A novel hydroxyethyl starch (Voluven®) for effective perioperative plasma volume substitution in cardiac surgery

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Purpose: To compare the new hydroxyethyl starch HES 130/0.4 (Voluven®) and the standard HES 200/0.5 (pentastarch) regarding effectiveness for plasma volume substitution and safety of large volumes in heart surgery.

Methods: Fifty-nine patients scheduled for coronary artery bypass grafting were enrolled in a prospective, randomised, double-blind, parallel-group, multicentre, clinical, phase III study. Hydroxyethyl starch was used as the exclusive artificial colloid for acute normovolemic hemodilution, priming of the heart lung machine, and for intra- and postoperative plasma volume substitution from induction of anesthesia until 16 hr after the end of surgery. Efficacy was evaluated by comparing the amount of colloid infused, hemodynamics, and colloid osmotic pressure (COP). Safety endpoints were blood loss, the use of allogeneic blood products, coagulation variables, and adverse events.

Results: Effectiveness, as assessed by the total amount of infused HES volumes within the treatment period, was similar between HES 130/0.4 and HES 200/0.5 (2550 mL ± 561 mL *vs* 2466 mL ± 516 mL). Also, no differences were found for the use of other colloids (pasteurised plasma), hemodynamics, and COP. In HES 130/0.4 patients, the postoperative increase of von-Willebrand factor (vWF) was higher ($P < 0.01$), blood loss was lower, and less packed red blood cells were transfused.

Conclusion: Hydroxyethyl starch 130/0.4 is an effective plasma volume expander in heart surgery and may be used as the sole artificial colloid to cover the perioperative period. We found a reduced influence of HES 130/0.4 on the physiologic postoperative increase of vWF.

Objectif : Comparer le nouvel hydroxyéthylamidon HEA 130/0,4 (Voluven®) et l'HEA standard 200/0,5 (pentamidon) au plan de l'efficacité, quand on l'utilise comme substitution du volume plasmatique, et au plan sécuritaire de l'emploi de volumes importants en cardiochirurgie.

Méthode : Cinquante-neuf patients qui devaient subir un pontage aorto-coronarien ont participé à une étude clinique multicentrique, prospective, randomisée, à double insu et en groupes parallèles, de phase III. L'hydroxyéthylamidon a été utilisé comme colloïde artificiel exclusif pour l'hémodilution normovolémique pratiquée d'emblée, pour amorcer l'utilisation du coeur-poumon artificiel et pour le remplacement du volume plasmatique peropératoire et postopératoire depuis l'induction de l'anesthésie jusqu'à 16 h après la fin de l'opération. L'efficacité a été évaluée en comparant la quantité de colloïde perfusé, l'hémodynamie et la pression osmotique du colloïde (POC). Les paramètres mesurés ont été : la perte sanguine, l'utilisation de produits sanguins allogéniques, les variables de coagulation et les inconvénients.

Résultats : L'efficacité, évaluée selon la quantité totale d'HEA perfusé pendant le traitement, a été similaire pour l'HEA 130/0,4 et l'HEA 200/0,5 (2550 mL ± 561 mL *vs* 2466 mL ± 516 mL). De plus, il n'y a eu aucune différence quant à l'utilisation d'autres colloïdes (plasma pasteurisé), à l'hémodynamie et à la POC. Chez les patients qui ont reçu l'HEA 130/0,4, l'augmentation postopératoire du facteur de von Willebrand (vWF) a été plus élevée ($P < 0,01$), la perte sanguine plus faible et la transfusion de globules rouges concentrés moins importante.

Conclusion : L'hydroxyéthylamidon 130/0,4 représente un substitut du plasma sanguin efficace en cardiochirurgie et peut être utilisé comme colloïde artificiel unique pendant la période périopératoire complète. Nous avons constaté une action réduite de l'HEA 130/0,4 sur l'augmentation physiologique postopératoire du vWF.

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ALTHOUGH the use of colloids or crystalloids for plasma volume substitution is still controversial, in Europe colloids are usually given to prevent and treat hypovolemia during major surgery.

In heart surgery, gelatins and hydroxyethyl starches (HES) are among the most common artificial colloids and have been used for many years. Gelatins are often favoured because of their unlimited daily dose recommendation and presumed lack of effect on hemostasis, although this has been disputed in heart surgery at doses exceeding two litres.[1,2] A disadvantage of gelatin is the higher incidence of allergic reactions, e.g., in comparison with HES.[3]

Hydroxyethyl starch is a derivative of amylopectin, the highly branched polysaccharide component of waxy maize which closely resembles glycogen. Hydroxyethyl starch is manufactured through hydrolysis and subsequent hydroxyethylation of amylopectin, thereby cleavage of the molecule *in vivo* by serum alpha-amylase is delayed. In particular, the extent of hydroxyethylation (molar substitution) and its pattern determine the degradation and subsequent elimination of HES and, thus, account for the pharmacological differences between various HES specifications.[4,5]

With large volumes of HES infused perioperatively, inhibitory effects on hemostasis, most notably on the von- Willebrand factor, have been reported.[6–8] Impairment of hemostasis by HES is most pronounced with large and highly substituted HES molecules, such as hetastarch, which has an average molecular weight of 450,000 dalton and a degree of substitution of 0.7 (HES 450/0.7), or after long-term use of medium molecular weight starches with a high degree of substitution (200,000 dalton; 0.62-0.66).[9,10] These HES types are characterised by delayed degradation *in vivo* and accumulation of HES molecules in plasma and tissue.[11]

The development of a new HES specification, HES 130/0.4 (Voluven®, Fresenius Kabi, Bad Homburg, Germany), focused on the pharmacokinetic drug profile. Based on the European standard HES 200/0.5 (pentastarch), the molecule was modified through reduction of the average molecular weight to 130,000 dalton and the degree of substitution to 0.4. The pharmacological concept was to provide more osmotically effective small molecules (maintenance of effectiveness) but to enhance metabolism and renal elimination of the substance (improvement of drug safety). With studies in healthy volunteers, Waitzinger *et al.*[12,13] demonstrated a volume effect of HES 130/0.4 6% of about 100% of the infused volume and approximately four to six duration. In contrast to other HES specifications, HES 130/0.4 does not accumulate in plasma following repetitive doses.[14] In pre-clinical studies in animals, a 75% reduction in tissue storage could be demonstrated for HES 130/0.4 compared with HES 200/0.5.[15] A clinically important advantage of HES 130/0.4 is that coagulation *in vitro* and *in vivo* is less affected.[16–18] Overall, this profile may be particularly attractive in clinical settings where high doses and repetitive administrations are needed.

To evaluate the plasma substitution characteristics of HES 130/0.4, we performed a comparative clinical study in heart surgery. The control group received the standard HES 200/0.5 (pentastarch). We assessed also the safety of large volumes of HES 130/0.4 with emphasis on coagulation, blood loss, and transfusion requirements.

Methods

This study was designed as a prospective, randomised, double-blind, parallel-group, multicentre, clinical, phase III study to demonstrate equivalence of two hydroxyethyl starch specifications in prevention and treatment of hypovolemia in patients undergoing heart surgery.

The study was performed in strict accordance with the revised Declaration of Helsinki and with the principles of Good Clinical Practice (GCP). From June to December, 1996, fifty-nine patients scheduled for coronary artery bypass grafting (CABG) were recruited in two cardiac centres in the Netherlands. The Medical Ethics Committees approved the protocol and, for participation, written informed consent from the patients was obtained. Adult male and female patients with a body weight between 70 -100 kg and an expected time of cardiopulmonary bypass between 30 min and 3.5 hr were included. Exclusion criteria were a history of cardiac surgery, severe congestive heart failure, hemoglobin concentration < 7.5 or > 10.5 $mmol \cdot L^{-1}$, pancreatitis, known hypersensitivity to hydroxyethyl starch, coagulation disorders, renal or hepatic disorders, and pregnancy or lactation.

Anesthesia was induced with 0.03-0.1 $mg \cdot kg^{-1}$ midazolam, 1-3 $\mu g \cdot kg^{-1}$ sufentanil, and 0.1 $mg \cdot kg^{-1}$ pancuronium and maintained with an infusion of midazolam and sufentanil. All patients received 1 $mg \cdot kg^{-1}$ dexamethason. The heart lung machine (HLM) was prepared with one litre starch, 900 mL Ringer's lactate and 100 mL mannitol. During cardiopulmonary bypass (CPB) the patients were cooled to 28-30°C with either a membrane oxygenator and nonpulsatile flow (2.4 $L \cdot m^{-2} \cdot min^{-1}$) or a hollow fibre oxygenator with pulsatile flow. St-Thomas crystalloid cardioplegia solution was used in all cases.

The patients were randomised into two treatment groups and received either HES 130/0.4 6% (Voluven®, Fresenius Kabi, Bad Homburg, Germany) or HES 200/0.5 6%, (pentastarch, HAES steril® 6%, Fresenius Kabi, Bad Homburg, Germany) as the exclusive artificial colloid. The hydroxyethyl starches were used for acute normovolemic hemodiluton (limited to 500 mL HES/patient plus crystalloids), priming of the HLM (1 litre HES/patient plus crystalloids) and, generally, for intraoperative and postoperative plasma volume substitution. A maximum dose of three litres of either hydroxyethyl starch was provided for each patient. With this dose we planned to cover the total perioperative treatment period from induction of anesthesia until 16 hr after the end of surgery. However, if additional volume was needed beyond three litres, isotonic pasteurised plasma was administered. Colloid infusion was not targeted by a strict algorithm or supranormal hemodynamic values, but was individually adjusted for each patient to maintain colloid osmotic pressure, a cardiac index preferably > $2 L \cdot min^{-1} \cdot m^{-2}$ with normal hemodynamic filling pressures (CVP 4-12 mmHg and PCWP 6-12 mmHg), and urine output of $1\text{-}2 mL \cdot kg^{-1} \cdot hr^{-1}$. In order to preclude any bias regarding the decision for colloid infusion, the HES solutions were blinded by the manufacturer (Fresenius Kabi, Bad Homburg, Germany).

No cell saver or mediastinal re-transfusion device was used. After CPB, first the autologous blood and, thereafter, the HLM residue was re-transfused to the patient. In the ICU, the remaining HLM residue was transfused first, after which starch was supplemented with a basic crystalloid infusion of $250 mL \cdot h^{-1}$.

A hemoglobin concentration of $5.0 mmol \cdot L^{-1}$ ($8.0 g \cdot dL^{-1}$) was the trigger for allogeneic red blood cell (RBC) transfusion. Desmopressin acetate and tranexamic acid but not aprotinin were allowed to correct hemostasis.

All fluids administered (including blood products) were recorded. Pericardial and pleural fluid losses were collected in the cardiotomy reservoir and all blood swabs in the operating theatre were weighted. In the ICU, pleural and mediastinal chest tube drainages were measured. Colloid osmotic pressure was measured with an osmometer using a 30,000 dalton membrane. Hemodynamic measurements (HR, MAP, CVP, MPAP, PCWP, CI, SVR, PVR) and blood gas analysis (pH, PaO_2, $PaCO_2$, HCO_3, SaO_2, and FiO_2) were recorded after induction of anesthesia, before start of CPB, after CPB, on admission to the ICU, and 8 and 16 hr thereafter. Blood samples for evaluation of hematological and biochemical variables (hemoglobin, hematocrit, serum electrolytes, creatinine, alpha-amylase, LDH, ALT, AST) as well as coagulation variables (von-Willebrand factor antigen, aPTT, PT, platelet agglutination) were drawn after induction of anesthesia, after CPB, at admission to the ICU, and on the following morning. Patients were followed up for laboratory variables until the second postoperative day and for adverse events until discharge from the hospital.

Von Willebrand Factor (plasma) concentration was determined with an ELISA (Gradipore, North Ride, Australia). To determine the activated Partial Thromboplastin Time, platelet poor plasma and rabbit brain cephalin (Sigma Diagnostics, St. Louis, USA) suspended in ellagic acid was incubated for three minutes at 37°C; after adding $CaCl_2$, (final concentration 10 mM), the clotting time was recorded in seconds (Coagulometer, Amelung, Lieme, Germany). The Thrombin Time was determined by means of Atroxin thrombin time reagent (Sigma). The Prothrombin Time was determined by means of rabbit thromboplastin (Kordia, Leiden, The Netherlands) and $CaCl_2$ (final concentration 10 mM). Platelet agglutination was performed by means of an (electrical) impedance measurement in citrated whole blood samples. Platelet agglutination was induced by the agonist ristocetin (Sigma Diagnostics, St. Louis, MO, USA), final concentration $0.75 mg \cdot ml^{-1}$.

The primary effectiveness parameter of the study was the total volume of colloids (HES plus isotonic pasteurised plasma) infused per treatment group within the treatment period (from induction of anesthesia until 16 hr after the end of surgery). Secondary efficacy parameters were hemodynamics, blood gases, and fluid balance. Safety parameters were coagulation variables, blood loss, the use of allogeneic blood products, hematological and biochemical laboratory parameters, and adverse events. With regard to patient outcome, the duration of mechanical ventilation, length of ICU stay and hospital stay were evaluated.

The hypothesis of this study was that the volume of colloids required in both treatment groups would be equivalent within a range of ±500 mL, thus, indicating comparable effectiveness of both HES specifications (calculation of two-sided 95% confidence intervals on an intent-to-treat basis, ANOVA with effects for treatment and centre). All analyses were performed using SAS®, version 6.09, on a DECstation 5000/200. The expected standard deviation (SD) was ±600 mL. With a total of 50 patients, the power of this study was estimated at 84%. A P value < 0.05 was considered statistically significant. By explorative data analyses (ANOVA with effects for treatment and centre), differences in coagulation variables, blood loss, use of allogeneic blood products, and in laboratory parameters were evaluated.

Results

Fifty nine patients were included in the study, 30 of whom received HES 130/0.4 while 29 patients were treated with HES 200/0.5. There were no differences in demographic variables, concomitant diseases or medication between the treatment groups. All patients were receiving nitrate therapy. In both groups, 83% of the patients were male. Also, no relevant differences were found for the cardiopulmonary bypass period, the duration of aortic cross clamping, and the duration of surgery (Table I). The time from induction of anesthesia to admission to ICU was 205 min (HES 130/0.4) *vs* 191 min (HES 200/0.5). All patients were included in the statistical analysis on an intent-to-treat basis.

The mean infused volume of HES was comparable between the treatment groups within the treatment period from induction of anesthesia until 16 hr after the end of surgery (2550 ± 561 mL of HES 130/0.4 and 2466 ± 516 mL of HES 200/0.5). The same was true for the mean infused volume of total colloids (2913 ± 779 mL in HES 130/0.4 patients and 2884 ± 1175 mL in HES 200/0.5 patients). In the ANOVA, the estimated treatment contrast HES 130-HES 200 was 23.9 mL, with a 95% confidence interval of [-488 mL; 535 mL]. This interval was not entirely included in the estimated equivalence range [-500 mL; 500 mL] and equivalence could not be statistically proven. However, the difference between the actual and the targeted interval was marginal (35 mL) and is clinically irrelevant. Importantly, the volume of crystalloid given throughout the treatment period was virtually identical between the treatment groups (4187 ± 615 mL in HES 130/0.4 patients and 4193 ± 735 mL in HES 200/0.5 patients).

Twelve patients in the HES 130/0.4 group (40%) and 11 patients in the HES 200/0.5 group (38%) needed additional colloid after the dose limit of three litres study drug was reached. When the mean infused dose of HES was expressed in $kg \cdot day^{-1}$, patients received 31.0 $mL \cdot kg^{-1}$ of HES 130/0.4 compared with 30.6 $mL \cdot kg^{-1}$ of HES 200/0.5. The maximum dose of either HES solution given was 42.9 $mL \cdot kg^{-1}$ (Table II).

In both treatment groups, colloid osmotic pressure remained within the normal range except for the initial period during CPB (Figure). No additional colloid or crystalloid were needed to control the venous blood supply during the period of CPB.

Hemodynamic filling pressures, cardiac index, and urine output were very similar between the two treatment groups throughout the treatment period (Table II, III). Also, for blood gas parameters no clinical differences were found.

We observed a lower mean total blood loss in HES 130/0.4 patients (HES 130/0.4: 1301 ± 551 mL, median 1182 mL, range 550-2605 mL *vs* HES 200/0.5: 1821 ± 1222 mL, median 1516 mL, range 470-6630 mL) which was reflected by a lower use of packed red blood cells (RBCs: 241 ± 419 mL in HES 130/0.4 patients *vs* 405±757 mL in HES 200/0.5 patients). The data are skewed due to two patients with extensive postoperative blood losses in the HES 200/0.5 group. The difference in blood loss was statistically significant in the ANOVA ($P = 0.046$) but non-significant with the Wilcoxon rank-sum test ($P = 0.052$). Thirteen patients (43.3%) in the HES 130/0.4 group and 14 patients (48.3%) in the HES 200/0.5 group received allogeneic blood products. Total perioperative allogeneic donor exposure (packed red blood cells, fresh frozen plasma, platelets) was 2.3 ± 3.5 units (range 0-12 units) in HES 130/0.4 patients and 3.0 ± 3.5 units (range 0-40 units) in HES 200/0.5 patients.

Postoperatively, the von-Willebrand factor increased to supranormal levels. This increase was higher in the HES 130/0.4 group than in HES 200/0.5 patients ($P = 0.0001$). For all other coagulation parameters (platelet agglutination, aPTT, TT, PT) no significant differences were found (Table IV). A few patients in this study received desmopressin and/or tranexamic acid (HES 130/0.4: four patients; HES 200/0.5: three patients).

TABLE I Patient characteristics and outcome (mean ± standard deviation)

Variable	*HES 130/0.4 n = 30*	*HES 200/0.5 n = 29*
Gender (m/f)	25/5	24/5
Age (yr)	63.5 ± 9.0	61.0 ± 10.3
Weight (kg)	83.0 ± 8.5	81.4 ± 9.3
Height (cm)	174 ± 7.0	176 ± 10.0
Concomitant diseases; no. of patients (%)		
- infarction	9 (30.0)	8 (27.6)
- hypertension	7 (23.3)	7 (24.1)
- COPD	4 (13.3)	5 (17.2)
- diabetes	6 (20.0)	4 (13.8)
Concomitant medication; no. of patients (%)		
- nitrates	30 (100)	29 (100)
- ß-blocker	23 (76.7)	24 (82.8)
- Ca-antagonist	17 (56.7)	17 (58.6)
- ASS or heparin	4 (13.3)	6 (20.7)
Aortic cross-clamping (min)	53.7 ± 25.8	44.6 ± 16.6
CPB (min)	88.9 ± 50.3	78.0 ± 30.8
Operation (min)	196.7 ± 65.2	177.9 ± 47.9
Mechanical ventilation (hr)	16.8 ± 14.8	16.6 ± 10.3
ICU stay (dy)	1.3 ± 0.8	1.1 ± 0.6
Hospital stay (dy)	6.7 ± 4.5	7.7 ± 5.1
Rethoracotomy; no. of patients (%)	2 (6.7)	3 (10.3)

CPB = cardiopulmonary bypass, ICU = intensive care unit

TABLE II Fluid balance (mean ± standard deviation)

Variable		*OR*	*ICU*	*OR + ICU*
Study colloid (mL)	HES 130/0.4	1475 ± 100	1150 ± 511	2550 ± 561
	HES 200/0.5	1500 ± 189	966 ± 516	2466 ± 516
Study colloid (mL·kg^{-1})	HES 130/0.4			31.0 ± 7.4
	HES 200/0.5			30.6 ± 7.3
Addit. colloids (mL)	HES 130/0.4	0	116 ± 268	116 ± 268
	HES 200/0.5	0	52 ± 155	52 ± 155
Crystalloids (mL)	HES 130/0.4	2167 ± 630	2020 ± 500	4187 ± 615
	HES 200/0.5	2327 ± 743	1866 ± 467	4193 ± 735
ANH (mL)	HES 130/0.4	746 ± 363		
	HES 200/0.5	710 ± 492		
RBC (mL)	HES 130/0.4	21 ± 113	220 ± 387	241 ± 419
	HES 200/0.5	9 ± 46	397 ± 757	405 ± 757
FFP (mL)	HES 130/0.4	0	116 ± 231	116 ± 231
	HES 200/0.5	0	229 ± 660	229 ± 660
Platelets (mL)	HES 130/0.4	0	20 ± 72	20 ± 72
	HES 200/0.5	0	38 ± 118	38 ± 118
Blood loss (mL)	HES 130/0.4	501 ± 287	800 ± 486	1301 ± 551
	HES 200/0.5	629 ± 326	1192 ±1225	1821 ±1222*
Urine output (mL)	HES 130/0.4	634 ± 233	3001 ± 956	3635 ± 1015
	HES 200/0.5	748 ± 417	2833 ± 774	3581 ± 941
Fluid balance (mL)	HES 130/0.4			3292 ±1387
	HES 200/0.5			3212 ±1654

HES 130/0.4: n=30 ; HES 200/0.5: n=29

OR = operating room, ICU = intensive care unit, RBC = red blood cells, FFP = fresh frozen plasma ANH= acute normovolemic hemodilution

* $P < 0.05$ for difference between groups (ANOVA)

Changes in hematological and biochemical variables during the study were similar between the treatment groups, except for alpha-amylase (Table V). Here, the mean increase was lower in HES 130/0.4 patients postoperatively (HES 130/0.4: from 72 ± 44 U·L^{-1} at baseline to 315 ± 193 U·L^{-1} on the 1st postoperative morning; HES 200/0.5: from 87 ± 75 U·L^{-1} at baseline to 558 ± 605 U·L^{-1} on the 1st postoperative morning; $P = 0.045$).

Five Serious Adverse Events (SAE) were reported in the study. In the HES 130/0.4 group, one patient had a cerebellar infarction on the 1st postoperative day, and two had severe heart failure after surgery. None of these events was considered to be related to the treatment with HES. In the HES 200/0.5 group, two patients had extensive postoperative blood losses which were primarily considered related to surgical problems.

With regard to outcome parameters, there were no major differences between the treatment groups (Table I). Two patients in the HES 130/0.4 group and three patients in the HES 200/0.5 group had to undergo re-thoracotomy because of postsurgical bleeding. No patient died in the study.

Discussion

This study in heart surgery was designed as a prospective, randomised, double-blind, multicentre study to investigate the plasma substitution effectiveness of a new generation hydroxyethyl starch HES 130/0.4. Heart surgery was chosen as a frequent surgical setting where routine procedures are implemented. The commonly used standard HES 200/0.5 (pentastarch) was used as control. We exclusively used hydroxyethyl starch as artificial colloid for plasma volume substitution within the treatment period from induction of anesthesia until 16 hr after end of surgery. Coagulation parameters, blood loss and transfusion requirements were major safety endpoints.

Within seven months, we recruited 59 patients undergoing elective coronary artery bypass grafting in two centres in the Netherlands. Demographic data and other patient characteristics were comparable in either group.

As shown in phase I studies by Waitzinger *et al.*,[1,2] HES 130/0.4 has an increased metabolic turnover and enhanced plasma elimination compared with conventional HES types such as HES 200/0.5 (pentastarch). Intuitively, one might expect that this

TABLE III Perioperative hemodynamics (mean ± standard deviation)

Variable	*HES 130/0.4 n = 30*	*HES 200/0.5 n = 29*
Heart rate (HR), beat/min		
after induction of anesthesia	60.6 ± 11.2	60.0 ± 8.8
after bypass	84.4 ± 12.8	88.7 ± 16.4
at arrival on ICU	79.8 ± 17.4	75.0 ± 14.6
8 hr postoperatively	86.4 ± 15.7	81.6 ± 11.6
16 hr postoperatively	89.4 ± 14.4	84.0 ± 13.0
Mean arterial pressure (MAP), mmHg		
after induction of anesthesia	75.4 ± 13.2	77.0 ± 13.8
after bypass	69.9 ± 9.0	69.6 ± 10.1
at arrival on ICU	72.2 ± 11.1	73.1 ± 9.8
8 hr postoperatively	80.6 ± 10.9	77.4 ± 9.2
16 hr postoperatively	81.4 ± 17.9	79.3 ± 15.5
Central venous pressure (CVP), mmHg		
after induction of anesthesia	8.5 ± 3.0	7.3 ± 2.9
after bypass	8.8 ± 2.8	8.0 ± 2.9
at arrival on ICU	8.9 ± 3.2	8.9 ± 3.0
8 hr postoperatively	8.0 ± 3.4	8.6 ± 2.8
16 hr postoperatively	8.1 ± 3.8	7.9 ± 3.0
Pulmonary capillary wedge pressure (PCWP), mmHg		
after induction of anesthesia	10.1 ± 3.1	8.7 ± 3.4
after bypass	9.8 ± 2.0	10.0 ± 3.4
at arrival on ICU	8.8 ± 2.4	9.1 ± 3.4
8 hr postoperatively	8.2 ± 3.3	8.3 ± 2.8
16 hr postoperatively	7.4 ± 3.8	8.2 ± 3.3
Cardiac index (CI), L·min^{-1}·m^{-2}		
after induction of anesthesia	2.2 ± 0.5	2.4 ± 0.6
after bypass	3.4 ± 0.8	3.4 ± 0.9
at arrival on ICU	3.0 ± 0.7	2.9 ± 0.8
8 hr postoperatively	3.2 ± 0.6	3.3 ± 0.9
16 hr postoperatively	3.2 ± 0.9	3.2 ± 0.5

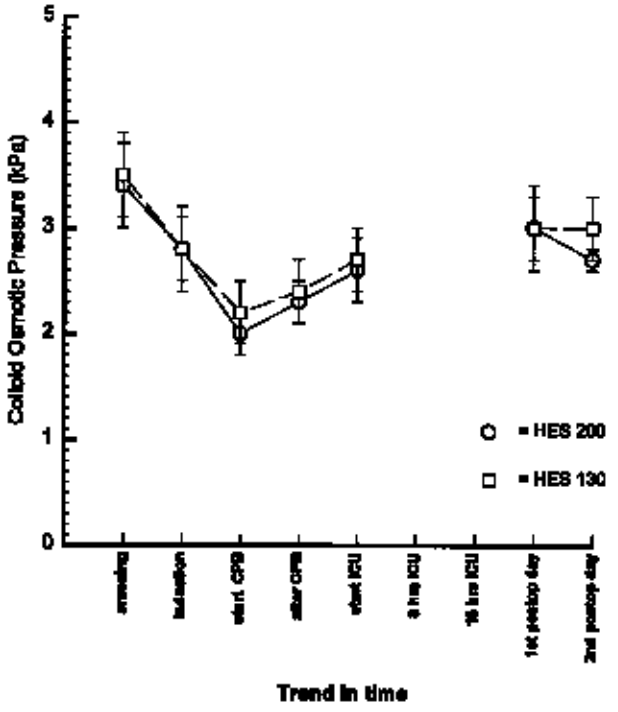

FIGURE Colloid osmotic pressure (mean ± standard deviation)

pharmacokinetic profile would result in less effectiveness regarding plasma volume substitution. However, the water binding effect of different HES types primarily depends on the number of molecules rather than on their size. The number of molecules in HES 130/0.4 is relatively high due to its lower average molecular weight and narrow molecular weight distribution. The greater number of osmotically effective molecules in HES 130/0.4 is thought to counterbalance its more rapid elimination. The major finding in this study is that the effectiveness of the new hydroxyethyl starch is indeed not compromised. We needed comparable volumes of both (blinded) HES solutions as well as of total colloids (HES plus isotonic pasteurised plasma) in either treatment group within the treatment period. Importantly, the amount of blood collected by ANH, the volumes of crystalloids infused perioperatively, and the overall fluid balance were comparable between the groups. Colloid osmotic pressure, hemodynamics, and urine output were also very similar. Meanwhile, comparable effectiveness of these two HES specifications has been demonstrated by other groups.[16,17,19] In our study, we used an extended treatment period comprising intra- and postoperative phase to look for any difference in effectiveness to become evident. In literature, usually either the intra- or postoperative period is evaluated.

Negative effects on hemostasis have been reported after using high molecular weight HES (450,000 dalton) and/or medium molecular weight HES with a high degree of substitution (0.6).[6,9,10] Treib *et al.*,[22] showed a relationship between the persistence of large HES molecules in plasma and the inhibited release of the von-Willebrand factor (vWF). Despite of the high dose of hydroxyethyl starch used in our study, coagulation parameters almost returned to baseline values on the first postoperative day. In both treatment groups, we found an increase in the vWF postoperatively. This increase was higher in patients receiving HES 130/0.4. A postoperative increase in vWF is part of the physiologic acute phase reaction to surgical stress.[23,24] Large and highly substituted HES molecules (hetastarch, HES 450/0.7) attenuate this physiological response as compared with human albumin[24] or crystalloids,[25] although the mechanism is not known.[10] Similarly, in

TABLE IV Coagulation variables (mean ± standard deviation)

Variable		*Time point*			
		induction	*post CPB*	*ICU*	*1st post-op.day*
vWF (%)	HES 130/0.4	151.0 ± 46.8	128.6 ± 47	141.7 ± 52.6	223.0 ± 40.5*
	HES 200/0.5	167.0 ± 60.8	143.7 ± 52.7	151.4 ± 61.6	185.0 ± 63.0
aPTT (sec)	HES 130/0.4	40.3 ± 11.1	50.9 ± 7.4	45.3 ± 7.7	37.1 ± 6.6
	HES 200/0.5	39.2 ± 6.0	57.4 ± 28.3	47.6 ± 8.8	30.9 ± 4.9
TT (sec)	HES 130/0.4	12.3 ± 1.1	11.2 ± 0.9	10.8 ± 0.8	10.7 ± 1.0
	HES 200/0.5	12.3 ± 1.2	11.1 ± 1.3	10.7 ± 0.7	10.3 ± 1.1
PT (sec)	HES 130/0.4	17.7 ± 1.1	24.ß ± 2.1	21.3 ± 3.2	17.8 ± 1.4
	HES 200/0.5	17.9 ± 1.3	23.8 ± 3.0	22.2 ± 2.5	18.0 ± 1.3
Platelet agglutination ($\%\cdot min^{-1}$)	HES 130/0.4	38.8 ± 20.9	42.5 ± 17.7	37.5 ± 18.8	43.0 ± 19.0
	HES 200/0.5	46.1 ± 19.3	44.9 ± 20.2	41.9 ± 17.5	44.0 ± 16.1
Platelets ($10^9 \cdot L^{-1}$)	HES 130/0.4	195.5 ± 51.7	115.2 ± 37.1	135.3 ± 36.5	174.3 ± 47.2
	HES 200/0.5	187.4 ± 75.9	114.6 ± 55.0	122.0 ± 46.7	153.4 ± 73.5

HES 130/0.4 n=30 ; HES 200/0.5 n=29
vWF = von-Willebrand factor, aPTT = activated partial thromboplastin time, TT = thrombin time,
PT = prothrombin time, CPB = cardiopulmonary bypass, ICU = intensive care unit
* $P < 0.05$ for difference between groups (ANOVA)

TABLE V Laboratory variables (mean ± standard deviation)

Variable		*Time point*		
		Baseline†	*1st post-op day*	*2nd post-op day*
Hemoglobin ($mmol \cdot L^{-1}$)	HES 130/0.4	7.9 ± 0.6	6.8 ± 0.6	6.9 ± 0.8
	HES 200/0.5	8.0 ± 0.7	6.6 ± 0.7	6.6 ± 0.5
Leucocytes ($10^9 \cdot L^{-1}$)	HES 130/0.4	7.3 ± 1.4	14.0 ± 3.7	18.1 ± 4.1
	HES 200/0.5	7.7 ± 2.4	13.6 ± 3.0	15.2 ± 4.2
Total protein (%)	HES 130/0.4	68.8 ± 6.6	51.8 ± 7.2	60.0 ± 9.5
	HES 200/0.5	69.4 ± 6.0	48.5 ± 5.7	51.4 ± 1.5
Creatinine ($\mu mol \cdot L^{-1}$)	HES 130/0.4	96.4 ± 14.3	84.1 ± 15.7	108.5 ± 17.3
	HES 200/0.5	98.2 ± 13.8	83.9 ± 15.5	94.0 ± 20.6
GOT ($U \cdot L^{-1}$)	HES 130/0.4	15.5 ± 5.9	35.1 ± 22.8	32.6 ± 8.4
	HES 200/0.5	20.4 ± 9.5	36.6 ± 23.7	31.6 ± 12.0
GPT ($U \cdot L^{-1}$)	HES 130/0.4	18.7 ± 7.7	16.5 ± 7.2	19.3 ± 6.7
	HES 200/0.5	30.9 ± 22.0	22.7 ± 14.3	23.6 ± 15.6
LDH ($U \cdot L^{-1}$)	HES 130/0.4	209.0 ± 32.5	332.5 ± 99.9	337.3 ± 43.8
	HES 200/0.5	221.7 ± 55.8	316.2 ± 102.6	307.9 ± 84.2
α-amylase ($U \cdot L^{-1}$)	HES 130/0.4	72.4 ± 43.6	315.3 ± 192.9*	202.3 ± 106.4
	HES 200/0.5	87.3 ± 74.5	557.5 ± 605.2	451.4 ± 313.1

HES 130/0.4 n=30 ; HES 200/0.5 n=29
GOT = glutamate oxalo-acetate transaminase (AST), GPT = glutamate pyruvate transaminase (ALT), LDH = lactate dehydrogenase
* $P < 0.05$ for difference between groups (ANOVA)
† = after induction of anesthesia

our study the control HES 200/0.5 attentuated the response as compared with HES 130/0.4. We conclude from our finding that HES 130/0.4 has a reduced influence on the physiologic postoperative increase of vWF. This result is consistent with the fact that HES 130/0.4 has a reduced fraction of large HES molecules and is more rapidly eliminated from the body than conventional HES types.[12,14,15]

Patients receiving HES 130/0.4 had a considerably lower perioperative blood loss which was consistent with a lower amount of allogeneic RBCs transfused. Interpretation of these findings is limited since statistics were only explorative. However, our findings are in accordance with the results of others. Vogt *et al.*[16] and Langeron *et al.*,[17] compared HES 130/0.4 and HES 200/0.5 in orthopedic surgery patients and

found similar differences for coagulation factors, total blood loss and need for allogeneic blood products.

A non-serious, well known side effect of all HES specifications is the transient increase of alpha-amylase following HES exposure which is caused by the formation of a HES-amylase complex resulting in a decreased renal elimination of alpha-amylase.[5,11] Again, in accordance with its improved pharmacokinetic profile, in HES 130/0.4 patients a lower increase in alpha-amylase was found postoperatively. However, postoperative increased plasma alpha-amylase remains an unreliable diagnostic marker for pancreatitis after cardiac surgery until the third postoperative day, this is also true with the new HES specification.

No anaphylactoid reaction or other serious adverse events related to hydroxyethyl starch were seen in this study. As expected, we did not find any differences in outcome variables. The period of mechanical ventilation as well as the length of ICU stay and hospital stay were comparable between the groups. The overall percentage of re-thoracotomies (8.4%) due to postoperative bleeding in this study may appear too high considering other reports.[21,22] A uniform trigger for re-thoracotomy could not be defined before the study and all re-thoracotomies for excessive blood loss occurred in the same study centre where, retrospectively, the rate was not increased compared with the rate in non-study patients.

Overall, our findings indicate that the new generation hydroxyethyl starch HES 130/0.4 6% (Voluven®) is an effective plasma volume expander compared to the standard HES 200/0.5 6% (pentastarch) in heart surgery. We infused up to three litres of HES/patient. Thereby, we almost covered the perioperative period with a single artificial colloid. Hydroxyethyl starch HES 130/0.4 has a reduced influence on hemostasis which is advantageous in a setting where the coagulation system is extensively affected. Further studies will show whether HES 130/0.4 can be used safely at even higher doses.

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