Implementing a Statistical Model for Protamine Titration: Effects on Coagulation in Cardiac Surgical Patients

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Objectives: To implement a statistical model for protamine titration.

Design: Prospective randomized trial.

Setting: University hospital.

Participants: Sixty ($n = 30 + 30$) patients scheduled for elective coronary artery bypass surgery were randomly assigned to 2 groups.

Interventions: Protamine dose calculated according to an algorithm established from a statistical model or to a fixed protamine-heparin dose ratio (1:1).

Measurements and Main Results: Both groups demonstrated comparable patient demographics and intraoperative data. Coagulation effects were evaluated using rotational thromboelastometry. Using the statistical model reduced ($p < 0.01$) the protamine dose from 426 ± 43 mg to 251 ± 66 mg, followed by significantly ($p < 0.01$) shorter intrinsic clotting time (208 ± 29 seconds versus 244 ± 52 seconds) and stronger clot firmness ($p = 0.01$), and effects on indices of extrinsic or fibrinogen coagulation pathways were insignificant. Test of residual heparin was negative in all patients after protamine administration, aligned with insignificant ($p = 0.27$) intergroup heparinase-verified clotting time differences.

Conclusions: The statistical model for protamine titration is clinically feasible and protects the patient from exposure to excessive doses of protamine, with advantageous effects on coagulation as measured using rotational thromboelastometry. Significance regarding clinical outcome is yet to be defined.

KEY WORDS: cardiac surgery, cardiopulmonary bypass, heparin, protamine, statistical model

DOSING OF PROTAMINE to reverse the effect of heparin after cardiopulmonary bypass (CPB) follows a number of different regimens,[1–3] in which a fixed dose in relation to heparin at 1:1 is a commonly used method.[4] The use of point-of-care (POC) devices offers an alternative, in which the instrument uses a specific algorithm to obtain an appropriate protamine dose. The hemostasis management system (HMS Plus; Medtronic, Minneapolis, MN) is a POC device with universal recognition.[1,2,5] The instrument calculates the protamine dose by assessing the concentration of heparin in a device-specific cartridge filled with a small volume of whole blood. The concentration measure of heparin and the estimated patient blood volume obtained using Allen's formula[6] are used to finalize the patient's protamine requirement.

In a recent report, the authors used the HMS Plus instrument as reference to develop a statistical model (SM) for protamine dosing.[7] The protamine dose derived from this SM reached a bias of 3 ± 23 mg compared with the dose calculated using the HMS Plus device. In the study presented here, the SM for protamine dosing was implemented clinically and compared with the results of using a fixed-dose protamine regimen.

METHODS

Patient Population

Sixty ($n = 60$) patients ages 20 to 80 years old scheduled from October 14, 2014, until July 1, 2015, for elective coronary artery bypass graft surgery were enrolled after obtaining Regional Ethical Review Board (DNr 2014311-31) approval and patients' informed written consent. Patients who demonstrated evidence of abnormal coagulation, who were taking warfarin, and who were allergic to fish or protamine were not included in the study.

Anesthesia and Surgery

Standard monitoring comprised radial arterial and central venous blood pressures, 5-lead electrocardiography, and pulse oximetry (Philips IntelliVue MX800; Philips Healthcare, Andover, MA). Anesthesia was induced with propofol, fentanyl, and rocuronium bromide and was maintained with isoflurane and propofol infusion. Supplemental doses of fentanyl and rocuronium bromide were administered as indicated. Systemic vascular resistance was maintained by using either phenylephrine or norepinephrine. Preferred pharmacologic intervention to support cardiac function included epinephrine and milrinone or levosimendan.

Surgery was performed according to standard procedures for coronary artery bypass grafting, during which peripheral anastomoses were performed during aortic cross-clamp and cardioplegic arrest using St Thomas II crystalloid solution. Central anastomoses were sutured behind a side-biting clamp. In all the patients, the left internal mammary artery was attached to the anterior descending branch of the left coronary artery.

Conduct of CPB

CPB was accomplished using the Stöckert S5 (Sorin Group, Munich, Germany) heart-lung machine, roller pumps set to nonpulsatile mode, and the Affinity Fusion (Medtronic Inc, Minneapolis, MN) or Quadrox-i (Maquet Cardiopulmonary GmbH, Rastatt, Germany) oxygenator, connecting the polyvinylchloride tubing and integrated venous-cardiotomy reservoir. The circuit was flushed with carbon dioxide before priming with 1,000 mL of Ringer's acetate, 60 g of mannitol, 160 mmol of sodium chloride, and 10,000 IU of mucosal heparin (Leo Pharma AB, Malmö, Sweden). A 350-IU/kg body

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weight bolus of mucosal heparin was given intravenously to prolong the activated clotting time above 480 seconds before initiation of CPB and thereafter as indicated.

CPB was established from the right atrium to the ascending aorta using a 2-stage venous (36/46 or 32/40 Fr) and a curved arterial cannula (24 Fr) (Medtronic Inc), respectively. Moderate hypothermia at 34°C was induced, adjusting arterial pump flow in accordance with the venous oxygen saturation at >75%.[8] Mean arterial blood pressure was controlled at >50 mmHg using preferred vasopressors. Cardiotomy suction was used in all cases. After CPB completion, connecting cannulae were removed, followed by administration of the precalculated protamine dose. Residual blood in the CPB circuit was transferred to a transfusion bag and thereafter retransfused via a peripheral vein.

Study Design

Block randomization formed 2 equally sized groups. Thirty (n = 30) patients from the study cohort received a patient-specific calculated protamine dose using the SM. The remaining 30 patients (n = 30) served as the reference group (reference) and received protamine in a ratio of 1 mg of protamine/100 IU heparin (bolus + prime).

Patient records were examined to collect sufficient patient-specific perioperative background information.

Statistical Model for Protamine Titration

The patient-specific protamine dose was calculated using a previously described SM.[7] The model was developed using the HMS Plus (Medtronic Inc) as reference.[5] Obtained systematic deviation and accuracy measures for the SM compared with the HMS Plus protamine dose calculation was 3 ± 23 mg. Predictors of significance to project the protamine dose were as follows: the administered dose of heparin, the patient's body surface area, heparin clearance, and the preoperative platelet count level.

$$\textit{Projected protamine dose (SM)} = -468.528 + 192.796 \times \textit{Body Surface Area} + 0.300 \times \textit{Total Heparin dose/kg} + 0.317 \times \textit{Heparin Clearance} + 0.147 \times \textit{Platelet Count}$$

Thromboelastometry

Thromboelastometry (ROTEM; Tem group, Basel, Switzerland) was performed at induction of anesthesia and repeated after protamine administration at sternum closure.[9,10] The following analyses were executed to evaluate intrinsic (INTEM), extrinsic (EXTEM), and fibrogen-mediated (FIBTEM) coagulation patterns.[11] To investigate the platelet contribution to clot firmness, clot elasticity was calculated by combining results from the EXTEM and FIBTEM analyses.[12]

Residual Heparin Analysis

The residual heparin concentration after protamine administration was analyzed using thromboelastometry (HEPTEM: intrinsic assay including heparinase) and the HMS Plus test for residual heparin at 0.0-to-1.2 μg/mL.[13]

Statistics

Statistical analysis included an initial evaluation of distribution patterns for continuous variables. Variables fulfilling the requirements for normal distribution (Shapiro-Wilk test) were analyzed using the Student *t*-test to identify intergroup differences. Repeated measurement and 2-way analysis of variance were implemented for variables analyzed over time to delineate intergroup interactions and main effects. Nominal data were cross-tabulated using the chi-square test to identify significant differences in the distribution of cell frequencies. Results are presented as means ± standard deviation, if not otherwise stated. A p value <0.05 was set as statistically significant. Power analysis based on the intergroup mean difference of the post-CPB expected clotting time extension (40 ± 50 seconds) gave a sample size estimate of 30 patients in each group to attain a power of at least 80%. SPSS, Version 18, (SPSS Inc, Chicago, IL) software was used for all statistical computations.

RESULTS

Patient Demographics and Intraoperative Data

No significant demographic or intraoperative differences were detected between the SM and reference groups, except for the 1.7-times higher protamine dose (Tables 1 and 2).

Thromboelastometry: Time-Dependent Indices

The clotting time increased significantly ($p < 0.01$) after completion of CPB and protamine administration, independently of group allocation, as verified using indicators of intrinsic-, extrinsic-, and fibrinogen-mediated coagulation. The intrinsic-mediated clotting time was significantly ($p < 0.01$) shorter in the SM group (23.3 ± 27.2 seconds) compared with the reference group (66.3 ± 52.9 seconds). Other time-dependent thromboelastometric indices of coagulation demonstrated insignificant intergroup differences (Table 3).

Table 1. Patient Demographics

Characteristics	SM (n = 30)	Reference (n = 30)	p Value
Age (years)	64.1 ± 8.3	66.3 ± 6.8	0.25
Sex (M/F)	26/4	26/4	1.00
Weight (kg)	86.9 ± 18.6	85.4 ± 12.2	0.71
Length (cm)	174 ± 9.1	174 ± 7.1	0.93
Body surface area (m^2)	2.0 ± 0.23	1.99 ± 0.15	0.85
Estimated blood volume* (mL)	5,289 ± 892	5,240 ± 594	0.80
Hemoglobin (g/L)	144 ± 13.9	140 ± 12.4	0.26
Erythrocyte volume fraction	0.43 ± 0.04	0.42 ± 0.03	0.85
Platelet count (10^9/L)	242 ± 51	236 ± 47	0.66
International normalized ratio	0.96 ± 0.06	0.99 ± 0.08	0.22
Activated thromboplastin time (s)	27.8 ± 2.6	28.1 ± 3.3	0.66
Fibrinogen (g/L)	3.36 ± 0.67	3.52 ± 0.97	0.47
Dual-antiplatelet therapy† (n)	12	9	0.42

*Nadler's formulae.

†Acetylsalicylic acid + clopidogrel *or* acetylsalicylic acid + ticagrelor.