WHITE PAPER: i-STAT SYSTEM COMPARATIVE VERIFICATION STUDY IN TWO CANADIAN HOSPITALS

Comparing precision and reliability of the i-STAT Kaolin ACT test with Hemochron Signature Elite and Medtronic ACT Plus

The results shown here are specific to one health care facility and may differ from those achieved by other institutions.
For In Vitro Diagnostic Use Only.
INTRODUCTION
The activated clotting time (ACT) measures the time required for whole blood clotting after activation of the intrinsic pathway of the coagulation cascade. The ACT test is commonly performed during invasive cardiac procedures such as cardiopulmonary bypass to monitor heparin anticoagulation therapy. Precision and reliability of the ACT test gives clinicians the confidence to make appropriate heparin dosage adjustments. However, there is no internationally accepted "gold standard" for ACT measurement and no "true" ACT value. As a result, ACT reference range and target range are method dependent and typically not interchangeable.

The majority of ACT systems, including the Hemochron Signature Elite and Medtronic ACT Plus, use mechanical methods to detect physical clot formation. In comparison, the i-STAT Kaolin Activated Clotting Time test (ACTk) uses an electrochemical sensor to amperometrically detect the conversion of thrombin substrate. Because the i-STAT System provides a direct chemical assessment of the presence of thrombin, it is less affected by environmental factors such as temperature and fibrinogen, when compared with mechanical clot detection systems.

This white paper summarizes a recent clinical study evaluating the precision and reliability of the i-STAT System's ACTk test with two other Point-of-Care (POC) systems – Hemochron Signature Elite and Medtronic ACT Plus.

OVERVIEW AND RATIONALE
This study was conducted at two tertiary teaching hospitals, which are part of Alberta Health Services. The University of Alberta Hospital in Edmonton has Canada’s largest heart transplantation program and performs more than 1300 open heart surgeries and 4000 cardiac catheterizations annually. The second site, Foothills Medical Centre in Calgary is another highly recognized Canadian teaching hospital, performing annually more than 1200 cardiopulmonary bypass procedures and 3800 cardiac catheterizations.

Prior to this study, the University of Alberta Hospital had years of experience using the i-STAT System for pediatric and adult intensive care patients. Following abbreviated studies that documented the i-STAT System's high precision and accuracy, it was implemented in the cardiology unit.

This study was initiated by the Laboratory Medicine and Perfusion Department of the hospital to verify the performance of the i-STAT System in the cardiac surgery unit and based on the findings, consolidate and standardize ACT POC testing across Alberta Health Services in the cities of Edmonton and Calgary.

The hypothesis tested in this clinical study is that the i-STAT ACTk test would demonstrate good correlation with improved precision and reliability when compared with Hemochron Signature Elite (ACT+ cartridges) and Medtronic ACT Plus (HR-ACT cartridges) across the range of potential values observed in clinical practice.

METHODS
Adults undergoing elective cardiac surgery were studied. Testing was conducted in the cardiac surgery unit of University of Alberta Hospital (48 tests) and Foothills Medical Centre (59 tests).

At University of Alberta Hospital, two i-STAT analyzers and two Hemochron Signature Elite analyzers provided all duplicate ACT results. At Foothills Medical Centre, the i-STAT System was compared with Medtronic ACT Plus. Two i-STAT analyzers were used to run all samples while a single Medtronic analyzer provided duplicate results which were statistically evaluated.

Quality control, calibration procedures and method comparison evaluation were performed as prescribed in the respective operator manuals and in accordance with CLSI guidelines.
Imprecision Analysis was conducted using the duplicate test results. Standard deviation of the duplicates can be calculated from the differences of each pair. This measure of dispersion is attractive because it is obtained from actual patient specimens. This standard deviation of duplicates provides the same standard deviation as that obtained from a single analyzer measuring a patient specimen multiple times. The imprecision calculations are made according to formulae in the book Laboratory Quality Management. In determination of imprecisions, duplicate measurements were grouped into 3 ranges: 90 to <400 seconds, 400 to 600 seconds and >600 seconds.

Accuracy Analysis was conducted to determine the strength of correlation between the i-STAT System and either the Hemochron or Medtronic systems. As there are no “standard” ACT measurements, the reference on the x-axis is defined as the median of the paired i-STAT ACT and paired comparator ACT values.

System Difference Analysis was represented with Bland-Altman plots, demonstrating the deviation of each of the systems from the median ACT.

RESULTS

A. University of Alberta Hospital, Edmonton
Imprecision Analysis
Table 1 below compares the approximate imprecisions of the i-STAT System and Hemochron Signature Elite for the 3 ranges. The coefficient of variation (CV) for the i-STAT System was less than 6% for the entire range, giving clinicians the confidence in the interpretation of results. In comparison, Hemochron Signature Elite exhibited a larger CV, which may cause misinterpretation of the heparin status, especially at higher ACT values.

Table 1

<table>
<thead>
<tr>
<th>ACT Range (s)</th>
<th>Mean (s)</th>
<th>SD (s)</th>
<th>CV (%)</th>
<th>Mean (s)</th>
<th>SD (s)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 - &lt;400</td>
<td>114</td>
<td>3.5</td>
<td>3.1</td>
<td>113</td>
<td>5.7</td>
<td>5.1</td>
</tr>
<tr>
<td>400 - 600</td>
<td>464</td>
<td>17.5</td>
<td>3.8</td>
<td>553</td>
<td>51</td>
<td>9.2</td>
</tr>
<tr>
<td>&gt;600</td>
<td>728</td>
<td>41.1</td>
<td>5.6</td>
<td>761</td>
<td>154</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Figure 1 below demonstrates the high precision of the i-STAT System with 71% of the duplicate samples varying less than 5% from each other. In comparison, Hemochron Signature Elite samples had more divergent duplicates with a fifth of the samples exceeding 15%.

![FIGURE 1: IMPRECISION ANALYSIS OF i-STAT SYSTEM AND HEMOCHRON SIGNATURE ELITE](chart_image)
Accuracy Analysis

Figure 2 demonstrates that the ACTs for both Hemochron Signature Elite and i-STAT System were highly correlated to the median ACT. The regression lines are both curvilinear with the i-STAT System values closer fitted in the 400-600s range. For values greater than 600s, Hemochron Signature Elite values appear to be dispersed and lower than the i-STAT System.

System Difference Analysis

The information provided by the difference plot (Bland Altman plot) in Figure 3 is analogous to that provided by the regression analysis. For values in 400-600s range, Hemochron Signature Elite exceeded the median ACT by up to 18% compared to i-STAT’s maximum negative difference of around 12%. For values greater than 600s, Hemochron Signature Elite was lower than the median by 20 to 30%, while the i-STAT System had similar positive deviation from the median ACT.
B. Foothills Medical Centre, Calgary

Imprecision Analysis

The *i-STAT System* and *Medtronic ACT Plus* reported comparable variation and distribution.

Of note, the *i-STAT System* duplicate testing was performed using two separate analyzers whereas the *Medtronic ACT Plus* results were from a single analyzer, running each test sample twice for duplicate results.

Table 2

<table>
<thead>
<tr>
<th>ACT Range (s)</th>
<th>Mean (s)</th>
<th>SD (s)</th>
<th>CV (%)</th>
<th>Mean (s)</th>
<th>SD (s)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 - &lt;400</td>
<td>114.3</td>
<td>0</td>
<td>0</td>
<td>172.9</td>
<td>8.5</td>
<td>4.9</td>
</tr>
<tr>
<td>400 - 600</td>
<td>458</td>
<td>16.9</td>
<td>3.7</td>
<td>503</td>
<td>14.6</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;600</td>
<td>729.1</td>
<td>28.2</td>
<td>3.9</td>
<td>694</td>
<td>38.9</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**FIGURE 4: IMPRECISION ANALYSIS OF i-STAT SYSTEM AND MEDTRONIC ACT PLUS**

Accuracy Analysis

From Figure 5, ACTs for both *Medtronic ACT Plus* and *i-STAT System* were highly correlated to the median ACT. There is little noticeable bias between the *i-STAT System* and *Medtronic ACT Plus* between 400-600s range. For values greater than 600s, *Medtronic ACT Plus* values appear to be lower than the *i-STAT System*. 
System Difference Analysis

As noted in Figure 6, for ACT values less than 400s, the i-STAT System was lower than Medtronic ACT Plus. For values in 400-600s range, Medtronic ACT Plus and i-STAT System demonstrated no definitive bias. For values greater than 600s, Medtronic ACT Plus values were lower than the median by up to 25%, compared to similar positive deviations by the i-STAT System.
DISCUSSION

The lack of an accepted gold standard for ACT makes method comparison of different systems important for clinical implementation purposes. The literature reporting such comparisons is relatively sparse. The present study was conducted as a comparison of three different POC ACT systems, including the i-STAT System, Hemochron Signature Elite and Medtronic ACT Plus at two clinical sites in Canada.

The study results demonstrate that the i-STAT ACTk test showed good correlation with improved precision and reliability when compared with Hemochron Signature Elite (ACT+ cartridge) and Medtronic ACT Plus (HR-ACT cartridge). This suggests that the therapeutic range used with the comparator products can be applied to the i-STAT System. These findings are consistent with results of two other comparison studies using the same systems, as described below.

In the first comparison study, Hemochron Signature Elite and i-STAT System duplicates showed mean differences of 9.1% and 4.3% respectively. This difference between the systems was statistically significant (p=0.0002) indicating better reproducibility with the i-STAT System (p=0.0002). Further, Hemochron Signature Elite duplicates became less precise at higher values. In another study comparing the i-STAT System with Medtronic ACT Plus, the Medtronic and i-STAT System duplicates showed mean differences of 4.9% and 3.5% respectively, indicating statistically significant difference (p=0.047). The authors noted that in their experience, duplicate Medtronic ACT Plus values failed to agree within a 12% limit approximately 13% to 15% of the time, needing to reject the test result.

Additionally, both of these studies reported that the i-STAT System was much less affected by external factors such as temperature, dilution, hematocrit, and fibrinogen levels and less dependent on user technique.

Precision of ACT results is of utmost importance in order to give clinicians the confidence to manage heparin dosing of patients undergoing invasive cardiac procedures. In this study, the i-STAT System was found to be a precise and reliable means of POC ACT testing. It correlated strongly with traditional mechanical systems for ACT measurement. In addition, the i-STAT System provides a single platform for measuring other levels monitored in the acute-care setting, such as blood gas, electrolytes, creatinine, and troponin which may help streamline POC testing within an institution.

CONCLUSIONS

• In this study, the i-STAT System demonstrated improved precision and reliability when compared with mechanical methods of POC ACT measurement, which can help clinicians make more accurate heparin dose adjustments.

• The i-STAT System is less susceptible to external factors such as temperature, dilution, hematocrit, fibrinogen levels and user technique.

• Advantages of the i-STAT System, as confirmed through this study, may allow clinicians to consolidate and standardize POC testing across tests and clinics.

KEY CONTRIBUTOR

The scientific leader and data analyst for this study at Alberta Health Services is Dr. George Cembrowski, Director of Medicinal Biochemistry, University of Alberta Hospital, Edmonton, Alberta, Canada

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Intended Use Information

The i-STAT Kaolin Activated Clotting Time (Kaolin ACT) test is an in vitro diagnostic test that uses fresh, whole blood, and is used to monitor high-dose heparin anticoagulation frequently associated with cardiovascular surgery.