Reversal of Heparin After Cardiac Surgery: Protamine Titration Using a Statistical Model

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Objective: **To establish a statistical model for determination of protamine dose in conjunction with cardiopulmonary bypass.**

Design: **Prospective.**

Setting: **University hospital.**

Participants: **Ninety consecutive cardiac surgical patients.**

Interventions: **None.**

Measurements and Main Results: **A series of clinically oriented variables were introduced into a statistical model for projection of the protamine dose after cardiopulmonary bypass. The following significant predictors were identified using multivariable regression analysis: The patient's body surface area, the administered dose of heparin, heparin clearance, and the preoperative platelet count. The statistical model projected the protamine dose within 3 ± 23 mg of the point-of-care test used as reference.**

Conclusion: **Protamine dosing based on statistical modeling represents an alternative to point-of-care tests.**

KEY WORDS: cardiac surgery, cardiopulmonary bypass, protamine, heparin, point-of-care testing, statistical modeling

DOSING OF PROTAMINE typically is performed empirically, which is why the dose administered may vary according to personal preference or hospital guidelines. Point-of-care systems enable patient-specific dose calculations with reference to a given algorithm.[1,2] In the present investigation, the Hemostasis Management System (HMS) (Medtronic, Minneapolis, MN) was used. The instrument measures the concentration of circulating heparin from which the required protamine dose is calculated, with adjustments for patient characteristics and the desired protamine-to-heparin ratio. The HMS is validated against anti-X_a as reference, with good agreement.[3] The projected dose of protamine based on HMS calculations tends to lower the general protamine dose, with possible favorable effects on normal coagulation activity.[4,5]

The aim of the present study was to develop a statistical model (SM) based on a number of patient-related clinical variables easily accessible in the operating room as input information for projection of the protamine dose requirement after cardiopulmonary bypass (CPB). It was hypothesized that the SM should project the dose of protamine with the precision of the HMS reference method.

METHODS

Patient Population

Ninety (n = 90) consecutive patients admitted for elective cardiac surgery requiring CPB were enrolled after obtaining written informed consent. Patients requiring acute surgical interventions were not included. The initial 60 patients (n = 60) formed a reference group for developing the SM; the next 30 patients (n = 30) served as test group for the established SM. The investigation was approved by the Ethical Review Board at Umeå University, Sweden (2014-94-31M).

Surgery and Anesthesia

Surgery was performed using standard techniques appropriate for the patient-specific diagnosis and indication. Anesthesia was induced using propofol and fentanyl, combined with rocuronium bromide to facilitate tracheal intubation. Maintenance of anesthesia was accomplished by iterated doses of fentanyl and rocuronium bromide as indicated, combined with isoflurane added to the mixture of oxygen in air used to ventilate the patient's lungs (Dräger Primus, Dräger Medical AB, Sweden). Standard monitoring (Philips Intellivue MX 800, Philips Healthcare, The Netherlands) included mean arterial and central venous pressures, pulse oximetry, 5-lead electrocardiogram, and nasopharyngeal temperature. Transesophageal echocardiography was performed routinely. Systemic vascular resistance was adjusted using phenylephrine or norepinephrine as indicated. Preferred inotropic medication included epinephrine, milrinone, and levosimendan. Most patients received (2 + 2 g) tranexamic acid intraoperatively. As a rule, platelet inhibitors were withdrawn 3-5 days before surgery.

Conduct of CPB

The CPB circuit was comprised of the Affinity Fusion® membrane oxygenator, with integrated venous-cardiotomy reservoir (Medtronic, Minneapolis, MA), connecting polyvinylchloride tubing, and venous-arterial cannulae. The circuit was primed with Ringer's acetate, 1,000 mL, mannitol, 400 mL, sodium chloride, 160 mg, and heparin, 10,000 IU. Pump blood flow (Stöckert S5, Sorin Group Mirandola, Italy) was controlled by maintaining the venous oxygen saturation >70%[6] and the mean arterial blood pressure above 50 mmHg. Re-transfusion of blood from the pericardial cavity was performed using roller pumps. The target body temperature was set at 34°C in most cases. Remaining blood volume in the CPB circuit after bypass was transfused after complete protamine reversal. Intervention and monitoring parameters related to the conduct of CPB were registered online using Stöckert data management system (Sorin Group Mirandola, Italy).

Anticoagulation Management

The activated coagulation time (ACT) (HemoTec ACT II, Medtronic, Minneapolis, MA) was measured before the induction

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of anesthesia and repeated after completion of CPB as verification. A standard dose of 350 IU/kg of porcine mucosal heparin (Leo Pharma AB, Malmö, Sweden) was administered intravenously before initiation of CPB. The effect was verified by ACT >480 seconds and maintained throughout the course of CPB. Supplemental doses of heparin were administered as indicated. Before completion of CPB, a heparin/protamine titration test was performed using HMS (Medtronic, Minneapolis, MA).[3] This specific test calculates the dose of protamine needed to neutralize the effect of heparin based on the plasma concentration of heparin and the patient's theoretical blood volume. The precision of the heparin concentration calculation is ±7 IU/mL or ±50 IU per kilogram body weight for the specific 6-channel (2.0-5.4 IU/mL) cartridge used. The HMS protamine: heparin ratio was set at 1:1. The effect of heparin reversal by protamine was verified by repeating the heparin/protamine titration test. Residual concentrations of heparin were counteracted by supplement doses of protamine.

The Statistical Model for Protamine Titration

Information of interest relating to dosing of heparin and protamine was scrutinized based on the first 60 (n = 60) patients' preoperative and intraoperative characteristic. A selection of predictors was introduced into a multivariable linear regression model, with the calculated HMS protamine dose as dependent variable. The dataset comprised the following presumed predictors: Patient age, gender, body weight, height, body mass index, body surface area, preoperative hemoglobin, albumin, platelet and granulocyte count, type of surgical intervention, duration of CPB and clamping of the aorta, body temperature (lowest nasopharyngeal), ACT registrations, heparin bolus and iteration doses, total heparin dose, time points for heparin and protamine administration, protamine dose calculated according to the formulae of Bull,[7] theoretical blood volume,[8] heparin concentration (per kg body weight and per mL blood volume), heparin clearance ($C_T = C_0\, e^{(-kT)}$, where C_T concentration of heparin at time T was defined as the time elapsed from administration of heparin to protamine, and C_0 initial heparin concentration was defined as the total administered dose of heparin), and platelet inhibitor medication.

The aim was to establish an SM, by which the protamine dose calculation derived from HMS could be explained with as high a degree of agreement as possible.

Testing the Statistical Model

The established SM (n = 60) was implemented and tested for robustness in the remaining patient sample of 30 (n = 30) patients. Predictors derived from the initial multivariable regression analysis formed the equation used to define the linear relationship with the dose of protamine calculated by the HMS. The predicted dose of protamine based on the SM then was compared with the HMS protamine dose by performing Bland-Altman analysis.[9] Hereby, the deviation between the 2 dose alternatives of protamine is illustrated within the dosing range. The null hypothesis would be accepted if the SM predicts the HMS protamine dose, with a precision (≤ ±2 standard deviations) and bias <50 mg.

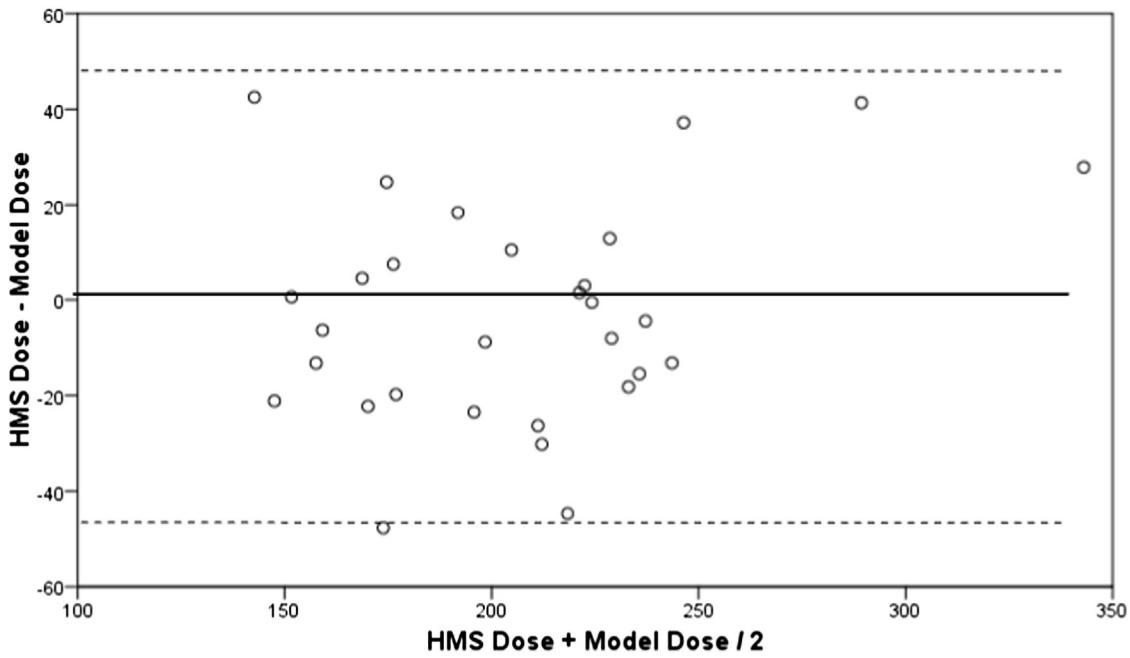

Fig 1. Dosing of protamine: HMS versus SM using Bland-Altman statistics. The protamine doses derived from the SM and HMS are depicted, with the deviation between the methods on the y-axes and the mean SM-HMS protamine dose on the x-axes. Solid horizontal line indicates the bias (3.04 mg) and the 2 dotted lines indicate limits of agreement, within 2 standard deviations or ±46 mg. Abbreviations: HMS, hemostasis management system; SM, statistical model.