Individualized Heparin and Protamine Management Improves Rotational Thromboelastometric Parameters and Postoperative Hemostasis in Valve Surgery

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Objectives: **This study investigated whether a tailored approach to heparin and protamine management improved thromboelastometric parameters after cardiopulmonary bypass and reduced postoperative blood loss compared with activated coagulation time (ACT)-based fixed target heparin and protamine management.**

Design: **Randomized controlled study.**

Setting: **Tertiary university hospital.**

Participants: **Patients undergoing elective valve surgery (n = 38).**

Interventions: **Heparin and protamine management were based either on the ACT (n = 19) or hemostasis management system (HMS) measurements (n = 19; HMS Plus; Medtronic, Minneapolis, MN).**

Measurements and Main Results: **The target ACT for initiation of cardiopulmonary bypass was 480 seconds. Study variables included rotational thromboelastometry EXTEM (extrinsic coagulation), HEPTEM (intrinsic coagulation with heparinase), and FIBTEM (fibrin part of clot formation) tests and 24-hour blood loss. The use of HMS reduced the median protamine-to-heparin ratio from 1.00 (1.00-1.00) to 0.62 (0.56-0.66; $p < 0.001$). The ACT group showed a prolonged postbypass clotting time for both EXTEM (86 ± 13 seconds *v* 78 ± 10 seconds; $p = 0.05$) and HEPTEM (217 ± 58 seconds *v* 183 ± 24 seconds; $p = 0.03$) tests. There was a moderate correlation between protamine dosing with the EXTEM and HEPTEM clotting time ($r = 0.42$; $p = 0.009$ and $r = 0.38$; $p = 0.02$, respectively). The number of patients with more than 450 mL/24 hours was higher in the ACT than in the HMS group (42% *v* 12%; $p = 0.04$).**

Conclusions: **Individualized heparin and protamine management decreased the protamine-to-heparin ratio, improved postbypass thromboelastometric hemostatic parameters, and reduced the incidence of severe blood loss compared with an ACT-based strategy, supporting the added value of this approach for hemostatic optimization during cardiac surgery.**

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HEPARIN DOSING for full anticoagulation during cardiopulmonary bypass (CPB) generally is based on patient weight, aiming at a target activated coagulation time (ACT) exceeding 480 seconds.[1,2] However, heparin requirements are influenced by individual sensitivity to heparin, which is altered by nonspecific binding of heparin to endothelial cells and plasma proteins and reduced antithrombin III availability.[1,3] Heparin-insensitive patients require more heparin for full anticoagulation, and this subsequently necessitates the use of a higher dose of its antidote, protamine, which itself exerts anticoagulant effects at high concentrations.[4–6] Although individualized heparin and protamine management using a point-of-care hemostasis management system (HMS) may contribute to a reduction in postoperative hemostatic abnormalities and blood loss when compared with ACT-based anticoagulation, this anticoagulation strategy generally is not applied. Some studies particularly focused on the benefits of HMS-guided anticoagulation in the pediatric population or in case of a target ACT below 400 seconds. Only a few studies investigated the effects of HMS-based management on perioperative hemostasis in adult cardiac surgery with a target ACT of 480 seconds.[7–10] These studies showed a reduction in thrombin generation, fibrinolysis, neutrophil activation,[7] higher postbypass platelet concentrations,[8] a reduced bleeding time, and fewer blood transfusion requirements.[9,10] Interestingly, these advantageous effects of HMS-based anticoagulation management on postoperative hemostasis were at the expense of higher heparin dosing and a reduction in the administration of protamine. This increase in heparin dosing, suggesting increased inhibition of coagulation and inflammation in HMS-based strategies, pleads against current trends towards low heparinization strategies during cardiac surgery.

The aforementioned studies were limited by the use of classic coagulation test findings only, which are known to be influenced by residual heparin. This randomized controlled trial compared the effects of individualized heparin and protamine management in cardiac valve surgery using the HMS system with ACT-based heparin and protamine management, and focused on alterations in rotational thromboelastometry hemostatic parameters and blood loss.

METHODS

This study was approved by the local Institutional Review Board (NL32254.029.10). Forty-four patients aged 18-85 years undergoing single heart valve replacement or valve repair surgery randomly were assigned by envelope drawing to 1 of the 2 study groups after written informed consent. Exclusion criteria were emergency surgery, reoperations, a history of hematologic, hepatic or renal diseases, insulin-dependent diabetes mellitus, a body mass index (BMI) ≥ 30 kg/m^2, and preoperative use of heparin or vitamin K antagonists.

Anesthesia was induced using sufentanil (3-7 μg/kg), rocuronium (0.5-1.0 mg/kg) and midazolam (0.1 mg/kg), and subsequently maintained with propofol (200-400 mg/h). All patients received dexamethasone (1 mg/kg)

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and cefazoline (1,000 mg; Eli Lilly, Nieuwegein, The Netherlands). Tranexamic acid was given after induction of general anesthesia (1,000 mg) and after reversal of heparin with protamine (2,000 mg).

The extracorporeal circulation system consisted of an S3/S5 heart-lung machine (Stöckert Instrumente GmBH, Munich, Germany) with a biocompatible coated centrifugal pump (Revolution, Sorin, Mirandola, Italy) using a heparin-coated polyvinyl extracorporeal circuit with an Affinity hollow-fiber oxygenator, an MVR 1600 soft shell collapsible venous reservoir (all Medtronic, Minneapolis, MN). The priming solution contained 1,000 mL of gelatin solution (Gelofusin, Braun Melsungen AG, Melsungen, Germany), 500 mL of lactated Ringer's solution (Baxter BV, Utrecht, The Netherlands), 100 mL of 20% mannitol (Baxter BV, Utrecht, The Netherlands), 50 mL of 8.4% sodium bicarbonate (Braun Melsungen AG), and 5,000 IU of porcine heparin (LEO Pharma, Amsterdam, The Netherlands). After heparinization, cardiopulmonary bypass (CPB) was performed using an aortic cannula (24 French), two-stage venous cannula in the right atrium (36 French) or 2 single cannulae in both vena cavae. Myocardial protection was achieved by using cold (4°C) crystalloid cardioplegia solution (St. Thomas). Patient temperature was maintained between 34°C and 36°C, and blood flow was kept between 2.4-2.6 L/min/m^2. A cell-saving device (Autolog, Medtronic, Minneapolis, MN) was used to process red blood cells during the whole procedure.

HEPARIN AND PROTAMINE MANAGEMENT

ACT Group

In the ACT group, an initial heparin therapy dose of at least 300 IU/kg was given before aortic cannulation to achieve a target celite ACT $\geq$480 seconds (HEMOCHRON, ITC Medical, Edison, NY). Cardiopulmonary bypass was initiated as soon as the ACT was $\geq$480 seconds. If required, additional doses of heparin (5,000 IU) were given during CPB to maintain an ACT $\geq$480 seconds. After termination of CPB, heparin was reversed with protamine in a 1:1 ratio, after which the ACT was measured to exclude residual heparin.

HMS Group

The HepCon Hemostasis Management System (HMS, Medtronic, Minneapolis, MN) first measured an individual heparin dose response (HDR) to calculate a target heparin concentration that was maintained during CPB. The heparin-protamine titration (HPT) test, conventional ACT, and HMS high range ACT (HR-ACT) were measured after administration of the primary heparin bolus, after administering cardioplegia, 30 minutes after initiating CPB and every 30 minutes thereafter, and after removal of the aortic clamp. After reversal of heparin with protamine, an HPT test was performed to exclude residual heparin.

All recommended heparin doses were calculated based on the total circulating volume, which consists of the estimated blood volume of the patient[11] and the pump volume. The pump volume during CPB was defined as the priming volume of the extracorporeal circuit plus other additional fluids minus urine output. In accord with Koster et al, the heparin dose in the priming volume was not subtracted from the calculated heparin bolus.[7]

Blood samples were taken after insertion of the radial artery catheter, 3 minutes after administering the heparin bolus, 3 minutes after administering cardioplegia, 30 minutes after initiating bypass (repeated every 30 minutes thereafter), after removal of the cross-clamp, and 3 minutes after administering protamine.

Routine coagulation tests included the activated partial thromboplastin time (aPTT), international normalized ratio of the prothrombin time (INR), platelet count, and fibrinogen levels. The aPTT (cefaline/microcrystalline) and PT (calcium thromboplastin) were performed with a STA-R instrument (Roche Diagnostics FmbH, Basel, Switzerland). Fibrinogen was determined by the Clauss fibrinogen assay, a functional assay based on the time for fibrin clot formation. Antithrombin activity was determined in platelet-free plasma.

Rotational thromboelastometry (ROTEM; TEM International Gmbh, Munich, Germany) was used to measure the viscoelastic properties of a blood clot after induction of anesthesia and 3 minutes after protamine administration. Rotational thromboelastometry assesses clot formation, clot stability, and fibrinolysis, as well as the inhibition of the clotting cascade by anticoagulants. Thromboelastometry tests included the intrinsic coagulation test in the presence of heparinase (HEPTEM; ellagic acid), the extrinsic coagulation test (EXTEM; tissue factor), and fibrin polymerization test (FIBTEM; EXTEM in the presence of cytochalasin) test. Study variables included the clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF).

Statistical analysis was performed on a personal computer using the SPSS statistical software package version 17.0 (IBM, New York, NY). The study endpoint was a significant difference in protamine dosing between the ACT and HMS groups of 100 mg, with an estimated sample size of 24 patients per group. Fewer patients were required to reach the primary endpoint. Descriptive statistics were calculated for all group parameters and included frequencies, mean with standard deviation, or median with interquartile ranges. Frequencies were evaluated using a χ^2 test. The Levene's test for equality of variances was nonsignificant for all parametric data. Numeric data, including the primary endpoint, were evaluated by a Student's t test. Ordinal data were analyzed using a Mann-Whitney U test. Pearson correlations were used to assess the association between heparin and protamine dosing with hemostatic parameters. Statistical significance was defined as a p value <0.05.

RESULTS

After exclusion of 6 patients because of a deviation from the study protocol caused by a change in the surgical strategy data, 38 patients were eligible for further analysis. The patient groups were similar with respect to demographic characteristics, preoperative hemoglobin levels and coagulation parameters, the use of antiplatelet drugs, type of surgical procedures, cardiopulmonary bypass (CPB) time, and duration of mechanical ventilation between the ACT- (n = 19) and HMS- (n = 19) guided groups (Table 1). The duration of mechanical ventilation after ICU admission tended to be lower in the HMS group. There were no differences in baseline ROTEM data between groups (Table 2).

Table 3 shows the doses of administered heparin and protamine, the protamine-to-heparin ratio, and the ACT as measured before surgery and after heparin or protamine administration, respectively. The total intraoperative dose of

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