Biphasic aPTT Waveform and Adverse Events in Non-Intensive Care Unit Patients

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Activated Partial Thromboplastin Time (aPTT) Waveform.

The waveform represents the change in light transmittance through a plasma specimen as the aPTT reaction takes place. [A] Normal waveform: The first phase (pre-coagulation phase) is a plateau which shows no change in light transmittance from baseline (100% transmittance [T]). Once a clot begins to form, the light transmittance abruptly decreases as fibrin is polymerized. The number of seconds until this abrupt drop in light transmittance is the aPTT result in seconds. [B] Biphasic waveform: In the presence of disseminated intravascular coagulation (DIC), the waveform can become "biphasic", with an initially steep negative slope (called "slope 1") prior to clot formation.

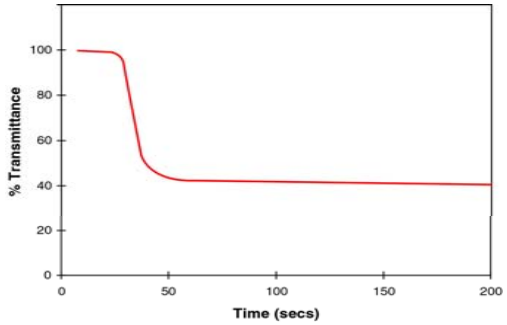

Figure 1A. Normal aPTT Waveform

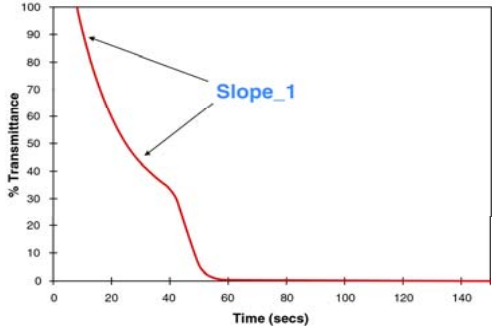

Figure 1B. Biphasic aPTT Waveform (BPW)

Table 1 Adverse Outcomes and Biphasic aPTT Waveform

Adverse Outcome	Biphasic Waveform Patients	Normal Waveform Control Patients	p value <0.05*
Length of stay mean (median) days†	16.9 (11)	4.9 (2.5)	0.011*
Mortality‡	3/24	0/24	0.12
Red blood cell transfusion‡	11/24	5/24	0.047*
Fresh frozen plasma transfusion ‡	5/24	0/24	0.025*
Platelet transfusion‡	1/24	0/24	0.50
Positive microbial culture‡	16/24	3/24	0.00013*
Transfer to an ICU‡	6/24	0/24	0.010*
Admission from ED‡	11/11	5/11	0.018*
PT; mean (median), seconds†	14.3 (14.2)	14.1 (13.3)	0.82
APTT; mean (median), seconds†	39.7 (32.2)	38.4 (33.2)	0.81
Platelets; mean (median), 1000/mm²†	317 (295)	248 (243)	0.071

ICU = intensive care unit; ED = emergency department, PT = prothrombin time (normal 11.1-13.1); aPTT = activated partial thromboplastin time (normal 22.1-35.1)
* Differences were statistically different at p<0.05
† P values determined by Student's T-test
‡ P values determined by Fisher Exact Test

INTRODUCTION

- The biphasic aPTT waveform (BPW), available on the MDA-180 (bioMérieux, Durham, NC), is a relatively new marker of disseminated intravascular coagulation (DIC)[1-4] and sepsis[5] (figure 1). It is associated with increased mortality among patients in intensive care units (ICU)[5]. The purpose of the present study was to determine whether the presence of a biphasic aPTT waveform is associated with adverse clinical outcomes among patients who are not in an ICU.

METHODS

- Consecutive non-ICU patients with a BPW (n=24) and 24 control patients with a normal aPTT waveform, matched for age, gender, and hospital location were prospectively enrolled at Massachusetts General Hospital. All waveform analyses were performed on clinician ordered aPTTs from patients who were located either in the emergency department or on non-ICU inpatient floors. For this study, a BPW was defined as an aPTT waveform with a slope_1 value more negative than -0.25 %T/sec. Clinicians caring for the patients and controls were unaware of the aPTT waveform results. The hospital course for the patients and controls were followed for adverse outcomes, including mortality, hospital length of stay, positive microbial cultures, transfusions, transfer into ICUs and admissions to an inpatient floor from the emergency department. Available data on clinician ordered assays for DIC were collected (PT, aPTT, platelet count, fibrinogen, and D-dimers).[6] Discharge diagnoses were also collected. Institutional Review Board (IRB) approval was obtained for this study.

RESULTS

- The mean (median, range) age was 68 (73, 21-90) years for patients with a biphasic aPTT waveform and 69 (73, 21-92) years for control patients. The mean slope_1 of the aPTT waveforms was -0.495 %T/sec among patients with a biphasic aPTT waveform and -0.021 %T/sec among controls. A comparison of results of non-ICU patients and controls is presented in Table 1. Patients with a BPW had a significantly longer length of hospital stay (mean [median] 16.9 [11] versus 4.9 [2.5] days, P=0.01), were more likely to have a positive microbial culture (16/24 [67%] versus 3/24 [13%], P = 0.00013), were more often transferred to an ICU (6/24 [25%] versus 0/24 [0%], P = 0.01), and were more likely to receive a red blood cell transfusion (11/24 [46%] versus 5/24 [21%], P = 0.047) and fresh frozen plasma transfusion (5/24 [21%] versus 0/24 [0%], P= 0.025). Among emergency department patients, those with a BPW were more likely to be admitted (11/11 versus 5/11, P = 0.018). There were three deaths among patients with a biphasic waveform versus no deaths among the control patients, but the difference in mortality was not statistically significant (3/24 [13%] versus 0/24 [0%], P = 0.12).
- Only one patient with a biphasic aPTT waveform and no control patients received transfusions of platelets. The one patient received a total of 72 units of platelets, 69 units of fresh frozen plasma, and 49 red blood cell transfusions.
- All subjects in this study had PT, aPTT and platelet counts measured. There were no significant differences between patients with a biphasic waveform and controls for these routinely available markers of DIC (PT, aPTT, platelet count).
- Among the 16 patients with a biphasic aPTT waveform and positive cultures, 6 had the biphasic waveform identified prior to the culture or gram stain result. In the remaining 10 cases, data on the timing was insufficient to determine which event came first.

DISCUSSION

This study finds that the presence of a BPW in non-ICU patients was associated with several adverse outcomes possibly related to sepsis and/or DIC. Specifically, the patients with a BPW had a longer length of hospital stay, were more likely to be transferred to an ICU, more often had positive microbiological cultures, and more often received a red blood cell and/or fresh frozen plasma transfusion. Among patients presenting to an emergency department, patients with a BPW were more likely to be admitted to an inpatient floor. There were more deaths among the patients with a BPW, but this was not statistically significant, likely due to the small population. The overall mortality among patients with a BPW (13%) was lower than in the previously studied ICU population (44%)[5]. This was expected, as the target population in the present study (non-ICU) was expected to be overall healthier than the previously studied ICU population.

Interestingly, there were no significant differences between the other routinely available coagulation assays (PT, aPTT or platelet count) when comparing patients with BPWs and normal aPTT waveforms. This suggests that these routinely available coagulation tests alone could not be used in place of identification of a BPW to predict adverse outcomes in non-ICU patients.

One limitation of the present study is that D-dimers and fibrinogen were performed only if requested by the clinician, and were requested for only 4 patients and no controls. In all four patients, the D-dimer was positive. Fibrinogen was elevated in two patients and normal in two, suggesting that fibrinogen would not be a predictor of DIC in these patients. We suspect that the D-dimer may not be as useful as the aPTT waveform in predicting DIC-related adverse outcomes because it lacks specificity, in that it may be positive in liver disease, thrombosis, recent surgery, or other conditions in addition to DIC/sepsis. The fact that clinicians ordered D-dimers and fibrinogen on only 4 of the 24 BPW patients indicates that in the remaining 20 patients, the diagnosis of DIC was likely not under consideration. Therefore, the aPTT waveform information (from a test that was already ordered by the clinicians) could provide a clue to a diagnosis of DIC that would otherwise be missed, thereby alerting the physicians to monitor the patient more closely, potentially resulting in earlier intervention.

A discharge diagnosis possibly associated with DIC and/or a positive microbial culture was identified in 20/24 (83%) of BPW patients versus 11/24 (46%) of control patients. Therefore, diagnosis alone may be insufficient to predict the presence of the waveform. The results of this study suggest that a biphasic aPTT waveform has the potential to identify non-ICU patients with an increased risk for complications and adverse outcomes.

CONCLUSIONS - These results suggest that a biphasic aPTT waveform is associated with an increased rate of adverse events among non-ICU patients, and further study in this population is warranted.

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