Comparison of Point-of-Care Activated Clotting Time Systems Utilized in a Single Pediatric Institution

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Abstract: This study compares four different activated clotting time (ACT) point-of-care (POC) testing systems used at our institution for the management of patients undergoing heparin therapy. We evaluated these systems under identical conditions to determine their accuracy, reproducibility, ease of use, and cost. Two separate testing stations containing four ACT systems were used. The testing order was randomized for every sample and performed by two trained individuals. Samples of fresh heparinized whole blood were taken at regular intervals and distributed to each station. Each operator tested 50 samples, totaling 400 ACT tests. The ACT value was significantly affected by the type of machine used at both stations 1 and 2 \((p < .001)\). Compared with all systems, the Medtronic ACT Plus Automated Coagulation Timer System (ACT Plus) resulted in the most consistent ACT values (median = 171, Interquartile Range (IQR): 169–175) and least variability (172.17 ± 5.24). The Hemochron Signature Elite Whole Blood Microcoagulation System had the most variability (221.10 ± 14.78) and yielded consistently higher ACT values (median = 220, IQR: 210–229.5) compared with other systems. The ACT values reported by the i-STAT Handheld and Test Cartridge Blood Analysis System (153.30 ± 7.87) were consistently lower (median = 154, IQR: 147–161) in comparison to the ACT Plus and Medtronic HMS Plus Hemostasis Management System (180.60 ± 7.60, median = 181, IQR: 175–186). There was no statistical difference in results between the two testing sites \((p > .05)\) or the operators \((p > .05)\). The significant finding of this study was the affect each system has on the ACT value. This investigation demonstrates the variability that exists among different ACT monitoring systems at our institution. The discrepant variation in ACT values that exists with the Hemochron system questions the reliability of its use in the management of patients undergoing heparin therapy. Keywords: activated clotting time, point-of-care, heparin, anticoagulation. JECT. 2012;44:15–20

The ability to quickly and reliably monitor whole blood coagulation time is crucial for the safe management of patients undergoing heparin therapy. This is especially true in the settings of the operating room during cardiopulmonary bypass, the catheterization laboratory during an intervention, or the cardiac intensive care unit while on extracorporeal life support. Hemostasis is appropriately and most simply managed with point-of-care (POC) activated clotting time (ACT) testing at the bedside. Four different POC ACT testing systems are currently being used at our institution. These include the Medtronic HMS Plus Hemostasis Management System (HMS) (Medtronic Perfusion Systems, Minneapolis, MN), ACT Plus® Automated Coagulation Timer System (ACT Plus) (Medtronic Perfusion Systems, Minneapolis, MN), Hemochron® Signature Elite Whole Blood Microcoagulation System (Hemochron) (International Technidyne Corp, Edison, NJ), and i-STAT® Handheld and Test Cartridge Blood Analysis System (i-STAT) (Abbott Point of Care Inc., Princeton, NJ). Each system has a unique testing method, which we suspect produces substantial variations in ACT measurement.

The objective of this investigation was to ascertain the degree of variation and reliability of each system. Utilizing the same fresh whole blood, we tested each of the four POC systems at two separate testing stations and compared the results.

MATERIALS AND METHODS

Our Institutional Research Ethics Board granted approval for this investigation. Consent for human blood donation was obtained at the time of study. Six hundred
milliliters of fresh whole blood was collected in a bag containing 1000 IU of porcine heparin. This achieved an approximate concentration of 1.7 IU of heparin per mL of blood. Using 1/4 inch tubing the bag was connected to a roller pump and the blood was continuously circulated at a rate of 200 mL per minute (Figure 1). Samples were collected during the study via a single port on the tubing containing a double lumen connector. Two testing stations, each containing four ACT systems, were established. Prior to the experiment all of the machines passed quality control testing. Each respective cartridge was handled and prepared per manufacturer recommendation. Simultaneous sampling was performed using two syringes. The heparinized fresh whole blood was sampled 50 times at regular intervals and distributed between the two sites. The order of systems tested was determined using a random number generator (1–4) for every sample. A trained individual performed the testing at each station. After evaluating the initial 25 samples the operators switched stations and tested the remaining 25 samples.

The HMS is a six-channel clot-timing instrument that automatically dispenses a blood sample from a syringe into an assay cartridge. This system has the ability to measure heparin dose response, heparin concentration, platelet function, ACT, and calculate protamine dose with respect to a specified cartridge and patient body surface area. Fresh whole blood is dispensed into each channel of the cartridge, which contains a flag with a daisy-shaped disc at the bottom. This mechanism enables the plunger to mix the sample and a reagent. During testing the unit continuously raises and drops the flag-plunger assembly until a photo optical sensor detects impedance in the rate of fall as a clot forms. During this study we used the two-channel high-range ACT cartridge to which .4 mL of fresh whole blood was dispensed in each channel and mixed with the activating reagents, kaolin in hydroxyethyl piperazineethanesulfonic acid buffer, calcium, and sodium azide. The ACT from each channel is determined and the machine reports the average.

The ACT Plus is a dual-channel instrument designed to determine the ACT of whole blood. The operator manually fills each of two channels between marked lines on the cartridge that indicate the limit of the sample volume. The cartridge is then placed in a receptacle on the actuator heat block of the machine and tested. The unit utilizes the same flag-plunger cartridge design as the HMS system. Similarly, the end point is reported upon the detection of a drop in the rate of fall of the plunger by a photo optical sensor. For this study, we used the high-range ACT cartridge in which the reagent chamber contains kaolin in hydroxyethyl piperazineethanesulfonic acid buffer, calcium, and sodium azide. Clot time for each channel is displayed at the end of testing and the average is reported.

Hemochron is a hand-held, battery-operated, single-channel unit capable of performing several coagulation tests on whole blood. Using test specific disposable cuvettes, the system can compute ACT, activated partial thromboplastin time (aPTT), and prothrombin time (PT). The cartridge contains a sample well to which a drop of blood is added. From this sample, a precisely measured amount is automatically extracted and dispensed into a testing channel where it is mixed in the cuvette that contains reagents. The sample gradually oscillates forward and backward inside the channel. The light-emitting diode optical sensor detects a reduction in flow rate of the blood sample as clot formation begins. The test endpoint occurs when movement slows to a predetermined rate at which the blood sample has achieved a clot, and thus an ACT value is reported. We used the low range activated clotting time assay that contains Celite® (World Minerals Inc., Santa Barbara, CA) as the activator for this study.

The i-STAT system is a battery-operated, hand-held blood analyzer that can perform a variety of diagnostic tests on whole blood, such as blood gases, chemistries and
electrolytes, lactate, hematology, cardiac markers, and coagulation. Using a test specific disposable cartridge the operator manually dispenses the sample into a well until the indicated fill mark is attained. A cover is snapped over the sample well and the cartridge is inserted into the machine where the sample is mixed with specific activators and evaluated. Unlike the other systems, which rely on mechanical detection of a clot, i-STAT uses an electrochemical sensor to detect the conversion of a thrombin substrate for the determination of the ACT. We used the kaolin ACT cartridges for this study.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS, PASW 19®, Chicago, IL) was used to organize, validate, and analyze the data collected. Indicators of central tendency and dispersion, including the median, mean, standard deviation, standard error of the mean, and 95% confident interval were estimated for quantitative variables. Outliers were eliminated from the data set. In addition, frequency and percentage were used for qualitative variables. Repeated-measures analysis of variance was performed to detect significant differences between selected systems. Differences were considered significant at a level of \( p < .05 \).

RESULTS

The results of each station were analyzed and summarized in Figure 2. As a result of a cartridge error at station 2 with the HMS system, one data entry was omitted. There was no significant difference between the machine operators (\( p > .05 \)). Variation is inherent to the machine and not attributed to operator bias (\( p > .05 \)). Furthermore, there was no significant difference between stations regarding mean ACT for the type of system used (\( p > .05 \)). Medians (square) and interquartile ranges (IQR) (box) in the plot are reported in Figure 3. The whiskers

![Figure 2](image-url)
in the plots display the range of non-outlier values and the diamonds denote outliers. When comparing ACT values, variation in the results of the Hemochron system (median = 220, IQR: 210–229.5) was most pronounced and it showed consistently higher ACT values than the other three systems (Table 1). The use of HMS (median = 181, IQR: 175–186) and ACT Plus (median = 171, IQR: 169–175) produced the least variation in ACT results. The ACT values acquired with the i-STAT system (median = 154, IQR: 147–161) were consistently lower. Within both stations, the results show ACT measurements are significantly affected by the type of system used ($p < .001$). There is a significant difference regarding test results from the four types of systems used at station 1 and station 2 ($p < .001$), respectively (Table 1).

**DISCUSSION**

Anticoagulation therapy has been used and managed for many years. Long-term anticoagulation employs the use of Coumadin (Bristol-Myers Squibb, New York, NY) and is monitored with PT.

The international normalized ratio (INR) was adopted for Coumadin management when discrepancies in PT were discovered while using different analytical machines. Heparin is the most widely used anticoagulant in the clinical setting (1). Activated partial thromboplastin time is sensitive to heparin and was initially used to measure the effect of heparin, but is nonspecific (2). Furthermore, aPTT does not accurately evaluate high blood concentrations of heparin (3). To confirm adequate anticoagulation, the ACT has been established as the metric in which to verify anticoagulation related to the individual response to heparin. The ACT is the most ubiquitous clinical test to assess heparinization (4). Heparin therapy is applied in the operating room, catheterization laboratory, and the cardiac intensive care unit, each with a different ACT target range to maintain adequate anticoagulation. With the advent of POC testing, the ACT has become the simple, safe, and cost-effective strategy.
to measure anticoagulation when heparin is administered (5–7). POC devices monitoring hemostatic function (ACT, aPTT, PT), when guided by algorithms, have improved care in terms of reducing transfusion rates (8,9). However, standardization similar to that of the INR has not been established for the ACT and the systems used to measure it.

It has been suggested that individualized heparin dosing is superior in achieving anticoagulation therapy (10). Several investigators reported the importance of maintaining a minimum heparin level as a more reliable standard for adequate heparinization (11). The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recognize the importance of the HMS for anticoagulation management for its ability to predict individual heparin dose response via specific assay thus conserving adequate heparinization, using heparin protamine titration-guided protamine calculations for heparin reversal, and ACT measurements (12).

**Figure 3.** The distribution of ACT Values for each system. Square, median; boxes, quartiles; whiskers, non-outliers range; diamonds, outliers.

**Table 1.** The ACT values at station 1 (A), station 2 (B), and in aggregate (C).

<table>
<thead>
<tr>
<th></th>
<th>ACT (s)</th>
<th>n</th>
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<tbody>
<tr>
<td>A</td>
<td>HMS</td>
<td>175.88 ± 6.51</td>
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<tr>
<td></td>
<td>ACT Plus</td>
<td>172.02 ± 7.64</td>
</tr>
<tr>
<td></td>
<td>Hemochron</td>
<td>220.06 ± 14.18</td>
</tr>
<tr>
<td></td>
<td>i-STAT</td>
<td>151.76 ± 7.54</td>
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</tbody>
</table>

| B   | HMS     | 185.52 ± 6.04 | 48 |
|     | ACT Plus| 173.17 ± 5.30 | 48 |
|     | Hemochron| 222.12 ± 15.42 | 50 |
|     | i-STAT  | 155.00 ± 7.96 | 50 |

| C   | HMS     | 180.60 ± 7.60 | 98 |
|     | ACT Plus| 172.17 ± 5.24 | 98 |
|     | Hemochron| 221.10 ± 14.78 | 99 |
|     | i-STAT  | 153.30 ± 7.87 | 100 |

Values are presented as mean ± SD.
Newer ACT systems feature reduced sample volume requirements, electronic quality control, electronic data base management, ease of use, and speed (13) (see Appendix). In spite of smaller sample volumes, results are less consistent and are more varied. This study showed the type of system used influences ACT measurements. It is apparent that the variability in ACT observed between the four systems has important implications for heparin therapy. The implications of using different systems within one institution could result in critically important over- or under-anticoagulation especially when maintaining a tight ACT range. The Hemochron system showed the highest variation in the same blood sample and suggests that this system is least reliable compared with the other systems.

Pre and post heparin ACT measurements should be performed on all patients undergoing heparin therapy and tailored not only to the patient, but also to the system used. It would be beneficial to streamline and limit the number of different ACT measuring systems within an institution. All clinicians need to be well informed of the variations when using different systems to measure ACT. Maintaining an ACT within a specific target range will be more easily achieved with one system within an institution. Furthermore, a standardization of ACT measuring systems should be established.

The present study demonstrates the necessity of a universal approach to POC ACT monitoring. The variability associated with the four systems in this study is cogent evidence that the ACT alone is not indicative of the full extent of anticoagulation in an individual patient. Since variability is inherent in the devices, using a singular device to monitor ACT for all settings in which heparin is used therapeutically would eliminate the variability between devices. An approach to standardizing the ACT between different devices much like the way the INR was established would decrease the misleading margin of variability in ACT measurements. In instances where the ACT is variable, thus less reliable, keeping the heparin level consistent would withstand the inaccurate depiction of anticoagulation by ACT exclusive based anticoagulation management. Further studies need to be conducted to identify the potential benefit of standardizing the systems.

REFERENCES


APPENDIX

<table>
<thead>
<tr>
<th>List Price ($</th>
<th>Weight (pounds)</th>
<th>Total ACT Sample Size (mL)</th>
<th>List Price per Cartridge ($)</th>
<th>Average Time for Results (seconds)</th>
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<td>Hemochron</td>
<td>7900</td>
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Relative specifications for each system used at our institution including list price, weight, ACT sample size, list price per cartridge, and average time for results as of January 1, 2011.