Heparinase Thromboelastography Compared With Activated Coagulation Time for Protamine Titration After Cardiopulmonary Bypass

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Objective: **The present study is a comparison of two point-of-care (POC) tests as endpoints of protamine titration after CPB. The authors hypothesized that using the heparinase-kaolin thromboelastography (TEG-HK) R-time difference would more readily identify residual heparin necessitating additional protamine than when using activated coagulation time (ACT). The primary endpoint was the between-group difference in protamine dose. Whether this approach would lessen postoperative bleeding and sequelae also was investigated.**

Design: **Single center, blinded, prospective, randomized study.**

Setting: **University teaching hospital.**

Participants: **Eighty-two adult patients for on-pump coronary artery bypass and/or valve surgery.**

Interventions: **Patients were randomized. In the ACT group, protamine was titrated until ACT did not exceed baseline by more than 10%. In the TEG group, a TEG-HK R-time difference less than 20% was targeted. Protamine was repeated to achieve the endpoints. Clinicians in the ACT group were blinded to TEG data and vice versa.**

Measurements and Main Results: **There was no between-group difference in total protamine dose (3.9 ± 0.6 and 4.2 ± 0.7; 95% CI of the difference between means: –0.544 to 0.008 mg/kg; $p = 0.057$) or protamine:heparin ratios (1.3:1 and 1.4:1; 95% CI of the difference between means: –0.05 to 0.03 mg/mg; $p = 0.653$). In the ACT group, 17% of patients required a second protamine dose, and in the TEG group, 24% of patients required a second protamine dose. No between-group differences in the postoperative transfusion requirements or intensive care unit length of stay were demonstrated.**

Conclusion: **No difference was identified in protamine dosing using either ACT or TEG-HK R-time difference as endpoints. Heparinase TEG may be useful for monitoring heparin reversal.**

KEY WORDS: thromboelastography, heparin, protamine, heparinase, activated coagulation time, cardiopulmonary bypass, postoperative bleeding, point-of-care test

METHODS OF ACHIEVING adequate heparin reversal after cardiopulmonary bypass (CPB) have been researched extensively. Both inadequate and excessive dosages of protamine are undesirable; the latter may contribute to postoperative coagulopathy by inhibiting platelet function and clot formation and structure.[1–3] At protamine-heparin ratios exceeding 2.6:1 and 5:1, ACT increases and platelet aggregation is impaired.[1,2]

Bull et al described an approach to calculating the protamine dose at the end of CPB, assuming that a similar relationship exists between ACT and heparin concentrations at the beginning and end of CPB.[4] This assumption is not always valid, because the relationship is altered by numerous factors, including platelet number and function, clotting factor and red cell dilution,[4,5] hypothermia, protamine, and even surgical stress.[6] ACT also has been reported to be an insensitive indicator of the presence of residual heparin.[7–15]

A difference in reaction time (R-time) between simultaneously performed kaolin-activated thromboelastography (TEG) and kaolin-activated TEG with heparinase added to the cuvettes ("heparinase TEG") (Fig 1) has been attributed to the presence of residual heparin, an observation that has been used on occasion to facilitate therapy.[16–20]

These observations led to the present investigation of the hypothesis that titrating protamine after CPB using the R-time difference between heparinase and kaolin TEG compared with standard ACT-based practice would increase the total protamine dose administered. The rationale was that the TEG-based test would more readily identify residual heparin, necessitating additional protamine. The authors also hypothesized that the TEG-based method would result in less postoperative bleeding and fewer postoperative complications.

METHODS

After institutional ethics committee approval (reference number N10/05/165) and obtaining informed consent, patients meeting inclusion and exclusion criteria were invited to take part in this study. A predetermined randomization protocol generated at www.randomization.com was used to assign patients to the ACT or TEG group. The research was conducted over 2 consecutive months, but only when members of the trained data collection team were available.

The primary endpoints were to identify differences in the dose of protamine (expressed as mg, mg/kg, and the heparin-protamine ratio) and the necessity for repeated protamine dosages when either the TEG or the ACT was used to titrate protamine after CPB. The secondary endpoints were to identify whether the use of TEG to guide the reversal of heparin with protamine would lessen postoperative bleeding and/or the associated complications, such as blood product or resuscitation fluid utilization and length of intensive care unit (ICU) stay. The predictive value of a surgical scoring system that rated the degree of microvascular bleeding after protamine administration had been completed and also was investigated.

Inclusion criteria were procedures requiring cardiopulmonary bypass (CPB), including valve replacement and/or repair and coronary

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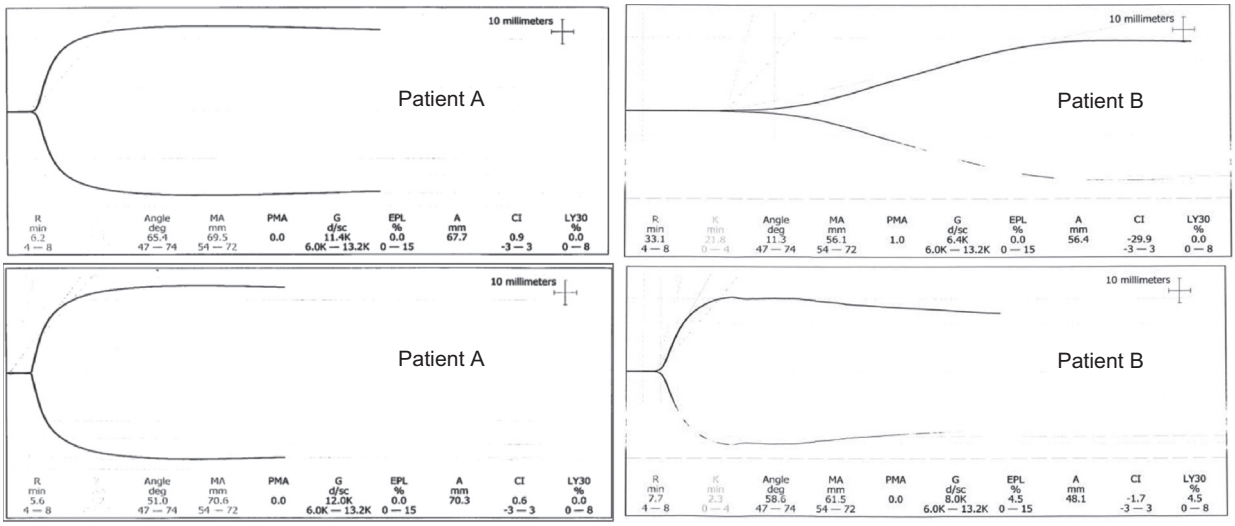

Fig 1. Concurrent kaolin (top) and kaolin-heparinase (bottom) TEG tracings after protamine administration from two patients. The similarity of R-times (and other parameters) suggest that heparin neutralization is adequate in patient A but not in patient B.

artery bypass grafting (CABG). Exclusion criteria were administration of heparin or oral anticoagulants in the 72 hours before surgery, known allergies or adverse reactions to heparin or protamine, known preexisting coagulation defects, liver dysfunction (defined as liver function poor enough to increase the international normalized ratio to greater than 1.6), severe renal dysfunction (defined as a blood urea greater than 12 mmol/L and/or creatinine greater than 200 μmol/L), urgent reinstitution of cardiopulmonary bypass at any time between induction of anesthesia until after protamine administration, trauma patients requiring CPB, deep hypothermic arrest, patients younger than 18 years of age, and patients weighing less than 45 kilograms. Patients on cardiac low-dose aspirin were included in the study, whereas patients who received any other antiplatelet drug in the week before surgery were excluded.

Anesthetic and monitoring techniques were at the discretion of the attending anesthesiologist. The conduct of CPB was standardized, with a CPB circuit of nonheparin-bonded tubing and a membrane oxygenator primed with 2 L of Balsol (Fresenius Kabi, Port Elizabeth, South Africa) to which heparin 5,000 IU had been added. Patient anticoagulation before CPB comprised administration of 300 IU/kg of unfractionated heparin (Fresenius Kabi, Bodene Limited trading as Intramed, South Africa). If ACT did not exceed 400 seconds before or during CPB, additional heparin boluses of 70 IU/kg were administered. Tranexamic acid, 70 mg/kg (Cyklokapron IV 500, Pfizer, NY), was administered just before initiation of CPB. The minimum hematocrit tolerated during hypothermic CPB (32°C) was 22%.

The initial protamine dose (Prosulf, Wockhardt, Wrexham, UK) was 1.3 milligram per milligram of heparin needed to achieve an initial preCPB ACT exceeding 400 seconds. ACT and TEG were performed 5 minutes after completion of protamine administration. In the ACT group, the endpoint of protamine administration was an ACT not exceeding baseline preCPB values by more than 10%. In the TEG group, the kaolin TEG (TEG-K) R-time was not to exceed that in the heparinase TEG (TEG-H) by more than 20%. If these endpoints were not attained, one third of the initial dose of protamine was administered again. This cycle was repeated until the relevant endpoints were achieved or a predetermined maximum dose of protamine (6 mg/kg) was reached.[2] Because only 4 TEG channels were available, only R-time was recorded to facilitate repeated cycles of point-of-care (POC) testing. All tests (TEG with and without heparinase; ACT before and after CPB) were performed in each patient, blood being withdrawn 5 minutes after completion of protamine administration. However, the attending anesthesiologists in the ACT group were blinded with regard to the TEG results and vice versa. If the attending anesthesiologists opined it was in the patient's best interests, they could request the blinded test results.

ACT was measured using an Actalyke MINI II Activated Coagulation Time (ACT) Analyzer and Celite Actalyke tubes (Helena Laboratories, TX). The ACT blood sampling method was standardized. After withdrawal of 10 mL of blood via the arterial catheter, a specimen was aspirated into a new 2-mL plastic syringe and transferred immediately to an adjoining room housing the ACT apparatus.

TEG was performed using the TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemonetics Corporation, MA) connected via serial cable to a Windows XP personal computer running version 3 of the TEG analytical software. All TEG channels were subject to the recommended manufacturer's calibration procedures twice weekly. Two dedicated clinical technologists, each with a minimum of 4 years' experience of performing TEG, performed all ACT and TEG tests immediately after blood sampling according to manufacturer-defined procedures. The TEG apparatus was readied before withdrawal of blood samples to ensure the cups reached 37°C. Blood sampling for TEG was standardized. After withdrawal of 20 mL of blood via the central venous catheter, a specimen was aspirated into a new 2-mL plastic syringe and transferred immediately to an adjoining room housing the TEG apparatus.

After protamine administration, the senior surgeon rated the degree of microvascular bleeding according to the following scale: (1) no bleeding, driest field imaginable; (2) some bleeding, acceptable; (3) bleeding unacceptable, please do something!; and (4) severe bleeding, not able to close chest.

In the absence of published data when this study was conceived, it was presumed that using TEG rather than ACT as the endpoint would result in a 30% larger protamine dose. Assuming mean (standard deviation) protamine:heparin dose ratios in the control (ACT) and TEG groups of 1.3 (0.6) and 1.7 (0.6), respectively, and accepting an alpha error of 0.05, power of 0.8, PASS (NCSS Statistical Software, Kaysville, UT), indicated that 78 patients would need to be studied. Allowing a 5% dropout rate, 82 patients were enrolled.

Data analysis was performed using SigmaStat version 2.03 (Systat Software, San Jose, CA). The data were analyzed for normality of distribution and equality of variance using the Kolmogorov-Smirnov and Levene-Median tests, respectively. Numeric data that were