Clinical Evaluation of the *i-STAT* Kaolin Activated Clotting Time (ACT) Test in Different Clinical Settings in a Large Academic Urban Medical Center

Comparison With the Medtronic ACT Plus

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Abstract

Historically, it has been difficult for hospitals to change methods for activated clotting time (ACT) testing because of differences in ACT values obtained with different instruments, wide differences in target ranges used in different procedures, and the difficulty of performing crossover studies at the bedside in critical care situations. There are limited published data comparing the *i-STAT* (Abbott Point of Care, Princeton, NJ) kaolin ACT with the Medtronic ACT Plus (Medtronic, Minneapolis, MN). The *i-STAT* system can perform ACT testing in addition to testing of a number of critical care analytes and may offer potential advantages over other ACT analyzers.

Comparison of ACT values on 121 simultaneous split-sample tests yielded an $R^2$ of 0.88 with *i-STAT* = 0.79 Medtronic + 72.0. The Pearson correlation was $R = 0.94$, indicating statistically significant correlation between the 2 methods. Based on this comparison, we were able to implement the *i-STAT* ACT throughout our institution without changing target ranges for any individual procedure.

The activated clotting time (ACT) measures the time required for whole blood clotting after activation of the intrinsic pathway of the coagulation cascade. The test is virtually always performed at the point of care, primarily to monitor heparin anticoagulation therapy, especially at high heparin concentrations when the partial thromboplastin time cannot be used. The ACT can also be used to monitor therapy with argatroban or other thrombin inhibitors.

The ACT is one of the more commonly performed point-of-care tests in settings including cardiopulmonary bypass and during invasive intravascular procedures such as percutaneous transluminal coronary angioplasty. According to a recent College of American Pathologists proficiency test survey, the most common sites where the ACT is performed include cardiopulmonary bypass (32.4% of reporting sites), cardiac catheterization (32.3%), intensive or coronary care unit (13.8%), vascular surgery or catheterization (10.1%), hemodialysis (1.1%), and other (10.2%).

The ACT is based on initiating the clotting cascade using an activator of the intrinsic coagulation pathway such as Celite or kaolin followed by measurement of the time required for clotting to occur. The reference range and therapeutic target ranges are method-dependent. ACT results obtained by different methods are not interchangeable.

Most ACT assays detect clot formation by mechanical methods including the use of a mechanical plunger (ACT Plus, Medtronic, Minneapolis, MN) or the use of displacement of a magnet (Hemochrono, ITC, Edison, NJ). In contrast, the Abbott *i-STAT* (Abbott Point of Care, Princeton, NJ) ACT uses a thrombin substrate with amperometric detection of an electrochemical product resulting from thrombin cleavage of the substrate. The *i-STAT* kaolin ACT...
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The Medtronic ACT test result was more than the results with the intraoperative hemoglobin concentration, which affects the surgery. Much of the disagreement could be attributed to the method. In another study, Medtronic high-range cartridge ACT values were lower than corresponding Hemochron 401 Celite ACT values in patients receiving heparin during cardiac catheterization.10

Of note there is no “gold standard” ACT method, and, therefore, there is no “true” ACT. For this reason, method comparisons between different test systems are particularly important. Historically, it has often been difficult for institutions to change ACT methods once an incumbent system has been in practice for a substantial period. This results from differences in the ACT values obtained on different systems and the difficulty of performing crossover studies in critical care situations. We report a comparison of the i-STAT and Medtronic ACT tests using kaolin cartridges in the settings of cardiac surgery, cardiac catheterization, and the electrophysiology laboratory.

Materials and Methods

We performed 121 simultaneous split-sample tests for ACT in our cardiac surgery unit (62 tests) and cardiac catheterization and electrophysiology laboratories (59 tests) in duplicate on the Medtronic ACT Plus using a high-range kaolin cartridge and on the i-STAT using the kaolin cartridge in the prewarm mode. Samples were collected at baseline and at varying clinically indicated time points during and/or after the procedure. Heparin was the only anticoagulant in use during the study. (None of the specimens contained direct thrombin inhibitors, such as argatroban or bivalirudin.)

All tests were performed according to manufacturers’ instructions. Medtronic tests were performed by operating room nursing personnel as part of regular patient care, whereas i-STAT tests were performed by our point-of-care coordinators or, in some cases, by Abbott implementation specialists. Specifically, arterial blood was drawn into a plastic syringe without any anticoagulant and immediately dispensed into the Medtronic sample vial and the i-STAT test cartridge. The respective devices perform the tests automatically.

A t test was used to determine the statistical significance between Medtronic and i-STAT regarding the percentage difference between duplicate test results. Linear regression and Pearson correlation coefficients were generated to assess agreement between the 2 ACT methods. A Bland-Altman plot was generated to assess for bias.

Results

Table II shows the current target ranges for ACT in use in our hospital using the Medtronic ACT along with specific qualifiers for different procedures. Of note, a wide range of ACT values are used depending on the procedure, and, in some settings, the range may be patient-specific or subject to the discretion of the individual physician. For this reason, the evaluation of the i-STAT ACT test should include the full range of potential ACT values that might be encountered across the institution. Very high ACT values beyond the reportable range of the Medtronic ACT (>999 seconds) occur relatively often in the setting of cardiac surgery, necessitating evaluation of the i-STAT up to this range.

Analysis of duplicate samples performed on the Medtronic showed a mean percentage difference between duplicates of 4.9% (range, 0%-29%), whereas for the i-STAT, the mean percentage difference was 3.5% (range, 0%-17%). This difference was statistically significant ($P = .047$), indicating that the i-STAT ACT test has slightly less imprecision than the Medtronic when testing actual patient samples. In addition, in our experience, when duplicate Medtronic values are compared with each other (as is the standard protocol), the duplicates fail to agree within a limit of 12% about 13% to 15% of the time, necessitating rejection of the Medtronic test result. Of note, assessment of imprecision for ACT cannot be made using anticoagulated samples, so an analysis of duplicate samples was used.

Figure 1A and Figure 1B show a comparison of the i-STAT ACT with the Medtronic ACT. Figure 1A includes all data points except points above 999 seconds on the Medtronic and above 1,000 seconds on the i-STAT, which occurred with 7 (5.8%) of 121 samples. Of note, in all 7 cases in which the Medtronic result was more than 999 seconds, the i-STAT result was more than 1,000 seconds. As shown in Figure 1A, we validated by crossover method the full analytic and reportable range of 70 to more than 1,000 seconds on the i-STAT. (The i-STAT literature reports a reportable range of 77-1,000 seconds.)

Defining a “normal range” for ACT testing is generally not clinically relevant. Rather, the normal range is patient-specific and clinically is interpreted to mean the patient’s
“baseline value.” For general guidance, we used a baseline range of 90 to 130 seconds on the Medtronic. Based on the data in Figure 1, this baseline range is also reasonable for use on the i-STAT. The range recommended by i-STAT is similar (74-137 seconds). The actual baseline value is patient-specific depending on the type of procedure, administration of prior anticoagulants, and other factors. In this study, we did not validate the normal reference range because it is not clinically relevant and because the collection of a large number of arterial samples from healthy donors would present a significant challenge.

Figure 1B shows an elimination regression using only the points less than 450 seconds. A cutoff of 450 seconds was chosen because this was the existing target Medtronic ACT value for surgery with cardiopulmonary bypass. Outlier values were not excluded from either analysis. Linear regression across the full range of measured values (Medtronic 70 to >999 seconds) showed an $R^2$ of 0.88, with $i$-STAT = 0.79 Medtronic + 72.0. Overall, the $i$-STAT tends to yield lower values than the Medtronic, which might be explained by the fact that the i-STAT method is not based on the detection of a stable thrombus. The Pearson correlation was $R = 0.94$ ($P < .0001$), indicating a statistically significant correlation between the 2 methods. The mean Medtronic value was 320 seconds (95% confidence interval, 284-356 seconds) compared with the mean $i$-STAT value of 312 seconds (95% confidence interval, 270-355 seconds), but this difference was not significant (2-tailed $P = .31$). With a standard target range of greater than 450 seconds for cardiopulmonary bypass, all but 2 points were in agreement (above or below target level); 2 discrepant points were close to the target cutoff. For values less than 450 seconds (Figure 1B), as typically used for ACT applications other than cardiopulmonary bypass, the comparison of the Medtronic with $i$-STAT ACT tests is more complex. ACT values in the 130- to 450-second range seem to be reasonably linear. Linear regression of the values less than 450 seconds yielded $i$-STAT = 0.85 Medtronic + 53.5. The Pearson correlation was $R = 0.84$ ($P < .0001$), again indicating a statistically significant correlation between the methods.

To illustrate the issues in comparing the 2 methods, Figure 1C shows the target range used in our electrophysiology laboratory (250-330 seconds). A total of 23 discrepant data points of 88 samples were observed (26% of samples). There was no clear bias concerning the distribution of the discrepant values. In all but a few of these, one device reported a value slightly above the target range and the other a value within the target range. Given the combined imprecision of the devices and the relatively narrow target ranges, discrepant results would be expected. This would also be true when comparing any single device against itself using duplicate values as shown in Figure 2B. By comparing Medtronic with itself in the range below 450 seconds with the target range used in our electrophysiology laboratory, we found 10 of 88 discrepant values (11%). In 1 case comparing the Medtronic with the $i$-STAT, 1 $i$-STAT value was slightly above the target range and the Medtronic value was slightly below the target range, resulting in a different classification of the patient’s heparin status with regard to target ranges.

A Bland-Altman plot Figure 3 demonstrates some negative bias for ACT values up to 800 seconds in that $i$-STAT values tend to be lower than Medtronic values, as
Figure 1. Comparison of the Medtronic and i-STAT kaolin activated clotting times for the full range of reportable values (A), for values <450 seconds (B), and using the target range for electrophysiology procedures (C).
Figure 1 (cont) Box represents the target range for Medtronic and the corresponding i-STAT values. **A**, $y = 0.7945x + 72.044$; $R^2 = 0.8776$. **B**, $y = 0.8526x + 53.5$. **C**, $y = 0.8526x + 53.5$; $R^2 = 0.8205$.

Figure 2 Comparison of duplicate Medtronic activated clotting time values using the target range (box) for electrophysiology procedures. $y = 0.9853x + 6.8795$; $R^2 = 0.9764$. 
noted. At more than 800 seconds, \textit{i-STAT} values tend to be higher than Medtronic values. However, differences in the 800-second range have less clinical relevance because they are not near a clinical decision cutoff.

**Discussion**

In this study, we evaluated the \textit{i-STAT} kaolin ACT in the prewarm mode in comparison with the Medtronic HemoTec ACT across a full range of reportable values in different clinical applications, including cardiac surgery, cardiac catheterization, and the electrophysiology laboratory. Studies comparing different ACT methods are complicated by several factors. First, the validations must be carried out at the bedside in critical care situations. Second, the target ranges vary significantly depending on the clinical procedure, requiring crossover of different methods over a wide analytic range. Finally, ACT tests may use different activators such as Celite or kaolin, some devices such as the Medtronic use a high-range and a low-range cartridge, and some devices offer the option of prewarm and no prewarm modes. Consequently, there are a number of permutations that could be evaluated.

A limited amount of published data exist comparing the \textit{i-STAT} Celite cartridge ACT test with the Hemochron method. Schussler et al\textsuperscript{7} compared the \textit{i-STAT} ACT with the Hemochron ACT in 128 cases but did not specify which cartridge (Celite or kaolin) was used or the \textit{i-STAT} mode (prewarm or no prewarm). They reported an overall high degree of correlation ($R^2 = 0.8$) with excellent agreement in the low range (<250 seconds). Values in the higher range were statistically different but showed a high degree of correlation. They interpreted the difference as small and not clinically significant. Schussler et al\textsuperscript{7} also reported a high level of correlation between the Hemochron and the \textit{i-STAT} ACT in patients receiving bivalirudin. Finally, Paniccia et al\textsuperscript{8} reported a comparison of the Hemochron with the \textit{i-STAT} ACT using Celite cartridges on 168 samples. They concluded that the \textit{i-STAT} ACT values were "quite similar to the Hemochron ACT."\textsuperscript{8}

There are relatively limited published data comparing the \textit{i-STAT} ACT with the Medtronic device. One study compared the \textit{i-STAT} Celite ACT test with the Medtronic device in children and showed poor agreement, but the data were largely limited to ACT values less than 250 seconds and much of the difference in the methods was attributed to the effect of variable hemoglobin concentrations on the Medtronic.\textsuperscript{9} We were not able to find published data comparing the Medtronic ACT with the \textit{i-STAT} at values more than 250 seconds or any published data using kaolin cartridges. At the start of our study, Medtronic kaolin cartridges were in clinical use throughout our institution for ACT testing.

The results from our study comparing the Medtronic with the \textit{i-STAT} ACT for the full range of values (70 to >999 seconds) showed excellent correlation ($R^2 = 0.88$ and $R = 0.94$). For values up to 800 seconds, a negative bias favoring lower values on the \textit{i-STAT} was observed. Presumably, this was because the \textit{i-STAT} detects the formation of thrombin, which occurs sooner than the formation of a stable clot as
detected by mechanical clot detection methods. The correlation between the 2 methods was statistically significant, and the difference in values between the Medtronic and i-STAT was not significant.

By using a target range of more than 450 seconds for cardiopulmonary bypass, we found only 2 discrepant values, but these values were close to the target and, therefore, clinically irrelevant. For values less than 450 seconds, the comparison of methods is more complex. Many procedures use target values in this lower range (Table 1), and some are fairly tightly defined. Overall, there was good correlation (\(R^2 = 0.82\)) with a statistically significant correlation. However, for any given procedure (eg, electrophysiology as discussed in the “Results” section), there will be discrepant values at which the 2 methods may classify a patient’s heparin status differently (ie, above vs below target). In most cases, one method will be within the target range and the other slightly above the target range. However, there was 1 value reported by one system as below target and by the other system as above target. Nevertheless, for values less than 450 seconds, the agreement was not as good as for values more than 450 seconds.

Because there is no true ACT value, there is no way to ascertain which method is “correct.” The important point is whether there is enough general agreement between the 2 methods to permit changing from one method to another without jeopardizing clinical care. In our hospital, all of the specialty units participating in this study (cardiac surgery, cardiac catheterization, and electrophysiology) determined that the ACT correlation is clinically acceptable and have subsequently transitioned from the Medtronic to the i-STAT method with no need to change the target ranges shown in Table 1.

The i-STAT ACT test has a number of advantages compared with ACT tests based on mechanical clot detection as described by Schussler et al. First, the i-STAT is much less affected by temperature, dilution, and fibrinogen levels and is less dependent on user technique (although, in some circumstances, insensitivity to fibrinogen could also be a disadvantage). In addition, in our experience, when duplicate Medtronic values were compared with each other, the duplicates failed to agree within a limit of 12% about 13% to 15% of the time, necessitating rejection of the Medtronic test results. Finally, the i-STAT requires less liquid quality control (once per month or with each new lot vs weekly for Medtronic), which simplifies regulatory compliance.

The i-STAT can also perform other tests that may be useful in the acute care setting, such as blood gas levels, electrolyte levels, lactate levels, international normalized ratios, and creatinine and troponin levels. The i-STAT, therefore, offers many potential advantages over mechanical clot detection methods and may permit consolidation of point-of-care testing in critical care settings to a single instrument platform.

This latter feature streamlines management of the point-of-care testing program and simplifies regulatory compliance. As a final caveat, we point out that our data are limited to i-STAT kaolin cartridges in the prewarm mode. We also have not evaluated the i-STAT ACT for use in extracorporeal membrane oxygenation. For these reasons, each institution must evaluate its intended ACT method under the specific conditions of use (eg, kaolin vs Celite and prewarm vs no prewarm) for the specific clinical indication for which it will be used.

Concerning the comparative cost of the Medtronic vs the i-STAT ACT tests, at first glance, the Medtronic seems less expensive (Medtronic, $1.98 per cartridge; i-STAT, $4.10 per cartridge). However, the Medtronic requires 2 levels of liquid quality control every week, whereas the i-STAT requires liquid quality control only every month. Furthermore, the Medtronic quality control is difficult to run, and there are many failures. For these reasons, the i-STAT would be slightly less expensive in low- to moderate-volume settings and slightly more expensive in high-volume settings.

Further study is needed to determine i-STAT ACT responses to direct thrombin inhibitors such as argatroban. Previous work revealed that ACT responses to the direct thrombin inhibitor argatroban were much different from the responses to heparin when comparing the Medtronic (high-range cartridge) with the Hemochron 401 (Celite CA519 tube). Clinicians might also wonder how well the i-STAT ACT compares with the Medtronic ACT in “problem” patient cases, for example, patients in whom the ACT prolongs much more than expected or patients with heparin resistance, in whom the ACT does not prolong as much as expected (as can be seen during acute phase reactions). The results of the present study suggest that the Medtronic and i-STAT ACT behave similarly at very prolonged levels because all Medtronic ACT values of more than 999 seconds were more than 1,000 seconds on the i-STAT. Between 800 and 1,000 seconds, the i-STAT values tended to be lower than those of the Medtronic. Further study can be performed in specific patients with heparin resistance, but there is no reason at this time to suspect that the i-STAT ACT will behave differently from the Medtronic ACT because the correlation of the 2 devices in the low range was acceptable.

Excellent correlation was found between the i-STAT ACT (kaolin cartridge in the prewarm mode) and the Medtronic ACT (high-range cartridge). The agreement between the methods was acceptable for clinical use.
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References