Use of the Activated Partial Thromboplastin Time for Heparin Monitoring

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Abstract

The objectives of the present study were to evaluate the relationship between heparin concentration and activated partial thromboplastin time (aPTT) results, define a heparin concentration–derived therapeutic range for each aPTT instrument, compare aPTT- and heparin concentration–guided dosage adjustment decisions, and compare laboratory- and bedside aPTT–guided decisions. In phase 1, 102 blood samples were analyzed for bedside and laboratory aPTTs and heparin concentration (used to establish aPTT therapeutic range). In phase 2, 100 samples were analyzed in the same manner. Correlations for aPTT compared with heparin ranged from 0.36 to 0.82. Dosage adjustment decisions guided by the aPTT agreed with those based on heparin concentration 63% to 80% of the time. Laboratory and bedside aPTT dosage adjustment decisions agreed 59% to 68% of the time. The correlation of aPTT with heparin concentration and agreement between aPTT- and heparin-guided decisions vary with the aPTT instrument. Decisions guided by laboratory aPTT results often disagree with decisions guided by bedside aPTT results.

Unfractionated heparin therapy most often is monitored using the activated partial thromboplastin time (aPTT).1 The aPTT traditionally was conducted in a central laboratory, but technology has allowed it to become a portable bedside anticoagulation test. Historically, the aPTT therapeutic range was defined empirically as 1.5 to 2.5 times a control. During the past several years, limitations to using an empiric aPTT therapeautic range have been recognized.2 The College of American Pathologists (CAP) has provided consensus recommendations about the establishment of the aPTT therapeutic range. Individual laboratories should define the aPTT therapeutic range as the range that corresponds to a heparin concentration of 0.2 to 0.4 U/mL by protamine titration or 0.3 to 0.7 U/mL by anti–factor Xa analysis.2 With this approach, the aPTT serves as a surrogate marker for heparin concentration.

Several investigators have assessed the relationship between heparin concentration and aPTT results. Regression analysis has been performed on heparin concentration vs aPTT and heparin concentration vs log aPTT. The $r^2$ values have ranged from 0.17 to 0.79 for heparin and aPTT and 0.38 to 0.77 for heparin and log aPTT.3-10 The variability in the reported strength of the relationship between heparin and aPTT can be explained by methodologic differences, including type of heparin assays, aPTT instruments and reagents, sample size, and data transformation techniques. It is evident that the relationship between heparin and aPTT is not always strong.

Another approach to evaluating the use of aPTT for heparin monitoring is to compare clinical decisions based on aPTT with those based on heparin levels. Studies that have compared aPTT-derived decisions using an empiric therapeutic range (1.5-2.5 times control) with those based on heparin have reported agreements of 57% to 68%.3,11 One
would suspect the use of a heparin concentration–derived aPTT therapeutic range would provide a higher level of agreement between aPTT- and heparin concentration–guided decisions. Unfortunately, the results of one clinical trial using a heparin concentration–defined aPTT therapeutic range reported an agreement of only 47%.4 The overall goal of the present study was to assess the performance of several aPTT instruments for monitoring unfractionated heparin therapy. The optimal aPTT instrument would be defined as that with the highest correlation with heparin concentration and the best level of agreement with heparin concentration in clinical decision making.

The objectives of the present study were to evaluate the relationship between heparin concentration and aPTT results using laboratory-based and bedside instruments, define a heparin concentration–derived therapeutic range for each aPTT instrument, compare aPTT-guided and heparin concentration–guided dosage adjustment decisions, and assess the level of agreement between the laboratory-based and bedside aPTT results.

Materials and Methods

This prospective study was approved by the human investigation committee at William Beaumont Hospital, Royal Oak, MI. Informed consent was obtained from all patients before enrollment. All patients for whom continuous-infusion intravenous heparin therapy was initiated were screened for inclusion. Patients were excluded for the following reasons: (1) receipt of continuous heparin infusion for longer than 48 hours, (2) receipt of (within the past 7 days) any agents that may have affected the aPTT (ie, nonsteroidal anti-inflammatory drugs, antplatelet agents, glycoprotein IIb/IIIa inhibitors, or thrombolytics), (3) receipt of more than 325 mg of aspirin daily, (4) receipt of more than 1 dose of warfarin, or (5) known coagulation disorders (including anticardiolipin antibodies, lupus anticoagulants, and antithrombin deficiency). The study was conducted in 2 phases. In phase 1, 100 patients were to be enrolled. The goals of phase 1 were to determine correlations between each aPTT test and plasma heparin concentration and to determine a heparin concentration–defined therapeutic range for each aPTT instrument. One blood sample from each patient receiving heparin was obtained. Two bedside aPTTs, a laboratory-based aPTT, and a plasma heparin concentration were performed on each blood sample.

Venous blood samples were obtained from each patient during a scheduled venipuncture, using standard-of-care techniques. Since one of the aPTT bedside devices used whole blood, all blood samples were initially drawn into a syringe and then transferred to the appropriate container. A 2-mL flush syringe was drawn and discarded. A second plastic syringe was then used to draw a total of 5 mL of blood. The first bedside aPTT was performed on the CoaguChek Plus System (CPS, Boehringer Mannheim, Indianapolis, IN) immediately after the specimen was drawn, using 1 drop of nonanticoagulated whole blood. The average time from sample acquisition to the performance of the CPS test was less than 30 seconds.

The balance of the whole blood specimen was transferred via a 21- to 23-gauge needle into a glass Vacutainer tube (Becton Dickinson, Franklin Lakes, NJ) containing 3.2% buffered sodium citrate within 60 seconds of obtaining the specimen. The whole blood and anticoagulant were gently mixed by slowly inverting the tube 4 to 6 times.

The second bedside aPTT was then performed using the Thrombolytic Assessment System (TAS, Cardiovascular Diagnostics, Raleigh, NC). A drop of blood from the Vacutainer tube was removed via transfer pipette and placed on the TAS aPTT test card.

The balance of the citrated whole blood was transported at room temperature to the central coagulation laboratory where an automated aPTT was performed. The whole blood was first centrifuged at 3,500 rpm (2,450g) for 10 minutes to provide platelet-poor plasma. Most samples (>95%) were centrifuged within 1 hour of sample collection. Platelet counts were performed randomly on plasma samples to ensure platelets remained fewer than 10 × 10^9/L. The laboratory-based aPTT then was performed using the Organon MDA-180 Analyzer (MDA) and MDA Platelin L reagents (Organon Teknika, Durham, NC). The remaining plasma was transferred to a clean plastic tube and centrifuged again at 3,500 rpm for 10 minutes to obtain platelet-free plasma. The top portion of the plasma sample was then transferred to a second plastic tube, which was frozen at −70°C for batch analysis of heparin concentration.

In phase 2, 100 patients were to be enrolled. The goals of phase 2 were to assess the appropriateness of dosage adjustment decisions in heparin therapy based on the aPTT test result compared with the corresponding plasma heparin concentration and to assess the level of agreement between laboratory-based and bedside aPTT results. Blood sampling and testing techniques were identical to those in phase 1. Once all samples from both phases were collected, the plasma was analyzed for heparin concentration. Plasma heparin concentration was determined by anti–factor Xa activity on the MDA.

The CPS was performed using 1 lot of cartridges; the TAS, using 2 lots of cards; and the MDA, using 1 lot of thromboplastin reagent throughout the study. All heparin curves and plasma concentrations were performed using the same lot of reagent (Coatest Heparin, Chromogenix AB, Möln达尔, Sweden). Two lots of heparin (39-724-FW for
Data Analysis

The data from phase 1 were analyzed for correlation between each aPTT test and plasma heparin concentration using the Pearson product moment correlation test. Correlations were performed on linear and log-transformed aPTT results. A Fisher z transformation was performed to determine whether there was a significant difference between the linear and log correlation coefficient for each aPTT instrument and whether the correlation for any one aPTT instrument was significantly stronger.12,13 Regression analysis was performed on both sets of data (linear and log transformed) to determine the heparin concentration–derived therapeutic range (aPTT results that correspond to plasma heparin concentrations of 0.3-0.7 U/mL by anti–factor Xa assay). Outliers (defined as data points whose vertical distance from the regression line was greater than 3 times the SD) were removed from the analysis. Calculated linear therapeutic ranges were used in the analysis of phase 2 data. By changing the regression so that the heparin concentration became the dependent variable, the 95% confidence and prediction intervals around the predicted heparin level (for a given aPTT) were calculated. The confidence interval estimates the mean heparin concentration for any given aPTT value (ie, for a given aPTT, you would be 95% confident that the mean would fall within this interval). The prediction interval estimates the range of heparin concentration for any given aPTT value (ie, for a given aPTT you would be 95% confident that the actual heparin level would fall within this interval).

A decision analysis for the appropriateness of a dosage adjustment decision based on an aPTT test result compared with the decision using the paired plasma heparin concentration was conducted on data from phase 2. A dosage adjustment decision was defined as the action taken on receipt of an aPTT or heparin assay result. This analysis assumes that the decision about dosage adjustment based on heparin concentration is the correct decision. A decision based on the aPTT test result could agree with the corresponding decision based on the plasma heparin concentration (ie, both increase, decrease, or indicate no change necessary) or disagree. Disagreement could result in potential over- or underanticoagulation. For example, an aPTT test result of 45 seconds (assuming a therapeutic aPTT range of 50-100 seconds) indicates a dosage increase is needed, while the corresponding plasma heparin concentration of 0.4 U/mL indicates a change is not required. This creates a scenario in which the heparin dose is increased when the heparin level is therapeutic, resulting in potential overanticoagulation. Fisher exact tests were performed on the number of agreements and disagreements resulting from the decision analysis between aPTT result and plasma heparin concentration and the number of disagreements resulting in potential underanticoagulation and potential overanticoagulation.

The relationship between bedside aPTT instruments (TAS and CPS) and the laboratory-based aPTT instrument (MDA) was assessed by the Pearson product moment correlation, the Fisher exact test to assess agreement in decisions guided by laboratory aPTT results vs beside aPTT results (assuming the laboratory aPTT result as the “gold standard”), and Bland-Altman analysis.14 The Bland-Altman analysis was performed to determine the bias (mean difference) and limits of agreement (bias ± 2 SDs).

Results

Demographic data are shown in Table 1. A total of 106 patients were enrolled in phase 1; however, only 102 patients were evaluated. Reasons for exclusion were as follows: the blood sample was lost, 1; no heparin assay performed, 1; hyperlipidemic sample, 1; and hemolyzed sample, 1. A total of 103 patients were enrolled in phase 2, of whom 100 were evaluated. Two excluded blood samples were hemolyzed, and 1 was hyperlipidemic.

The interrun coefficients of variation (CVs) were calculated for each aPTT test and heparin assay. CVs were obtained from liquid quality control plasma samples run daily throughout the study. The CVs were 6% to 12%, 3% to 6%, 2% to 4%, and 2.3% for the TAS, CPS, MDA, and heparin assay, respectively.

Phase 1

Correlation coefficients for linear and log-transformed data are shown in Table 2. No significant differences were found between the linear and log correlation coefficients for
any individual aPTT instrument. The linear correlation between the aPTT result and heparin concentration was significantly stronger for the MDA compared with the TAS (\(P < .0001\)) and the CPS (\(P = .0013\)). The regression lines and equations are shown in **Figure 1**, **Figure 2**, and **Figure 3** for the linear relationship. The linear and log-derived therapeutic ranges for each test are shown in **Table 3**. Assuming an aPTT of 60 seconds, the 95% confidence and prediction intervals around the predicted heparin level were 0.33 to 0.45 U/mL and –0.05 to 0.83 U/mL for the CPS, 0.54 to 0.62 U/mL and 0.01 to 1.15 U/mL for the TAS, and 0.36 to 0.44 U/mL and 0.09 to 0.71 U/mL for the MDA.

**Phase 2**

Results of the agreement between heparin dosage adjustment decisions based on the aPTT result compared with heparin concentration are shown in **Table 4**. Decisions based on the MDA agreed with the heparin concentration more often than decisions based on the CPS (\(P = .0098\)) or TAS (\(P = .0097\)). The level of agreement was not different between the CPS and the TAS (\(P = 1.00\)). When aPTT-guided decisions disagreed with heparin concentration–guided decisions, the potential for underanticoagulation occurred more frequently with the TAS compared with the laboratory aPTT (\(P < .0011\)).

The linear correlation between the laboratory aPTT instrument (MDA) compared with the bedside aPTT instruments was 0.82 for the CPS and 0.76 for the TAS. The agreement between the laboratory and bedside instruments is shown in **Table 5**. The CPS result would lead to the same clinical decision as the MDA aPTT in 68% of cases, while the TAS would agree with the MDA aPTT in 59.2% of cases. The level of agreement did not differ between bedside instruments (\(P = .2375\)). Bland-Altman plots of bedside vs laboratory aPTT instruments are shown in **Figure 4** and **Figure 5**. Evaluation of Figure 5 reveals a noticeable increase in bias between the MDA and TAS as the level of anticoagulation increases. Bias (and limits of agreement) for the CPS was –8.0 seconds (–48.3 to 32.3 seconds) and for the TAS was 12.4 seconds (–35.6 to 60.5 seconds). Biases were different (\(P < .001\)) between the two bedside instruments.
Discussion

Several factors, such as alterations in the level of heparin-binding proteins, antithrombin deficiency, and prothrombotic conditions, are known to affect the use of aPTT for heparin monitoring and contribute to the variable strength of the relationship between aPTT and heparin concentration. The CAP consensus conference on heparin monitoring suggests that less than half of the variability of aPTT can be explained by differences in heparin concentration. In the literature, coefficients of determination ($r^2$) for the aPTT–heparin concentration relationship have varied significantly. In the present study, $r^2$ values ranged from 0.13 to 0.67. In addition to the aforementioned physiologic factors, the aPTT result also may be affected by sample collection, transportation, and preparation techniques. An effect on the aPTT result then would influence the relationship between aPTT and heparin concentration. Guidelines for performing the laboratory-based aPTT test are available from the National Committee for Clinical Laboratory Standards (NCCLS). In the present study, blood was collected into syringes for all anticoagulation tests. Since one of the bedside aPTT tests (CPS) requires whole blood, the syringe system allowed all coagulation tests to be run on the same sample of blood. The current NCCLS guidelines recommend that blood for coagulation testing be collected directly into a tube containing an anticoagulant; however, the syringe system is not prohibited. To minimize variability in aPTT results from sample processing, efforts should be made to adhere to the NCCLS guidelines whenever possible. In the present study, the length of time from sample acquisition to placement in a tube containing an anticoagulant was within NCCLS guidelines. In addition, more than 95% of samples were transported to and processed by the central coagulation laboratory within 1 hour as recommended.

Two studies have evaluated the predictability of a heparin level from the aPTT. Rosborough evaluated results of paired aPTT and heparin levels in 694 patients receiving unfractionated heparin. By using a Bland-Altman analysis, the heparin level predicted by the aPTT value had a 95% limit of agreement with the actual heparin level of ± 0.39 U/mL. Baker et al found that for a reported aPTT of 60 seconds, the predicted heparin level was 0.53 U/mL with a 95% confidence interval of 0.44 to 0.63 U/mL and a prediction interval (estimate of the anti–factor Xa level for a given patient from an aPTT value) of 0.05 to 1 U/mL. In the
present study, an aPTT of 60 seconds for the MDA corresponded to a heparin level of 0.4 U/mL with a 95% confidence interval for the predicted heparin level of 0.37 to 0.44 U/mL and a prediction interval of 0.09 to 0.71 U/mL. The wide variability in the strength of the relationship between aPTT and heparin concentration and the poor ability to predict heparin levels from aPTT raises concern.

The present study established a heparin concentration–defined therapeutic range for each aPTT instrument. The width of the therapeutic range varied from a low of 8 seconds for the TAS to a high of 42 seconds for the MDA. Taylor et al determined a heparin concentration–defined aPTT therapeutic range for the MDA and TAS instruments. The ranges were 61 to 93 seconds for the MDA and 56 to 73 seconds for the TAS. The differences in the therapeutic range demonstrate the lack of interchangeability of aPTT instruments and interinstitutional variation.

The agreement between aPTT-guided heparin dosage adjustment decisions and those guided by heparin concentrations also was evaluated. The laboratory-based aPTT decisions agreed with the heparin concentration 82% of the time, while the bedside aPTT decisions agreed 64% to 65% of the time. The agreement with the laboratory-based instrument was significantly better than either bedside instrument ($P < .01$). Results from the TAS instrument were more likely to result in potential underanticoagulation compared with the laboratory aPTT. The higher level of agreement between aPTT- and heparin concentration–guided decisions in our study compared with that reported by Baker et al (47%) may be related to the sample size. Thirty-eight patients were used to establish the therapeutic range in the study by Baker et al, while 80 or more (depending on instrument) were used in the present study. The agreement between heparin

Table 4
Decision Analysis for Activated Partial Thromboplastin Time Result vs Heparin Concentration*

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Potential Underanticoagulation</th>
<th>Potential Overanticoagulation</th>
</tr>
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<tbody>
<tr>
<td>CPS (n = 99)$^\dagger$</td>
<td>64 (65)</td>
<td>15 (15)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>TAS (n = 98)$^\ddagger$</td>
<td>63 (64)</td>
<td>23 (23)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>MDA (n = 98)$^\S$</td>
<td>80 (82)$^|$</td>
<td>3 (3)$^|$</td>
<td>15 (15)</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage). For names of instruments and manufacturer information, see Table 2.
$^\dagger$ One outlier was removed from analysis.
$^\ddagger$ One outlier and 1 machine default were removed from analysis.
$^\S$ Two outliers were removed from analysis.
$^\|$ $P = .0099$ for MDA vs CPS; $P = .0097$ for MDA vs TAS.
$^\|$ $P = .0011$ for MDA vs TAS.

Table 5
Decision Analysis for Laboratory vs Bedside Activated Partial Thromboplastin Time*

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Potential Underanticoagulation</th>
<th>Potential Overanticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS vs MDA (n = 100)</td>
<td>68 (68)</td>
<td>19 (19)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>TAS vs MDA (n = 98)$^\dagger$</td>
<td>58 (59)</td>
<td>30 (31)</td>
<td>10 (10)</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage). For names of instruments and manufacturer information, see Table 2.
$^\dagger$ Two outliers were removed from analysis.
level-guided decisions and aPTT-guided decisions using a heparin concentration–defined therapeutic range varies from 47% to 82%. The reported agreement between heparin level–guided decisions and aPTT-guided decisions using an empiric aPTT therapeutic range varies from 57% to 68%. To fully evaluate the recommendation to define a heparin concentration–derived aPTT therapeutic range, decisions guided by empiric and heparin concentration–derived ranges need to be compared in the same patient population. As baseline aPTT values and normal ranges for each instrument were not available at the time of the study, we were unable to assess this.

In addition to comparing how well the aPTT correlates with heparin, one should assess how well bedside aPTT results correlate with laboratory-based aPTT results, the standard laboratory test used in patient care for heparin monitoring. Reported correlations (r) between bedside and laboratory aPTT results vary from 0.73 to 0.95.6,9,10,16-19 High correlations, however, do not necessarily indicate a high level of agreement between instruments.6 The mean bias in aPTT results between bedside and laboratory instruments varies from –8 seconds to +12 seconds.5,19 Limits of agreement (± 2 SDs of the bias) between instruments vary widely, with bedside instruments producing results as much as 28 seconds lower than and 52 seconds higher than results from laboratory instruments.6 In the present study, the correlation of bedside aPTT with laboratory-based aPTT was 0.83 for the CPS and 0.57 for the TAS. The TAS instrument was more biased than the CPS, and both instruments displayed significant variation in the limits of agreement. In addition, patient care decisions directed by bedside aPTT results differed from those directed by laboratory aPTT results 32% to 41% of the time. Despite high correlations between laboratory and bedside aPTT results and the use of a therapeutic range designed for each instrument, laboratory and bedside aPTT testing often do not result in the same patient care decisions.

The laboratory-based aPTT demonstrated the highest correlation with the plasma heparin concentration. Heparin dosage adjustment decisions guided by the laboratory-based aPTT agreed with those guided by plasma heparin concentration more often than the bedside aPTT results. When aPTT instruments are selected based on the best correlation with heparin and the highest agreement in clinical decisions with heparin, the laboratory aPTT instrument is superior to bedside instruments. Nevertheless, even when establishing a heparin concentration–defined aPTT therapeutic range for the central laboratory, heparin dosage adjustment decisions differ from decisions based on heparin concentration approximately 20% of the time. Prospective studies assessing heparin dosage adjustments guided by an empiric aPTT therapeutic range vs adjustments guided by a heparin concentration–derived therapeutic range need to be conducted. Such studies would permit evaluation of the benefit of defining a heparin concentration–derived aPTT therapeutic range. Until such data are available, following the CAP recommendation to establish a heparin concentration–derived aPTT therapeutic range is recommended.

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* At the time of the study, Ms Nowak was a PharmD student.

References


