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Alternative Methods for Anticoagulation Monitoring in Pediatric Patients with Applicability to a Patient with Severe Hemophilia A and Circulating Inhibitor

Jerri L. McNamara, BA, BS, CCP; John P. Lombardi, CCP; Robert Ferguson, CCP; Peter B. Manning, MD; Ralph A. Gruppo, MD

Division of Pediatric Cardiothoracic Surgery, Children's Hospital Medical Center, Cincinnati, Ohio

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Abstract: Anticoagulation monitoring in pediatric patients can be problematic because of the immaturity of the coagulation system in this population. In addition, the hemodilution required to place a small patient on bypass can interfere with standard monitoring methods. In this institution, the Hemochron Jr. ACT (activated clotting time)+ assay has been the standard of care for anticoagulation monitoring since 1997. This assay, with a target ACT of 400 s for initiating bypass, was compared to both the Medtronic HMS system ($N = 7$) and the Hemochron HiTT assay ($N = 6$) in pediatric patients. All three assays were then employed to monitor a pediatric Hemophilia A patient (Factor VIII <1%) with high inhibitor titer. Both the HiTT clotting time and the HMS heparin level showed statistically significant correlation to the ACT+ (HiTT, $N = 24$, $r = 0.761$; HMS, $N = 31$, $r = 0.818$). An HMS target heparin level of 1.5 mg/kg and a HiTT target clotting time of 180 s were found to be clinically equivalent to the 400-s ACT+ as indicators of the need for additional heparin. When a 7-year-old male with severe hemophilia A and high inhibitor titer required tricuspid valve replacement, all three assays were used to ensure appropriate anticoagulation management. During bypass, this patient's ACT+ remained out of range (>1005 s). The HiTT was maintained at >180 s and the HMS heparin level at >1.5 mg/kg. Heparin was administered when any single parameter was below the cutoff value. The use of the combination of three distinct monitoring assays for this patient allowed the surgical team an added level of confidence that appropriate anticoagulation had been maintained. *JECT. 2001;33:239–242*

Anticoagulation management in the routine pediatric patient requiring cardiopulmonary bypass (CPB) is a clinical challenge. Because both the immaturity of the patient's hemostatic systems and the great degree of hemodilution employed as compared to adult patients, the validity of traditional activated clotting time (ACT) testing for monitoring this patient population has been questioned (1). In 1997, the Children's Hospital Medical Center in Cincinnati, Ohio implemented the use of the Hemochron® Jr. ACT+ assay for monitoring heparin administration during CPB for all pediatric patients. At that time, a target ACT+ of 400 s was determined to be optimal for ensuring appropriate anticoagulation in this population.

The current study was initiated to compare two anticoagulation monitoring systems (HiTT and HMS) to the institutional standard (ACT+). Whereas, the ACT+ is based on the measurement of the intrinsic coagulation path, the HiTT and the HMS were chosen, because they examine different portions of the coagulation cascade (Table 1).

These three methods (ACT+, HiTT, and HMS) were then employed in concert for managing heparin administration during CPB for a pediatric patient with severe hemophilia A and high inhibitor titer. Hemophilia A is a sex-linked trait associated with the reduced levels of blood coagulation factor VIII. Approximately 15% of severe hemophilia A patients (coagulation factor VIII levels <0.01 IU/mL) develop antibodies (inhibitors) directed toward the substitution factor infused to maintain normal hemostasis. In these patients, the standard preprocedural use of large factor VIII infusions to minimize bleeding complications is frequently ineffective. Instead, infusions of recombinant factor VIIa and/or anti-inhibitor coagulant complex can be used to normalize clotting. There is no established procedure for anticoagulation management of

Address correspondence to: J.L. McNamara, BA, BS, CCP, Division of Pediatric Cardiothoracic Surgery, Children's Hospital Medical Center, Cincinnati, OH 45229-3039, e-mail: Jmcnamara@chmcc.ors
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Table 1. Comparison of alternative monitoring methods.

Assay	Activation Method	Coagulation Pathway Monitored
ACT+	Silica/kaolin	Intrinsic
HPT	Thromboplastin	Extrinsic
HiTT	Thrombin	Common

the severe hemophilia A patient with high inhibitor titer. The planned infusion of factor concentrates known to influence intrinsic pathway clotting times before surgery also increases the level of uncertainty surrounding the proper method for monitoring heparinization in this patient population.

MATERIALS AND METHODS

Medical Chart review was carried out in accordance with the Institutional Review Board policies at Children's Hospital Medical Center.

This study was performed in three phases. Phases I and II involved comparisons of each alternative monitoring method with the institutional standard, the ACT+. All data collected during these two phases were examined to determine clinical relevant ranges with which to perform the third phase, a case study, monitoring a severe hemophilia A patient with high inhibitor titer.

All patients included in the evaluations were pediatric patients undergoing elective cardiac surgery requiring cardiopulmonary bypass. All patients received an initial heparin bolus of 300 units/kg before CPB with subsequent heparin doses given when the ACT+ [International Technidyne Corporation (ITC), Edison, NJ] was below 400 s. Data collected in all studies included clotting times for ACT+ and HiTT (High-dose thrombin time, ITC, Edison, NJ) and heparin level for the HMS (Medtronic, Parker, CO).

The ACT+ assay, performed on the Hemochron® Jr. (ITC, Edison, NJ) series of analyzers, utilizes a combination of silica and kaolin to activate coagulation. The instrument reports the result as a clotting time in seconds. The HiTT assay, performed on hemochron test tube systems, is thrombin time based. Results are reported as clotting time in seconds, and, in some instrument models, as heparin level. Only the clotting time results were available during this study. The HMS assay employed (HPT) (Medronic, Parker, CO) uses a thromboplastin activator to perform a protamine titration and report a heparin level in mg/kg.

The comparison between the ACT+ and the HMS system was conducted as part of a clinical comparison of the methodologies. Simultaneous samples were taken from seven patients and analyzed by the two methods after heparin bolus, every 30 min on bypass, and postprotamine administration. Baseline HMS values were not obtained during this portion of the evaluation. A total of 31 evaluable sample pairs were analyzed.

For the evaluation of the HiTT assay, six pediatric patients were studied using simultaneous sampling between the HiTT and ACT+ assays at the same intervals as used in the HMS comparison, plus baseline. These patients were different from those observed in the HMS comparison and yielded 24 evaluable sample pairs.

In June 2000, a 7-year-old boy with severe hemophilia A and high inhibitor was referred to the cardiothoracic surgery service for evaluation of tricuspid valve regurgitation secondary to endocarditis. At 2 years of age, the patient received his first MediPort for factor replacement. This port was removed and replaced secondary to an infection 2 years after its placement. With his hemophilia A, the patient developed an inhibitor that destroys factor VIII. His medical history is further complicated by an episode of intracranial bleeding. Because the patient continues to receive routine factor replacement and would require presurgical factor infusions for hemostasis management during bypass, a decision was made to use multiple methods of heparin management to ensure adequate levels of systemic anticoagulation.

To address the patient's coagulation management during the perioperative period, the hematology/oncology and cardiothoracic surgery teams worked closely together. Porcine factor VIII and recombinant factor VIIa were given immediately before surgery. After a median sternotomy was performed, the patient was systemically heparinized (300 IU/kg). Cardiopulmonary bypass with moderate hypothermia was employed. During bypass, additional factor VIII was administered. The extracorporeal circuit consisted of a hollow fiber oxygenator (COBE Cardiovascular, Arvada, CO), 40-micron arterial line filter (Terumo Corporation, Ann Arbor, MI), hemofilter (Ashai Medical, Tokyo, Japan), a 4:1 blood to crystalloid cardioplegia device (COBE Cardiovascular, Arvada, CO) and a roller pump (Stockert, COBE Cardiovascular, Arvada, CO). The aortic cross clamp was applied and cold blood cardioplegia solution (30 mL/kg) was delivered into the aortic root. Additional half doses of cardioplegia were given at 15–20-min intervals during the clamp time. The tricuspid valve was replaced with a bovine Mitral Perimount Pericardial Valve (Edwards Life Sciences, Zurich, Switzerland) following IRB and FDA review and approval. A terminal dose of warm cardioplegia was delivered before the cross clamp removal. Conventional ultrafiltration (CUF) was employed during rewarming. After successfully weaning from cardiopulmonary bypass, modified ultrafiltration (MUF) was performed for 20 min. Protamine was administered for heparin reversal, and a second perioperative dose of porcine factor VIII and recombinant factor VIIa was given. The patient was transported to the intensive care unit in stable condition.

RESULTS

During phases I and II, a single fresh whole blood sample was obtained and used to perform two tests. This procedure led to the collection of 31 paired samples for comparison of the ACT+ and HMS (phase I) and 24 paired samples using the ACT+ and HiTT assay (phase II). Standard linear regression analyses showed strong statistical correlation ($p \ll .001$) between the ACT+ clotting times and both the HMS heparin level and the HiTT clotting time (r = 0.761 and 0.818 for HiTT and HMS, respectively). Removal of a single statistical outlier from each dataset improved these correlations further ((r = 0.840 and 0.862 for HiTT and HMS, respectively, (Figure 1).

To establish clinically equivalent target times on the two new test systems, the correlation graphs were marked with a vertical line corresponding to the ACT+ target time of 400 s. By placing a horizontal line at the target level of the comparative assay predicted from the regression analysis, the graph is divided into four quadrants. Two quadrants represent clinical equivalence (bottom left and upper right) and two clinical disagreement (top left and bottom right). A target time of 180 s for the HiTT test and a target heparin level of 1.5 mg/kg on the HMS showed only two values clinically different from the ACT+. In all these cases, the alternative assay would have predicted the need for more heparin than indicated by the ACT+.

A further examination of the results of each assay at each timepoint tested reconfirmed these results (Figure 2). The mean and standard deviation of each test type was determined and plotted against time during the procedure. The mean value for each test remained above the test specific target level at all timepoints.

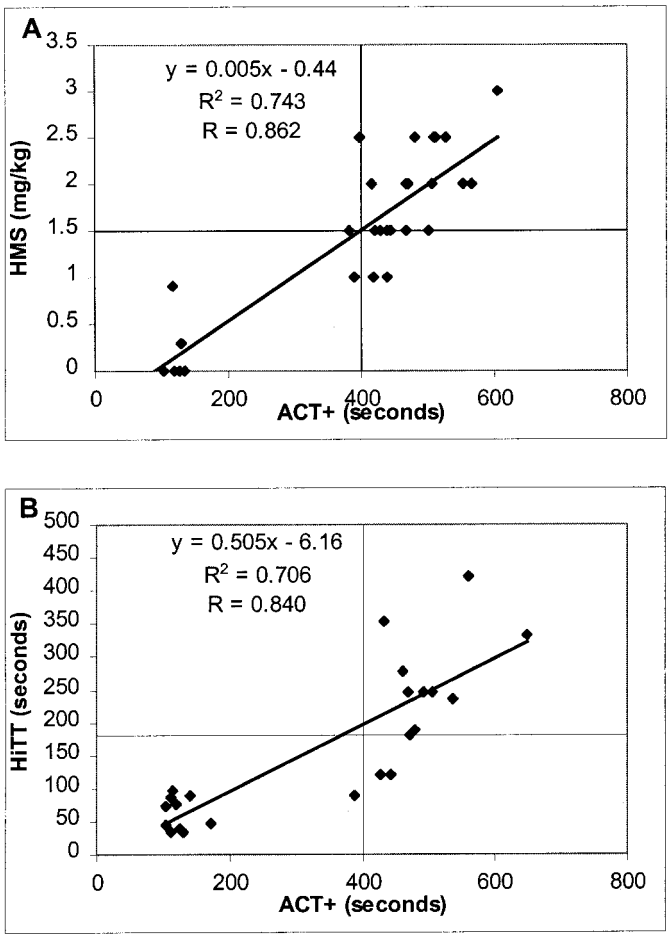

Figure 1. Correlation of the HMS heparin level and HiTT clotting time to the ACT+ clotting time. Split samples were analyzed with the HMS heparin assay (A) or the HiTT test tube assay (B) and the ACT+ cuvette. Good statistical correlation was observed between the HMS result and the ACT+ and the HiTT result and the ACT+. The institutional standard target time of 400 s on the ACT+ is indicated by a vertical line. The horizontal lines indicate the clinically equivalent target times for the HMS system (A, 1.5 mg/kg) and the HiTT assay (B, 180 s).

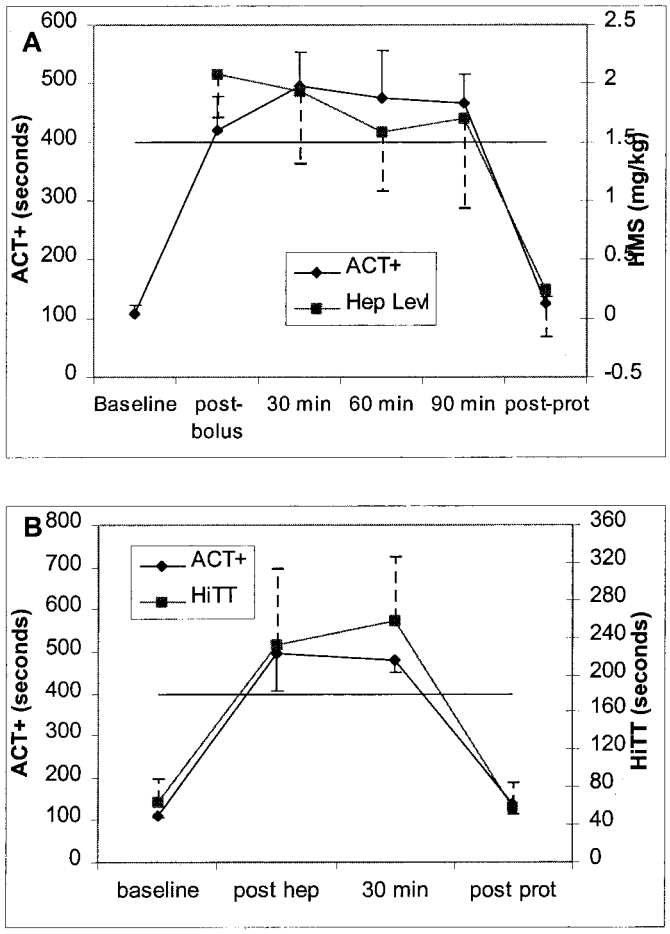

Figure 2. Clinical correlation between the HMS heparin level and HiTT clotting time to the ACT+ clotting time. The data shown in Figure 1 were analyzed by sample time during each case. (Baseline, postheparin bolus, 30-min intervals on bypass and postprotamine). The mean and one standard deviation are shown for each assay. Error bars are indicated in a single direction for clarity. A. HMS heparin level (right axis) compared to ACT+ clotting time (left axis). B. HiTT clotting time (right axis) compared to ACT+ clotting time (left axis). All axes are scaled so that the horizontal line corresponds to the test specific target time.

These analyses allowed the surgical team to proceed with the case of the 7-year-old hemophiliac boy with high inhibitor titer with multiple monitoring methods. At the time of surgery, the patient was 120 cm tall, weighing 24 kg. All three monitoring methods were employed at 20-min intervals throughout surgery. Additional heparin was administered when any of the three assays fell below the predetermined targets (ACT+, 400 s; HiTT, 180 s; HMS, 1.5 mg/kg).

As demonstrated in Figure 3, the ACT+ rose significantly higher than the 400-s target time immediately postbolus and remained high out of range (>1005 s) throughout the bypass period. Both the HiTT and the HMS readings were below target immediately postbolus and at the first sampling time on pump (CPB1). An additional 4000 units of heparin was given postheparin bolus at the initiation of CPB and after the first test on bypass in response to these values. After 80 min on bypass (CPB4) the HMS result lowered slightly to 2 mg/kg. An additional 3500 units of heparin was then administered. Following rewarming, the patient was weaned from bypass without complication, and protamine was administered. The ACT measurements returned to baseline.

DISCUSSION

The challenges associated with the monitoring of anticoagulation in a pediatric patient were exacerbated, in the case described, by the diagnosis of severe hemophilia A with high inhibitor titer. Standard presurgical prophylaxis for hemophilia A patients includes factor VIII infusion to reach serum factor levels of 50–100 IU/mL (2). In addition to Factor VIII replacement, several alternative therapies exist; namely, the use of factor IX concentrates, recombinant factor VIIa infusions (NovoSeven®) (Novo Nordisk Pharmaceuticals, Inc, Princeton, NJ) or the use of anti-inhibitor coagulation complex (Feiba) (Baxter Healthcare, Deerfield, IL) (2). This patient was receiving Feiba infusions at home three times each week. Both these pharmaceuticals are known to lead to decreases in the aPTT in hemophilia A patients (3, 4). Despite the infusion of porcine factor VIII, it was questionable how the inhibitor antibodies would effect the ACT that monitors the intrinsic coagulation pathway. Investigation into alternative monitoring methods led to two candidates, the HMS heparin assay (HPT) and the hemochron HiTT assay (5).

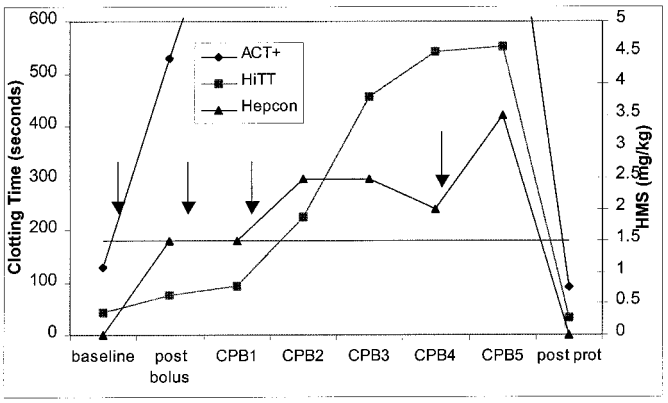

Figure 3. Assay results for Hemophilia A patient with high titer inhibitors. Test results for ACT+, HMS heparin level, and HiTT clotting time are shown for each testing interval (baseline, postheparin bolus, every 20 min on bypass and postprotamine). The horizontal line indicates the target levels for the HMS heparin level (right axis) and the HiTT assay (left axis). The ACT+ clotting time exceeded 600 s throughout the bypass interval. Arrows indicate additional heparin administration.

The ACT+ assay used as part of this institution's standard practice utilizes a combination of silica and kaolin to activate coagulation. Particulate activation is the definition of an ACT (6) that works primarily through the intrinsic or contact factor pathway. The HMS system uses a thromboplastin activator that generally works through the extrinsic, or tissue factor pathway. The HiTT assay is thrombin time based and thus affected predominantly by the common pathway of coagulation. By using these three distinct pathways, the surgical team felt that this patient could be managed with a level of confidence unattainable by any one system.

The preliminary evaluations revealed that these assays that employ unique mechanisms exhibit statistical comparability. Evaluation of routine pediatric cases demonstrated the clinical utility of all three tests. The successful use of the tests in the unique pediatric patient with challenging hemostasis management provides a validation of the use of these assays to manage anticoagulation safely during cardiac surgery.

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