Correlation Between Platelet Aggregation Test With Maximum Amplitude Of Thromboelastography (Ma-Teg) Parameters In Covid-19 Patients At Rsu Dr. Soetomo Surabaya In Assessing The Function Of Platel

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Correlation Between Platelet Aggregation Test With Maximum Amplitude Of Thromboelastography (Ma-Teg) Parameters In Covid-19 Patients At Rsu Dr. Soetomo Surabaya In Assessing The Function Of Platelet

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Abstract

Background: Examination of the platelet aggregation test (PAT) and Maximum Amplitude – Thromboelastography (MA-TEG) are two ways of assessing platelet function. Examination of the platelet aggregation test aims to detect any disturbance of platelet function based on changes in light transmission after adding an agonist. At the same time, the MA parameter of TEG shows the strength of the clot, which is related to platelet count and function, as well as their interaction with fibrin. This study aims to analyze the relationship between the results of the platelet aggregation test and the MA parameter of TEG in assessing platelet function in COVID-19 patients. **Method**: The type of research used is correlation research with a sampling technique, purposive sampling. Examination of PAT used the Aggregometer Chrono-Log Model 490 while checking MA values used a Thromboelastography 5000. The correlations for the variables studied were analyzed statistically. **Results**: The results of PAT in COVID-19 patients for each agonist showed different results. Most of the epinephrine and ADP agonists (60%) showed normoaggregation. In comparison, most collagen agonists (66.6%) showed hypoaggregation, while the value of the parameter MA-TEG in COVID-19 patients showed increased results: 75.2 (34.8 – 82.2). The correlation between each PAT agonist and MA-TEG showed no correlation. This conclusion is drawn based on the p-value > 0.05. Each p-value between variables is epinephrine with MA-TEG = 0.689, ADP with MA-TEG = 0.945 and collagen with MA-TEG) = 0.282.**Conclusion**: There is no significant correlation between PAT and TEG's MA parameter in assessing platelet function in COVID-19 patients.

Keywords: COVID-19, Platelet Function, Platelet Aggregation Test, Maximum Amplitude, Thromboelastography

INTRODUCTION

COVID-19 has affected more than 200 countries, with more than 219 million cases, 4.55 million deaths, and a 4.3% mortality rate. In Southeast Asia, Indonesia is ranked first as the country with the most COVID-19 cases, with 4.2 million COVID-19 cases. The total number of deaths due to COVID-19 in Indonesia is 141 thousand and is the first rank for most deaths in Southeast Asia [1]. Case of coagulopathy in critically ill Covid-19 patients is an emergency for immediate treatment because it can cause morbidity and mortality. COVID-19 can significantly affect the hematopoiesis and hemostasis systems [2]. is due to increased proinflammatory cytokines such as IL-6, IL-10, and tumour necrosis factor (TNF). Then this cytokine storm will cause hyperinflammation, which is a condition where

there is an excessive and uncontrolled immune response. The hyperinflammation that occurs in COVID-19 causes increased activation of the coagulation cascade and excessive thrombin production. Hemostatic/coagulation disorders in COVID-19 cause a prothrombotic state, increasing the risk of thrombosis and venous and arterial thromboembolism [3]. This is associated with a significant increase in mortality[3] because thrombosis can trigger acute respiratory distress syndrome (ARDS), multiorgan failure, respiratory failure, and death. Despite receiving prophylactic anticoagulant therapy, an increase in thrombosis was found widely in critically ill COVID-19 patients [4].

One of the causes of thrombosis in COVID-19 patients is hyperactivity of platelet function. Where are conventional tests/screening for hemostatic examination such as platelet count, activated partial thromboplastin time (aPTT) for intrinsic pathway examination, international normalized ratio (INR), prothrombin time (PT) for extrinsic pathway examination, thrombin time (TT), fibrinogen level, and fibrin degradation products (FDPs), these tests examine the coagulation cascade separately, are time-consuming, slow therapy, and are unable to assess thrombotic function [5].

Examination of the platelet aggregation test and the maximum amplitude parameter from thromboelastography (MA-TEG) are two ways of assessing platelet function. Examination of the platelet aggregation test aims to detect platelet function disorders based on changes in light transmission after adding an agonist. This test is still the gold standard for assessing various platelet functions [6]. Agonists used to examine platelet aggregation tests include ADP (adenosine diphosphate), epinephrine, and collagen. At the same time, the MA parameter of TEG shows the strength of the clot, which is related to platelet count and function, as well as their interaction with fibrin. The MA value is strongly influenced by the number and function of platelets and is slightly affected by fibrinogen levels [5]. So far, no study in Indonesia has researched the correlation/relationship between the platelet aggregation test and the MA parameter of TEG in assessing platelet function in COVID-19 patients or the correlation/relationship of these two examination methods in assessing platelet function in certain diseases.

This study aimed to analyze the relationship between the results of the platelet aggregation test and the MA parameter of TEG in assessing function in COVID-19 patients at Dr Soetomo General Hospital Surabaya.

METHODS

Design and participants

A total of 30 patients were seen at RSU, Dr. Soetomo Surabaya. Sample collection was carried out based on the Polymerase Chain Reaction (PCR) test from April to September 2022. The type of study used was a correlation study that aimed to see the relationship between the results of the platelet aggregation test and Maximum Amplitude – Thromboelastography (MA-TEG) in assessing platelet function. In COVID-19 patients with a purposive sampling technique. The inclusion criteria in this study were patients who were on heparin therapy or not, patients over the age of 18 years, patients who had undergone treatment for ≥ the first 24 hours, patients who showed mild, moderate, severe, and critical symptoms and patients showing D-Dimer results ≥ 500 ng/mL, including patients showing increased D-dimer results ≥ 500 ng/mL at control/evaluation. Patients whose D-dimer results were within the normal range and pregnant women were excluded.

Platelet aggregation test: Citrate entire blood samples were centrifuged for 15 minutes at 1000 rpm to get platelet-rich plasma (PRP). The PRP obtained was then transferred to a plastic tube. The remaining blood from the first centrifugation was centrifuged for 15 minutes at 3500 rpm to get platelet-poor plasma (PPP). PRP as sample and PPP as control each amounted to 500 μL, then examined using the Aggregometer Chrono-Log Model 490 to see platelet aggregation with the addition of 10 μM Epinephrine agonist, 10 μM ADP (Adenosine diphosphate) and 2 μg/ml Collagen. Platelet aggregation results are expressed in percent units.

Maximum Amplitude - Thromboelastography (MA-TEG): As much as 1 cc of whole blood was put into kaolin and then homogenized. Then 20 micro CaCl2 was added to the heparin cup, and 340 micro kaolin citrate samples were added to the heparin cup. Then an examination was carried out using the Tromboelastogarfi 5000. The

measurement results of the electrical signal were then converted into a graphical display (graphic) and in the form of numbers. The MA value is expressed in mm.

Statistical Analysis

Continuous variables are expressed in mean ± standard deviation and IQR (Median, Min-Max), while categorical variables are expressed in percent. Test for normality using the Shapiro-Wilk test. The correlation between the 2 variables, namely between PAT agonists and MA-TEG parameters, was tested statistically using the Spearman rank correlation test with a significance level of $\alpha = 0.05$. To determine the correlation or not of the p-value sig (2-Tailed). Significant if the p-value < 0.05 and how big the relationship is seen from the value of r.

RESULTS

the data collection that was conducted from April 2022 to September 2022, the sample of 30 subjects was obtained who were infected with COVID-19 based on PCR results. Research subjects were determined based on predetermined inclusion and exclusion criteria. The table below contains a detailed descriptive explanation of the variables in this study.

Table 1: Characteristics of Research Subjects (n=30)

Characteristics	n (%)	Subjects (n=30)
Gender		
Male	21 (2.1)	
Female	9 (0.95)	
Age, years		
Mean ± SD		48.8±18.8
Median (IQR)		52.50 (20 – 84)
Body weight, Kg		
Mean ± SD		59.2±9.6
Median (IQR)		57 (45 – 81)
Height, cm		
Mean ± SD		161± 7.2
Median (IQR)		164 (150 – 172)
Body mass index		
Mean ± SD		22.8±3.4
Median (IQR)		21 (18 – 33)
Severity		
Mild	-	
Moderate	25 (83.3)	
Severe	5 (16.6)	
Critical	-	
Non-Comorbid	3 (8.8)	
Comorbid		
Hypertension *	7 (20.6)	
Diabetes *	5 (14.7)	
Kidney failure *	3 (8.8)	
Liver failure	2 (5.9)	
Tuberculosis	4 (11.8)	
HIV	2 (5.9)	

Characteristics	n (%)	Subjects (n=30)
Heart disease	2 (5.9)	
Stroke	2 (5.9)	
Malignancy	4 (11.8)	
Non-Anticoagulant	7 (23)	
Antikoagulan		
Heparin	7 (23)	
Enoxparin	4 (13)	
Lovenox	12 (40)	
Length of stay, day.		
Mean ± SD	10.57 ±5.87	
Median (IQR)	8.50 (5 – 32)	

Description: * 2 patients have two comorbidities: hypertension, and diabetes, while 2 other patients also have 2 comorbidities: kidney failure and hypertension.

Table 2: Platelet, D- dimer, MA-TEG, and platelet aggregation test (PAT) results.

Parameter	n (%)	Median (IQR)	Mean ± SD	Range
Platelet, (10^3 uL)	30 (100)	297 (153 – 530)	299.97± 102.07	150 - 450
D-dimer, (ng/mL)	30 (100)	1805 (600 – 4930)	2205 ± 1399.51	< 500
MA-TEG, (mm)	30 (100)	75.2 (34.8 – 82.2)	72.72 ± 10.10	51 – 69
PAT				
Epinephrine, (%)	30 (100)	25 (1 – 115)	37.57± 32.25	15 – 45
Normoaggeration	19 (63)			
Hypoaggertion	4 (13)			
Hyperaggeration	7 (23)			
ADP, (%)	30 (100)	55 (11 – 89)	52.03 ± 19.18	50 – 82
Normoaggeration	17 (56.7)			
Hypoaggertion	12 (40)			
Hyperaggeration	1 (3.3)			
Kolagen, (%)	30 (100)	21 (1 – 95)	32.20 ± 30.37	55 – 92
Normoaggeration	8 (26.7)			
Hypoaggertion	21 (70.0)			
Hyperaggeration	1 (3.3)			

Table 3: Statistical results of correlation between PAT agonists and MA-TEG

	Epinephrine		ADP		collagen	
	p	r_s	p	r	p	r_s
MA-TEG	0.689	0.076	0.945	-0.013	0.282	-0,203

The correlation between each PAT agonist and MA-TEG can be seen in table 3, where they all show no correlation. This conclusion is drawn based on the p-value > 0.05. Each p-value between variables is epinephrine with MA-TEG = 0.689 > 0.05, ADP with MA-TEG = 0.945 > 0.05 and collagen with MA-TEG) = 0.282 > 0.05

DISCUSSION

Results of Laboratory Examination of Research Subjects

In this study, the MA value increased by 75.2 (34.8 – 82.2) (**Table 2**). Some evidence suggests that an increase in MA can predict postoperative thrombotic complications because MA largely depends on platelet function and fibrinogen concentration [7], where an increase in the MA parameter (MA > 70) indicates hypercoagulation in COVID-19 patients [8–10]. This study is similar to previous studies. Research conducted by Panigada et al. (2020) explained that an increase in MA value is associated with an increased risk of thrombotic events [11]; even in other studies, TEG values (low K and R values and elevated MA values and angle) have been proposed as a high sensitivity and specificity predictor for thrombosis/thrombotic risk [12].

A hypercoagulable condition is also found in critically ill COVID-19 patients, as seen by an increase in clot strength as evidenced by an increase in the MA value in heparin samples above the normal value in 32 patients (80%). In contrast, the LY30 value was found to be 0%. This situation normalized after 14 days, although adding fibrin continues to strengthen the clot [9].

Previous studies have shown that VTE can occur in COVID-19 patients, even with standard thromboprophylaxis therapy.[13] It may be due to the ineffectiveness of using anticoagulants because the dose of anticoagulants is less [8], which can significantly impact TEG results. Several studies support this. According to the study of Bocci et al. (2020), there was no difference in the examination results on standard coagulation test examinations or TEG parameters in COVID-19 patients after 7 days with anticoagulant therapy (Enoxaparin 0.5 mg kg-1 subcutaneously every 2 times a day, unfractionated heparin 7500 units subcutaneously 3 times daily, or low-dose heparin infusion). On the other hand, laboratory findings from COVID-19 patients with acute respiratory distress syndrome demonstrate enhanced fibrinogen activity and elevated levels of D-dimer and MA. [10].

Statin et al. (2020) also reported hypercoagulation in COVID-19 patients with elevated MA levels. The anti-factor Xa and TEG tests were varied and inconsistent in detecting the effect of LMWH on thrombotic states, where monitoring of LMWH effects is crucial in COVID-19 patients but offers issues in interpreting the data about thromboembolic risk. [14]. And then, Saseedharan et al. (2020) data show hypercoagulation in COVID-19 patients even though a standard dose of enoxaparin has been given [13].

Other studies suggest evaluating TEG to detect clotting risk in people with severe COVID-19 and adjusting anticoagulant doses to prevent and treat thrombosis. Vatansev et al. (2020) suggested that the shorter the R and K time values , the greater the alpha angle at TEG, indicating that heparin administration is appropriate for patients with high D-dimer results. High MA results are related to excessive platelet activation. They indicate a prothrombotic state, and then Vatansev et al. added that patients with COVID-19 are not receiving intensive care and show high D-dimer results. TEG analysis results should be given heparin therapy [12].

Then in this study, each agonist from the platelet aggeration test examination showed different results where the epinephrine agonist obtained a median of 25 (1 – 115) (normal value 15 – 45%), and a collagen agonist obtained a median of 21 (1 – 95) (normal values were 55 – 92 %) where these two agonists mostly showed hypoaggregation, whereas ADP agonists with a median of 55 (11 – 89) (normal values 50 – 82 %) mostly showed normoaggregation. These findings are inconsistent with the literature. Platelet hyperactivity is characterized by enhanced platelet aggregation, fibrinogen and collagen dispersion via the mitogen-activated protein kinase (MAPK) pathway and thromboxane generation. Thus, the researchers concluded that platelet hyperactivity plays a role in the thrombotic symptoms found in COVID-19 patients [15]. COVID-19 has been linked to enhanced platelet activation, according to Holtz et al. (2020). They discovered that platelet aggregation was higher in severely sick COVID-19 intensive care unit (ICU)

patients than in individuals with mild COVID-19 infection. These findings are consistent with coagulation laboratory alterations in COVID-19 patients, such as elevated fibrinogen and D-dimer levels [16].

Other opinions add that infection and inflammation of the SARS-CoV-2 virus are known to cause lung damage. Damage to the tissues and endothelial cells of the lung can affect hematopoiesis and will activate platelets. Platelet activation will lead to microthrombus aggregation and formation, impacting megakaryocyte maturation and platelet production [17].

Correlation between PAT agonists and MA-TEG

Then to see the correlation between agonists in PAT and MA-TEG, the three agonists did not correlate with MA-TEG (**Table 3**).

This study is comparable to Koza et al., who observed no association between TEG and platelet function tests in preoperative and postoperative cardiac patients utilizing platelet-rich plasma (PRP) aggregometry with ADP, epinephrine, and ristocetin as agonists [18]. This study suggests that TEG may not be complete or sensitive to platelet activity and that coagulation factors influence TEG outcomes more than platelets [19].

In addition, these two tests use different samples; the MA-TEG uses whole citrate blood, which contains platelets, coagulation plasma, and other blood cell components. Platelet count, function, and fibrinogen levels impact the MA-TEG value. On the other hand, the platelet aggregation test employs platelet-rich plasma (PRP), and the administration of agonists altered platelet aggregation tests' findings. Additionally, most of the patients in this study had received prophylactic anticoagulant medication. In this study, the effect of heparin on the TEG examination could be eliminated because the heparin cup used contained heparinase, where this heparinase can break down and inactivate heparin [5]. In their research, Saba H et al. (1984) explained that heparin in PRP samples could change the membrane on platelets so that it can interfere with their ability and inhibit them in responding to agonists that play a role in platelet aggregation [20].

This study has limitations. Several factors can affect results, such as anticoagulant therapy or drugs. The sampling time for each study subject is different, in which the conditions of coagulopathy in research subjects differ.

CONCLUSION

In this research, there was no statistically significant correlation between the results of epinephrine, ADP, and collagen agonists on the platelet aggregation test with the MA parameter of TEG in assessing platelet function in COVID-19 patients, Dr. Soetomo Surabaya. However, MA and D-dimer values help detect the risk of thrombosis and a hypercoagulable state in COVID-19 patients, even on prophylactic therapy with LMWH or heparin. However, it is less sensitive in assessing platelet function. Besides helping to evaluate platelet function, platelet aggregation tests also help monitor treatment. Although the platelet aggregation test is the gold standard for platelet aggregation, it may be challenging to use it routinely in hospitals because it is a lengthy process and requires particular expertise.

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CONFLICT OF INTERESTS

The author declares that there is no conflict of interest.

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