

Original Article

Hemochron vs. Hemotec Kaolin ACT Comparison with Aprotinin Use in Congenital Heart Surgery

Jodie M. Ecklund, CCP; Mary M. McCall, CCP; Rhonda S. Southworth, CCP; Mindy M. Blackwell, CCP; Jeffrey B. Riley, CCT, CCP

Medical University of South Carolina, College of Health Professions, ECT Program, Charleston, South Carolina

Keywords: activated clotting time, celite, kaolin, aprotinin, cardiopulmonary bypass, congenital heart surgery

ABSTRACT

Between July 1994 and January 1995, ten patients underwent reoperative cardiac surgery with cardiopulmonary bypass for correction of various congenital anomalies. The patients' ages ranged from 0.17 to 34 years. Aprotinin was used according to surgeon protocol (200 mg/m² body surface area initial loading dose and in pump prime, and 50 mg/m² hourly infusion). The purpose of this study was to compare the simultaneous ACT values obtained from the Hemotec cartridge and the Hemochron kaolin tube.

A 3 ml blood sample was drawn and duplicate ACTs run at four time periods during the procedure: 2 ml in a prewarmed kaolin Hemochron tube and 0.4 ml in each well of a pre-warmed Hemotec cartridge. Information recorded at each time period included: event [pre-CPB, on-CPB hypothermia, on-CPB rewarming, post-CPB], temperature, and ACT values from each machine. A total of 74 paired samples were analyzed. Two-way ANOVA was used to compare the values. Multiple comparison tests using the Bonferonni method were performed to maintain the Type I error rate at 0.05. Regression, correlation, and residual analyses were performed. Cohen’s kappa statistic was used to assess the degree of agreement between the two devices.

There was a statistically significant difference between the ACT values obtained between the two devices (p<.01); however, the correlation between the values was high and significant (r=0.841, p<.01). The Hemotec was an average of 86 seconds lower than the Hemochron. The kappa statistic was 0.688, which indicates good agreement. The differences between these two devices have been previously reported using the celite Hemochron tubes, and it appears that there is still a difference when both tubes contain kaolin. Differences in the method of clot detection, differences in sample volume, and differences in the adsorption of aprotinin may explain the differences observed in this study. The Hemochron kaolin ACT is an acceptable alternative to the Hemotec ACT for monitoring heparinization when aprotinin is in use in congenital heart surgery.

Address correspondence to:
Jodie Ecklund, CCP
MUSC-ECT Program
101 Doughty St., 2nd floor
Charleston, SC 29401

Article available at https://j ect.edpsciences.org or https://doi.org/10.1051/ject/1996283123
INTRODUCTION

The activated clotting time (ACT) is a measure of the extrinsic clotting cascade and has been shown to be affected by many factors: temperature, levels of heparin and heparin cofactors, circulating anticoagulants, platelet count and activity, hemodilution, plasminogen, and calcium. There is also variation within an individual (patient and user), and variation due to differences in the devices. There are currently two automated systems available that measure the ACT: the Hemochron and the Hemotec.

The Hemochron utilizes 2 ml of whole blood added to a tube containing an activator. Celite, kaolin, and glass particles are all activators available for this device. A clot is detected when a magnet within the tube is displaced from a detector in the machine. The Hemotec utilizes 0.4 ml of whole blood added to each of two wells of a cartridge which contains an activator, a buffer, and calcium chloride. The activator used in this device is liquid kaolin. A clot is detected by a change in the rate of descent of a plunger in the cartridge.

In 1990, Dumond et al. correlated the values from the Hemotec kaolin cartridge, the Hemochron celite tube and the Sonoclot celite cup and found significant differences between both the means and standard deviations of the devices (1). The correlations between the devices were low, especially in the heparinized samples. They concluded that differences in the mechanism of clot formation and use of different activators may explain the differences between the devices as well as the differences in the reproducibility of the devices and that the values obtained from the three machines should not be interchanged.

In 1994, Avendano and Ferguson compared the Hemochron and Hemotec ACT values in patients having coronary angioplasties (2). They observed higher correlations than Dumond, but still reported significant differences between the machines and also concluded that the values should not be interchanged between the devices. Target values for one machine should not be used for the other.

With the introduction of aprotinin into cardiac surgery, the differences in the machines can be further evaluated. Aprotinin is a serine protease inhibitor which is isolated from bovine lung. Aprotinin was first introduced into cardiac surgery in Europe in the 1980s and in the United States in 1993. Since then, aprotinin has been used in increasingly greater frequency to decrease bleeding and blood product administration in both first time and reoperative cardiac procedures. Determination of the efficacy of aprotinin in pediatric patients has been limited to a few published studies; however, the results have been similar to results found in adult patients (3,4). The three interrelated mechanisms described to limit the bleeding during and after bypass procedures are: inhibition of contact activation, antifibrinolytic activity, and inhibition of platelet dysfunction.

Since the introduction of aprotinin into cardiac surgery, many studies have been published about the effect of aprotinin on anticoagulation as measured by the ACT. In 1990, deSmet and associates reported a prolongation of the celite ACT with aprotinin use and suggested that decreased heparinization may be possible with aprotinin use (5). However, further in vitro research by van Oeveren, et al. indicated that aprotinin affects the extrinsic coagulation system. They advised against the use of the ACT to monitor heparinization, since the ACT is a measure of the speed of extrinsic coagulation pathway activation (6). A study done by Najman, et al. concluded that the anticoagulant effect of aprotinin as determined by the celite ACT is not heparin-like and does not affect thrombin formation and the coagulation cascade as heparin does. Therefore, it is not appropriate to assume that the increased ACT warrants reduced heparinization (7).

MATERIALS AND METHODS

The study sample consisted of ten patients undergoing cardiopulmonary bypass (CPB) for reoperative cardiac procedures in whom aprotinin was used from July 1994 to January 1995. The patients’ ages ranged from 0.17 to 34 years. The extracorporeal circuits (ECC) consisted of a membrane oxygenator1 with venous reservoir, cardiotomy2, custom tubing pack3, 4:1 blood cardioplegia system4, and an ultra-filtrator5. Modified ultrafiltration was used in six of the patients after discontinuation of CPB.
as described by Groom, et al (11). Degree of hypothermia depended upon the complexity of the operative procedure and ranged from mild to extreme. Alpha-stat blood gas management was used in all patients. A heparin loading dose of 300 u/kg was administered to each patient by the anesthesiologist. Heparin was added to the ECC prime to obtain an on-bypass heparin concentration greater than 3.5 u/ml. Kaolin ACTs were maintained greater than 480 seconds throughout bypass and extra heparin was given only when the ACT fell below 480 seconds. The aprotinin protocol was as follows: 200 mg/m² body surface area loading dose, 200 mg/m² in the pump prime, and 50 mg/m²/hour continuous infusion until protamine administration.

A 3 ml blood sample was drawn from the radial arterial line or the ECC sampling manifold and duplicate ACTs were run at four time periods throughout the procedure. Two milliliters of blood was added to a pre-warmed gold topped kaolin Hemochron tube and 0.2 ml was added to each well of a pre-warmed Hemotec cartridge. Low range Hemotec cartridges were used for non-heparinized samples. The following information was recorded at each sample period: event, temperature, Hemochron ACT value, and Hemotec value. The events of interest were pre-CPB, on-CPB during hypothermia, on-CPB during rewarming, and post-CPB post-protamine administration. Demographic information from each patient was also recorded.

**DATA ANALYSIS**

The data were entered into a computerized spreadsheet and transferred to a statistical program for analysis. All Hemochron ACT values >1000 seconds were converted to 999 seconds. ACT values of 999 seconds and >1000 seconds have no clinical difference. Converting the Hemochron values will increase the correlations between the devices. Analysis of variance was used to compare the ACT values. Two-way analysis of variance was specifically chosen to compare the values and determine whether there was an event effect on the difference in the ACT values and whether there was an interaction. Multiple comparison tests with the Bonferonni method were used to maintain the Type I error rate at 0.05. Bartlett’s F test was used to compare the standard deviations. Regression, correlation, and residual analysis were performed. Cohen’s kappa statistic (k) was also used to assess the degree of agreement between the two devices. A p < 0.05 was chosen to assess statistical significance.

**RESULTS**

Demographic information for the ten patients is shown in Table 1. Descriptive statistics for all ACT values are shown in Table 2. There are no significant differences in the means or standard deviations between the two devices. Figure 1 is a scatterplot of all of the ACT values. The correlation between the two devices when all of the values are included is significant at 0.81 (p < 0.01). The values fall into three distinct groupings: non-heparinized values, heparinized values, and “faulted” values. Descriptive statistics for the non-heparinized ACT values are shown in Table 3 and the heparinized ACT values are shown in Table 4. Both the heparinized and non-heparinized ACT values are significantly different between the two devices (p < 0.05). Analysis of variance revealed significant differences between the devices, but there was no significant interaction between device and event. The standard deviations were not significantly different for the non-...
heparinized samples, but were significantly greater in the Hemochron group for the heparinized samples (p < 0.05). Figure 2 is a scatterplot of the non-heparinized values (r=0.85, p < 0.01) and Figure 3 is a scatterplot of the heparinized values (r=0.66, p < 0.01). Removing all of the faulted values from the heparinized values does not increase the correlation between these values. Figure 4 plots the difference between the ACT values against the Hemochron ACT value. The increased variation at higher ACT values can be more easily seen here. This graph also shows that the Hemochron usually read higher than the Hemotec value. It can also be seen in Figure 4 that at ACT values less than 600 seconds, the variation around the zero line is minimal (10-15% of an acceptable ACT on bypass of 480 seconds).

Cohen's kappa statistic was calculated using the following formula (12):

\[
k = \frac{p_o - p_e}{1 - p_e}
\]

where \( p_o \) is the observed probability of agreement and \( p_e \) is the expected probability of agreement by chance. The computed statistic was 0.688, which indicates "good agreement."

**DISCUSSION**

Several hypotheses have been offered to explain the differences in the ACT values obtained from the various automated machines available including: differences in sample volume, activators, and mechanisms of clot formation (1). For this study, both devices utilized kaolin as their activator, so this cannot explain all of the differences found in this study; however, the other differences between devices still exist.

Two ml of cold blood may take longer to warm to 37°C than 0.2 ml, even in pre-warmed tubes; therefore, the effect that hypothermia has on the ACT may be more evident in the device that uses the larger volume. This would result in higher ACTs in the Hemochron device which has been reported in several studies.

The Hemochron requires a clot to form that breaks the magnet in the tube away from a detector in the machine. This may require a stronger clot than is necessary for the Hemotec device to signal a clot. The Hemotec may be more sensitive to clot formation and detect a clot before the Hemochron would. This

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**Table 3: Descriptive statistics for non-heparinized ACT values. **

<table>
<thead>
<tr>
<th>DEVICE</th>
<th>n</th>
<th>MEAN*</th>
<th>STD DEV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochron</td>
<td>15</td>
<td>121.5</td>
<td>27.7</td>
</tr>
<tr>
<td>Hemotec</td>
<td>14</td>
<td>106</td>
<td>25.6</td>
</tr>
</tbody>
</table>

*p<0.01

**Table 4: Descriptive statistics for heparinized ACT values. **

<table>
<thead>
<tr>
<th>DEVICE</th>
<th>n</th>
<th>MEAN*</th>
<th>STD DEV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochron</td>
<td>59</td>
<td>913</td>
<td>435.8</td>
</tr>
<tr>
<td>Hemotec</td>
<td>55</td>
<td>644</td>
<td>248.8</td>
</tr>
</tbody>
</table>

*p<0.01

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**Figure 2: Scatterplot of unheparinized ACT values for Hemochron and Hemotec**

![Figure 2: Scatterplot of unheparinized ACT values for Hemochron and Hemotec](image)

\( r = 0.845, p < 0.01, n = 14 \)

**Figure 2: Scatterplot of heparinized ACT values for each device**

![Figure 2: Scatterplot of heparinized ACT values for each device](image)

\( r = 0.658, p < 0.01, n = 55 \)
would result in lower ACT values in the Hemotec machines.

Both devices use 12 mg kaolin as the activator (low range Hemotec cartridges use 7 mg); however, the Hemotec kaolin is liquid, and the Hemochron kaolin is solid. The liquid activator appeared to mix more completely with the blood than the solid activator. It was noted in this study that even after vigorously shaking the Hemochron kaolin tube 10 times, there would still be visible undissolved kaolin sticking to the sides of the tube. This would result in variable adsorption of the aprotinin from the sample, which would leave varying aprotinin concentration left in the blood sample to increase the ACT.

The instructions for use from both device disposables state that the kaolin tubes/cartridges are precise in low to moderate aprotinin levels (<180 KIU/ml). As the aprotinin concentration increases (toward 500 KIU/ml), the ACT values become less precise. The aprotinin concentrations were not measured in this study, but were estimated by dividing the sum of the aprotinin loading dose and the ECC prime dose by the estimated patient blood volume. The average estimated concentration was 818 KIU/ml, which is greater than the upper limit on the kaolin tubes. However, this estimate does not take into account the pharmacokinetics of aprotinin or the fact that ultrafiltration was used in all cases (ultrafiltration removes aprotinin (13)), so this may not have actually had an effect on the ACT values recorded. Aprotinin concentrations would have to be measured to evaluate the possibility of confounding due to this variable.

There are many variables that affect an ACT measurement. Further study would have to be done to evaluate the effect of each of the possible confounders discussed on the differences between the values from each machine. The ACT values obtained from the two machines using kaolin as the activator were significantly different from each other, but the correlations were high and significant. The correlations were improved over those found in Dumond’s study, which suggests that the differences in the type of activator did contribute to the differences observed between machines. The values should not be interchanged between machines, but since they highly correlate and the differences are small at ACT <600 seconds, Hemochron kaolin tubes are an acceptable method of measuring the ACT when aprotinin is in use.

ACKNOWLEDGEMENTS

The authors would like to thank the faculty and students in the MUSC Extracorporeal Circulation Technology Program for their assistance in data collection and for their helpful critiques during the preparation of this manuscript.

REFERENCES