Clinical Research

Thromboelastographic method for early decision on anticoagulant therapy in moderate to severe COVID-19 patients

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pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.oa.225890
Med J Indones. 2022;31:96–101

Received: November 09, 2021
Accepted: June 01, 2022
Published online: July 14, 2022

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ABSTRACT

BACKGROUND Coagulopathy is a serious COVID-19 complication that requires rapid diagnosis and anticoagulation. This study aimed to determine the role of coagulation examination using thromboelastography (TEG) on the decision-making time of anticoagulant therapy in COVID-19 patients and its clinical outcomes.

METHODS A prospective observational study was conducted in Cipto Mangunkusumo Hospital, Indonesia, from October 2020 to March 2021. We consecutively recruited moderate and severe COVID-19 patients in the high and intensive care units. Turnaround time, time to anticoagulant therapy decision, and clinical outcomes (length of stay and 30-day mortality) were compared between those who had a TEG examination in addition to the standard coagulation profile examination (thrombocyte count, PT, APTT, D-dimer, and fibrinogen) and those who had only a standard coagulation profile laboratory examination.

RESULTS Among 100 moderate to severe COVID-19 patients recruited, 50 patients had a TEG examination. The turnaround time of TEG was 45 (15–102) min *versus* 82 (19–164) min in the standard examination ($p<0.001$). The time to decision was significantly faster in the TEG group than the standard group (75 [42–133] min *versus* 184 [92–353] min, $p<0.001$). The turnaround time was positively correlated with time to decision ($r = 0.760$, $p<0.001$). However, TEG did not improve clinical outcomes such as length of stay (10.5 [3–20] *versus* 9 [2–39] days) and 30-day mortality (66% *versus* 64%).

CONCLUSIONS The TEG method significantly enables quicker decision-making time for moderate to severe coagulation disorder in COVID-19 patients.

KEYWORDS blood coagulation disorder, COVID-19, intensive care unit, mortality, thromboelastography

Coagulopathy is a serious complication in coronavirus disease 2019 (COVID-19). Severe COVID-19 patients have all of the Virchow triad factors consisting of endothelial injury, stasis due to immobilization, and hypercoagulable state.[1] They had been found to have a hypercoagulable state along with severe inflammation, indicated by an increase in coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), platelets, factor VIII activity, fibrinogen, and D-dimer as well as clot strength.[2,3] Hypercoagulability justified the increased rate of thromboembolic events in major venous and arterial vessels, such as pulmonary embolism, deep vein thrombosis, and stroke in COVID-19 patients.[4,5] Moreover, post-mortem examinations showed that COVID-19 patients also have microthrombus in the alveolar capillaries or thrombosis in medium-sized vessels.[6–9] These findings prompted clinicians to support anticoagulation use for COVID-19 patients, but the

type, duration, and dose of the anticoagulant should be adjusted based on individual's risk of bleeding, age, weight, and creatinine clearance.[10]

Due to its association with life-threatening thromboembolic events and mortality, prompt and accurate investigations are needed to diagnose coagulation disorders, make personalized decisions for anticoagulant therapy, and monitor the outcomes. Rapid diagnosis and subsequent therapy are important because the improvement of coagulation derangements after anticoagulant therapy showed a time-related pattern, although clinical evidence regarding the timing of anticoagulation administration in COVID-19 patients remains scarce.[3,11] The standard diagnostic tests for COVID-19 patients' coagulation status are blood platelet count, PT, APTT, D-dimer, and fibrinogen level. Unfortunately, these tests are usually done in a centralized hospital laboratory, with results received after 4–6 hours. In a setting during peaks of the COVID-19 pandemic, the turnaround time for even routine laboratory tests would be longer, making it nearly impossible to initiate individualized anticoagulant therapy immediately.[12]

Thromboelastography (TEG) is an alternative method to measure clotting capacity that is superior for comprehensiveness, practicality, and time efficiency because it uses whole blood samples instead of plasma in a standard coagulation panel.[13] TEG gives a more comprehensive coagulation function because it considers viscoelastic clot characteristics, platelet function, and fibrinolysis activity from whole blood.[13] A systematic review concluded that TEG parameters, such as high maximum amplitude (MA) and clot lysis at 30 min (LY30), showed a consistent pattern in COVID-19 coagulopathy.[14] Moreover, the examination can be done at the patient's bedside, and the results are relatively quick. The results are relatively simple and conclusive to be interpreted by any health worker.[13] Thus, TEG is useful for assessing the hypercoagulable state, enabling early diagnosis and treatment, and subsequently lowering complications and mortality in COVID-19 patients.[14] However, no studies have established and quantified the time efficiency of TEG and its effects on clinical outcomes in COVID-19 patients. This study aimed to compare the role of TEG *versus* standard coagulation panel for determinig the turn around time, decission making time, and clinical outcomesin moderate to severe COVID-19 patients.

METHODS

Study design

This prospective observational study was conducted from October 2020 to March 2021 in the high care unit (HCU) and intensive care unit (ICU) at Kiara Ultimate, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. This research was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital (No: KET-1023/UN2.F1/ETIK/PPM.00.02/2020). Informed consent was provided to the patient's family. This study was retrospectively registered in ClinicalTrials.gov with the registration number (NCT05343728).

Population and samples

The study population was patients who had confirmed COVID-19 and underwent treatment at Cipto Mangunkusumo Hospital from October 2020 to March 2021. Subjects were eligible if they were adults (aged >18 years) who had positive severe acute respiratory syndrome coronavirus 2 nasopharyngeal swab examination with moderate to severe clinical symptoms. We defined moderate COVID-19 as patients with clinical signs of pneumonia with SpO_2 >93% in room air and severe COVID-19 as pneumonia with SpO_2 ≤93% in room air or ventilator support requirement.[15] The exclusion criteria were pregnant women, patients with a history of blood clotting disorders, and patients who had contraindications to anticoagulant therapy, such as platelet count <25×10⁹/l, bleeding manifestations, or history of allergy to heparin or heparin-induced thrombocytopenia. Subjects were removed from the study if the data on length of stay in the higher care and death within 30 days were not available. We calculated the minimum sample requirement with an expected improvement of 25% with α of 5% and β of 20%, consisting of 96 patients. The samples were enrolled by the consecutive sampling method.

Data collection

The baseline characteristic data collection was carried out when the patient was admitted to the ICU or HCU. Then, venous blood was taken by nurses within 30 min of admission. The samples were sent to the centralized hospital laboratory for a standard hemostasis panel that consisted of platelets, PT/APTT, fibrinogen, and D-dimer. The hospital used Sysmex® CS-2500 and 5100 (Sysmex Corp., Japan) for coagulation

tests using plasma-derived from centrifuged whole blood samples.

In the TEG group, we performed a bedside TEG examination using TEG 5000 Hemostasis Analyzer (Haemonetics Corp., USA) with 2.5 ml of a whole blood sample. Samples of patients with heparin thromboprophylaxis were given heparinase, which binds to heparin so that the coagulation profile can be assessed. Except for the TEG group, all patients received equal diagnostic tests and treatment, including anticoagulant therapy, as indicated according to the national guideline.[15] However, the guideline did not provide the algorithm for anticoagulation use based on the TEG result. Thus, the decision of anticoagulant therapy was made by an attending anesthesiologist with >5 years of experience based on clinical presentation, TEG pattern, and parameters such as shortened reaction time (R) and clot formation time (K).[2,16] The type and dose of anticoagulant were determined based on kidney function and body mass index.[15] Moreover, MA and alpha angle values that indicated any sign of thrombocyte dysfunction were used as a basis to avoid heparin.[16] The decision would be modified if needed after a complete laboratory result was obtained.

A trained doctor from the research team recorded the time from blood samples taken until the coagulation panel or TEG results were obtained (result turnaround time). We also recorded the time from the samples obtained to the time of the anticoagulant therapy decision made by the attending physician (time to anticoagulation decision) based on the national guideline. The test result timestamp, anticoagulant therapy decision timestamp, mortality, and length of stay in the higher care were objectively retrieved through online medical records.

Statistical analysis

The data analysis was performed using SPSS software version 22.0 (IBM Corp., USA) for Mac. On numerical data, a normality test was performed using the Kolmogorov–Smirnov test. The data were normally distributed if *p*-value was >0.05. Data were presented with a mean (standard deviation) if the distribution was normal or median (min–max) if the distribution was not normal. The analysis for numerical outcome was performed using the student's *t*-test or Mann–Whitney *U* test. Nominal outcomes were analyzed using the Chi-square or Fischer's exact tests. Correlation between numerical variables was done using Pearson or Spearman correlation.

RESULTS

A total of 100 subjects, consisting of 50 patients with TEG and 50 patients without TEG, were included. No samples were dropped out. The demographic and clinical characteristics of the subjects in the TEG and standard groups showed that data tended to be comparable. The demographic, clinical, and laboratory characteristics of each group can be seen in Table 1. Only 4% of samples had no known comorbidities.

Table 2 summarizes the outcomes of the research. This study found that the TEG group had a shorter coagulation test turnaround time than the standard group. Patients in the TEG group also had a similarly shorter time to anticoagulant therapy decision by the attendings compared with the control. Spearman correlation test revealed a positive linear correlation between the turnaround time and time to therapy decision ($r = 0.760$, $p<0.001$). However, there was no difference in length of stay in higher care nor mortality risk in 30 days between the TEG and standard groups, with a relative risk for mortality of 1.03 (95% confidence interval: 0.77–1.38).

DISCUSSION

Rapid recognition of hypercoagulable state and subsequent prompt decision-making for anticoagulant therapy in moderate to severe COVID-19 patients are important in reducing the risk of life-threatening thrombotic events and mortality.[17] This study included 100 cases of COVID-19 with moderate to severe clinical symptoms treated in the ICU and HCU in a tertiary-level hospital from October 2020 to March 2021 to explore the feasibility and benefit of TEG as an alternative to the standard coagulation panel for recognizing hypercoagulability. To the best of our knowledge, this study was the first to establish the role of TEG *versus* standard coagulation panel for faster turnaround time and faster time to anticoagulant therapy decision in moderate to severe COVID-19 patients. However, this study did not find the effect of TEG on clinical outcomes, such as 30-days mortality and length of stay in the higher care units.

This study established that TEG produced a significantly faster result than the standard laboratory

Table 1. Demographic, clinical, and laboratory characteristics of the subjects

Variables	TEG group (N = 50)	Standard group (N = 50)	*p*
Age (years), mean (SD)	56.62 (13.14)	58.0 (10.88)	0.569
Male sex, n (%)	22 (44)	39 (78)	**<0.001**†
Height (cm), median (min–max)	159 (149–175)	165 (150–178)	0.053
Weight (kg), mean (SD)	65.0 (12.09)	68.24 (12.55)	0.192
BMI, median (min–max)	24.75 (17.8–40)	24.30 (18.40–40.1)	0.751
Comorbidities, n (%)			
Hypertension	23 (46)	26 (52)	0.548
Heart failure	1 (2)	1 (2)	1.000
DM	19 (38)	28 (56)	0.071
Previous lung disease	1 (2)	0 (0)	1.000
Malignancy	1 (2)	1 (2)	1.000
Others*	7 (14)	3 (6)	0.182
Anticoagulants, n (%)	30 (60)	37 (74)	0.137
Types of anticoagulants, n (%)			0.213
Enoxaparin	1 (3)	5 (14)	
Heparin	29 (97)	32 (86)	
Severity of COVID-19, n (%)			0.275
Severe	44 (88)	40 (80)	
Moderate	6 (12)	10 (20)	
Hemostasis and coagulation parameters			
Platelets ($\times 10^9$/l), mean (SD)	237.53 (111.51)	258.13 (140.94)	0.500
PT (vs. control), median (min–max)	1.00 (0.80–2.2)	1.00 (0.04–1.70)	0.378
APTT (vs. control), median (min–max)	1.20 (0.60–5.50)	1.20 (0.01–3.80)	0.207
Fibrinogen (g/l), median (min–max)	549.95 (408.98–745.55)	595.10 (441.70–780.20)	0.493
D-dimer (µg/ml), median (min–max)	3,520 (160.0–35,200)	2,550 (227–35,200)	0.554
TEG profile, median (min–max)			
R time (min)	6.80 (1.0–24.10)	-	-
K time (min)	1.80 (0.80–9.10)	-	-
Alpha angle (°)	65.50 (9.60–79.50)	-	-
MA (mm)	61.70 (9.20–78.60)	-	-
G (dynes/cm^2)	8.05 (0.50–18.40)	-	-
EPL	0.80 (0.0–72.20)	-	-
A (mm)	56.05 (8.20–74.90)	-	-
CI	-0.15 (-16.0–13.70)	-	-
LY30 (%)	1.10 (0.0–12.10)	-	-

A=amplitude; APTT=activated partial thromboplastin time; BMI=body mass index; CI=coagulation index; COVID-19=coronavirus disease 2019; DM=diabetes mellitus; EPL=estimated percent lysis; G=generated value; HCU=high care unit; ICU=intensive care unit; K time=clot formation time; LY30=clot lysis at 30 min; MA=maximum amplitude; PT=prothrombin time; R time=reaction time; SD=standard deviation; TEG=thromboelastography
*Other comorbidities included obesity, myasthenia gravis, systemic lupus erythematosus, chronic kidney disease, and severe pre-eclampsia; †Chi-square test, $p<0.05$ was considered significant

Table 2. Clinical and laboratory outcomes measured in TEG *versus* standard groups

Outcomes	TEG group	Standard group	*p*
The turnaround time to the result of the coagulation profile (min), median (min-max)	45 (15–102)	82 (19–164)	**<0.001***
The time to anticoagulant therapy decision by HCU/ICU attendings (min), median (min-max)	75 (42–133)	184 (92–353)	**<0.001***
Severe COVID-19 patients	72 (42–133)	181 (92–353)	**<0.001***
Moderate COVID-19 patients	65.50 (52–112)	187.50 (165–277)	**0.001***
Length of stay in the higher care (days)	9 (2–39)	10.50 (3–20)	0.316
Death, n (%)	33 (66)	32 (64)	0.834

COVID-19=coronavirus disease 2019; HCU=high care unit; ICU=intensive care unit; TEG=thromboelastography
*Mann–Whitney *U* test, $p<0.05$ was considered significant. All timing parameters on the outcomes were counted since the blood samples were taken

to guide on the coagulation profile in COVID-19 patients. This finding might be caused by its feasibility to be performed at the bedside. Previously, TEG was used to help rapidly manage trauma-associated hemorrhage and cardiac surgery.[13] According to Galvez and Cortes,[16] the TEG examination performed at the bedside could be finished in 45–60 min. In this study, the median time required to obtain the coagulation profile results using the bedside TEG method was similar (45 [15–102] min). On the other hand, the time required for the standard laboratory results to be released was 82 (19–164) min. It is possible because TEG operates on whole blood samples compared to plasma for the standard coagulation laboratory, eliminating the need for centrifugation and other pre-analytical preparations. This benefit is especially highlighted in the pandemic setting, where a high volume of patients caused laboratories to be overflown with samples and made the result turnaround time more delayed.[12] This study found that the TEG method could be performed at the bedside as point-of-care testing for coagulation profile with a quicker result.

This study found a shorter decision time for anticoagulant therapy in patients whose coagulation profile was determined by TEG, compared with the standard coagulation panel. Further correlation analysis revealed a positive association between the time to anticoagulation decision and result turnaround time. The TEG test's comprehensive yet specific clotting capacity pattern may cause this result, compared with the standard panel. The standard coagulation panel showed the typical hypercoagulability profiles commonly found in COVID-19, such as a high D-dimer level on admission.[4] The samples also had increased fibrinogen levels that were unique to the hemostasis disorder in COVID-19 patients compared with the normal disseminated intravascular coagulation, as previously studied by Panigada et al.[2] Meanwhile, PT and APTT values were still within normal limits in both groups. So, it can be argued that the standard coagulation profile markers could not comprehensively capture the actual hypercoagulable state of COVID-19 patients. In contrast, TEG offers practical interpretation by assessing global coagulation function that is not covered by the standard coagulation panels and presenting easily recognizable patterns for specific conditions.[16] In this study, the patients' TEG examination showed a decrease in the profile of R time, K time, LY30, and an increase in MA, similar to previous studies.[5,14] These findings showed that TEG displayed a consistent pattern that could enable clinicians to recognize the pattern faster and accurately assess coagulation disorders in COVID-19 patients.

Finally, even though this study demonstrated that TEG enabled faster results and decision making, we found no associations between TEG for initiating anticoagulation and clinical outcomes, such as length of stay in the higher care and mortality in 30 days. Three possibilities might affect the result. Firstly, the baseline characteristic data showed that most patients were older adults and had multiple comorbidities. Therefore, although early diagnosis and subsequent treatment of COVID-19 coagulopathy would be beneficial for the patients, they were already at high risk of thrombotic complications and mortality.[7] Secondly, we did not record the exact timing of anticoagulation and could not rule out any delay in anticoagulant administration that requires manual labor from healthcare providers. Thirdly, faster decision-making found in this study

might not reach clinical significance because both groups had their anticoagulant decided in less than 24 hours. Previously, a large cohort found that prophylactic anticoagulation initiated within the first 24 hours of admission was vital to reducing 30-days mortality and deterioration.[11] However, the comparator in the study was no anticoagulation instead of delayed anticoagulation. Therefore, gaps remain for the best timing of anticoagulation initiation for moderate to severe COVID-19 patients to improve clinical outcomes.

Due to its nature as single-center data, this study had limitations on the variety of samples that could not yet represent the broader population in the ongoing pandemic conditions. Although this study clearly delineated inclusion and exclusion criteria, several other accompanying clinical conditions, such as impaired heart contractility, kidney function, and other conditions, might affect the process and results of the study, such as the accuracy of therapeutic decision-making, length of stay, and mortality in research subjects. Based on the result, we recommend doing a prospective multicenter study that explores the effect of TEG's role in enabling faster therapy decisions to more proximal outcomes, such as arterial or venous thrombotic events and bleeding incidence. The study should also delve deeper to find the best timing of starting anticoagulation to prevent thrombotic complications due to COVID-19.

In conclusion, the moderate to severe COVID-19 patients in the TEG group had a faster turnaround time than the standard group. The TEG method also enables a quicker decision-making time for anticoagulant therapy in moderate to severe COVID-19 patients. However, this study found no association between TEG use and mortality or length of stay.

Conflict of Interest

The authors affirm no conflict of interest in this study.

Acknowledgment

We would like to thank the Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital for helping to conduct this research and supporting the publication.

Funding Sources

None.

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