ORIGINAL ARTICLE

Comparing the effects of 5% albumin and 6% hydroxyethyl starch 130/0.4 on coagulation and inflammatory response when used as priming solutions for cardiopulmonary bypass

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ABSTRACT

Aim. This prospective, randomized and controlled trial compares the use of human albumin (HA) and hydroxyethyl starch (HES) 130/0.4 in the priming solution for a non-biocompatible cardiopulmonary bypass (CPB) circuit. The effects of each substance on coagulation, postoperative blood loss and pro-inflammatory activities were examined.

Methods. Thirty-six adult patients undergoing mitral valvular heart surgery were randomly assigned to either the HA or HES group; 500 mL of 5% HA or 6% HES 130/0.4 were added to the priming solution of the CPB circuit for each group, respectively. Coagulation variables were measured perioperatively; these variables included thromboelastographic (TEG) parameters and pro-inflammatory markers such as interleukin (IL)-6, IL-8 and tumor necrotic factor (TNF)-α. Postoperative blood loss and transfusion requirements were also assessed.

Results. There were no significant intergroup differences in the coagulation variables (including TEG parameters), serum concentrations of IL-6, IL-8 and TNF-α, and blood loss or transfusion requirements. TEG parameters, which indicate the speed of solid clot formation and the strength of the fibrin clot, decreased up to 4 hours after CPB in both groups. Serum concentrations of IL-6, IL-8 and TNF-α were higher up to 12 hours after surgery compared to baseline values in both groups. Hemoglobin levels and platelet counts were lower up to 12 hours after surgery compared to baseline values in both groups.

Conclusion. HES 130/0.4 was comparable to albumin as a component of the priming solution for a non-biocompatible CPB circuit. The two substances showed similar effects on coagulation variables, blood loss and pro-inflammatory activities in adult patients undergoing mitral valvular heart surgery. *(Minerva Anestesiol 2010;76:584-91)*

Key words: Cardiopulmonary bypass - Blood coagulation - Postoperative hemorrhage.

The cardiopulmonary bypass (CPB) circuit can have adverse effects on coagulation and systemic inflammatory response. However, a variety of colloids are available to prime this circuit.[1, 2] Human albumin (HA) is a naturally-occurring colloid that has been reported to reduce inflammatory response and to minimize neutrophil activation and adhesion.[3, 4] In several meta-analyses, the use of HA in cardiac surgery was compared to hydroxyethyl starch (HES) and was shown to better reduce postoperative bleeding and preserve the coagulation system.[5, 6] These characteristics could

be of particular value when non-biocompatible circuits are used. Although biocompatible circuits are beneficial for inflammation and the coagulation system, their real clinical efficacy is unclear.[7] Non-biocompatible circuits are more cost-effective and are therefore widely used in cardiac surgeries that require a relatively short duration of CPB (i.e., less than 2 hours). Because synthetic colloids cost less, HES has been identified as a valuable alternative to HA. However, HES may significantly affect the coagulation system, which is already negatively affected by CPB.[8]

The HES solution that is currently used has a low molecular weight and molar substitutions. This solution, HES 130/0.4 (Voluven Inj., Fresenius Kabi, Germany), has less of an effect on coagulation than its congeners but provides a similar volume expanding effect.[9] Studies have demonstrated its safety in pediatric cardiac surgery; these studies showed that, compared to HA, HES 130/0.4 is associated with a smaller transfusion requirement and a more favorable intraoperative fluid balance.[10, 11] However, evidence for the safety of HES 130/0.4 in adult cardiac surgery is limited.

In this study, we evaluated whether HES 130/0.4 was comparable to HA as a component of the priming solution for patients undergoing mitral valvular heart surgery using conventional non-biocompatible circuits. This randomized, prospective and controlled study examined the association of each primer with coagulation, postoperative blood loss and pro-inflammatory activities.

Materials and methods

A total of 36 patients consecutively scheduled for elective mitral valvular heart surgery between January 2008 and November 2008 were included in this prospective study. The study was approved by the Institutional Review Board, and all patients gave their consent before participation. Patients were excluded from the study if they underwent an emergency operation or had any of the following indicators: concomitant coronary arterial occlusive disease, infective endocarditis, other signs of inflammation, preoperative coagulation disorder, a history of receiving medication with antiplatelet agents within the previous five days, liver insufficiency, elevated serum creatinine (over 1.4 mg dL^{-1}) before the operation, a left ventricular ejection fraction of less than 50%, previous cardiac surgery or a hemoglobin level of less than 10 mg dL^{-1} before surgery.

A computerized randomization table was used to assign patients to two groups. Patients received 500 mL of either 5% HA (HA group) or 6% HES 130/0.4 (HES group) as part of the 1,600 mL total priming solution used for the CPB circuit. The final priming solution consisted of the randomized colloids, 20% mannitol (5 mL kg^{-1}), $NaHCO_3$ (40 mEq), heparin (10 mg L^{-1}), sufentanil (1.5 μg kg^{-1}), midazolam (0.05 mg kg^{-1}) and acetated Ringer's solution (Plasma Solution A Inj., CJ Pharma, Korea). With the exception of the priming colloids, only crystalloid solutions were used during surgery. The priming solutions were prepared by a perfusionist who was not involved in the study, and physicians were not aware of the randomization results.

All patients received a standardized anesthetic and CPB management. Anesthesia was induced with intravenous midazolam (0.03-0.05 mg kg^{-1}), sufentanil (1.5-2 μg kg^{-1}) and rocuronium (50 mg). Anesthesia was maintained with a continuous infusion of sufentanil (0.2-0.3 μg kg^{-1} h^{-1}), vecuronium (1-2 μg kg^{-1} min^{-1}), and sevoflurane (1.5-2.5%) in 50% oxygen with air.

Heparin (initial bolus 3 mg kg^{-1}) was administered before CPB was established. CPB was instituted with a membrane oxygenator (Edwards Vital™, Edwards Lifesciences, USA) with non-pulsatile flow (2.2-2.4 L min^{-1} m^{-2}). To maintain the filling volume of the circuit, acetated Ringer's solution was added. Packed red blood cells (pRBC) were only added if the patient's hematocrit was less than 20%. Moderate hypothermia (33-34 °C) and cold blood cardioplegia were used in all cases. In addition, α-stat acid-base gas management was used, and the target range for PaO_2 was 200-300 mmHg. During CPB, norepinephrine or sodium nitroprusside were used to maintain arterial pressure between 60 and 80 mmHg. After CPB was terminated, the effects of heparin were reversed with protamine (1 mg per 1 mg of heparin). In addition, blood from the CPB circuit was salvaged with a cell salvage device and retransfused after sternal closure.

After surgery, all patients were transferred to

the intensive care unit where controlled mechanical ventilation was continued. Tracheal extubation was performed when the patients' hemodynamics were stable and they were able to breathe spontaneously and reach adequate blood gas levels. Postoperatively, fluid therapy was used to keep the pulmonary artery occlusion pressure between 10 and 14 mm Hg, the cardiac index above 2 L min^{-1} m^{-2}, and urine output at more than 0.5 mL kg^{-1} h^{-1}; HES 130/0.4 (maximum of 20 mL kg^{-1}) and/or crystalloid solutions were used for fluid therapy in both groups. In the intensive care unit, HES 130/0.4 was given only to the defined colloid dose limits. Fresh frozen plasma (FFP) was transfused when the INR was more than 1.5. Platelet concentrates were transfused when a platelet count of less than 50000 μL^{-1} after surgery was accompanied by excessive bleeding (*i.e.*, more than 200 mL h^{-1} for 2 consecutive hours). The threshold for transfusion of pRBCs was a hematocrit of less than 25%. Physicians who were not involved in the study and who did not know its purpose directed postoperative management for all of the patients.

Thromboelastographic (TEG®, Hellige Co., Germany) tracings

TEG tracings were obtained from venous whole blood and analyzed with native whole blood without an activator. The following variables were measured: reaction time (*r*), coagulation time (*r*+*k*), clot formation rate (α-angle), maximum amplitude (MA), and shear elastic modulus (G=5000× MA/[100 – MA]). These variables were measured after the induction of anesthesia (baseline) and 4 hours after the end of CPB. All TEG assays were performed by the same investigator who was unaware of the patient's assigned group.

Hemostatic variables

Laboratory measurements, including hematocrit, platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT), were performed the day before surgery, immediately after surgery, 8 hours after surgery and 24 hours after surgery. Fluid administration, urine output and blood loss were carefully measured in the perioperative period for up to 24 hours after surgery. The amounts of pRBCs, FFP and platelets transfused were also recorded.

Inflammatory markers

Serum concentrations of interleukin (IL)-6, IL-8, tumor necrosic factor (TNF)-α and white blood cells (WBC) were measured after the induction of anesthesia (baseline) and at 0.5 hours, 4 hours and 12 hours after the end of CPB. The samples used to analyze IL-6, IL-8, and TNF-α were placed on ice after they were collected and were centrifuged immediately. The serum was separated and stored in the freezer at -70 °C. Serum concentrations of IL-6, IL-8, and TNF-α were assayed using enzyme-linked immunosorbent assay (Quantikine® human IL-6, human CXCL8/IL-8, human TNF-α Immunoassay; R&D Systems, USA). The assay has a detection limit of 0.05, 1.5 and 0.5 pg mL^{-1} for IL-6, IL-8, and TNF-α, respectively. All of the blood samples used for biochemistry assays were obtained through the arterial line. All assays were controlled according to the manufacturer's instructions.

Statistical analysis

The sample size was estimated with a two-sided α level of 0.05 and a power of 0.8. A 20% decrease in the MA of the TEG tracing (TEG: MA, i.e., the strength of the fibrin clot) with the use of HES was assumed, and the power analysis indicated that 18 patients needed to be included in each group.

The data were analyzed with SPSS 14.0 (SPSS Inc., USA) and expressed as the mean±SD or the number of patients. Data between the groups were compared using a chi-squared test, Fisher's exact test, independent t-test or Mann-Whitney *U* test, as appropriate. For intragroup comparisons of variables to baseline values, repeated measures analysis of variance followed by a post hoc Dunnett's test were used. A p value of less than 0.05 was considered to be statistically significant.

Results

Table I shows patient characteristics and operative data. There were no significant differences between the groups.

TABLE I.—*Demographics and operative data.*

	HA group (N=18)	HES group (N=18)	P value
Age (yr)	55±14	54±12	0.909
Sex (M/F)	6/12	5/13	0.717
Weight (kg)	59±12	60±10	0.736
Body mass index (kg m^{-2})	22.7±2.4	23.1±3.0	0.642
Left ventricular ejection fraction (%)	62±9	65±5	0.253
Hypertension (n.)	3	2	1.0
Diabetes mellitus (n.)	3	2	1.0
Atrial fibrillation (n.)	6	4	0.457
Preoperative heparin use (n.)	5	4	0.71
Cardiopulmonary bypass time (min)	94±30	88±32	0.593
Aortic cross-clamping time (min)	66±22	64±20	0.719

Data are mean±SD or number of patients. HA group: priming with 5% human albumin; HES group: priming with 6% hydroxyethyl starch 130/0.4.

TEG variables were similar between the groups before and after surgery. In both groups, TEG variables showed that initial fibrin formation (r time) and fibrin buildup (r+k time) were prolonged 4 hours after CPB compared to the baseline values. TEG variables also showed that, in both groups, the speed at which a solid clot forms (α-angle) and the strength of the fibrin clot (MA and G) were significantly depressed 4 hours after CPB compared to the baseline values (Table II).

There were no significant differences in the coagulation variables between the groups throughout the study period. When compared to the baseline values of each group, hematocrit and platelet counts were significantly reduced until 24 hours after surgery. Compared to the preoperative baseline values, PT was significantly prolonged until 8 hours after surgery. In the HA group, aPTT was significantly shortened only immediately after surgery (Table III).

There was no difference in the intraoperative and postoperative blood loss measured for the two groups. There were also no differences in the amounts of infused crystalloids and colloids or urine output until 24 hours after surgery. The number of patients transfused and the amount of pRBC, FFP and platelets did not differ between the groups (Table IV).

There were no significant differences in serum concentrations of pro-inflammatory markers between the groups throughout the study period. IL-6, IL-8, and TNF-α were significantly increased compared to their baseline values in both groups throughout the postoperative period. IL-6, IL-8, and TNF-α were highest at 0.5 hours after CPB and decreased as time passed; however, these values were still higher than the baseline in both groups at 12 hours after CPB (Table V).

Hemodynamic variables and the use of vasoactive drugs also did not differ between the two groups throughout the study period. No differences were found in the duration of mechanical ventilation (12.8±4.6 *vs.* 14.1±5.1 h), duration of ICU stay (1.4±0.6 *vs.* 1.7±0.8 day) or duration of hospital stay (11.6±3.0 *vs.* 12.0±3.7 day) between the two groups.

TABLE II.—*Thromboelastographic tracings (TEG).*

		Baseline	4 h after CPB	Reference value
TEG: γ (min)	HA	17±5	43±21*	12-27
	HES	15±3	39±22*	
TEG: γ+κ (min)	HA	26±8	43±21*	15-39
	HES	22±5	39±22*	
TEG: α (°)	HA	26±8	14±4*	14-46
	HES	32±10	15±7*	
TEG: MA (mm)	HA	48±8	34±7*	42-63
	HES	51±7	31±10*	
TEG: G (dynes cm^{-2})	HA	4887±1542	2553±816*	3591-8514
	HES	5361±1523	2502±1237*	

Data are mean±SD. HA group priming with 5% human albumin; HES group priming with 6% hydroxyethyl starch 130/0.4; TEG: r reaction time; TEG: r+k coagulation time; TEG: α α –angle; TEG: MA maximal amplitude; TEG: G shear elastic modules. *P<0.05 compared with baseline values.

TABLE III.—*Changes in hemostatic variables.*

		Baseline	End of CPB	8 h after CPB	24 h after CPB
Hematocrit (%)	HA	36±4	30±5*	28±5*	27±5*
	HES	37±4	28±3*	28±3*	27±4*
Platelet count (10^3 μL^{-1})	HA	246±73	116±42*	118±36*	107±35*
	HES	242±59	118±37*	126±37*	123±30*
Prothrombin time (s)	HA	12±2	15±1*	13±1*	13±1
	HES	12±3	15±2*	14±1*	13±1
aPTT (s)	HA	38±16	30±5*	34±14	40±10
	HES	33±4	30±3	31±3	39±7

Data are mean±SD. HA group: priming with 5% human albumin; HES group: priming with 6% hydroxyethyl starch 130/0.4. aPTT: activated partial thromboplastin time. *P<0.05 compared with baseline values.

TABLE IV.—*Fluid in-and output and use of blood and blood products.*

		Until end of CPB	8 h after CPB	16 h after CPB	24 h after CPB
Crystalloids (mL)	HA	1711±523	332±160	118±100	98±106
	HES	1571±941	497±372	219±276	141±139
Colloids (mL)	HA	—	799±241	14±42	0
	HES	—	921±361	15±45	0
Total blood loss (mL)	HA	573±201	161±119	133±111	107±45
	HES	471±187	213±204	151±99	103±143
Urine output (mL)	HA	898±415	1194±445	974±385	744±423
	HES	1127±666	1320±433	1012±316	750±205
Blood products					
pRBC (total units, n. of patients)	HA	15 (11)	3 (3)	5 (4)	2 (1)
	HES	9 (7)	2 (2)	0	1 (1)
FFP (total units, n. of patients)	HA	0	10 (3)	6 (1)	0
	HES	0	4 (2)	1 (1)	0
Platelets (total units, n. of patients)	HA	0	6 (1)	1 (1)	0
	HES	0	0	0	0

Data are mean±SD or number of patients. HA group: priming with 5% human albumin; HES group: priming with 6% hydroxyethyl starch 130/0.4. pRBC: packed red blood cell; FFP: fresh frozen plasma. There were no significant differences between the two groups.

TABLE V.—*Changes in inflammatory markers.*

		Baseline	0.5 h after CPB	4 h after CPB	12 h after CPB
WBC (10^3 mL^{-1})	HA	6.2±1.8	5.8±3.8	17.2±6.0*	16.3±7.4*
	HES	6.8±1.8	5.1±2.9	17.8±8.3*	19.1±8.7*
IL-6 (pg mL^{-1})	HA	1.6±2.1	565.3±48.4*	525.4±122.3*	280.6±192.2*
	HES	1.2±0.7	509.4±136.6*	505.7±150.7*	204.0±151.8*
IL-8 (pg mL^{-1})	HA	3.6±0.6	1527.0±737.6*	1028.6±826.7*	60.8±53.5*
	HES	3.6±0.6	1307.6±838.5*	561.7±642.8*	35.6±30.7*
TNF-α (pg mL^{-1})	HA	1.6±0.0	1085.3±795.1*	129.0±124.8*	9.8±16.8*
	HES	1.6±0.0	939.8±581.5*	70.6±69.2*	8.7±11.7*

Data are mean±SD or number of patients. HA group: priming with 5% human albumin; HES group: priming with 6% hydroxyethyl starch 130/0.4. WBC: white blood cell; IL: interleukin; TNF: tumor necrosis factor. *P<0.05 compared with baseline values.

Discussion

This study compared the use of 6% HES 130/0.4 to HA as a component of the priming solution for non-biocompatible CPB circuits in patients undergoing mitral valvular heart surgery. No significant differences could be observed between the two colloids with regard to coagulation variables (including TEG parameters), postoperative blood loss, transfusion requirements and inflammatory response.

Increased bleeding after cardiac surgery continues to be a problem. Significant hemodilution, excessive activation of the coagulation system and fibrinolysis occur with CPB,[12, 13] and the priming solution used for the CPB circuit has been known to further affect coagulation status.[14] Although this priming solution may vary widely among institutions, colloid solutions, including HA and HES, are generally added in an attempt to reduce fluid retention after CPB.[15] Because the adverse hemostatic effects of HA seem to be limited to inevitable hemodilution,[16] HA is often used for circuit priming. In addition, it is assumed that HA forms an almost nonthrombogenic layer on surfaces in the CPB circuit so that pre-exposure of the synthetic surfaces of the CPB circuit to HA decreases the affinity of platelets to these surfaces.[17, 18] This effect of mimicking the endothelial surface may be especially beneficial when non-biocompatible circuits are employed.

Various biocompatible CPB circuits are also available; these circuits have beneficial effects on inflammation and the coagulation system. However, no definite evidence has shown improved clinical outcomes with biocompatible circuits.[7] Non-biocompatible circuits are therefore still widely used because they are cost-effective. In an effort to reduce health costs, HA has increasingly been replaced with a non-protein colloid like HES or gelatin. This replacement raises concerns about the potential hazards of a biological product using allogenic blood.[19, 20]

The safety and efficacy of HES as an intravascular volume expander have been well documented in clinical studies.[21] However, the effects of HES on the coagulation system are a primary concern when HES is added to the priming solution of a CPB circuit because the deleterious effects of extracorporeal circulation already compromise effective hemostasis.[22] The effects of HES on hemostasis have been shown to be closely related to its *in vivo* molecular weight, which mainly depends on its *in vitro* molecular weight, molar substitution ratio, and C2/C6 ratio.[23] With a lower molecular weight and molar substitution ratio, HES 130/0.4 appears to have a minimal effect on hemostasis. However, clinical studies examining the use of HES 130/0.4 as a component of priming solutions have been limited.[10, 11] In hypoalbuminemic cardiac surgical patients over the age of 80 years, HES 130/0.4 was shown to have a comparable effect as HA on the amount of postoperative blood loss and the necessary transfusion of allogenic blood products.[10] In addition, perioperative volume replacement with a maximum of 50 mL/kg of HES 130/0.4 in congenital cardiac surgery resulted in a lower number of patients transfused and better fluid balance compared to HA.[11] In those studies, however, only routine coagulation tests were performed; these tests could not precisely reveal the effects of HES on the coagulation system.

This study found that TEG parameters and the results of routine coagulation tests were comparable between the HA and HES 130/0.4 groups. These findings suggest that HES 130/0.4 has a minimal effect on coagulation. Furthermore, in earlier studies comparing the effects of HES and HA priming solutions on hemostasis, HES and HA were also used as volume expanders during the perioperative period. This study used HES 130/0.4 as a volume expander in both groups after surgery, allowing us to examine only the effects of the different priming solutions.

An earlier clinical trial of small infants undergoing surgery found different results than this study. In this earlier trial, the coagulation variables obtained from a modified TEG were significantly impaired in the HES 130/0.4 group compared to the HA group; however, changes in routine coagulation tests were comparable between the two groups.[24] This discrepancy might be attributable to the degree of hemodilution and duration of elimination. In two *in vitro* studies, HES 130/0.4 diluents significantly compromised TEG parameters when compared with HA or gelatin diluents.[25,26] The most significant deterioration of TEG parameters, however, occurred when blood was diluted by more than 40% with HES 130/0.4. TEG parameters

tested with 20% or 40% HES 130/0.4 dilutions were comparable to those seen with diluted solutions of HA or gelatin.[25, 26] In the previous study, 15 mL/kg of HES 130/0.4 were administered within 1 hour and the TEG assay was performed immediately. In the current study, 500 mL of HES 130/0.4 in the priming solution may not result in significant hemodilution even with the addition of approximately 15 mL/kg of HES 130/0.4. The 24-hour postoperative time period may provide enough time for complete elimination.

In addition to its beneficial hemostatic effects, HA also has anti-inflammatory and antioxidant effects that make it advantageous when compared to non-protein colloid solutions.[27] Inflammatory reaction plays a pivotal role in the development of postoperative morbidity and mortality in cardiac surgery.[28] A positive effect of colloids on inflammatory reaction could therefore benefit a patient undergoing CPB. In recent studies, HES 130/0.4 was also reported to have beneficial anti-inflammatory effects.[10, 29] In these studies involving elderly patients undergoing various types of cardiac surgeries including coronary artery bypass graft surgery, HES 130/0.4 resulted in a similar degree of inflammatory response and endothelial activation as HA[10] and produced a less marked endothelial inflammatory response than gelatin.[29] HES 130/0.4 also reduced capillary leakage by modulating the inflammatory response in a rat model of polymicrobial sepsis.[30] The current trial involved a more homogenous study population because only patients undergoing isolated mitral valvular surgery were included. Nevertheless, similar effects of HES 130/0.4 and HA on the activities of pro-inflammatory mediators were observed in this study as in previous studies.

This study has some limitations. The lower activities of IL-8 and TNF-α in the HES 130/0.4 group were not statistically significant when compared to the HA group, which may be the result of a large SD. Additional studies are necessary to validate the effects of HES 130/0.4 on inflammatory reaction in a larger number of patients.

Conclusions

When used as a component of the priming solution for a non-biocompatible CPB circuit in patients undergoing mitral valvular heart surgery, HES 130/0.4 and HA demonstrated similar efficacy in terms of coagulation, postoperative blood loss and transfusion requirements. In addition, HES 130/0.4 appeared to have a similar effect as HA on pro-inflammatory activities and patient outcomes.

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