The Effect of Intraoperative 6% Balanced Hydroxyethyl Starch (130/0.4) During Cardiac Surgery on Transfusion Requirements

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Objectives: **To compare transfusion requirements in adult cardiac surgery patients when balanced hydroxyethyl starches (HES) (130/0.4) or balanced crystalloids is used for pump prime and intraoperative fluid therapy.**

Design: **Data were obtained retrospectively from medical records and perfusion charts. Matching based on propensity scores was used to adjust for potential confounders.**

Setting: **A university hospital.**

Participants: **Adult patients undergoing cardiac surgery with the use of cardiopulmonary bypass.**

Interventions: **Allocation to one of the study groups according to whether balanced HES or balanced crystalloids was used for pump prime and intraoperative fluid therapy.**

Measurements and Main Results: **240 propensity-matched patients were retained for final analyses. Forty-eight patients (40%) of the colloid group and 28 patients (23.3%) of the crystalloid group received blood products, with an odd ratio (95% CI) of 2.1(1.2-3.8 ($P = 0.009$). After bypass HES patients had lower hemoglobin levels (8.4 [1.3] gr/dL vs 9.6 [2] gr/dL; $P < 0.001$) and a higher cumulative chest drain output after 3 hours (180 [210] mL vs 140 [100] mL, $P < 0.001$]. Heparinase thromboelastogram (TEG®) showed longer K times (2.5[1.1] vs 1.6[0.8], $P < 0.001$) and lower maximal amplitudes (55.1[12.5] vs 63.4[9.8], $P = 0.008$).**

Conclusions: **HES patients required more transfusions, owing to greater hemodilution, HES-induced clotting disturbances, and bleeding.**

KEY WORDS: Hydroxyethyl starch, cardiac surgery, transfusion, bleeding, crystalloid, cardiopulmonary bypass

INTRODUCTION

COLLOIDS STILL ARE USED widely for priming of the cardiopulmonary bypass (CPB) circuit. They maintain a higher colloid osmotic pressure than crystalloids. Consequently, the fluid balance is less positive, the weight gain is lower and there is less pulmonary fluid accumulation when colloids are added to the pump prime.[1,2] Among colloids hydroxyethyl starches (HES) and gelatins have gained the wider popularity.[3] They are much cheaper than human albumin and less likely to lead to allergic reactions than dextrans.

Although newer generations of HES (130/0.38-0.45) had been claimed to be safer with regard to their effects on blood coagulation[4] and kidney function, increasing concerns were raised recently. Several studies performed in critically ill patients have, indeed, reported that fluid resuscitation with HES (130/0.4) resulted in a higher risk of renal failure requiring renal replacement therapy than fluid resuscitation with crystalloids.[5] Whether these concerns also apply to the perioperative setting remains debated.[6,7] In patients undergoing on-pump cardiac surgery some data suggest that the use HES (130/0.4) may adversely affect renal function.[8] A recent meta-analysis also showed that the use of HES resulted in a higher chest drain output and in an increased risk of re-exploration for bleeding and of transfusion than the use of albumin.[9] No difference between newer and older HES generation was observed.

At this institution, HES had long been used both for pump prime and intraoperative fluid therapy in cardiac surgery patients. However, owing to above-mentioned safety issues, HES has been replaced completely by a balanced crystalloid solution since August 2013.

The authors tested the hypothesis that the new crystalloid fluid regimen reduced the risk of blood products transfusion. Secondarily, they assessed the effect of the type of fluid used intraoperatively on blood losses, coagulation analyses, incidence of complications, length of intensive care unit, and hospital stays and 30-day mortality.

METHODS

The IRB (B707201420116) approved the study. Data from 432 consecutive adult patients who had cardiac surgery at this institution between April 2013 and January 2014 were analyzed retrospectively. The only exclusion criterion was a surgery performed without use of cardiopulmonary bypass.

Clinical management remained unchanged over the study period. Whenever possible, clopidogrel, prasugrel, and ticagrelor were stopped 5 days before surgery. Aspirin usually was continued until the day before surgery. New oral anticoagulants and vitamin K inhibitors were interrupted at least 5 days before surgery. Therapeutic doses of low-molecular-weight heparin were used for bridging and an international normalized ratio and a platelet count were obtained the day before surgery in these patients.

Preoperative medications included midazolam, morphine, hydroxyzine, and atropine. All patients were monitored with an arterial line and a pulmonary artery catheter was inserted after induction of anesthesia. Propofol and remifentanil infusions were used to induce and maintain general anesthesia. Rocuronium was used to achieve full muscle relaxation. After tracheal intubation, lungs were ventilated with a tidal volume of 8 mL/kg and a positive end–expiratory pressure of 5 cm H_2O until establishment of full-flow cardiopulmonary bypass. Inspired oxygen fraction was adjusted to keep the arterial oxygen

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saturation above 97%. Transesophageal echocardiography was used in case of valve surgery and when considered necessary by the attending anesthesiologist. Antibiotic prophylaxis consisted of a 1.5-gr bolus of cefuroxime at induction followed by a continuous infusion of 140 mg/h over 21 hours to achieve a total dose of 4.5 gr. A 2.5-gr bolus of tranexamic acid was given after induction of anesthesia and repeated after complete separation from cardiopulmonary bypass.

Full anticoagulation was achieved with 300 UI/kg of unfractionated heparin. Repeated injections of heparin were given when necessary to keep the activated coagulation time (ACT) (Hemochron® Signature Elite, International Technidyne Corporation, Edison, NJ) ≥ 420 seconds. Extracorporeal circuits with hollow-fiber oxygenators and integrated cardiotomy reservoir were used (Quadrox-i®, Maquet Getinge Group, Rastatt, Germany or Sorin Apex HP®, Sorin Group, Milano, Italy). For patients managed with colloids, the priming consisted of 1,500 mL of 6% HES 130/0.4 in a balanced solution (Volulyte®, Fresenius Kabi AG, Bad Homburg, Germany) with added 150 mL of 20% mannitol, 1 gr of tranexamic acid, and 5,000 IU of unfractionated heparin before reducing the volume to the minimal amount acceptable for use with an open venous reservoir. Six percent HES 130/0.4 also was infused through the Swan sheath and through the peripheral catheter at a rate of 50 mL per hour on each line until the end of surgery. In the group of patients managed with crystalloids, a balanced crystalloid solution (Plasmalyte A®, Baxter SA, Lessines, Belgium) were used instead of HES both for pump priming and intravenous infusions. After complete separation from cardiopulmonary bypass, protamine was given to reverse the effect of heparin and the ACT was checked. Additional doses of protamine were given if necessary. In patients who were at high risk of excessive bleeding or actually bleeding abnormally, usual clotting tests and a thromboelastogram (TEG® 5000, Haemonetics Corporation, Braintree, MA) were requested.

Postoperatively, patients were ventilated 4 to 6 hours in the intensive care unit (ICU). No synthetic colloid was used during the ICU stay. In the absence of complication, they were discharged to the ward after chest drain removal on the second postoperative day.

A cell saver was used intraoperatively for all patients. Allogeneic packed red blood cells were transfused to maintain a minimal hemoglobin level of 7 gr/dL. In case of excessive bleeding or hemodynamic compromise, the transfusion trigger was raised to 8 gr/dL. The transfusion of any other blood product was restricted to patients bleeding excessively, which was identified either by the surgeon while the chest was still open or based on a chest drain output rate greater than 100 mL/hour. Indications for platelets were a platelet count less than 100,000/μL after CPB, a TEG maximal amplitude less than 55 mm, and antiplatelet agents other than aspirin stopped fewer than 5 days before surgery. Fresh frozen plasma (FFP) was considered in case of increased R time on the heparinase TEG, prolonged activated partial thrombin time or prothrombin time after CPB. Fibrinogen level below 1.5 gr/L was corrected either with FFP or with fibrinogen concentrates. Use of prothrombin complex concentrates was considered in patients treated with vitamin k antagonists who had an abnormal international normalized ratio.

The primary endpoint was the transfusion of any blood product including allogeneic red blood cells, fresh frozen plasma, platelet concentrates, fibrinogen concentrates, and prothrombin complex concentrates in the operating room or during the intensive care unit stay. Secondary outcomes were results of the usual clotting tests and thromboelastograms, chest drain output, postoperative renal function, postoperative respiratory complications, lengths of ICU and hospital stays, and 30-day mortality. Postoperative respiratory complications were defined as pneumonia requiring prolongation of the ICU stay, atelectasis, need for reintubation or noninvasive ventilation.

The exposure of interest was the type of fluid used for pump priming and intraoperative fluid infusion. It was retrieved easily both from the perfusion charts and the anesthetic records. Propensity scores for the type of fluid were estimated in a multivariate logistic regression model including potential confounders (Table 1). The authors used 1:1 nearest-neighbor matching without replacement on propensity scores to within 0.01 units. Balance of the covariates was assessed using the standardized mean difference (SMD). Imbalance was defined as an SMD ≥ 0.1 in absolute value. Final analyses for the primary and secondary outcomes were performed on the propensity-matched data. The association between the type of fluid administered and transfusion of any blood product was assessed by multivariate logistic regression, which enabled adjustment for imbalanced covariates after propensity matching. For secondary outcome data, chi square test, Mann-Whitney U-test, and Student's t-test were used as appropriate. Data are presented as median [IQR] unless otherwise stated. A P values ≤ 0.05 was considered statistically significant. Statistical analyses were performed with Stata 13.1 (StatCorp LP, Texas). The "PSMATCH2" Stata module was used for propensity score matching.[10]

RESULTS

There were 432 patients who met inclusion criteria. Seventy-nine patients with missing values for covariates incorporated into the estimation model of the propensity score had to be excluded. Successful matches were obtained for 120 patients managed with crystalloids. Consequently, the final analyses were performed on 240 propensity-matched patients. Additional patient and procedure characteristics not used for the estimation of the propensity scores are provided in Table 2. Twenty-eight patients (23.3%) of the crystalloid group and 48 patients (40%) of the colloid group were transfused blood products, corresponding to an odds ratio of 2.1 (95% CI; 1.2-3.8), which was statistically significant (P = 0.009). Detailed breakdown of transfusion with the different blood products in the two groups is provided in Table 3.

The intraoperative fluid balance was 2,305 ± 1,111 mL in the crystalloid group and 1,036 ± 1,040 mL in the colloid group (P < 0.001). The hemoglobin level after separation from CPB was 9.6 [2] g/dL in the crystalloid group and 8.4 [1.3] g/dL in the colloid group (P < 0.001). The cumulative chest drain output after 3 hours was 180 [210] mL in colloid patients and 140 [100] mL in crystalloid patients (P < 0.001). In the subgroup of patients in whom a heparinase TEG was performed after separation from CPB and protamine administration, the K time was significantly lower (P < 0.001) and the maximal amplitude was significantly higher in the crystalloid group than in the colloid group (P = 0.007). Platelet counts and fibrinogen levels obtained at the same time were similar between groups. A summary of the TEG and laboratory clotting tests obtained after separation from CPB in the two groups is provided in Table 4.

Diuresis during CPB was higher in the crystalloid group than in the colloid group (P = 0.0004); however, creatinine levels at postoperative day one and day seven and the proportion of patients requiring postoperative renal replacement therapy did not differ between groups. The incidence of postoperative respiratory complications, lengths of ICU and hospital stay, and 30-day mortality were similar between groups. The outcome data are summarized in Table 5.

DISCUSSION

These data suggested that the use of HES (130/0.4) for pump prime and intraoperative fluid therapy in adult patients