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Accuracy of aPTT monitoring in critically ill patients treated with unfractionated heparin

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ABSTRACT

Introduction: The anticoagulant effect of unfractionated heparin (UFH) is usually monitored by means of the activated partial thromboplastin time (aPTT). In critically ill patients, however, increased levels of acute phase proteins may decrease the accuracy of the aPTT, leading to inadequate UFH dosing. In these circumstances, the anti-Xa assay is recommended for monitoring.

Objective: We aimed to analyse the accuracy of the aPTT for the monitoring of UFH dosing in critically ill patients.

Methods: In critically ill patients treated with therapeutic doses of UFH, we compared aPTT levels with simultaneously measured anti-Xa levels as the gold standard. Sensitivity and specificity of the aPTT were determined for different cut-off points, receiver operating characteristic (ROC) curves were constructed and their areas under the curve (AUCs) were calculated.

Results: A total of 171 paired blood samples from 58 patients were analysed. Concordant aPTT and anti-Xa values were observed in 108 (63.2%) data pairs. In 33 data pairs (19.3%) the aPTT was discordantly high and in 30 data pairs (17.5%) discordantly low. The sensitivity of the aPTT in detecting UFH underdosing and overdosing was 0.63 and 0.37, respectively. When considering alternative thresholds, ROC curves for underdosing and overdosing had AUCs of 0.71 and 0.81, respectively.

Conclusion: In this small cohort of critically ill patients, the aPTT was accurate in 63.2% of the blood samples. Its sensitivity to detect UFH underdosing and overdosing was low (0.63 and 0.37, respectively). We conclude that in critically ill patients, the aPTT is not accurate enough to detect UFH underdosing and overdosing.

KEYWORDS

Heparin/therapeutic use, partial thromboplastin time, factor Xa/analysis, drug monitoring/methods, critical care

INTRODUCTION

Although unfractionated heparin (UFH) has been replaced by low-molecular-weight heparin (LMWH) for many indications, it remains the anticoagulant of choice among selected patient groups because of its short half-life and its possibility to be reversed by protamine sulphate.[1] The indications for UFH may ultimately be limited to clinical environments in which rapid reversal of the anticoagulant effect is required, e.g. the intensive care unit (ICU). Despite being a cornerstone of anticoagulation, UFH is limited by its unpredictable pharmacokinetic profile. The complex kinetics of clearance render the anticoagulant response to heparin nonlinear at therapeutic doses, with both the intensity and duration of the effect rising disproportionately with increasing dose.[2] The anticoagulant and pharmacological properties of UFH vary among patients as well as within individuals over time, as a consequence of the binding of UFH to various plasma proteins.[3]

Because of its unpredictable anticoagulant effect, close monitoring of UFH treatment is crucial. Historically, the activated partial thromboplastin time (aPTT) has been the primary laboratory test used to monitor and adjust UFH.[4] A therapeutic aPTT range of 1.5-2.5 times baseline has gained wide acceptance in daily clinical practice.[2,5]

Monitoring of the anti-factor Xa effect has been suggested as an alternative to the aPTT because the assay is based on enzymatic inhibition, which can be accurately measured spectrophotometrically using well-defined chemical reagents that are not biologically derived.[6] Since the anti-factor Xa assay measures the inhibition of a single enzyme, it reflects the UFH activity more directly than the aPTT. Accordingly, it demonstrates less variability and exhibits minimal interference from the presence of biological factors, such as acute phase reactants.[7] Disadvantages of the anti-factor Xa assay are its relative expense and limited laboratory availability.

Because of their complex clinical presentation, critically ill patients are particularly vulnerable and difficult to manage. These patients have a predisposition for thrombosis due to acquired risk factors including indwelling central venous catheters, prolonged immobilisation and acquired coagulation disorders.[8] They are also susceptible to bleeding complications because of acquired coagulopathy, drug interactions, recent surgery or invasive procedures and concomitant organ failure, especially of the liver or kidney. Renal failure affects the anticoagulant effect of UFH due to decreased clearance. Moreover, critically ill patients often have decreased levels of albumin, increasing the serum concentration of unbound drugs and thus the risk of toxicity. On the other hand, critically ill patients often have elevated levels of acute phase proteins such as factor VIII. Binding of UFH to these acute phase proteins may contribute to heparin resistance, resulting in an even more unpredictable response of UFH in critically ill patients. Aforementioned complications contribute to the morbidity and mortality in critical care patients and close monitoring is required to protect these patients against adverse outcomes.

The accuracy of the aPTT for monitoring of UFH dosing in critically ill patients is currently not well-known and we hypothesised that it is insufficient. Therefore, we assessed the accuracy of the aPTT in terms of sensitivity and specificity for detecting underdosing and overdosing of UFH in critically ill patients.

MATERIALS AND METHODS

Study design

We conducted a retrospective observational study using the data of critically ill patients admitted to the Academic Medical Center (AMC), a 1000-bed university hospital in Amsterdam, the Netherlands. All patients who received intravenous UFH in the intensive care unit and medium care unit of the AMC between January 2010 and January 2012 were eligible for this study. We identified patients by a query in the hospital laboratory database, searching for patients in whom both an aPTT and an anti-Xa level were measured. We excluded patients aged under 18 years and patients treated with anticoagulants other than UFH.

Laboratory assays

In all patients, we compared the results of aPTT and anti-Xa levels performed on the same blood sample in our routine haemostasis laboratory. All blood samples were drawn into sodium citrate tubes (BD Vacutainer, Becton Dickinson Co.) then centrifuged at 2680 g at 20 °C for 15 minutes to separate blood cells from platelet-poor plasma; the aPTT was then analysed. To obtain platelet-free plasma the plasma was transferred into another tube and further centrifuged for 5 minutes at 13,000 g at 20 °C followed by storage at -30 °C until anti-Xa assays were performed. Coagulation parameters were measured using a Sysmex CA-7000 system (Siemens AG, Erlangen, Germany) with Dade Actin FS activated PTT reagent (Siemens AG, Erlangen, Germany) for the aPTT and STA liquid anti-Xa reagent (Diagnostica Stago SAS, Asnières sur Seine, France) for the anti-Xa. aPTT levels between 45-60 seconds and anti-Xa levels between 0.3-0.7 IU/ml were defined as therapeutic.

Protocols

According to the ICU heparin dosing protocol, the treating physician sets and documents the target aPTT level for each patient in the patient data management system. Depending on indication and risk of bleeding, a loading dose of 1000-5000 units is administered, followed by a continuous infusion of 1000 units/hour. The aPTT is measured four times a day starting four hours after the start of infusion, even when the aPTT result is within the therapeutic range. The dose-adjustment protocol is shown in *table 1*.

Data collection and outcomes

The primary outcome assessed in this study was the accuracy of the aPTT in monitoring UFH dosing, using the anti-Xa level (0.3-0.7 IU/ml) as gold standard. Paired aPTT and anti-Xa measurements were grouped according to their concordance. Discordantly paired measurements were divided into two subgroups:

- Disproportionately low aPTT values (i.e. a subtherapeutic aPTT with a therapeutic or high anti-Xa level or a therapeutic aPTT with a supratherapeutic anti-Xa level);

Table 1. *Protocol for the intravenous dosing of unfractionated heparin – ICU Academic Medical Center Amsterdam*

aPTT result	Dose modification*	Follow-up after
< 39	Increase drip by 150 IU/h, consider bolus 1000-5000 IU	6 h
39-44	Increase drip by 100 IU/h	6 h
45-59	–	6 h
60-74	Decrease drip by 50 IU/h	6 h
75-89	Decrease drip by 100 IU/h, stop infusion for ½ hour	6 h
> 89	Decrease drip by 150 IU/h, stop infusion for 1 hour	6 h

***Initial dosing: infusion rate of 1000 IU/h or 5 ml/h with a concentration of 200 IU/ml. Bolus: administration of a bolus depends on the indication and is not given without consultation of the treating physician.**

- Disproportionately high aPTT values (i.e. a therapeutic aPTT with a subtherapeutic anti-Xa level or a supratherapeutic aPTT with a subtherapeutic or therapeutic anti-Xa level).

Since a disproportionately low aPTT value is unable to detect UFH overdosing, this result represents a risk of bleeding. The opposite is true for a disproportionately high aPTT value, which represents a risk of thrombosis. Patients were divided into groups according to their concordance status and clinical outcomes were assessed.
For further assessment of the diagnostic value of the aPTT, we determined the sensitivity and specificity of the aPTT for detecting underdosing and overdosing of UFH, using the anti-Xa as a gold standard.

Statistical analysis
Statistical analysis was conducted with SPSS version 20.0 (IBM Inc., Chicago, Illinois, USA). Because there were multiple measurements per patient and the number of aPTT and anti-Xa measurements differed between patients, we used a generalised linear mixed model to estimate specificity and sensitivity. Data are presented as median and range. Instead of the commonly used thresholds to define normal aPTT levels, we also determined sensitivity and specificity for both detecting underdosing and overdosing by means of the aPTT for multiple cut-off values. Based on these data, receiver operating characteristic (ROC) curves were constructed and for each of them the area under the curve (AUC) was calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

Fifty-eight patients met the inclusion criteria and were enrolled in the study (*table 2*). Concomitant use of LMWH was the most prevalent reason for exclusion. The main indications for UFH therapy were venous thromboembolism (41.4%) and atrial fibrillation (32.8%).
Paired measurements of aPTT and anti-Xa were performed on 171 samples and plotted as an x-y scatterplot. The distribution of aPTT and anti-Xa levels is shown in *figure 1*. The median aPTT was 48 seconds (range: 22-96), the median anti-Xa level was 0.3 IU/ml (range: 0.1-1.0) and the median administered UFH dose was 1600 IU/hour (range: 900-2600 IU/hour). For each anti-Xa value, a wide range of aPTT values was measured. For an anti-Xa level of 0.4 IU/ml, for example, the corresponding aPTT values ranged from 32-65 seconds.
In *table 3*, the concordance of the test results is shown. Concordant aPTT and anti-Xa values were observed in 108 (63.2%) data pairs, whereas in 33 data pairs (19.3%) the aPTT was discordantly high and in 30 data pairs (17.5%) discordantly low.
When UFH was monitored by the aPTT, underdosing was detected in 32 out of 56 samples (57%), whereas the anticoagulant efficacy was underestimated in 22 of 115 samples (19%). Using the generalised mixed model, we calculated the sensitivity and specificity of the aPTT to detect UFH underdosing to be 0.63 and 0.82, respectively.

Table 2. *Baseline characteristics*

Patients, n	**58**
Age in years, median (range)	61 (25-86)
Male, n (%)	37 (64)
Weight in kg, median (range)	85 (50-134)
Indication for anticoagulation	
VTE, n (%)	24 (41.4)
Atrial fibrillation, n (%)	19 (32.8)
Mechanical heart valve, n (%)	10 (17.2)
Acute coronary syndrome, n (%)	2 (3.4)
Unknown, n (%)	3 (5.2)
Admission diagnosis	
Infection or inflammation, n (%)	27 (46.6)
Heart valve replacement, n (%)	8 (13.8)
Acute coronary syndrome, n (%)	6 (10.3)
Arterial thrombosis, n (%)	6 (10.3)
Other cardiovascular, n (%)	5 (8.6)
Malignant neoplasm, n(%)	2 (3.4)
Other, n (%)	4 (6.9)
Severity score (APACHE II)	
< 12, n (%)	6 (10.3)
12-17, n (%)	22 (37.9)
18-22, n (%)	10 (17.2)
> 22, n (%)	14 (24.1)
Unknown, n (%)	6 (10.3)

APACHE II = Acute Physiology and Chronic Health Evaluation II; VTE = venous thromboembolism.

Figure 1. *Distribution of aPTT and anti-Xa levels in an XY scatter plot*

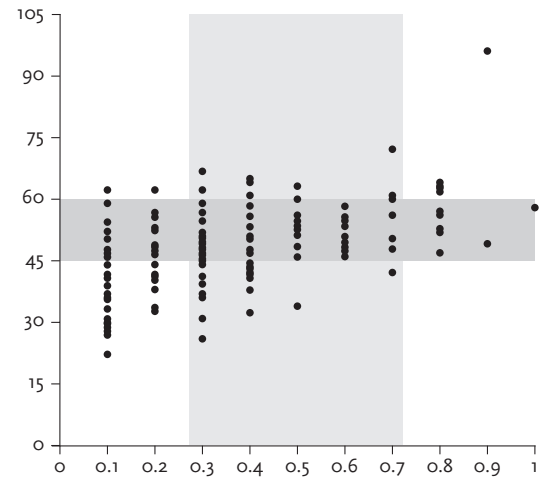

Table 3. *Cross-tabulation of clinically relevant aPTT and anti-Xa levels*

aPTT, s	Total	anti-Xa <0.3 IU/ml	anti-Xa 0.3-0.7 IU/ml	anti-Xa > 0.7 IU/ml
< 45	54	32	22	0
45-60	102	22	72	8
> 60	15	2	9	4
Total	171	56	103	12
Detecting heparin underdoing and overdosing with the aPTT			Sensitivity (GLMM)	Specificity (GLMM)
UFH underdosing (anti-Xa < 0.3 IU/ml)			0.63	0.82
UFH overdosing (anti-Xa > 0.7 IU/ml)			0.37	0.94

GLMM = general linear mixed model; UFH = unfractionated heparin.

UFH overdosing was detected by means of the aPTT in four out of 12 samples (33%), whereas in 11 out of 159 samples, overdosing was falsely diagnosed (7%). After statistical correction for repeated measurements, we found a sensitivity of 0.37 and specificity of 0.94 for detecting UFH overdosing by means of the aPTT. ROC curves for detecting UFH underdosing and overdosing had AUCs of 0.71 and 0.81, respectively (*figure 2*). The highest combination of sensitivity and specificity was reached with an aPTT cut-off value of 45 seconds for detecting UFH underdosing (sensitivity 0.81, specificity 0.57) and 51 seconds for detecting UFH overdosing (sensitivity 0.83, specificity 0.69).

To further evaluate the accuracy of the aPTT, the occurrence of thrombosis and bleeding was assessed. In *table 4*, the number of thrombotic and bleeding events is related to the concordance status of the patients. Forty-three patients (74.1%) had mainly concordant aPTT and anti-Xa values, nine patients (15.5%) had mainly disproportionately low aPTT values and six patients (10.3%) had mainly disproportionately high aPTT values. There was no statistically significant difference in the occurrence of thrombotic and bleeding events between these three groups.

We also calculated the sensitivity and specificity of the aPTT and anti-Xa for detecting thrombotic and bleeding events. The results of these calculations are shown in *table 4*. The majority of bleeding events were haematomas without further adverse outcomes. One patient suffered from gastrointestinal bleeding causing a decrease in haemoglobin concentration, for which an intervention was required.

DISCUSSION

The aim of laboratory monitoring of anticoagulation is to ensure an optimal antithrombotic effect while minimising the risk of bleeding.[1] In the present retrospective study, we examined the accuracy of the aPTT in critically ill patients requiring high doses of UFH, using the anti-Xa level as gold standard. In patients on UFH, we noted discordance between aPTT and anti-Xa assays in 36.8% of the paired measurements. Discordantly high and low aPTT values were found in 19.3 and 17.5% of the blood samples, respectively. The aPTT had a sensitivity of 0.63 and a

Figure 2. *ROC curve for A) Detecting UFH underdosing (anti-Xa < 0.3 IU/ml) by means of the aPTT, B) Detecting UFH overdosing (anti-Xa > 0.7 IU/ml) by means of the aPTT*

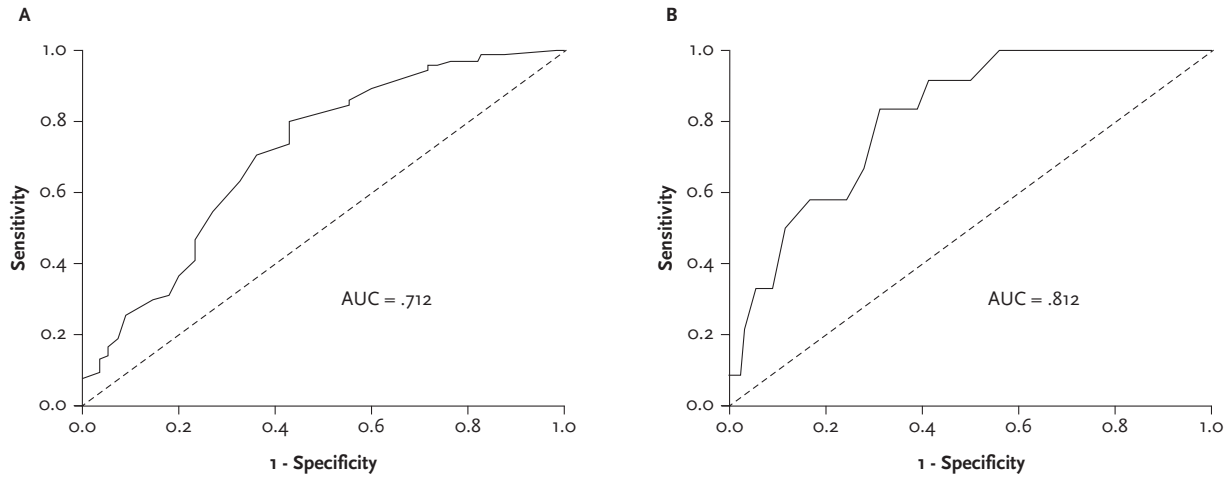

Table 4. *Clinical outcome of the patients according to their concordance status*

Group of patients	Number of patients	Thrombotic events	Bleeding events
Discordantly high aPTT levels			
aPTT > 60 and anti-Xa < 0.7 or	2	-	2
aPTT > 45 and anti-Xa < 0.3	7	1	-
Concordant aPTT levels			
Subtherapeutic (anti-Xa < 0.3)	11	2	-
Therapeutic (anti-Xa 0.3-0.7)	31	2	5
Supratherapeutic (anti-Xa > 0.7)	1	-	1
Discordantly low aPTT levels			
aPTT < 45 and anti-Xa > 0.3 or	4	-	-
aPTT < 60 and anti-Xa > 0.7	2	-	1
Total	58	5	9
		Sensitivity	Specificity
Detecting a thrombotic event			
By means of the aPTT		0.40 (2 out of 5)	0.81 (43 out of 53)
By means of the anti-Xa		0.60 (3 out of 5)	0.68 (36 out of 53)
Detecting a bleeding event			
By means of the aPTT		0.33 (3 out of 9)	0.96 (47 out of 49)
By means of the anti-Xa		0.22 (2 out of 9)	0.96 (47 out of 49)

specificity of 0.82 for detecting UFH underdosing. In order to detect UFH overdosing, we found a low sensitivity (0.37) but a high specificity (0.94). Considering other aPTT thresholds to define overdosing or underdosing, the ROC curves for underdosing and overdosing had AUCs of 0.71 and 0.81, respectively. The highest combination of sensitivity and specificity for detecting underdosing and overdosing was reached with an aPTT cut-off value of 45 and 51 seconds, respectively.

The results of our study are in line with results of previous studies on this subject.[9,10] Takemoto *et al.* found a poor correlation between aPTT and anti-Xa and elucidated which acute phase reactants were associated with a disproportionately low and high aPTT. The study demonstrated that low factor II activity resulted in a discordantly high aPTT for a given anti-Xa activity level. Conversely, discordantly low aPTT values were noted for a given anti-Xa in the presence of elevated factor VIII activity.[10] Since our study had a retrospective nature, we were unable to investigate the interaction with acute phase reactants in our patients. According to other studies, critically ill patients often have aberrant levels of acute phase proteins, which may lead to a shortened or a prolonged aPTT.[11-13] Although there is a relationship between the UFH level and the aPTT, the relationship is weak and the aPTT is associated with both significant intra- and inter-patient variability.[7,14]

Although the aPTT is considered a global assessment of coagulation status, it is not designed to detect either a thrombotic or a bleeding event. The anti-Xa level represents the level of heparinisation and does not reflect either thrombosis or bleeding. Therefore, the cross-tabulation with clinical outcomes should be considered an overview of the clinical outcomes according to the patient's coagulation status rather than an evaluation of the diagnostic value to detect thrombosis or a bleeding. Conflicting data exist about higher heparin doses or excessively prolonged aPTT and its effect on haemorrhagic risk.[15-17] However, patient-specific factors are likely to be important contributors to the bleeding risk in patients on UFH treatment, with increased risk of bleeding seen in the context of older age,[18] concomitant treatment with antiplatelet drugs[19] and the presence of other haemostatic defects.[20]

Since our study involved multiple measurements per patient, we had to conduct a specific statistical analysis to reduce the potential bias of repeated measurements. There was no significant bias from multiple measurements per patient, suggesting that multiple measurements were included from individuals with both concordance and discordance. However, the analysis of variance did slightly increase the sensitivities of detecting both UFH underdosing and overdosing with the aPTT when compared with the raw statistics. This is the result of a situation with a smaller intra-patient variability than the inter-patient variability. A repeated measurements design increases the sensitivity of a test when subjects serve as their own controls, and thus inter-subject variation is not a problem.[21]

The limitations of our study merit some consideration. First, this analysis was designed as a pilot study to investigate the accuracy of the aPTT in patients admitted to the ICU. Because of the small sample size, the probability of a type II error is conceivable. Consequently, it should be recognised that showing a reduction in thrombosis or bleeding according to the patient's coagulation status based on the aPTT or anti-Xa would require an extremely large, prospective study design. Second, anti-Xa assays were only performed in patients in whom a discordantly low aPTT was suspected. This may have caused a significant bias in the selection of patients. To obtain an unbiased judgment of the value of the aPTT, paired measurements of aPTT and anti-Xa should be compared in all patients treated with UFH.

Another limitation is that the outcomes analysed in this study are based on surrogate markers of heparin effect, rather than in terms of clinical outcomes such as rates of thrombosis and bleeding. Since there is a lack of evidence about clinical outcomes related to anti-Xa levels, open questions remain about whether the anti-Xa should be considered to be the gold standard. In a population of patients aged less than 1 year, Gruenwald *et al.* found no correlation between whole blood heparin concentrations and anti-Xa levels.[22]

Although UFH overdosing does not occur often, the aPTT is not adequate to detect UFH overdosing, with a low sensitivity of 0.37. Conversely, UFH underdosing occurs more often, but the aPTT is also unreliable to detect this effect, with a sensitivity of 0.63. Although an AUC of 0.81 seems somehow reliable for detecting overdosing by means of the aPTT, it should be considered that the ROC curve is a combination of sensitivity and specificity. Therefore, a high specificity for several cut-off values can result in a reasonable AUC, despite the fact the sensitivity is dramatic for most cut-off values.

In conclusion, in critically ill patients, the aPTT is less accurate than the anti-Xa in detecting UFH underdosing and overdosing. We suggest to use the anti-Xa assay for the monitoring of UFH treatment in critically ill patients with an increased risk of bleeding.

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DISCLOSURE

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