase III study in strict accordance with the revised Declaration of Helsinki and with the principles of Good Clinical Practice. The study was approved by the local IRB (ethics committee of La Pitié-Salpêtrière). Written, informed consent was obtained from each patient before inclusion into the study.

Adult male and female patients scheduled for elective major orthopedic surgery with an expected blood loss of more than 2.0 L were included. Exclusion criteria were ASA physical status classification $>$ III; hematocrit $<$ 30% or hemoglobin $<$ 10 g/dL; cardiac insufficiency (New York Heart Association $>$ II); myocardial infarction during the last 6 mo; unstable angina pectoris; renal dysfunction (serum creatinine $>$ 1.2 mg/dL or $>$ 106 μmol/L for women, $>$ 1.3 mg/dL or $>$ 115 μmol/L for men); severe hepatic disorders (bilirubin $>$ 1.5 times upper limit of normal, or aspartate aminotransferase or alanine aminotransferase $>$ 2 times upper limit of normal); diabetes insipidus; severe infectious diseases; history of coagulation disorders; known allergy to starch; body weight $>$ 100 kg; pregnancy or lactation.

There were no restrictions with regard to concomitant medication. Patients were premedicated with 5 mg of midazolam orally. All patients underwent general anesthesia, which was induced with propofol (2–3 mg/kg) and sufentanil (1 μg/kg). Muscular relaxation for tracheal intubation was achieved with vecuronium 0.1 mg/kg. Anesthesia was maintained with isoflurane, sufentanil (0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and 60% N_2O in oxygen. Ventilation was adjusted to keep end tidal CO_2 at 35–40 mm Hg. Hypothermia was prevented during the surgery and the recovery period by using a heating blanket and perfusion warming. No acute normovolemic hemodilution was done. Crystalloid solutions were infused at a constant rate of approximately 10 $mL \cdot kg^{-1} \cdot h^{-1}$. Triggers for the administration of blood components were a hematocrit $<$ 25% for red blood cells transfusion and a platelet count $<$ 80 G/L for platelets transfusion.

Plasma volume replacement for treatment of perioperative hypovolemia was performed either with 6% Voluven® or with the control solution 6% HAES-steril®. The solutions were blinded by the manufacturer. The treatment period started after the induction of anesthesia and ended 5 h after the end of surgery. During this period, the triggers for infusion of the study HES solutions were a systolic blood pressure of $<$90 mm Hg and/or a decrease of $>$20% from baseline, a heart rate of $>$100 bpm and/or an increase of $>$30% from baseline, and/or a urine output of $<0.4\ mL \cdot kg^{-1} \cdot h^{-1}$. The infusion was continued until these hemodynamic goals were met. The maximum dose of Voluven® or HAES-steril® was 33 mL/kg body weight (e.g., 2.5 L for a patient of 75 kg), which is the maximum dose that is approved for HAES-steril® (pentastarch) in Europe. If larger doses were required, any other routinely used colloid than HES had to be administered. The IV fluid input and the complete fluid output were documented.

Other data recorded were adverse events, preexisting diseases, concomitant medication administered, systolic and diastolic blood pressure, heart rate, and body temperature. Laboratory tests included: red blood cells, hemoglobin, hematocrit, leukocytes, platelets, Quick, thrombin time, partial thromboplastin time (PTT), factor VIII concentration (chronometry with factor VIII deficient plasma, Behring, Germany), factor VIII-associated antigen/von Willebrand factor (ELISA test; Diagnostica Stago, Asnières, France), factor VIII ristocetin cofactor (agglutination test, Behring, Germany), blood gases, serum electrolytes, creatinine, lactate, bilirubin, glucose, lactate dehydrogenase, α-amylase, γ-glutamyl transferase, and liver transaminases. Measurements were performed 1 day before surgery, after the induction of anesthesia, every hour after incision, at the end of surgery, 5 h after the end of surgery, and 1 day after surgery. Not all of the variables were determined at each time point.

The primary efficacy variable was the total volume of colloids (as described above) required during the treatment period, i.e., from the induction of anesthesia until 5 h after the end of surgery. The hypothesis was that the volume need in both groups would be equivalent within a range of ±500 mL (corresponding to one HES bottle), indicating equal efficacy of both HES specifications (calculation of two-sided 95% confidence intervals on an intent-to-treat basis, analysis of variance [ANOVA] with effects for treatment and center [$\alpha = 0.05$ and $\beta = 0.01$]). All analyses were performed by using SAS®, version 6.09 (SAS Institute, Cary, NC), on a DECstation 5000/200. The expected standard deviation as deduced from previous observations in orthopedic patients was ±600 mL (11). With 100 patients included, the power of this confirmatory study was calculated at 99%. Blood transfusion and blood loss data were not normally distributed. For blood transfusion, the majority of values was zero. Therefore, standard nonparametric tests (problem of ties) or standard log transformation were not appropriate. For those endpoints, a Van-der-Waerden two-sample test was calculated after processing of the ties by either random procedure or mean ranks procedure. In addition, we performed a classification according to the distribution of the amount of red blood cells transfused according to 5 "classes" (0 mL, 1 to 500 mL, 501 to 1000 mL, 1001 to 2000 mL, and more than 2000 mL) for homologous, autologous, or total blood transfusion. Then, a Mantel-Haenszel test of the classified data was calculated to compare the distribution of red blood cells transfused between groups. A P value <0.05 was considered statistically significant.

Results

One hundred patients were included in the study (52 in the Voluven® group, 48 in the control group HAES-steril®). The groups were well matched with regard to demographics, type of surgery, and duration of surgery (Table 1), as well as preexisting diseases and concomitant medication. No significant differences in hemodynamics or body temperature (Table 2) were seen during the entire colloid treatment period, i.e., from the induction of anesthesia until 5 h after surgery. All patients received one of the two HES solutions. Because no major protocol violation was observed, no separate per protocol analysis was required in addition to the intent-to-treat analysis.

The mean infused volume of HES was not significantly different between the two groups: the Voluven® group received 1662 ± 641 mL (median, 1750 mL), and the control group received 1696 ± 675 mL (median, 1950 mL) (Fig. 1). Moreover, no significant difference was observed for the mean infused volume of total colloids (1960 ± 971 mL in the Voluven® group, 1928 ± 901 mL in the control group). An ANOVA with effects for treatment and center was calculated. Based on this ANOVA, the 95% confidence interval for the treatment contrast Voluven®–HAES-steril® was [−330 mL; +284 mL]. Because it was entirely included in the predefined equivalence range [−500 mL; 500 mL], equivalence of the two HES specifications with regard to efficacy was clearly proven ($P = 0.001$).

If colloid doses larger than 33 mL/kg were needed for intravascular volume replacement, the investigator had to switch to any other colloid than HES. Sixteen patients in the Voluven® group and 14 patients in the HAES-steril® group received additional colloids for this reason. Depending on the routine procedure in the respective hospital, these additional colloids were either fresh-frozen plasma or gelatin (no significant differences between groups) (Fig. 1). No albumin was used in any patient. Mean infused volumes of crystalloid solutions were similar in both groups (3030 ± 1138 mL in the Voluven® group versus 2971 ± 1752 mL in the HAES-steril® group, Fig. 1). When expressed in mL per kg body weight, mean infused volumes of HES were 24.2 mL/kg for Voluven® and 24.5 mL/kg for HAES-steril®. In 7 Voluven® patients and in 9 HAES-steril® patients, the HES dose limit of 33 mL/kg was exceeded, but mostly by <0.5 mL/kg. Maximum doses were 38.5 mL/kg for Voluven® and 40.8 mL/kg for HAES-steril®.

Table 1. Patient Demographics

	Voluven® ($n = 52$)	HAES-steril® ($n = 48$)
Age (yr)		
Mean	52	61
Range	18–83	19–86
Sex [n (%)]		
Male	21 (40)	17 (35)
Female	31 (60)	31 (65)
Weight (kg)		
Mean	70	69
Range	46–96	45–99
Height (cm)		
Mean	167	165
Range	146–197	146–188
Broca index[a]		
Mean	1.14	1.16
Range	0.72–1.93	0.85–1.80
Type of surgery [n (%)]		
Hip	22 (42)	26 (54)
Spine	26 (50)	19 (40)
Knee or femoral	4 (8)	3 (6)
Duration of surgery (min)		
Mean	241	219
Range	120–540	80–450

Voluven® (Fresenius Kabi, Bad Homburg, Germany); HAES-steril® (Fresenius Kabi).

[a] Weight (kg)/[height (cm) − 100] for men. Weight (kg)/([height (cm) − 100] × 0.9) for women.

Table 2. Perioperative Hemodynamics (mean ± SD)

	Voluven® (n = 52)	HAES-steril® (n = 48)
Heart rate (bpm)		
1 day before surgery	76 ± 10	73 ± 8
After induction of anesthesia (baseline)	68 ± 14	65 ± 10
1 h after incision	64 ± 11	61 ± 9
2 h after incision	68 ± 13	65 ± 11
3 h after incision	72 ± 12	69 ± 14
End of surgery	71 ± 14	69 ± 16
5 h after end of surgery	84 ± 16	83 ± 16
1 day after end of surgery	81 ± 16	78 ± 12
Systolic blood pressure (mm Hg)		
1 day before surgery	137 ± 17	135 ± 15
After induction of anesthesia (baseline)	108 ± 16	107 ± 21
1 h after incision	96 ± 12	98 ± 12
2 h after incision	98 ± 12	98 ± 16
3 h after incision	97 ± 12	99 ± 17
End of surgery	105 ± 15	102 ± 20
5 h after end of surgery	126 ± 19	127 ± 19
1 day after end of surgery	127 ± 14	125 ± 15
Diastolic blood pressure (mm Hg)		
1 day before surgery	78 ± 11	77 ± 9
After induction of anesthesia (baseline)	62 ± 12	61 ± 14
1 h after incision	58 ± 9	58 ± 8
2 h after incision	60 ± 9	57 ± 10
3 h after incision	57 ± 8	57 ± 12
End of surgery	61 ± 11	58 ± 11
5 h after end of surgery	66 ± 11	64 ± 12
1 day after end of surgery	70 ± 12	68 ± 11
Body temperature (°C)		
After induction of anesthesia (baseline)	35.8 ± 0.6	35.9 ± 0.5
1 h after incision	35.3 ± 0.7	35.4 ± 0.6
2 h after incision	35.2 ± 0.9	35.2 ± 0.7
3 h after incision	35.0 ± 0.9	35.3 ± 0.8
End of surgery	35.2 ± 1.0	35.3 ± 0.9
5 h after end of surgery	36.9 ± 0.5	36.5 ± 0.6

Voluven® (Fresenius Kabi, Bad Homburg, Germany); HAES-steril® (Fresenius Kabi).

The total blood loss (i.e., sum of cell saver, drainage, and estimated other blood loss) was not significantly different between groups (medians, 1800 mL in Voluven® group versus 2350 mL in control group) by using a modified Van-der-Waerden two-sample test. The total amount of autologous and homologous red blood cells transfused was not significantly different between groups by using a modified Van-der-Waerden two-sample test and a Mantel-Haenszel test of the classified data (Fig. 1 and Table 3, respectively). Patients in the Voluven® group required significantly less homologous red blood cells than those in the control group (Fig. 1 and Table 3). Only one patient (control group) received platelets.

Differences between treatment groups were also found for some coagulation variables (Table 4 and Fig. 2). Five hours after the end of surgery, PTT had slightly decreased in the Voluven® group but increased in the control group as compared with baseline (Table 4). This difference between groups was significant in the ANOVA (P = 0.002). Factor VIII concentration showed a significantly larger mean increase with Voluven® than with HAES-steril® 5 hs after the end of surgery (P = 0.04, Table 4 and Fig. 2). For all other coagulation variables, differences between treatment groups did not reach statistical significance. The degree of hemodilution as reflected by the perioperative hematocrit was very similar in both groups (Table 4).

There was an increase in α-amylase in both treatment groups. However, the mean increase in Voluven® patients (from 74 U/L at baseline to 158 U/L 1 day after surgery) was significantly smaller (P = 0.04) than that in HAES-steril® patients (from 74 U/L to 255 U/L). With regard to all other laboratory variables, both groups were comparable.

There were no major differences between treatment groups regarding adverse events. No patient died. Study drug relationship as judged by the investigators was probable for only one adverse event (postoperative hemorrhage, control group).

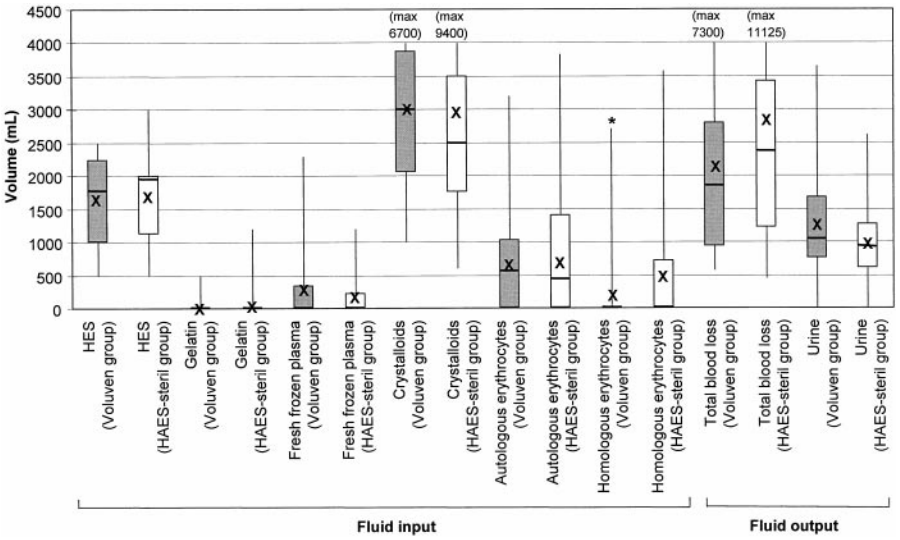

Figure 1. Fluid input and output from the induction of anesthesia until 5 h after the end of surgery in the Voluven® (Fresenius Kabi, Bad Homburg, Germany) group (n = 52) and the HAES-steril® (Fresenius Kabi) group (n = 48). Vertical lines = minimum/maximum, boxes = 25%/75% percentiles, horizontal line within column = median, X = mean. *P < 0.05 versus HAES-steril® group.

Table 3. Red Blood Cell Transfusion [number of patients (%)]

	Voluven® (n = 52)	HAES-steril® (n = 48)
Homologous blood transfusion*		
0 mL	40 (77)	30 (63)
1–500 mL	3 (6)	1 (2)
501–1000 mL	6 (11)	10 (21)
1001–2000 mL	2 (4)	2 (4)
>2000 mL	1 (2)	5 (10)
Autologous blood transfusion		
0 mL	19 (36)	20 (42)
1–500 mL	4 (8)	6 (12)
501–1000 mL	14 (27)	7 (15)
1001–2000 mL	10 (19)	10 (21)
>2000 mL	5 (10)	5 (10)
Total blood transfusion		
0 mL	11 (21)	11 (23)
1–500 mL	4 (8)	4 (8)
501–1000 mL	19 (37)	9 (19)
1001–2000 mL	12 (23)	14 (29)
>2000 mL	6 (11)	10 (21)

Voluven® (Fresenius Kabi, Bad Homburg, Germany); HAES-steril® (Fresenius Kabi).

*P = 0.042 for difference between treatment groups (Mantel-Haenszel test).

Discussion

This prospective, randomized, double-blinded, multicenter study in major orthopedic surgery patients was designed to investigate the clinical efficacy and safety of Voluven®, a novel HES preparation. It was demonstrated, in this largest study with Voluven® and one of the largest double-blinded trials in intravascular volume replacement therapy performed, that the perioperative administration of Voluven® is as efficient and at least as safe as that of the commonly used standard HAES-steril® (pentastarch). The primary efficacy endpoint was the colloid volume infused. Safety evaluation focused on coagulation, estimated blood loss, and blood transfusion requirements, as these are clearly the most relevant safety endpoints in intravascular fluid replacement studies.

Elective major orthopedic surgery was chosen because it offers a frequent and standardized surgical setting allowing the study design to be based largely on clinical routine. The study solutions were infused after a simple algorithm aimed at preventing hypovolemia. When a maximum HES dose of 33 mL/kg body weight was reached, any other common colloid could be used for further volume replacement. Importantly, the strictly double-blinded design of the study precluded any bias regarding the decision for colloid infusion. Also, the results were not influenced by different crystalloid use as crystalloid volumes infused were very similar in both groups. The primary efficacy variable was the total amount of colloids required perioperatively, namely from the induction of anesthesia until five hours after the end of surgery. With regard to efficacy, equivalence of Voluven® and HAES-steril® (pentastarch) was clearly demonstrated. This confirms previous observations in healthy volunteers after bleeding and using an isovolemic model (18), in autologous blood donation (19), and in cardiac surgery (16,21). However, those previous results had to be confirmed in a larger clinical setting as in the present study.

Patients treated with Voluven® had somewhat smaller blood loss (not significant) and received significantly less homologous red blood cells than the control group. In addition, the number of patients with the largest blood transfusion requirement (i.e., >2000 mL) was smaller in the Voluven® group compared with the control group for homologous and total blood transfusion (Table 3). The decreased homologous blood transfusion need in this subclass of

Table 4. Perioperative Coagulation Variables and Hematocrit (mean ± SD)

	Voluven® (n = 52)	HAES-steril® (n = 48)
Factor VIII concentration (%)		
After induction of anesthesia (baseline)	113 ± 45	129 ± 64
End of surgery	84 ± 40	94 ± 50
5 h after end of surgery	162 ± 68*	141 ± 51
Factor VIII/von Willebrand factor (%)		
After induction of anesthesia (baseline)	102 ± 41	105 ± 44
End of surgery	87 ± 42	84 ± 37
5 h after end of surgery	142 ± 50	130 ± 61
Factor VIII ristocetin cofactor (%)		
After induction of anesthesia (baseline)	94 ± 40	99 ± 47
End of surgery	84 ± 41	78 ± 43
5 h after end of surgery	136 ± 50	126 ± 58
Partial thromboplastin time (sec)		
After induction of anesthesia (baseline)	32 ± 5	32 ± 11
End of surgery	38 ± 10	40 ± 20
5 h after end of surgery	30 ± 5*	35 ± 14
Quick (%)		
After induction of anesthesia (baseline)	88 ± 9	92 ± 9
End of surgery	70 ± 17	71 ± 20
5 h after end of surgery	78 ± 16	77 ± 18
Thrombin time (sec)		
After induction of anesthesia (baseline)	23 ± 9	23 ± 9
End of surgery	21 ± 6	24 ± 16
5 h after end of surgery	22 ± 8	23 ± 15
Platelets (G/L)		
After induction of anesthesia (baseline)	239 ± 54	241 ± 56
End of surgery	179 ± 47	172 ± 58
5 h after end of surgery	185 ± 53	169 ± 56
Hematocrit (%)		
After induction of anesthesia (baseline)	33 ± 4	33 ± 4
End of surgery	26 ± 5	26 ± 4
5 h after end of surgery	29 ± 4	29 ± 4

Voluven® (Fresenius Kabi, Bad Homburg, Germany); HAES-steril® (Fresenius Kabi).
* $P < 0.05$ for difference between groups (baseline-corrected).

the Voluven® group contributed to making the difference between groups significant for the overall homologous blood transfusion. Furthermore, as it is mandatory, autologous transfusion is always performed before homologous transfusion; then differences in blood transfusion requirements will mainly become apparent for homologous blood. This may explain why homologous, but not autologous, blood transfusion was reduced in the Voluven® group compared with the control group. In a previous study (16) comparing Voluven® versus HAES-steril® in cardiac surgery, mean blood loss appeared also to be somewhat less in the Voluven® group (1301 mL vs 1821 mL, not significant) compared with the control group as in our study. In our study, the volumes of fresh-frozen plasma transfused were rather small, with no significant differences between groups (Fig. 1). Therefore, it is unlikely that the favorable red blood cell transfusion and coagulation results obtained with Voluven® were influenced by transfusion of fresh-frozen plasma. Furthermore, the types and duration of surgery were comparable between groups, indicating that the severity of the intervention did not differ between groups (Table 1). Thus, there is no indication that there was more surgical bleeding in the control group than in the Voluven® group.

The blood transfusion results discussed above are consistent with the finding that factor VIII concentration and PTT were significantly less compromised by Voluven® than by HAES-steril® in the early postoperative phase. These two coagulation variables are relevant for the evaluation of any new HES type, as it is known that higher substituted and higher molecular weight HES types lead to a prolonged PTT and a lower postoperative increase in factor VIII (6,8,22). Postoperative increases in factor VIII, von Willebrand factor, and ristocetin cofactor are part of the physiologic acute phase reaction to surgical stress (23–25). Large and highly substituted HES molecules (hetastarch, HES 450.000/0.7) attenuate this physiologic response as compared with human albumin (24) or crystalloids (25), although the mechanism is not

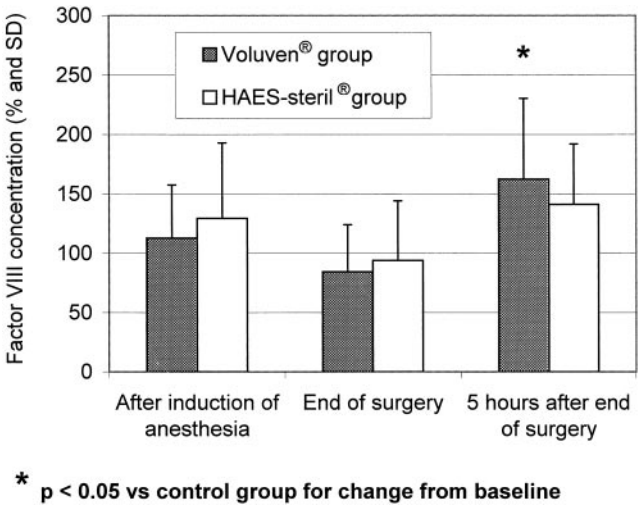

Figure 2. Perioperative factor VIII concentration (%) in the Voluven® (Fresenius Kabi, Bad Homburg, Germany) group ($n = 52$) and the HAES-steril® (Fresenius Kabi) group ($n = 48$). *$P < 0.05$ versus HAES-steril® group (baseline-corrected).

known (3,10). Similarly, in our study the control HES specification significantly attenuated the factor VIII response as compared with Voluven®. Very similar results were obtained in previous clinical studies with Voluven® (15,16). The reduced influence of Voluven® on coagulation was also shown in an *in vitro* study (17).

The increase observed in serum α-amylase was significantly less in Voluven® patients than in control patients. Serum α-amylase is transiently increased by all available HES solutions. This is because of the formation of a HES-amylase complex resulting in a decreased renal elimination of α-amylase. This effect is directly correlated with plasma HES concentration (5). Problems might result from interference with the diagnosis of pancreatitis. Therefore, the reduced influence of Voluven® on serum α-amylase is potentially beneficial. Furthermore, this observation confirms the improved pharmacokinetic profile of Voluven®.

All the above-mentioned data relating to improved safety are consistent with the fact that Voluven® is more rapidly eliminated from the body than conventional HES types (12–14). This is not in conflict with its evident equivalence in efficacy. The reason is that in older HES types, very high molecular weight molecules account for a large proportion of the total mass. These large molecules are thought to be responsible for the undesired storage and coagulation phenomena (3,10). However, the oncotic (water-binding) effect of colloids primarily depends on the number of molecules rather than on their size. The number of molecules in Voluven® is relatively large because of its lower average molecular weight and its narrow molecular weight distribution, which both result in a very small proportion of large molecules. This surplus oncotic effect of Voluven® counterbalances its more rapid elimination.

We conclude that in large-blood–loss surgery, Voluven® may have a favorable coagulation profile and may lead to less homologous blood consumption compared with HAES-steril® (pentastarch), while the efficacy of both solutions in restoring plasma volume is equivalent. Nevertheless, further studies are required to show whether Voluven® can safely be used at larger dosages than currently recommended.

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