Comparison of a Waxy Maize and a Potato Starch-Based Balanced Hydroxyethyl Starch for Priming in Patients Undergoing Coronary Artery Bypass Grafting

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Objective: **Concerns have been raised about differences in the safety profile of potato- versus waxy maize-derived hydroxyethyl starch (HES). The objective of this study was to compare 2 HES solutions derived from 2 different source materials (potato versus waxy maize) for their dose-related effects on hemostasis and organ function when used to prime the cardiopulmonary bypass circuit (CPB).**

Design: **A prospective, randomized, controlled study.**

Setting: **Tertiary care center.**

Participants: **Eighty patients undergoing coronary artery bypass grafting (CABG) on CPB.**

Interventions: **For priming the CPB circuit, the HES_PRL group received 1000 mL of potato-derived balanced 6% HES 130/0.42 along with 500 mL of Ringer's lactate; the HES_P group received 1,500 mL of potato-derived balanced 6% HES 130/0.42; the HES_MRL group received 1000 mL of waxy maize-derived balanced 6% HES 130/0.4 along with 500 mL of Ringer's lactate, and the HES_M group received 1500 mL of waxy maize-derived balanced 6% HES 130/0.4.**

Measurements and Main Results: **There were no significant differences in 24-hour mediastinal drainage, rate of re-exploration, blood product usage, coagulation parameters, and measures of pulmonary, renal, and hepatic function with respect to plant source of HES, when equivalent doses were used. Sonoclot activated clotting time (SonACT) was significantly higher and clot rate (CR) significantly lower at end of surgery (T_1) and 24 hours after surgery (T_2) in the HES_P and HES_M groups compared with the HES_PRL and HES_MRL groups. Compared with baseline, CR and platelet function were significantly lower at T_1, PaO_2/F_IO_2 ratio decreased significantly at T_1 and T_2, and serum bilirubin and transaminases increased significantly at T_2 in all 4 groups.**

Conclusions: **There was no significant difference in cumulative 24-hour mediastinal drainage when potato-derived balanced 6% HES 130/0.42 or waxy maize-derived balanced 6% HES 130/0.4 was used to prime the CPB circuit in patients undergoing CABG. In equal doses, both starches exerted the same effect on blood coagulation and pulmonary, renal, and hepatic function.**

KEY WORDS: ***cardiopulmonary bypass, coagulation, hemodilution, hydroxyethyl starch, priming, outcome***

THE EVOLUTION OF CARDIOPULMONARY BYPASS (CPB) circuit priming solutions from fresh whole blood to present-day asanguineous crystalloid or colloid solutions has been riddled with controversy.[1] The effects of CPB priming solution on coagulation system and organ function are of vital importance in influencing postoperative outcomes after cardiac surgery.[2–4]

The availability of a third-generation, balanced, low-molecular-weight, low molar substitution, rapidly degradable hydroxyethyl starch (HES) preparation for priming has added a colloid versus colloid debate to the ongoing crystalloid versus colloid debate.

The need to improve safety and pharmacologic properties while maintaining the volume expansion characteristics has led to the development of 2 new-generation HES solutions originating from 2 different plant sources. A waxy maize-derived balanced 6% HES (130/0.4/9:1) and a potato-derived balanced 6% HES (130/0.42/6:1) have been developed recently and are used for volume expansion and for priming the CPB circuit.[5,6]

The waxy maize- and potato starch-derived HES solutions differ in their finer chemical structure, area under the plasma concentration curve, and apparent plasma clearance.[7,8] The use of waxy maize starch is supported by a large evidence base; however, information supporting the use of potato-derived HES is limited.[9] Extrapolation of clinical data obtained from studies comparing one type of HES to the other would be highly inappropriate.

Concerns have been raised about the differences in the safety profile of potato-derived 6% HES 130/0.42 and waxy maize-derived 6% HES 130/0.4 with regard to blood coagulation[10], renal dysfunction,[11] and hepatic dysfunction.[12] There is a lack of clinical studies comparing the safety profile of the 2 HES solutions from different plant origin when used as priming solution for cardiac surgery on CPB. A recent editorial in a leading journal also lamented the lack of studies investigating whether the difference in molecular structure between potato- and maize-derived starch translates into differences in drug safety when these colloids are used in perioperative medicine.[13]

In this randomized prospective study, the authors aimed to test the hypothesis that, in patients undergoing coronary artery bypass grafting (CABG), priming the CPB circuit with waxy maize-derived balanced 6% HES 130/0.4 resulted in less postoperative blood loss in comparison with potato-derived balanced 6% HES 130/0.42. The effects on blood coagulation and renal, hepatic, and pulmonary function were compared, and the impact of 2 different doses of the study solutions was examined.

METHODS

After approval from the institute ethics committee and written informed consent from the patients, 80 consecutive patients undergoing elective CABG on CPB were recruited. Exclusion criteria were a

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history of previous cardiac surgery, severe congestive cardiac failure (ejection fraction <25%), known coagulation disorders, renal failure (serum creatinine >2 mg/dL, oliguria or anuria requiring dialysis), liver insufficiency (aspartate aminotransferase >40 U/L, alanine aminotransferase >40 U/L), known hypersensitivity to HES, and intracranial bleeding.

A computerized randomization table was used to assign patients to 1 of the 4 groups (n = 20 in each group). The total prime volume was 1,500 mL in all the groups. The HES_PRL group received 1,000 mL of potato-derived balanced 6% HES 130/0.42 (Tetraspan; B Braun, Melsungen, Germany) along with 500 mL of Ringer's lactate as CPB prime. The HES_P group received 1,500 mL of potato-derived balanced 6% HES 130/0.42 (Tetraspan) as CPB prime. The HES_MRL group received 1,000 mL of waxy maize-derived balanced 6% HES 130/0.4 (Volulyte; Fresenius Kabi, Bad Homburg, Germany) along with 500 mL of Ringer's lactate as CPB prime. The HES_M group received 1,500 mL of waxy maize-derived balanced 6% HES 130/0.4 (Volulyte) as CPB prime.

The priming solutions were prepared by a perfusionist who was not involved in the study, and the anesthesiologist was not aware of the randomization results. Anesthetic and surgical management were standardized in all groups. All the operations were performed by the same surgical team to eliminate the variations in CPB time and surgical technique as a cause of increased blood loss.

Anesthesia was induced with midazolam (0.05 mg/kg), thiopentone (4-5 mg/kg), fentanyl (3-5 mg/kg), and rocuronium (1 mg/kg) and maintained with isoflurane in an air–oxygen mixture and intermittent doses of midazolam, fentanyl, and vecuronium. All patients received Ringer's lactate solution via a peripheral line for maintenance and intraoperative volume replacement throughout the surgery. Mannitol 20% (100 mL) and heparin (5,000 IU) were added to the CPB prime in all 4 groups. Antifibrinolytics were not administered in any of the patients. Before establishing CPB, intravenous heparin (400 IU/Kg) was administered through a central line to achieve an activated clotting time (ACT) >480 seconds. CPB was performed using nonpulsatile flow at 2.5 L/min/m^2, a nonheparin coated circuit and a membrane oxygenator (Affinity NT Oxygenation System, Medtronic Inc, Minneapolis, MN). Mild hypothermia (32°C-34°C) and cold blood cardioplegia (4:1 dilution) were used in all patients for myocardial preservation. During CPB, phenylephrine or nitroglycerin was used to maintain a perfusion pressure between 60 and 80 mmHg. All patients were rewarmed to 36°C (nasopharyngeal temperature) before weaning from CPB. After termination of CPB, the effects of heparin were reversed with protamine (1 mg per 100 U of heparin). An additional dose of protamine, 0.2 mg/kg, was administered if ACT was more than 140 seconds.

HES solutions were not used in the postoperative period, and intravascular volume was maintained with either Ringer's lactate or blood products as required to maintain the central venous pressure (CVP) between 5-12 mmHg and urine output >0.5 mL/kg/min. Transfusion trigger for transfusion of packed red blood cells (PRBC) was a hemoglobin concentration of <8.0 g/dL during CPB and 10 g/dL after weaning from CPB. Fresh frozen plasma (FFP) and platelet concentrates (PC) were transfused for oozing from the surgical site or catheter site, increased chest tube drainage (>200 mL/hour for 2 consecutive hours) and deranged coagulation profile (ACT >140, clot rate <12 and platelet function <1.6) on SONOCLOT analysis (Sienco Inc, Arvada, CO). Re-exploration was considered when the chest tube drainage was >200 mL/hour for 2 consecutive hours with normal coagulation studies. The postoperative care was undertaken by a separate team of intensivists, unaware of the patient's assigned group.

Consecutive clinical variables were measured in the 4 groups in the preoperative period (T_0), at the end of surgery (T_1), and then 24 hours after surgery (T_2) in the intensive care unit (ICU). Hemoglobin, cumulative chest tube drainage in the first 24 hours after surgery, and SONOCLOT analysis were used to monitor coagulation. All SONOCLOT measurements were taken by the same investigator, who was unaware of the patient's assigned group.

The SONOCLOT analyzer is designed to detect and quantify viscoelastic changes in a whole-blood sample that occur throughout hemostasis.[14] As determined in other SONOCLOT-based trials,[15,16] SonACT, clot rate (CR) and platelet function (PF) were recorded at the 3 study time points and compared. The SonACT, a glass bead-based ACT (normal 117-195 seconds), is the time until the beginning of fibrin formation and corresponds to the conventional ACT measurements using the Hemochron method.[14] The CR (normal 7-23 clot signal units/minute) corresponds to the maximum slope of the SONOCLOT signature during the fibrin polymerization and clot development. The function of platelets is reported as PF and is derived from the timing and quality of clot retraction (0 represents no PF and 5 represents strong PF).[17]

Renal function was monitored by measuring the urine output (hourly and 24-hour cumulative) and serum creatinine. The RIFLE (risk, injury, failure, loss, and end stage) classification[18] for acute kidney injury (AKI) was used for assessment of renal function in the postoperative period.

Serum bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were measured at T_0 and T_2 to monitor liver function. Postoperative hyperbilirubinemia was defined as an increase of serum bilirubin levels to 3 mg/dL.[19] Threefold increase in serum transaminases from the preoperative level was considered significant.

The duration of mechanical ventilation, ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (PaO_2/F_IO_2), and the thoracic fluid content (TFC) using the Thoracic Electrical Bioimpedance (TEB)[20,21] monitor (ICON; Osypka, Berlin, Germany) was used to compare the pulmonary function among the groups. Acute respiratory distress syndrome (ARDS) was diagnosed based on the Berlin definition of ARDS.[22]

ICU stay, hospital stay, and in-hospital mortality were recorded as secondary measures of outcome. The patients were contacted by telephone 60 days after the surgery to inquire about delayed adverse events, especially renal failure requiring dialysis.

The primary outcome variable was cumulative chest tube drainage in 24 hours. Based on this pilot study, a standard deviation of 325 mL was expected for 24-hour chest tube drainage. The authors calculated that with 80% power and 5% α error, a minimum sample size of 20 patients per group was required to detect a 250-mL difference in chest tube drainage among the groups.

Data were analyzed using SPSS version 17.0 statistical software. Categoric data were compared using the Pearson χ^2 test. Continuous data comparison among the 4 groups was performed by applying one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as applicable. Post hoc comparison with Bonferroni correction was applied to adjust the level of significance. Continuous variables within a group were compared using a paired *t* test. A p value of <0.05 was considered statistically significant.

RESULTS

All 80 patients who were recruited completed the study. The 4 groups were comparable with respect to age, sex, weight, body mass index (BMI), concomitant diseases, number and origin of grafts, CPB, and aortic cross-clamp time (Table 1).

The cumulative 24-hour mediastinal drainage was higher in the HES_P (544 ± 301 mL) and HES_M (546 ± 227 mL) groups compared with the HES_PRL (456 ± 207 mL) and HES_MRL