Cardiothoracic Anesthesia, Respiration and Airway

3.5% urea-linked gelatin is as effective as 6% HES 200/0.5 for volume management in cardiac surgery patients

[La gélatine à pont d'urée à 3,5 % est aussi efficace que de l'HEA 200/0,5 à 6 % pour le remplissage vasculaire des patients de chirurgie cardiaque]

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Purpose: To compare the efficacy of volume expansion with 3.5% gelatin and 6% hydroxyethyl starch 200/0.5 in patients undergoing cardiac surgery. The second objective was to compare the two colloids in terms of blood losses and allogeneic blood transfusion exposure rate.

Methods: In this open-label controlled study, patients were randomly allocated to receive either 3.5% urea-linked gelatin (GEL group: $n = 55$) or 6% hydroxyethyl starch 200/0.5/5.1 (HES group: $n = 55$) for per- (including priming of the bypass machine) and postoperative volume management with a maximum dosage of 30 ± 3 $mL \cdot kg^{-1} \cdot day^{-1}$. Volume replacement was guided according to routine per- and postoperative care based on cardiac index, mixed venous oxygen saturation, and diuresis. If additional colloid was required, 4.5% albumin had to be given. The study period comprised per- and postoperative investigations up to 18 hr after surgery.

Results: All hemodynamic variables were comparable in both groups. Total study drug was 25.8 ± 4.8 $mL \cdot kg^{-1}$ in the GEL group and 24.5 ± 6.0 $mL \cdot kg^{-1}$ in the HES group. There was no difference in the number of patients receiving albumin solution or in the amount of albumin administered. Total blood loss was higher in the HES than in the GEL group (11.0 ± 7.8 $mL \cdot kg^{-1}$ *vs* 8.7 ± 4.0 $mL \cdot kg^{-1}$; $P < 0.05$) resulting in a higher need for allogeneic blood transfusion (HES: nine patients received 12 units, GEL two patients received 3 units; $P = 0.026$).

Conclusion: In the conditions of the present study, HES was not associated with a better plasma expansion effect than GEL. HES could result in a higher need for allogeneic blood transfusion.

Objectif : *Comparer l'efficacité de l'expansion volumique avec de la gélatine à 3,5 % et de l'hydroxyéthyl-amidon 200/0,5 à 6 % chez des patients de cardiochirurgie. Comparer aussi les colloïdes en termes de pertes sanguines et de taux d'exposition à une transfusion de sang allogénique.*

Méthode : *Pour notre étude ouverte et contrôlée, des patients ont été répartis au hasard et ont reçu soit de la gélatine à pont d'urée à 3,5 % (groupe GEL : n = 55), soit de l'hydroxyéthyl-amidon 200/0,5/5,1 à 6 % (groupe HEA : n = 55) pour le remplissage vasculaire peropératoire (incluant le volume d'amorçage de la CEC) et postopératoire avec une dose maximale de 30 ± 3 $mL \cdot kg^{-1} \cdot jour^{-1}$. Le remplissage vasculaire a été réalisé selon les méthodes habituelles fondées sur l'index cardiaque, la saturation en oxygène du sang veineux mêlé et la diurèse. Si un colloïde supplémentaire était nécessaire, de l'albumine à 4,5 % était administrée. L'étude comprenait les investigations peropératoires et postopératoires jusqu'à 18 h après l'opération.*

Résultats : *Toutes les variables hémodynamiques étaient comparables dans les deux groupes. La moyenne du total de médicament utilisé a été de 25,8 ± 4,8 $mL \cdot kg^{-1}$ dans le groupe GEL et de 24,5 ± 6,0 $mL \cdot kg^{-1}$ dans le groupe HEA. Il n'y a pas eu de différence quant au nombre de patients qui ont reçu une solution d'albumine ou quant à la quantité d'albumine administrée. Les pertes sanguines totales ont été plus élevées avec l'HEA qu'avec la GEL (11,0 ± 7,8 $mL \cdot kg^{-1}$ vs 8,7 ± 4,0 $mL \cdot kg^{-1}$; $P < 0,05$) provoquant une demande plus importante de transfusion de sang allogénique (groupe HEA : neuf patients ont reçu 12 unités ; groupe GEL : deux patients ont reçu 3 unités ; $P = 0,026$).*

Conclusion : *Dans les conditions de la présente étude, l'HEA n'a pas été associé à une meilleure expansion plasmatique que la GEL. L'HEA peut entraîner de plus grands besoins de transfusion sanguine allogénique.*

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Supported by a grant from Fresenius Kabi GmbH, Bad Homburg, Germany.

Accepted for publication August 26, 2003.

Revision accepted December 1, 2003.

THERE is increasing evidence that intraoperative intravascular volume optimization in high-risk surgical patients could decrease postoperative morbidity and reduce length of hospital stay.[1–3] In patients undergoing cardiac surgery, maximizing cardiac output through titrated perioperative volume expansion was associated with a lower postoperative morbidity and a reduced length of stay in the intensive care unit (ICU) and in the hospital.[4] In addition, regional tissue perfusion was better maintained as demonstrated by a lower incidence of gut mucosal hypoperfusion in the study group.[4]

The choice of the type of solution to be used for volume expansion in the perioperative period remains a point of debate. Numerous studies have addressed this question. Compared to crystalloids, the use of colloids offers the advantage of a lower net weight gain which could result in a shorter hospital stay.[5] Compared to the synthetic colloids, albumin has not been shown to offer any clinical advantage and its use could be associated with increased costs.[6] Gelatins and medium weight hydroxyethyl starches are the most widely used synthetic colloids in Western Europe. According to the available pharmacokinetic data, medium weight hydroxyethyl starches are expected to have a greater plasma expanding effect than gelatins, due to a higher *in vivo* molecular weight.[7,8] However, few studies have compared these two synthetic colloids in terms of volume expansion in the setting of cardiac surgery. In addition, interpretation of the available clinical data is hampered by a number of methodological issues such as the limited number of patients included, the use of different fluid regimens in the various clinical protocols, and the absence of well-defined endpoints.[9]

The aim of this randomized open-label controlled study was to compare 3.5% urea-linked gelatin (GEL) and 6% hydroxyethyl starch 200/0.5 (HES) administered for per- and postoperative volume management in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB). The first objective was to compare the efficacy of plasma volume expansion of these two colloids as defined by their ability to maintain cardiac output and oxygen delivery up to 18 hr postoperatively. Our hypothesis was that a higher volume of colloids would be required with GEL than with HES to achieve similar hemodynamic endpoints. The second objective was to compare the two colloids in terms of safety, evaluated by allogeneic blood transfusion exposure rate.

Methods

After approval by the Institutional Ethical Committee, this randomized open-label controlled study was conducted from January 1998 to September 1999. Written informed consent was obtained from all subjects. One hundred and ten patients with a preoperative left ventricular ejection fraction higher than 35% undergoing elective coronary artery or single valve surgery were included. Patients undergoing combined cardiac surgery or redo operations were excluded. A history of allergic reactions to either hydroxyethyl starches or gelatins and the presence of significant liver (SGOT and SGPT > 2.5 times normal) or renal (serum creatinin > 1.3 $mg \cdot dL^{-1}$) dysfunction were also exclusion criteria. All preoperative cardiac medication was continued until the morning of surgery, except for angiotensin converting enzyme inhibitors, angiotensin II antagonists and acetyl salicylic acid that were discontinued the day before surgery. Routine monitoring included five-lead electrocardiography, femoral and pulmonary artery catheters, pulse oximetry, capnography and blood and urine temperature monitoring. Anesthetic regimen was similar in all patients and consisted of high dose sufentanil (a bolus of 0.5 $\mu g \cdot kg^{-1}$ followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) and midazolam (a bolus of 0.5 $mg \cdot kg^{-1}$ followed by a continuous infusion of 0.2–0.3 $mg \cdot kg^{-1} \cdot hr^{-1}$). Pancuronium (0.1 $mg \cdot kg^{-1}$) was used for muscular relaxation. Routine surgical technique and cardioprotective strategies (cold crystalloid cardioplegia: 800 mL of Ringer's lactate containing 30 $mEq \cdot L^{-1}$ of potassium chloride) were used in all patients. Surgery was performed using non-pulsatile CPB (pump flow 2.4 $L \cdot min^{-1} \cdot m^{-2}$) under moderate hypothermia (valve surgery: 28°C; coronary surgery 32°C). All patients received aprotinin given as a bolus dose of 2.10^6 kallikrein inhibiting units (KIU) followed by a continuous infusion of 500,000 $KIU \cdot hr^{-1}$ until the end of the surgical procedure and an additional bolus of 2.10^6 KIU in the pump prime. The pump prime consisted of 1000 mL of the studied colloid, 200 mL of Ringer's lactate and 0.5 $g \cdot kg^{-1}$ of mannitol.

Patients were randomly allocated (by opening of an envelope) to receive either 6% hydroxyethyl starch 200/0.5/5.1 (Haesteril, Fresenius Kabi, Bad Hombourg, Germany) or 3.5% urea-linked gelatin (Haemaccel, Hoechst, Germany; GEL group: $n = 55$) for per- and postoperative volume management with a maximum dosage of 30 ± 3 $mL \cdot kg^{-1} \cdot day^{-1}$. Volume replacement was guided according to routine per- and postoperative care aimed at maintaining cardiac index > 2.4 $L \cdot min^{-1} \cdot kg^{-1}$, mixed venous oxygen saturation > 65% and diuresis > 0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$. If additional colloid was required, 4.5% albumin had to be given. Dobutamine infusion (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was initiated when cardiac index remained < 2.4 $L \cdot min^{-1} \cdot m^{-2}$ despite adequate filling pressures. Noradrenaline infu-

sion was started whenever mean systemic arterial pressure was below 60 mmHg despite adequate filling pressures. The study period comprised per- and postoperative investigations up to 18 hr after surgery.

Hemodynamic measurements included heart rate, mean arterial pressure, right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure, and cardiac output measured with the thermodilution technique. Three consecutive measurements were performed at each time point and averaged. Derived data were calculated using standard equations. Measurements were performed after induction of anesthesia, before the start of surgery (T1), after weaning of CPB (T2), at the end of surgery (T3), on arrival in the ICU (T4), and six (T5) and 18 hr (T6) later. Laboratory measurements included hemoglobin concentration, hematocrit, prothrombin time, activated partial thromboplastin time, platelet count, urea, creatinine, total serum protein, calcium, lactate, blood glucose, liver enzymes, and lactate dehydrogenase. These measurements were performed the day before surgery (T-1), and at T4, T5 and T6.

In each group, colloid osmotic pressure (COP) was measured in the first ten patients with an oncometer (cut-off membrane 30,000 Dalton) just before induction of anesthesia, prior to any colloid administration (T0), and at T4 and T6.

Fluid administration, diuresis, and blood losses were carefully measured in the perioperative period and up to 18 hr postoperatively. Transfusion policy was standardized and based not only on the hemoglobin level (ICU: 70 $g \cdot L^{-1}$; ward: 80 $g \cdot L^{-1}$) but also the general clinical status of the patient, as described previously.[10] Fresh frozen plasma and platelets were transfused in the presence of abnormal clinical bleeding, using the algorithm developed by Despotis *et al.*,[11] based on the platelet count, and prothrombin and partial thromboplastin times.

Statistical analysis

To determine the appropriate sample size, an interim analysis was performed after 20 patients (ten patients in each group). A difference of 10% in the number of patients necessitating 4.5% albumin between both groups was considered significant. For a power of 0.8 and $\alpha = 0.05$, a sample size of 50 patients in each group was calculated to be appropriate.

Demographic data and data on fluid management were compared between groups using Fisher's exact and unpaired t test where appropriate. Hemodynamic and laboratory data were compared using a two-way analysis of variance for repeated measurements followed by a post-hoc Tukey test. A P value < 0.05 was considered statistically significant.

The authors had full access to all the data.

Results

Table I summarizes the patients' characteristics in the study groups. Both groups were well balanced as far as demographic data, preoperative ejection fraction and medication are concerned. Number of grafts, aortic cross clamp time and duration of CPB did not differ between groups.

Hemodynamic data (Table A) are presented as "Additional Material" on the Journal's website (www.cja-jca.org). All variables measured up to 18 hr postoperatively were similar in both groups, except for arterial oxygen content that was significantly higher in the GEL group compared to the HES group at the end of surgery (T3).

Table II summarizes the data on per- and postoperative fluid balance. Total study drug administered was 24.5 ± 6.0 $mL \cdot kg^{-1}$ in the HES group and 25.8 ± 4.8 $mL \cdot kg^{-1}$ in the GEL group. There was no difference in the number of patients receiving albumin solution or in the amount of albumin administered. Total crystalloid administration also did not differ between groups. Per- and postoperative diuresis was similar in both groups. Per- and postoperative blood losses tended to be higher in the HES than in the GEL group, resulting in a significantly higher total blood loss in the HES group. Nine patients received a total of 12 units of packed red blood cell in the HES group, while two patients received a total of 3 units in the GEL group (P = 0.026). One patient in the HES group, and no patient in the GEL group received platelets.

During the study period, the number of patients requiring dobutamine and/or noradrenaline was not significantly different between groups (dobutamine: nine patients in the GEL group and 14 patients in the HES group; noradrenaline: five patients in the GEL group and two patients in the HES group).

Duration of ventilation and ICU length of stay were similar in both groups (Table III). Three patients in the HES group required re-operation for hemorrhage: in two of them a surgical origin (coronary suture leakage) was found. Two patients in the GEL group developed acute pulmonary edema. Two patients in the HES group and three patients in the GEL group presented transient diffuse skin oozing at the site of surgical incision. There was no mortality and total hospital length of stay was similar in both groups.

COP measured in ten patients of each group showed no significant differences between groups (Figure).

Laboratory data (Table B) are presented as "Additional Material" on the Journal's website

TABLE I Demographic data

	HES	*GEL*
Age (yr)	63 ± 8	63 ± 11
Gender (M/F)	35/20	37/18
Weight (kg)	74 ± 9	76 ± 8
LVEF (%)	61 ± 13	63 ± 13
HTA preop (% of patients)	55	45
ß blockers (% of patients)	62	64
Aspirin (% of patients)	64	62
Heparin preop (% of patients)	13	18
Duration of surgery (min)	232 ± 50	236 ± 48
Duration of CPB (min)	102 ± 30	104 ± 28
CABG/valve	40/15	40/15
Grafts (nb)	3.8 ± 1.2	3.8 ± 1.4

HES = 6% hydroxyethyl starch 200/0.5 group (n = 55); GEL = 3.5 urea-linked gelatin group (n = 55); LVEF = left ventricular ejection fraction; HTA preop = history of preoperative hypertension; CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafts.

TABLE II Fluid balance

	HES	*GEL*
Study drug intraop (mL·kg^{-1})	18.1 ± 3.6 (11.0–23.8)	19.0 ± 3.6 (11.8 ± 29.1)
Study drug postop (mL·kg^{-1})	6.4 ± 4.6 (0–17.1)	6.7 ± 4.1 (0–14.9)
4.5% albumin (patients)	21/55 (38%)	24/55 (44%)
4.5% albumin (mL·kg^{-1})	9.8 ± 5.4 (0–23.8)	9.3 ± 5.9 (0–21.3)
Total colloids (mL·kg^{-1})	28.2 ± 10.3 (11–31.7)	29.9 ± 9.4 (11.8–30.8)
Crystalloids intraop (mL·kg^{-1})	33.4 ± 8.0 (23.5–62.3)	32.8 ± 9.6 (23.3–63.8)
Crystalloids postop (mL·kg^{-1})	16.0 ± 4.9 (6.6–32.5)	16.3 ± 5.0 (7.7–34.4)
Total crystalloids (mL·kg^{-1})	49.4 ± 9.5 (33.8–76.1)	49.2 ± 10.9 (31.4–81.5)
Diuresis intraop (mL·kg^{-1})	17.4 ± 8.3 (4.2–37.7)	18.7 ± 8.2 (3.7–46.8)
Diuresis postop (mL·kg^{-1})	25.4 ± 11.7 (9.4–64.8)	25.3 ± 10.0 (8.6–57.3)
Total diuresis (mL·kg^{-1})	42.7 ± 15.2 (16.1–76.2)	44.0 ± 15.2 (12.4–90.7)
Blood loss intraop (mL·kg^{-1})	3.9 ± 2.9 (1.2–11.2)	3.5 ± 1.9 (1.4–11.7)
Blood loss postop (mL·kg^{-1})	7.1 ± 7.4 (1.1–40.1)	5.2 ± 3.6 (1.7–20.1)
Total blood loss (mL·kg^{-1})	11.0 ± 7.8 (4.9–43.4)	8.7 ± 4.0* (4.3–24.6)
Allogeneic blood exposure (%)	16.4 (9/55)	3.6 (2/55)*
Fresh frozen plasma (%)	10.9	3.6

HES = 6% hydroxyethyl starch 200/0.5 group (n = 55); GEL = 3.5 urea-linked gelatin group (n = 55). *P < 0.05 *vs* HES.

TABLE III Postoperative data

	HES	*GEL*
Ventilation (hr)	22 ± 5	22 ± 6
ICU LOS (hr)	40 ± 43	33 ± 23
Hospital LOS (days)	10 ± 7	9 ± 3
Re-operation	3	0
Acute pulmonary edema	0	2
Postop wound oozing	2	3

HES = 6% hydroxyethyl starch 200/0.5 group (n = 55); GEL = 3.5 urea-linked gelatin group (n = 55). ICU = intensive care unit; LOS = loss of stay.

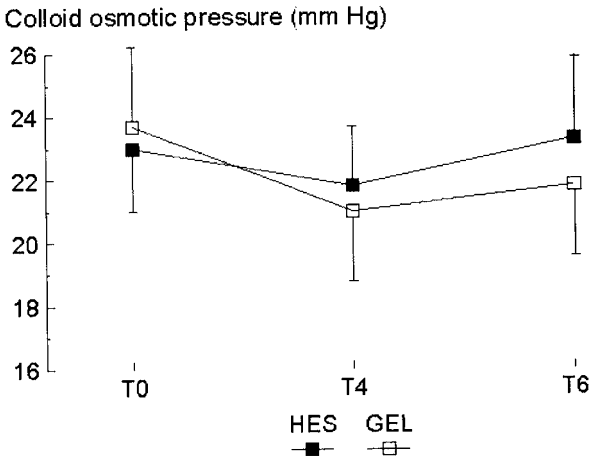

FIGURE Colloid osmotic pressure in the first ten patients of each group
HES = 6% hydroxyethyl starch 200/0.5 group; GEL = 3.5 urea-linked gelatin group; T0 = just before induction of anesthesia; T4 = at arrival in the intensive care unit (ICU); T6 = 18 hr after arrival in the ICU. No significant difference between groups at any time.

(www.cja-jca.org). There was no significant difference in any of the measured variables between the two groups throughout the study period, except for calcium concentration that was consistently higher in the GEL group than in the HES group after arrival in the ICU. Blood glucose, liver enzymes and LDH were also not different between the two groups (data not presented).

Discussion

The first objective of our study was to compare the efficacy of plasma volume expansion of 6% hydroxyethyl starch 200/0.5 and 3.5% urea-linked gelatin as defined

by the maintenance of cardiac output and oxygen delivery up to 18 hr postoperatively. The amount of colloids necessary to achieve a comparable per- and postoperative cardiac index and oxygen delivery did not differ between the two solutions investigated. In addition, the amount of rescue colloid (i.e., 4.5% albumin) was not different between the two groups. Therefore, in the conditions of the present study, the intravascular volume effect of GEL appeared similar to HES. According to the available pharmacokinetic data, these findings appear somewhat surprising. On the one hand gelatin consists of very small molecules, which are rapidly cleared from the circulation by renal filtration,[7] on the other hand, HES is expected to have a prolonged intravascular presence due to its higher *in vivo* molecular weight.[8] One should, therefore, expect a better plasma volume expansion with HES than with GEL as demonstrated by Mortelmans *et al.* in orthopedic surgery using an albumin marked technique.[12] Several factors may explain our observations. First, during cardiac surgery, the major fluid shifts that occur intraoperatively are mainly managed with the fluid from the CPB circuit so that the need for additional fluids during this period is probably limited. Second, in the immediate postoperative period, the possible higher plasma expanding effect of the starch could have been blunted by the higher postoperative blood loss observed in the HES group. Finally, plasma expanding effects of colloids closely depend on COP. Our results indicate that, in this specific patient population, COP was maintained similarly with both colloids. These findings confirm previous reports demonstrating that gelatin was able to achieve a similar COP as hydroxyethyl starch.[13]

The second objective of our study was to compare the effects on hemostasis of these two colloids as evaluated by perioperative blood losses and allogeneic blood transfusion exposure rate. Total blood losses were significantly greater in the HES group, resulting in a higher need for allogeneic blood transfusion. These results were obtained in the presence of a highly standardized multidisciplinary blood conservation strategy, which has been shown to significantly reduce allogeneic blood transfusion.[10] Our results are in agreement with those of Mortelmans *et al.*[12] showing a higher blood loss with 6% HES 200/0.5 in comparison with 3% modified fluid gelatin in patients undergoing primary total hip replacement. Colloids can affect coagulation through the hemodilution they induce and through their direct effect on coagulation factors. Since hematocrit remained similar in both groups throughout the observation period, it can be assumed that the degree of hemodilution achieved with the two colloids was comparable. Therefore, the difference in blood loss seems related to a different effect of both colloids on coagulation factors. Gelatins are generally considered to have minimal effects on hemostatic competence although impairment of ristocetin-induced platelet aggregation has been observed in healthy humans.[14,15] In addition, urea-linked gelatins have been shown *in vitro* to inhibit platelet aggregation occurring in response to other agonists like adenosine diphosphate, platelet-activating factor, collagen and epinephrine.[15] This effect appeared, at least partially, related to the high concentration of ionized calcium present in the urea-linked solutions.[15] In contrast to gelatins, starch preparations markedly affect hemostasis. They have been shown to induce a type I von Willebrandt syndrome with decreased factor VIII coagulant activity, decreased von Willebrandt factor antigen, and factor VIII-related ristocetin cofactor.[16,17] In addition they can also alter platelet function by inducing cellular abnormalities like a reduction in platelet membrane glycoprotein IIb-IIIa expression.[18] The effects of starches on coagulation appeared closely related to their *in vivo* molecular weight.[18,19] These different effects on coagulation cannot be detected by routine coagulation tests.

It must be noted that three patients in the HES group required re-operation for hemorrhage, and were transfused with allogeneic packed red blood cells. In two of them, a surgical origin was found, which may have contributed to the observation that transfusions were unequal between groups. If these two patients are excluded from the analysis, there is still a tendency for a higher need for transfusion in the HES group ($P = 0.082$). Interpretation of these data must also take into account the fact that global transfusion rate in this study was quite low (10%) and that sample size calculation was based on volume management, not on transfusion requirements.

No adverse reactions were observed in both groups. However, it should be noted that the sample size of the present study was not sufficient to address this question.

For technical reasons it was not possible to reliably blind the two colloids (different physical aspects of the solutions). The absence of blinding is a limitation of the study. However, as far as blood transfusion is concerned, physicians taking care of the patients on the ward were blinded to the type of solution used perioperatively. In addition, they were involved in the standardized multidisciplinary blood conservation strategy developed in the institution, which results in very strict criteria for postoperative blood transfusion.[10]

Finally, the choice of a synthetic colloid for perioperative volume replacement may also be influenced by the cost of the different solutions. In the conditions of

our study, Gelatins appear more cost-effective than HES as they present a similar volume effect as HES and are much less expensive (In Belgium, a bottle of 500 mL gelatin costs ≈ 4 ∈; while a bottle of 500 mL 6% HES 200/0.5 costs ≈ 11 ∈).

In conclusion, in the conditions of our study, the use of 6% HES 200/0.5 was not associated with a better plasma expansion effect than 3.5% urea-linked gelatin. HES could result in a higher allogeneic blood exposure rate due to higher total blood losses.

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