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Impact of 6 % hydroxyethyl starch (HES) 130/0.4 on the correlation between standard laboratory tests and thromboelastography (TEG®) after cardiopulmonary bypass

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ABSTRACT

Background: Hydroxyethyl starches (HES) affect the results of thromboelastography (TEG®). We sought to determine whether using HES rather than crystalloids for cardiopulmonary bypass (CPB) prime and intraoperative fluid therapy changes the TEG cutoff values best identifying patients with a low platelet count or a low fibrinogen level after CPB.

Methods: Data from 96 patients who had on-pump cardiac surgery, a TEG® (kaolin-heparinase) and standard investigations of blood clotting performed after separation from CPB and protamine administration were retrospectively reviewed. Patients were assigned to the HES or crystalloid group according to whether balanced 6% HES 130/0.4 or balanced crystalloids were used for intraoperative fluid therapy and pump prime. Mutlivariable linear regression models with computation of the standardized regression coefficients were used to identify independent associations between the four main TEG parameters (R time, alpha angle, K time and MA) and the type of fluid used, the INR, the aPTT, the fibrinogen level and the platelet count. Receiver-operating-characteristic curves were used to assess the effect of HES on the ability of TEG parameters to identify patients with a platelet count < 80.000 μl^{-1} or a fibrinogen level < 1.5 gr l^{-1} and on the cutoff values best identifying these patients.

Results: The type of fluid used significantly affected the MA ($P < 0.001$), the K time ($P < 0.001$) and the alpha angle ($P < 0.001$) regardless of the results of the standard clotting tests. According to standardized ß regression coefficients the platelet count and the type of fluid used were stronger predictors of the MA, the alpha angle and the K time than the fibrinogen level. MA better predicted platelets < 80.000 μl^{-1} than K time and alpha angle ($P = 0.023$). The best cutoff value of MA identifying patients with platelets < 80.000 μl^{-1} was 62 mm in the crystalloid group and 53 mm in the HES group. MA, K time and alpha angle were poor predictors of the postoperative fibrinogen level.

Conclusion: HES significantly changes the cutoff value of TEG® MA best identifying patients < 80.000 μl^{-1} after on-pump cardiac surgery.

Introduction

Postoperative bleeding and coagulopathy remain a significant problem after cardiovascular surgery, in particular when cardiopulmonary bypass is used [1]. Five to 10 percent of patients still experience significant blood loss after cardiovascular surgery [2] and up to 25 percent of blood products transfused worldwide are given in this clinical setting [3]. Tackling the problem of bleeding and transfusion is important for at least two reasons. First, blood and blood products are limited and expensive resources [4]. Second, bleeding and transfusion are associated with increased morbidity and mortality [5].

Compared with transfusions based on clinical judgment alone, transfusion protocols decrease transfusion requirements, postoperative bleeding and the need for surgical reexploration [6]. There is also some evidence that using viscoelastic tests such as TEG® or ROTEM® to guide the administration blood products is useful [7]. Indeed, TEG® or ROTEM® offer several advantages over standard laboratory investigations of coagulation. They are performed on whole blood and are commonly available as point-of-care tests with short turnaround times [8].

Several aspects of the interpretation of these tests still deserve investigation. Different TEG parameters are correlated to distinct aspects of

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the coagulation process [8]; transfusion thresholds can be derived from these correlations [9]. However, other factors, such as the use of hydroxyethyl starch (HES), also affect the results of viscoelastic tests [10] and therefore can possibly interfere with TEG-based indications for blood product transfusion.

Whether the use of HES alters the relationship between standard laboratory tests and viscoelastic tests has never been investigated. At our institution, HES 130/0.4 was used for intraoperative fluid therapy and pump prime until the end of July 2013. From August 2014 onwards, HES was entirely replaced by a balanced crystalloid solution.

In the present study, we retrospectively studied the effect of using HES as pump prime and for intraoperative fluid therapy on the relationship between the results of the TEG® and those from standard laboratory tests. This allowed assessment of its potential impact on the determination of transfusion thresholds.

Material and Methods

Study Design and Patients

Our institutional review board (B70720230288) approved the study and waive informed consent. Data from 735 adult patients who had cardiac surgery between April 2013 and July 2014 were reviewed retrospectively. Inclusion criteria were surgery involving the use of cardiopulmonary bypasss (CPB) and having TEG® and standard coagulation tests done 10 minutes after separation from CPB and protamine administration *as per* our local guidelines for patients presenting risk factors for postoperative bleeding. Exclusion criteria were the use of albumin or blood for pump priming and the use of bivalirudin for intraoperative anticoagulation.

Clinical management remained unchanged over the study period apart for the type of fluid used as a pump prime and intraoperative fluid therapy. Patients were premedicated with midazolam, morphine, hydroxyzine and atropine. Intraoperative monitoring included 5-lead electrocardiogram, non-invasive blood pressure cuff, pulse oximeter and an arterial line. A pulmonary artery catheter was inserted after induction of anesthesia. Target-controlled infusions of propofol and remifentanil were used to induce and maintain general anesthesia; rocuronium was given to achieve full muscle relaxation. Lungs were ventilated at a tidal volume of 8 mL/kg using an air:oxygen mixture. A positive end-expiratory pressure of 5 cmH_2O was applied. A 2.5 gr bolus of tranexamic acid was given after induction of anesthesia and repeated after complete separation from cardiopulmonary bypass. Before arterial canulation, full anticoagulation was achieved with a 300 UI/kg bolus of unfractionated heparin. Boluses of heparin were repeated if necessary to keep the activated clotting time (ACT) (Hemochron® Signature Elite, International Technidyne Corporation, Edison, NJ) ≥ 420 seconds. An extracorporeal circuit with hollow fiber oxygenator and integrated cardiotomy reservoir was used (Sorin Apex HP®, Sorin Group, Milano, Italy). For patients managed with HES, the priming consisted of 1500 mL of 6% HES 130/0.4 in balanced salt solution (Volulyte®, Fresenius Kabi AG, Bad Homburg, Germany) with 150 mL of 20 % mannitol, 1 gr of tranexamic acid and 5000 UI of unfractionated heparin added prior to reducing the volume to the minimal amount acceptable for use with an open venous reservoir. 6% HES 130/0.4 was also infused through the pulmonary artery catheter as well as 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 crystalloid, an equivalent amount of a balanced crystalloid solution (Plasmalyte A®, Baxter SA, Lessines, Belgium) was use 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.

TEG® and Standard Coagulation Tests

Blood for thromboelastography was drawn from the arterial line into a 20 mL plastic syringe 10 minutes after protamine administration. TEG® assays (TEG® 5000 Thromboelastograph Hemostasis system, Haemoscope Corp®, IL, USA) were immediately carried out by trained technicians in the perfusion room. Routine quality control of the machine was performed according to the manufacturer's instructions. One milliliter of whole blood was placed in a kaolin vial that was inverted several times, after which 360 μL were transferred to a cup containing 2.0 International Units of lyophylized heparinase. The assay was performed at a constant temperature of 37 °C. The R time (time to reach 2 mm of amplitude), the K time (time elapsed between 2 mm and 20 mm of amplitude), the alpha angle (angle between R and K) and the maximal amplitude (MA) were recorded in all patients (Fig. 1).

Blood for standard coagulation tests and full blood count was transferred into a citrated tube and a EDTA tube respectively, and was sent to the central laboratory. Platelet count was performed on an automated cell counter (Sysmex XE-5000®, Sysmex Corporation, Japan). Coagulation tests included activated partial thromboplastin time (aPTT), International Normalized Ratio (INR) and fibrinogen (Clauss method). These assays were performed on BCS® XP (Siemens Healthcare Diagnostics Products GmbH, Germany). Reagents for aPTT, INR and fibrinogen were respectively Actin FS, Thromborel® S and Multifibren® U (Siemens Healthcare Diagnostics Products GmbH, Germany).

Statistics

As a first step, we aimed at identifying which standard clotting test had an independent impact on the results of the four main TEG parameters and whether the type of fluid used affected this relationship. This was done by running four multivariable linear regression models, one for each TEG parameter. For each linear predictor, the standardized ß coefficient was estimated in order to rank the strength of their association with the TEG parameter of interest. The component plus residual plot was used to check the linearity assumption for each predictor and the normality of the residuals was assessed visually. In case of violation of one of these two assumptions, an appropriate transformation of the outcome variable was chosen. In a second step, we sought to determine whether the type of fluid used had an impact on the ability of TEG to predict a low platelet count arbitrarily defined as less than 80×10^3 platelets per μL or a low fibrinogen level defined as less than 1.5 gr/L of fibrinogen. Receiver operating characteristics (ROC) curves were used to identify which TEG parameter best predicted low platelets and low fibrinogen respectively. The effect of the type of fluid was then assessed by drawing separate ROC curves (one for each type of fluid) using the TEG parameter previously identified as the best predictor of low platelets or low fibrinogen. Area under the curve (AUC) was used to compare ROC curves. When appropriate the best cutoff value was determined for both types of fluid regimen using the Youden's Index. Data are presented as mean ± sd or median [range] unless otherwise stated.

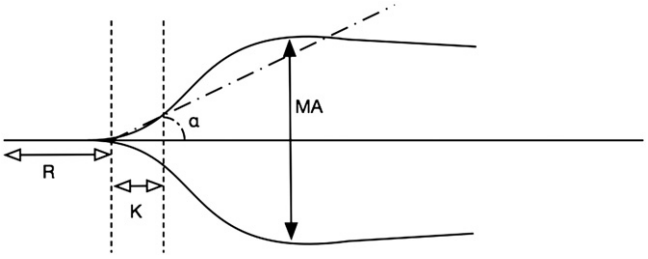

Fig. 1. Typical TEG® trace. R time = time to 2 mm of amplitude. K time = time from 2 mm to 20 mm of amplitude. MA = maximal amplitude reached. Alpha angle = Angle between amplitudes at 2 mm and at 20 mm.