Partial Thromboplastin Time

Prediction of Adverse Events and Poor Prognosis by Low Abnormal Values

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Background: Clinical observations suggest an increased incidence of bleeding and thrombosis in association with a shortened partial thromboplastin time (PTT).

Objective: To determine whether abnormally fast PTTs are associated with an increased risk of death, thromboses, bleeding, and the overall occurrence of morbid events.

Methods: The medical records of 199 patients admitted in a 1-year period to a Veterans Affairs medical center were reviewed for PTTs and the events of death, thromboses, and severe bleeding. Group 0 (n = 49) consisted of patients with abnormally fast PTTs (<23 seconds). Group 1 (n = 50) consisted of patients with fast normal PTTs (23-25 seconds), and the control group, group 2 (n = 100), contained patients with PTTs from 28 to 31 seconds. The Cox proportional hazards regression was used to analyze the time-independent covariates of PTT groups, surgery, cancer, and other clinical variables as predictors of 3 outcome variables: bleeding, thrombosis, and death.

Results: Of the covariates examined, the PTT was found to be the most significant predictor of poor outcome. A statistically significant association was found between the PTT and time to death (P<.001), thrombotic events (P<.001), and bleeding (P<.006), and between the PTT and overall occurrence of morbid events (P<.001). Furthermore, survival curves showed that the greatest hazards of death, thrombosis, bleeding, and overall morbidity consistently occurred in group 0 compared with groups 1 and 2.

Conclusions: Abnormally fast PTTs, particularly if confirmed on repeated testing, indicate a significant risk of subsequent death, thrombosis, bleeding, and overall morbidity. Careful examination of patients with low PTTs may reduce such associated morbidity and mortality.

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THE ACTIVATED partial thromboplastin time (PTT) is commonly used as part of a general screen for coagulation disorders in patients with abnormal bleeding. The PTT evaluates the intrinsic pathway of the coagulation cascade. It is very sensitive to coagulation disorders and deficiencies within the intrinsic pathway as well as to heparin sodium therapy. Thus, the PTT is abnormally prolonged in inherited coagulopathies such as hemophilia and in acquired coagulopathies such as disseminated intravascular coagulation (DIC) and acquired factor inhibitors. The PTT is also prolonged during heparin therapy and is used to monitor such therapeutic anticoagulation.

Although prolonged PTTs are often associated with abnormal bleeding^2 and even as predictors of poor outcome in such conditions as meningococcal sepsis in children,^3 the importance of the short PTT has not been fully explored or evaluated. Edson et al^4 suggested that short PTTs may be correlated with elevated levels of the factor VIII procoagulant and, possibly, a tendency for thrombosis. Previous studies have also suggested that short PTTs could be associated with an increased risk of thromboembolism^5 or bleeding.^6 This information, however, is generally not reflected in standard hematology texts. In addition, methods of performing the PTT have evolved, and the “normal range” is lower now than it was 25 years ago.

The purpose of the present study was to determine whether short PTTs have clinical significance, ie, whether they are associated with an increased risk of death, thromboses, bleeding, and overall occurrence of morbid events.
PATIENTS AND METHODS

We retrospectively reviewed the medical records of 199 patients admitted to a Veterans Affairs (VA) medical center during the period November 1995 to November 1996. These cases were identified by obtaining a computer-generated list of all patients who had had a PTT determination from November 26, 1995, through November 22, 1996.

We assigned these patients to 1 of 3 groups. Our first group consisted of all patients with PTTs less than 23 seconds. Because the normal range of the PTT at this VA medical center is 23.0 to 34.7 seconds, we considered this group to have the abnormally fast PTTs. Forty-nine patients fell into this group. The second group of 50 patients included all patients with fast normal PTTs, in the range of 23 to 25 seconds. The last group consisted of 100 patient controls selected randomly from more than 300 patients having PTTs in the range of 28 to 31 seconds.

Results of the patients were reviewed for pertinent medical history and medications as well as assessing survival and morbid or comorbid events. Morbid events included the presence of any severe bleeding or of any thrombotic event, such as DIC, thrombotic stroke, deep vein thrombosis, and arterial or venous emboli. Other clinical variables recorded and analyzed included age, concomitant surgery, infection, and cancer. Postoperative complications were also recorded for patients undergoing surgical procedures.

The time from the index PTT to the development of any of these morbid events and/or death was recorded. The time from the index PTT to the last documented visit to the VA medical center was also recorded for all patients. At our institution, PTTs are standardized in 3 ways. At 2-year intervals, a group of normal controls is tested to assess the range of test results to be found. Our normal ranges are also compared with those of other VA medical centers in our region and with the equipment manufacturer’s recommendations. The final decision as to the acceptable range is made by the chief chemist. During a 3-year period for which we have data, 5% of all PTT determinations fell in the range faster than 25 seconds, and fewer than 2% were less than 23 seconds.

Cox proportional hazards regression was considered the most appropriate method to analyze the time-dependent outcome events of bleeding, thrombosis, and death. All hazard function models included all relevant time-independent covariates, namely, the PTT group, surgery, infection, and cancer. Models with death as an end point also included thrombosis and bleeding as covariates. Patients’ ages were incorporated into the hazard function models as well. The form of the hazard function was \[ \lambda(t) = \lambda \exp(\beta X_1 + \beta X_2 + \ldots) \] so that the products of nonzero values of the covariates \( X \) and nonzero values of the regression coefficients \( \beta \) are added together in calculating the final hazard for a patient with multiple risk factors. This model takes into account the time at risk. We noted (data not shown) that the contribution of each covariate to the log likelihood in the resulting model was strikingly similar in univariate and multivariate analyses, suggesting that the significant covariates we identified are largely independent of each other. The method of Kaplan and Meier was also used to calculate and examine survival curves for the 3 PTT groups.

Table 1. Occurrences of Various Morbid Events in the 3 PTT Groups*

<table>
<thead>
<tr>
<th>Group No. (PTT)</th>
<th>No. of Patients</th>
<th>No. (%)</th>
<th>Deaths (No. (%)</th>
<th>Thrombotic Events (No. (%)</th>
<th>Bleeding Episodes (No. (%)</th>
<th>Infection (No. (%)</th>
<th>Cancer (No. (%)</th>
<th>Surgery, No. of Complications/Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (PTT &lt;23 s)</td>
<td>49</td>
<td>17 (35)</td>
<td>13 (27)</td>
<td>18 (37)</td>
<td>13 (27)</td>
<td>12 (25)</td>
<td>3/14</td>
<td></td>
</tr>
<tr>
<td>1 (PTT 23-25 s)</td>
<td>50</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td>9 (18)</td>
<td>9 (18)</td>
<td>9 (18)</td>
<td>3/19</td>
<td></td>
</tr>
<tr>
<td>2 (PTT 28-31 s)</td>
<td>100</td>
<td>6 (6)</td>
<td>3 (4)</td>
<td>14 (14)</td>
<td>24 (24)</td>
<td>15 (15)</td>
<td>7/45</td>
<td></td>
</tr>
</tbody>
</table>

*PTT indicates partial thromboplastin time.

RESULTS

Of the 199 patients from the retrospective study at this VA medical center, the occurrences of death, thrombotic events, bleeding episodes, significant infections, cancer, and surgical procedures with complications in each PTT group are shown in Table 1. The Cox proportional hazards results evaluating the relationship between the covariate of the PTT group and the time-dependent outcome variables of death, thrombotic events, bleeding episodes, and overall occurrence of morbid events are shown in Table 2. Also shown in Table 2 are the relationships between the covariates of cancer, surgery, and age with these same outcome variables.

An association between the PTT group and death was found to be significant at \( P<.001 \). Inspection of the Kaplan-Meier curves (Figure 1) shows that the death rate was greater for patients with PTTs less than 23 seconds (group 0, Figure 1) than that in the control group (group 2) and the group with PTTs of 23 to 25 seconds (group 1).

The association between the PTT and thrombotic outcome events was found to be statistically significant at \( P<.001 \). The Kaplan-Meier curves in Figure 2 illustrate the percentage of patients free of thrombosis from time zero (when the index PTT was measured) to the last patient follow-up or occurrence of thrombosis. The percentage of patients free of thrombosis in group 2 was 97% at time zero, with no further thrombotic events occurring. Group 1 exhibited a slight decrease in the percentage of patients free of thrombosis, from 94% at time zero to 86% at 30 months. Group 0, however, exhibited the
greatest hazard of thrombosis, with 74% of patients projected to be free of thrombosis at 30 months.

We recognized that in some instances the actual occurrence of a morbid event led to the measurement of the index PTT. Thus, we also analyzed the data set obtained by discarding all patients with “index events” (events occurring at time zero). After data for patients with index events were discarded, the Cox proportional hazards results evaluating the associations between the covariate of the PTT group–-and time-dependent outcome variables of thrombotic events, bleeding, and overall occurrence of morbid events are shown in Table 2. Table 2 also displays the associations between the covariates of cancer and surgery and the outcome variables of thrombosis, bleeding, and overall morbidity when index events are discarded.

Age did not provide a significant contribution to the hazard function in this analysis.

If thrombotic index events are ignored, the correlation between the PTT group and thrombosis remains significant at $P < .001$. The Kaplan-Meier curves illustrate that the percentage of patients free of thrombosis decreased as a function of time in all 3 PTT groups (Figure 3). Group 1 exhibited a 9% incidence of thrombosis; however, the abnormal PTT group exhibited the greatest hazard of thrombosis, with only 80% of patients projected to remain event-free at 30 months.

A correlation between the PTT and any bleeding event was found to be statistically significant at $P < .006$ when all events were analyzed. The Kaplan-Meier curves illustrate that the percentage of patients free of bleeding decreased as a function of time in all 3 PTT groups (Figure 4). The greatest hazard of bleeding, however, occurred in patients with PTTs less than 23 seconds. The correlation between the PTT group and bleeding lost statistical significance when index bleeding events were disregarded (Table 2).

A statistically significant association was found between PTT group and the overall occurrence of morbid events, which includes bleeding, thrombosis, or death (Table 2). Overall, all 3 PTT groups experienced an ongoing hazard of morbidity (Figure 5). The greatest hazard of morbidity, however, occurred in patients with PTTs less than 23 seconds (group 0). When index

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Table 2. Values of Regression Coefficients ($\beta$) and Corresponding $P$ Values for Statistically Significant Clinical Variables Associated With Each Time-Dependent Outcome Variable*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death</th>
<th>Thrombosis</th>
<th>Bleeding</th>
<th>Morbid Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT group</td>
<td>$-1.05, &lt; .001$</td>
<td>$-0.92, &lt; .001$</td>
<td>$-0.53, .006$</td>
<td>$-0.79, &lt; .001$</td>
</tr>
<tr>
<td>Cancer</td>
<td>$1.22, .002$</td>
<td>$1.02, .03$</td>
<td>$-0.71, .18$</td>
<td>$0.45, .09$</td>
</tr>
<tr>
<td>Surgery</td>
<td>$-1.41, .004$</td>
<td>$-1.34, .04$</td>
<td>$-0.64, .09$</td>
<td>$-0.97, .002$</td>
</tr>
<tr>
<td>Age</td>
<td>$0.043, .04$</td>
<td>$-0.009, .64$</td>
<td>$0.03, .05$</td>
<td>$0.025, .04$</td>
</tr>
</tbody>
</table>

With Index Events Disregarded

| PTT group | $-0.98, < .001$ | $-1.62, < .001$ | $-0.44, .24$ | $-1.1, < .001$ |
| Cancer    | $1.35, < .001$  | $1.27, .08$    | $-0.21, .78$ | $1.04, .005$  |
| Surgery   | $-1.28, .007$   | $-1.86, .04$   | $0.04, .94$  | $-1.05, .005$ |

*PTT indicates partial thromboplastin time.
†Data in boldface type are statistically significant.
events were ignored, a statistically significant correlation between the PTT and overall morbidity was maintained at P<.001 (Table 2). Figure 6 demonstrates that group 0 continued to display the greatest hazard of morbidity.

Among other clinical variables examined, 2 others—the presence of cancer and the absence of surgery—remained significant predictors of poor outcome in the multivariate analysis. The presence of cancer was found to be a statistically significant predictor of poor survival, of thrombosis, and of the overall occurrence of morbid events (Table 2). The covariate of the PTT group, however, maintained a stronger statistical association with these outcome variables than the presence of cancer; therefore, the PTT was the stronger predictor of poor survival, thrombosis, and overall morbidity. The analysis also showed that patients undergoing surgery had improved survival and reduced risk of thrombosis and overall morbidity. The absence of surgery was, thus, found to be a significant predictor of death as well as a significant predictor of thrombosis and overall occurrence of morbid events within this patient population (Table 2). The PTT group again exhibited a stronger statistical association with these outcome variables than the absence of surgery did and remained the stronger predictor of death, thrombosis, and overall morbidity.

Thrombosis and bleeding were also included in the multivariate analysis as covariates with the outcome event of death as the end point. At P>.3 and P>.15, respectively, thrombosis and bleeding were not considered to be significant predictors of death, even when the variable for the PTT group was excluded from the analysis.

The prothrombin and activated partial thromboplastin times remain standard screening tests for function of the coagulation system. Their utility in monitoring therapeutic anticoagulation is widely accepted. The usefulness of these tests as screening for bleeding or thrombotic risk in presurgical patients has come into question in part because of the high incidence of false-positive findings in patients whose history and physical examination do not disclose evident coagulation problems. However, discussion of the utility of these tests has focused on the significance of prolonged times in these tests. Little attention has been paid to the significance of the shortened PTT. Hume12 did call attention to shortened PTT as a predictor of thrombosis, as did Gallus et al.13 Pilgeram14 suggested an increased risk of stroke in patients with shortened PTT, and McKenna et al5 also found increased thrombosis in such patients. Landi et al15 found that shortened PTT was a predictor of deep vein thrombosis in patients with stroke. Belgueau6 reported a high risk of spontaneous bleeding in patients with a shortened PTT. Still, widely used textbooks of hematology7 and hemostasis and thrombosis8 do not comment on this phenomenon.

Several authors have described abnormalities in association with a fast PTT that may contribute to the laboratory finding and to the associated morbid events. Elevated factor VIII levels have been reported in association with shortened PTT and thrombosis. Others have found elevation of levels of factor V, factor X, or fibrinopeptide A to be associated with fast PTT and thrombosis. Salem et al19 described a subgroup of patients with glomerulonephritis with a thrombotic tendency associated with fast PTT and elevated levels of factor VIII coagulant activity above that of factor VIII antigen levels. Patients with cancer receiving chemotherapy are at high risk for thrombotic events, and this has been attributed by Gabazza et al20 to both increased procoagulant and decreased fibrinolytic activity.20 These findings were associated with shortened PTT, although not to the degree seen in our study group. Yamamoto et al21 found elevations of factor II and IX levels after mecloxyprogesterone administration to patients with breast cancer, leading to shortened PTT. However, thrombotic events were not observed in their patients.

Disseminated intravascular coagulation, a systemic thrombohemorrhagic disorder, is also a setting in
which short PTT can occur. Although PTT is typically prolonged in fulminant DIC, normal or fast PTTs are found in about 40% of patients.22 Bick23 believes that this is because of the presence of circulating activated clotting factors as well as the presence of early degradation products that are rapidly clotted by thrombin and quickly gel in the test system.

Thrombosis, bleeding, and death were not primarily linked to DIC in our patient population. Only 2 of the 49 patients with fast PTTs (group 0) had documented DIC, and only 1 of these had a low platelet count at the time of the index PTT. Thus, it seems unlikely that the risk of poor outcomes was primarily caused by DIC in our study population.

Our observations confirm and extend those of others and suggest that shortened PTT is an independent risk factor for thrombosis, bleeding, and death. Other clinical factors predictive of death in the population we studied included more advanced age and presence of cancer, as would be suspected. Interestingly, patients undergoing surgery had a lower risk of death. We believe that this reflects the relatively good health of patients without cancer whose PTT is determined as part of preoperative screening at our institution. Our surgical service does not handle trauma, neurosurgery, or cardiac surgery, and has relatively few emergency surgery cases of any sort.

The role of shortened PTT as a predictor of thrombosis or bleeding is certainly influenced by the setting in which PTT testing is done. Thus, perhaps it is not surprising that a proportion of patients with active bleeding or thrombosis will have a fast PTT. However, even when index events were disregarded, fast PTT remains a strong predictor of both thrombosis and death. It is also of interest that neither bleeding nor thrombosis was itself an independent predictor of death, even when the PTT group variable was not included. Even an artificial variable combining both types of events was not a predictor of death, yet the PTT group was the strongest predictor of high risk of death.

When analyses were performed comparing only the subset of patients with fast normal PTT (23-25 seconds; group 1) with controls (PTT, 28-31 seconds; group 2), comparisons generally lost statistical significance. This is in part because of the small number of events in such comparisons. Still, inspection of the relevant Kaplan-Meier curves (eg, Figures 1 and 5) generally demonstrates a consistent trend toward higher risk of events in the fast normal group (group 1).

Thus, we believe that the presence of a shortened PTT, either faster than the normal range or within 2 seconds of the lower limits of institutional normal values, indicates a significant risk of subsequent thrombosis and death, and may be associated with increased risk of bleeding as well. Although more formal prospectively designed studies should be carried out to fully evaluate the validity and significance of our observations, we believe that the presence of a shortened PTT should be considered to indicate higher-than-normal risk of thrombosis, bleeding, and death, and should promote careful examination of such patients with a view to minimizing morbidity from preventable adverse events.

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