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Original Article

Assessment of Heparin Anticoagulation Measured Using i-STAT and Hemochron Activated Clotting Time

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Objective: Adequate anticoagulation, measured using activated clotting time (ACT), is important during vascular and cardiac surgeries. Unfractionated heparin is the most common anticoagulant used. The purpose of this analysis was to compare the i-STAT ACT (iACT) to the Hemochron ACT (hACT), both of which were then compared to anti-factor Xa (anti-Xa) assay, a representation of heparin level and activity.
Design: Prospective study.
Setting: Tertiary care cardiovascular center.
Participants: Eleven consecutive elective adult cardiac surgical patients.
Interventions: Prior to cardiopulmonary bypass, ACTs were measured using i-STAT and Hemochron technologies and compared to each other and to anti-Xa assay prior to and during a cumulative administration of heparin. Data were compared using bias analyses.
Measurements and Main Results: Heparin (300 U/kg) was administered in quarterly doses. Coagulation labs were collected prior to and 3 minutes after each quarterly dose of heparin. The baseline ACTs for i-STAT and Hemochron were 147 and 142 seconds, respectively. A significant association was found between iACT and hACT ($p = 0.002$). The iACT measurements underestimated hACT at ACT levels > 180 seconds or anti-Xa levels > 0.75 U/mL. No significant difference was found between ACT data at anti-Xa levels < 0.5 U/mL.
Conclusion: There was a good association between the iACT and hACT; however, the 2 tests are not equivalent. Overall, the iACT underestimated the hACT. Agreement between the ACT technologies was good at lower ACTs and anti-Xa levels, but declined with an anti-Xa > 0.75 U/mL.

Key Words: anticoagulation; heparin; activated clotting time; anti-Xa; i-STAT

ADEQUATE ANTICOAGULATION is important during vascular and cardiac surgeries. Unfractionated heparin (UFH) is the most common anticoagulant used to achieve this goal. Because of interpatient variation in response to heparin, monitoring coagulation is important to avoid excess or deficient heparin administration, prevent bleeding and thrombotic complications, and reduce blood transfusions.[1–3]

Anticoagulation with heparin can be assessed using readily available point-of-care testing or, more specifically, by measuring the activated clotting time (ACT), which is a whole blood measure of clotting.[3–8] Different technologies can measure the ACT, including the Hemochron device (Accriva Diagnostics, San Diego, CA, or its subsidiary, International Technidyne Corporation, Bedford, MA), the Hepcon device (Medtronic, Minneapolis, MN), and the i-STAT device

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(iACT: Abbott, Princeton, NJ). The i-STAT is a compact, handheld device, recently introduced to the authors' practice, that has the ability to measure ACT and a number of other critical lab tests, helping to streamline point-of-care testing.

The purpose of this analysis was to report on the comparison of the i-STAT ACT (iACT) and the Hemochron ACT (hACT), both of which then were compared to anti-factor Xa (anti-Xa) assay, a representation of heparin levels and activity.[3,4] The authors hypothesized that the 2 ACT tests would yield similar data during heparin administration.

Methods

This study was reviewed and considered a quality assurance activity by the hospital institutional review board. The analysis was prompted by a concern that the i-STAT ACT (iACT) was not equivalent to hACT during lower-dose heparin administrations (eg, vascular surgery). To evaluate a range of heparin dosing, 11 consecutive patients scheduled for elective coronary artery bypass grafting were assessed. For patients receiving preoperative intravenous heparin, the heparin was discontinued 6 hours prior to surgery. Patients were without any oral anticoagulants prior to surgery, with the exception of aspirin. All patients had a preoperative platelet count (Plt) $>$ 120,000/mL.

Each patient received general anesthesia with endotracheal intubation and was monitored using the standard American Society of Anesthesiologists monitoring in addition to an intra-arterial line and pulmonary artery catheter. Saline (0.9%) was used for the flush systems. After sternotomy, baseline coagulation studies were obtained. Inclusion criteria were a baseline hACT $<$ 160 seconds. After dissection of the left internal mammary artery, heparin administration began. Heparin (3 mg/kg or 300 U/kg) was given in 4 divided doses at 5-minute intervals. Three minutes after each one-fourth dose, coagulation studies were obtained, making a total of 5 sampling periods (baseline, T1-T4). Blood specimens were obtained after removal of 3 $\times$ the dead space volume, which was measured to be 3.0 mL.

The analysis occurred prior to cardiopulmonary bypass (CPB) to reduce the impact of CPB on coagulation (eg, hemodilution and hypothermia).[4,5,9] Prior to CPB, there was a good correlation between heparin concentration (anti-Xa levels) and ACT data.[4]

Baseline hematologic data included iACT, hACT, hematocrit (Hct), white blood cell count, Plt, prothrombin and partial thromboplastic time, thromboelastogram, factor VIII activity, anti-thrombin III level, and anti-Xa concentration. At times 1-4 (T1-T4) iACT, hACT, and anti-Xa were assessed.

The Hct, white blood cell count, and Plt were measured using a Coulter Counter, Model DX 800 (Beckman Coulter, Indianapolis, IN). The prothrombin time and activated partial thromboplastin time were tested on the IL-ACL TOP 700 (Instrumentation Laboratory, Lexington, MA). Factor 8 activity was measured using a 1-stage chronometric method on the same IL-ACL TOP 700. The antithrombin III and anti-Xa levels were measured using a chromogenic method, also on the IL-ACL TOP 700 analyzer. Thromboelastography (TEG) was performed using kaolin activation on the TEG 5000 series analyzer (Haemonetics, Braintree, MA) to assess for baseline coagulation abnormalities, which could be relevant to the interpretation of the data.

hACT was performed by placing 2 mL of whole blood into a test tube that contained Celite, as an activator, and a precision magnet. The test tube was agitated by an operator and then placed in a well, where it was rotated at a controlled speed. The coagulation system was activated, resulting in fibrin clot, at which time the magnet was displaced within the tube. The time it takes to displace the magnet within the tube is coagulation time or ACT. The Hemochron system is sensitive for a range of heparin concentrations from 1.0 to 6.0 U/mL. The normal range of hACT is 96 to 152 seconds with a mean of 124 seconds and a standard deviation of 14 seconds. Variables that affect hACT data include high or low Hcts ($>$ 55% or $<$ 20%) and hypothermia.

Instead of converting fibrinogen into fibrin clot, the iACT converts a substrate that mimics the thrombin-cleaved amide linkage in fibrinogen.[5] The substrate is Phenylalanine-Pipecolic Acid-Arginine-NH-C_6H_4-NH-C_6H_4-OCH_3.

The product of the conversion results in an electronically active compound that can be electrically detected and measured: NH3+ - C6H4 - NH - C6H4 - OCH3.

The reportable range for the analyzer is 50 to 1000 seconds. The normal iACT ranges from 89 to 139 seconds.

Statistical Analysis

Differences Between iACT and HACT

Prior to use of i-STAT measures of ACT, the Hemochron technology was the standard at the authors' institution (ie, hACT was the reference measure). Although anti-Xa is a pharmacokinetic measure of heparin and reflects heparin concentration, it is used to guide heparin therapy. Therefore, anti-Xa assays were measured to give a unifying comparison between the 2 ACT measures and additional clinical significance to the ACT levels. A generalized linear mixed model (which accounts for repeated measures) for a lognormal distribution was used to test the relationship (slope) between ACT values for the 2 machines (i-STAT and Hemochron). Instead of evaluating the intercept of the model (because ACT values are not possible at 0), the minimum observed value of hACT (78 seconds) was chosen to evaluate the difference between iACT and hACT at a physiologic minimum value. Bland–Altman and modified Bland–Altman plots were used to evaluate agreement and further assess the machines for bias and precision relative to each other. Modified Bland-Altman plots were included because ACT was found to be nonparametric log-normal data (log ratio of iACT and hACT *v* the geometric mean of iACT and hACT).[9] Additionally, the y-axis of the modified Bland-Altman plot was plotted with an x-axis of increasing anti-Xa.

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