COMPARISON OF APTT AND THROMBOELASTOGRAPHY (TEG) TO BLEEDING TENDENCY IN CRITICALLY ILL COVID-19 PATIENTS TREATED WITH HEPARIN

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ABSTRACT

Background: Hypercoagulation in COVID-19 is known to increase the risk of vascular thromboembolism and mortality. Unfractionated Heparin (UFH) is an anticoagulant used to prevent venous thromboembolism. Inadequate dose causes unachieved therapeutic targets, while large dose increases the risk of bleeding. For this reason, the laboratory marker that has most sensitive to detect bleeding tendency is of utmost importance. APTT is a common laboratory test used to therapeutic targets but its sensitivity is still debatable. Thromboelastography (TEG) seems more promising for this purpose in other clinical condition. This study is aimed to compare APTT and Thromboelastography (TEG) in detecting bleeding tendency in critically ill COVID-19 patients treated with heparin.

Methods: This study is an analytic observational study in a retrospective design. The method used is total sampling, through several inclusion criteria. Inclusion criteria include: age >18-year-old, confirmed COVID-19 with RT-PCR results, hospitalized in Special Isolation Room, received UFH therapy, and examined for TEG and APTT at the same time. The subjects of this study were divided into two groups, the bleeding and non-bleeding groups. Suitability in APTT between the two groups were analyzed using the Kappa test, suitability in various TEG parameters were analyzed using the Kappa test, and differences APTT and TEG were analyzed using Fisher's exact test.

Results: This study showed that there were significant differences in the APTT and had a weak concordance for the incidence of bleeding in these two groups (p: 0,002; k: 0,340); significant differences in various TEG parameters ($p < 0,05$), namely R time (k: 0,340), K time (k: 1,0), α angle (k: 0,821), MA (k: 0,701) and CI (k: 1,0), but LY30 no significant difference ($p > 0,05$). K time and CI had a perfect concordance for the incidence of bleeding. In addition, there was a significant difference in APTT and TEG between the two groups (p: 0.000).

Conclusion: TEG shows better description the bleeding condition compared to APTT in critical COVID-19 patients treated with heparin.

Keywords: COVID-19, Hypercoagulation, Unfractionated Heparin (UFH), Thromboelastography (TEG), APTT, and bleeding conditions.

INTRODUCTION

The 2019 coronavirus disease (COVID-19) outbreak has contributed to significant deaths in several countries with the number of infected cases increasing exponentially worldwide (1). Several causes have contributed severe clinical conditions and one of them is coagulation

disorder that mimic systemic coagulopathy associated with severe infection, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. COVID-19 coagulopathy has distinct features (2). Most typical finding in patients with COVID-19 is an increase in the concentration of D-dimer (1). This indicates a hypercoagulable state that can increase the risk of venous and arterial thromboembolic complications in all organs including the lung and the heart, resulting in the increase of mortality (2,3).

The histologic features of the lung in fatal cases of COVID-19 are diffuse exudative or proliferative alveolar damage, with a viral cytopathic effect involving the alveolar epithelium and small airways, and slight lymphocytic infiltration. Pathological observations support the concept of hypercoagulation status in critically ill COVID-19 patients suggesting that the frequency of pulmonary micro thrombosis is high (4).

In hospitalized COVID-19 patients, it is important to provide prophylactic therapy to avoid vascular thromboembolism (5). Inadequate administration of hypercoagulation therapy may explain the high incidence of COVID-19 deaths. This may be associated with potentially preventable microvascular and macrovascular thrombosis (6). The drugs used to inhibit thrombus formation in general are anticoagulants such as Enoxaparin, Unfractionated Heparin (UFH) and Fondaparinux. One choice of heparin use in critical ill patient because it has a protamine antidote where if bleeding occurs, restoration of hemostasis is expected 3-4 hours after antidote administration and also of its anti-inflammatory effect (7).

APTT assay serves to measure the integrity of the intrinsic pathway and the general pathway by which heparin acts (8). Therefore, the APTT examination is commonly needed as a monitoring of the achievement of therapeutic doses and aims to minimalize bleeding. Latest studies showed that the response of patients receiving heparin therapy depict different levels of APTT, therefore parameter of successful therapy is also uncertain (7).

Thromboelastography (TEG) examination makes it possible to study the contribution of various cellular and enzymatic elements in the coagulation process and provides information about the strength of the blood clot. This continues until fibrinolysis occurs (9). TEG has several parameters such as R-time (coagulation initiation time), K-time (fibrin formation time), α angle (fibrin formation rate), MA (blood clotting diameter and strength), CI (coagulation index), and LY30 (degree of fibrinolysis) (10). Moreover, TEG is a test that can be performed at the bedside. This can indicate a more specific disorder such as a coagulation factor deficit and/or platelet deficiency or dysfunction. The disadvantage of this examination is a higher price than the APTT examination (11).

Another study of TEG's utility to detect hypercoagulability in adult patients at post cardiac surgery using Cardio Pulmonary Bypass in ICU was performed, and its result showed that 17 patients or 56,7% of the total TEG test results had hypercoagulability. An interesting thing found in this study was more than half of the patients had hypercoagulability characteristics in the TEG test. More than half of these patients had a history of CABG, whereas the rest of them had a history of valve surgery and TOF. This study results suggested that TEG was better in detecting hypercoagulability, consistent with the absence of clinically significant bleeding (12)

This observation has prompted researchers to know when a TEG examination is needed and to what extent TEG can assist the APTT examination to monitor of the effects of heparin administration. Therefore, this study was prepared with the aim to compare APTT and Thromboelastography (TEG) to the incidence of bleeding in critically ill COVID-19 patients treated with heparin.

METHOD

This study was an analytic observational study in a retrospective design. This research was conducted in the period of March-July 2021, with the study population including critically ill patients who were confirmed to have COVID-19 in Special Isolation Room 1 (RIK-1) Dr. Soetomo Hospital Surabaya. Inclusion criteria include: age >18 year-old, confirmed COVID-19 with RT-PCR results, hospitalized in Special Isolation Room, received UFH therapy, and examined for TEG and APTT at the same time

The study included total sampling of all patients met inclusion criteria in a period of 8 months from May to December 2020 through a consecutive sampling technique. Samples that met the inclusion and exclusion criteria were recorded for age, gender, comorbidities, D-dimer, presence of bleeding incidence, TEG and APTT results during ICU care in the data collection sheet. The D-dimer, APTT and TEG examination were checked at the same time and taken on day 3-7 during ICU care. It was processed with the SPSS Statistic Ver 26.

RESULT

Characteristics of Research Subjects

There were 79 of patient's medical record fulfilled the inclusion criteria. Data characteristic can be seen in table 1.

Table 1. Characteristics of Subjects.

Characteristics	N (%)	Mean ± SD	Median
Age (year)	79 (100%)	51,48 ± 11,434	53 (26 – 79)
Gender Male Female	 53 (67,1%) 26 (32,9%)		
BMI (kg/m^2)	79 (100%)	27,88 ± 5,740	26,67 (18,37 – 50,78)
Comorbidity Diabetes Mellitus Obesity Hypertension	 20(25,3%) 35(44,3%) 36(45,6%)		
Bleeding Incidence Yes No	 9 (11,4%) 70 (88,6%)		

D-dimer (ng/mL) Bleeding No	 9 (11,4%) 70 (88.6%)	 6485,56 ± 6594,33 4181,09 ± 5246,06	 4580 (620 –19150) 2310 (217 –29280)
TEG day-	79 (100%)	4,54 ± 1,631	5 (3 – 7)

TEG day- refers to the length of ICU stay (day) that TEG was performed

Based on table 1, the median age of the patients was 53 years with a range of 26 – 79 years old. The BMI mean was 27.88 kg/m2. TEG examination was performed between days 3-7 during ICU care. The mean level of D-dimer in the bleeding group was 6485,56 ng/mL, while in the non-bleeding group it was 4181.09 ng/ml. most of patients were male (67.1%). Frequency comorbidities of hypertension, obesity and Diabetes Mellitus are 45,6%, 44,3% and 25,3% respectively. Profile bleeding tendency was not observed in 88,6% of patients of APTT and TEG's parameters can be seen in table 2.

The parameters observed in this study were APTT and various TEG parameters such as R time, K time, angle, Maximum Amplitude (MA), Coagulation Index (CI), LY30 in both group (table 2).

Table 2. Data on Mean, Standard Deviation, Median, Minimum and Maximum Value of Variables in the Bleeding and Non-Bleeding Groups.

Variable	Bleeding	N = 79 (100%)	Mean ± SD	Median
APTT (<40 seconds)	Yes No	9 (11,4%) 70 (88,6%)	38,49 ± 11,82 29,54 ± 5,98	34,50 (26,8 – 62,6) 29,6 (18 – 51,2)
R (2-8 minutes)	Yes No	9 (11,4%) 70 (88,6%)	7,60 ± 2,08 4,28 ± 1,89	7,90 (4,2 – 10,6) 4,15 (0,2 – 9,7)
K (1-3 minutes)	Yes No	9 (11,4%) 70 (88,6%)	4,50 ± 1,24 1,32 ± 0,54	4,70 (3,2 –6,8) 1,20 (0,5 –3,0)
α angle (55^{o}-78^{o})	Yes No	9 (11,4%) 70 (88,6%)	42,64 ± 8,19 71,41 ± 8,09	41,60 (31,3 –55,6) 73,25 (43,7 –91,5)
MA (51-69 mm)	Yes No	9 (11,4%) 70 (88,6%)	47,13 ± 7,52 73,01 ± 1,24	45,50 (36,8 –62,4) 74,95 (43,1 –95,0)
CI (-3 – 3)	Yes No	9 (11,4%) 70 (88,6%)	-5,43 ±1,50 3,25 ± 2,30	-5,4 (-7,4 –-3,3) 3,60 (-2,5 –7,4)
LY30 (1-3%)	Yes No	9 (11,4%) 70 (88,6%)	8,20 ± 16,60 8,62 ± 1,40	0,8 (0 – 50,8) 3,70 (0 – 79,6)

Comparison of patients who were examined for APTT in the Bleeding and Non-Bleeding Groups showed in Table 3

Table 3. Comparison of Patients who were Examined for APTT in the Bleeding and Non-Bleeding Groups.

Bleeding	APTT		N (%)	P (k) value
	Suitable	Not suitable		
Yes	3 (33,3%)	6 (66,7%)	9 (100%)	0,002 (0,340)
No	67 (95,7%)	3 (4,3%)	70 (100%)	

APTT value suitable for bleeding group ≥ 40 second, and APTT value suitable for non-bleeding group < 40 detik

Table 3 shows the details of APTT value which is within normal range or already prolonged in patients who have bleeding tendency or not. In the bleeding group, 6 out of 9 (66,7%) patients have normal APTT (< 40 seconds), 3 out of 9 (33.3%) patients have APTT ≥ 40 seconds, which are in the expected range of APTT. In the non-bleeding group, 67 out of 70 (95,7%) patients have normal APTT (<40 seconds), 3 out of 70 (4.3%) patients have prolonged APTT (≥ 40 seconds). Statistically, the APTT can be used to identify abnormalities in hemostatic function, but when tested for kappa, it shows a weak concordance for the incidence of bleeding.

Comparison of patients with various TEG parameters in the bleeding and non-bleeding groups showed in table 4

Table 4. Comparison of patients with various TEG parameters in the bleeding and non-bleeding groups.

Bleeding	R time (minute)		N (%)	p (k) value
	Suitable	Not suitable		
Yes	3 (33,3%)	6 (66,7%)	9 (100%)	0,002 (0,340)
No	67 (95,7%)	3 (4,3%)	70 (100%)	
	K time (minute)			
	Suitable	Not suitable		
Yes	9 (100%)	0 (0%)	9 (100%)	<0,001 (1,0)
No	70 (100%)	0 (0%)	70 (100%)	
	α angle (°)			
	Suitable	Not suitable		
Yes	8 (88,9%)	1 (11,1%)	9 (100%)	<0,001 (0,821)
No	68 (97,1%)	2 (2,9%)	70 (100%)	
	MA (mm)			
	Suitable	Not suitable		
Yes	7 (77,8%)	2 (22,2%)	9 (100%)	<0,001 (0,701)
No	67 (95,7%)	3 (4,3%)	70 (100%)	
	CI			
	Suitable	Not suitable		
Yes	9 (100%)	0 (0%)	9 (100%)	<0,001 (1,0)
No	70 (100%)	0 (0%)	70 (100%)	

	LY30			
	Suitable	Not suitable		
Yes	3 (33,3%)	6 (66,7%)	9 (100%)	0,270 (-0,078)
No	33 (47,1%)	37 (52,9%)	70 (100%)	

Suitable criteria for bleeding group : R time > 8 minute, K time > 3 minute, α angle < 55º, MA < 51 mm, CI < -3, LY30 > 3% respectively whereas suitable criteria for non-bleeding group : R time ≤ 8 minute, K time ≤ 3 minute, α angle ≥ 55º, MA ≥ 51 mm, CI ≥ -3, LY30 ≤ 3% respectively.

From table 4, in the bleeding group where the TEG parameter indicates a condition of hypo-coagulation. We can see that R time >8 minutes (33.3%), K time >3 minutes (100%), α angle <55º (88.9%), MA <51 mm (77.8%), CI <-3 (100%), and LY30 >3% (33.3%). The calculation results show that there is match between R time, K time, α angle, MA and CI with expected bleeding ($p<0.05$) where K time and CI are the most reliable value with perfect strength ($k=1.0$). Meanwhile, LY30 did not ($p>0.05$).

Comparison of patients who were examined for APTT and TEG in the Bleeding and Non-Bleeding Groups

The results from Fisher's Exact test showed that there was a significant difference in APTT and TEG between the groups that experienced bleeding and those who did not (p: 0.000). The results showed that 9 out of 9 patients have bleeding (100% TEG showed hypo-coagulation according to TEG+ criteria), where 3 out of 9 patients (33.3%) have abnormal prolonged APTT (APTT+). Meanwhile, in the non-bleeding group, there were no TEG abnormalities or hypercoagulable conditions, but 3 out of 70 patients (4.3%) have abnormal prolonged APTT without bleeding. It is in determine of bleeding that the TEG parameter is superior to the APTT examination (table 5).

Table 5. Comparison of patients who were examined for APTT and TEG in the Bleeding and Non-Bleeding Groups

Bleeding	TEG + APTT +	TEG + APTT -	TEG - APTT +	TEG - APTT -	P value
Yes	3 (33,3%)	6 (66,7%)	0 (0%)	0 (0%)	0.000
No	0 (0%)	0 (0%)	3 (4,3%)	67 (95,7%)	

TEG + : hypocoagulation conditions (R time > 8 minute, K time > 3 minute, α angle < 55º, MA < 51 mm, CI < -3, LY30 > 3%); TEG - : hypercoagulable or normal condition (R time ≤ 8 minute, K time ≤ 3 minute, α angle ≥ 55º, MA ≥ 51 mm, CI ≥ -3, LY30 ≤ 3%); APTT + : ≥ 40 seconds, APTT - : < 40 seconds.

DISCUSSION

Comparison of APTT in the Bleeding and Non-Bleeding Groups

Heparin works by binding to antithrombin III (AT III) and accelerating the reaction of AT III to inhibit blood clotting factor proteases, namely thrombin (IIa), IXa, and Xa. The main complication of heparin administration is bleeding. The intrinsic pathway in the coagulation cascade begins with the activation of factors XIIa, XIa, and IXa. Then it enters the general pathway, namely activating factor Xa, IIa (thrombin), and converting fibrinogen into fibrin (13).

The APTT examination serves to measure the integrity of the intrinsic pathway and the general pathway where heparin works (8). Moreover, the APTT examination is needed to monitor the achievement of therapeutic doses and does not cause bleeding complications (7).

In this study, two-thirds of patients in the bleeding group did not show prolonged APTT (range <40 seconds) and only one-third were in accordance with the current practice. Meanwhile, not all the non-bleeding group have normal or hypocoagulation according to APTT examination. When tested for suitability (Kappa test), APTT can show the ability to identify abnormalities of hemostasis function but shows a weak correlation with bleeding conditions. Therefore, the APTT cannot adequately assess the state of bleeding due to heparin administration. Therefore, it indicates the failure of the APTT examination to identify the effect of heparin therapy and assess the coagulation state of the patient appropriately. Previous study by van Roesse et al., have shown that the accuracy of the APTT in critically ill patients requiring heparin therapy have a lower sensitivity than anti-Xa levels. Although the APTT is considered a global assessment of coagulation status, it is not designed to detect thrombotic or bleeding processes (14).

This refers that the APTT can show the suitability of the results to clinical patients without bleeding (95.7%). While the APTT (with normal range <40) could not show a significant match in the bleeding group. This study used a 40 second APTT cut-off to differentiate normal and prolonged APTT. Further studies, a larger sample, and a new APTT cut-off may be needed.

Comparison of Various Thromboelastography (TEG) Parameters in the Bleeding and Non-Bleeding Groups

Most of COVID-19 patients are in a hypercoagulable state, especially severe and critically ill cases. The pathogenesis of hypercoagulability in COVID-19 is thought to be due to systemic inflammation and endothelial disorders that cause hypercoagulability. These findings may explain the incidence of pulmonary embolism and/or venous thromboembolism (VTE) observed in some of these patients and support the administration of prophylactic/antithrombotic treatment with LMWH or unfractionated heparin (15).

In this study, the non-bleeding group was eight fold higher than the bleeding group when the TEG examination was performed. The results indicate that there is a suitability between R time, K time, α angle, MA and CI with bleeding condition where K time and CI have perfect strength. However, LY30 shows the opposite. It is parallel with previous study by Llitjos et al in France who reported a VTE incidence of COVID-19 patients in the ICU of 69% (16). In hypercoagulable conditions, the TEG image was obtained in the form of a decrease in R time and K time and an increase in angle, MA and CI. Several studies have shown that MA on TEG is used to monitor patients at risk for hypercoagulation during surgery (17).

Previous study by Al-Samkari et al reported 7.6% bleeding conditions in critically ill COVID-19 patients, with major bleeding (5.6%) (18). In conditions with deficiency of coagulation factors such as hypofibrinogenemia, thrombocytopenia or thrombocytopenia, an increase in R time, K time, LY30 and a decrease in angle, MA, and CI (19).

Comparison of APTT and TEG in the Bleeding and Non-Bleeding Groups

Thromboelastography (TEG) examination makes us possible to study the contribution of various cellular and enzymatic elements in the coagulation process and provides information about the strength of the blood clot. This continues until the occurrence of fibrinolysis, so that it can describe the details of coagulation (9). TEG has several parameters such as R-time, K-time, angle, Maximum Amplitude (MA), Coagulation Index (CI) and LY30 (10). These can indicate a more specific disorder such as a coagulation factor deficit and/or platelet deficiency or dysfunction (11).

Similar to the results of this study, where two thirds of patients with normal APTT had hypo-coagulation TEG (R time > 8 minutes, K time > 3 minutes, angle < 55^o, MA < 51 mm, CI < -3, LY30 > 3%). In the non-bleeding group, most of the APTT was normal and the TEG showed normal or hypercoagulable conditions (R time 8 minutes, K time 3 minutes, angle 55^o, MA 51 mm, CI -3, LY30 3%).

Examination of TEG parameters in patients with normal and prolonged APTT shows hypo-coagulable or hypercoagulable conditions. This is in accordance with the study of Kim et al who performed TEG examination in septic shock patients with normal PPT and APTT, but hypocoagulability or hypercoagulability conditions were obtained with TEG (20).

CONCLUSION

TEG shows better description of bleeding condition compared to APTT in critical COVID-19 patients treated with heparin.

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