LITERATURE REVIEW

The Role of Thromboelastography in Heparin Therapy for COVID-19 Patients

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ABSTRACT

The 2019 coronavirus disease (COVID-19)-associated coagulopathy one of the significant complications often found in hospitalized COVID-19 patients. A hypercoagulable and prothrombotic state characterize coagulopathy with an increased risk of thrombotic events. Abnormal coagulation tests could predict bleeding risk, thrombosis, and disease severity. In addition to increasing the D-dimer, prolonged prothrombin time has decreased survival and increased treatment requirements. Based on laboratory findings, it was reported that 70% of patients with COVID-19 had disseminated intravascular coagulation (DIC) and 30% had thrombosis. Approximately 8% of patients with COVID-19 have hemorrhagic complications, the most common one is gastrointestinal bleeding. Variations in hypercoagulability and bleeding occur in COVID-19 patients. Therefore, the anticoagulant drug should be considered to minimize bleeding risk. An anti-bleeding agent for bleeding complications should be considered for the potential increase of coagulopathy. Thromboelastography (TEG) is a tool that is used to analyze the characteristics of viscoelastic clots, platelet function, and fibrinolysis in whole blood, providing a complete picture of the patient's coagulation status. From various therapeutic guidelines for COVID-19 patients, heparin is used as an anticoagulant drug to prevent thrombosis in COVID-19 patients. Starting from prophylactic doses to therapeutic doses, heparin is used to prevent the severity of COVID-19 patient course. The effect of coagulation on COVID-19 patients varies from no impact to hypercoagulation in TEG results.

INTRODUCTION

Initially, 44 patients with severe pneumonia were found in Wuhan, Hubei Province, China, in December 2019 and were reported to World Health Organization (WHO) in early 2020. This disease was originally called 2019 novel coronavirus (2019-nCoV), then changed to coronavirus disease (COVID-19) and caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease is known to cause pulmonary alveolar thrombosis and cause airway obstruction. Infection can cause extensive thrombosis, not confined to the lungs, and induce a cytokine storm that can lead to death.[1]

The process of hemostasis runs dynamically, hence it can be used to monitor the infectious process and indicate suspicion about its severity. Laboratory abnormalities, especially parameters of hemostatic become abnormal, make it possible to examine the status of SARS-CoV-2 infection because the coagulation and hemostatic systems significantly support COVID-19 disease process.[2]

Given the ongoing global pandemic, it is urgently needed to understand the manifestations of the bleeding and thrombotic levels associated with COVID-19 coagulopathy: abnormal coagulation tests to predict

bleeding risk, thrombosis, and disease severity. In addition to the D-dimer, prolonged prothrombin time has decreased survival and increased treatment requirements. Based on laboratory findings, it was reported that 70% of patients with COVID-19 had disseminated intravascular coagulation (DIC) and 30% had thrombosis.[3–5]

Around 8% of patients with COVID-19 complained of hemorrhagic complications, the most common one is gastrointestinal bleeding. Variations in the type of hypercoagulability and bleeding were reported in COVID-19 patient. Therefore, treatment of anticoagulants should be considered for the potential increased risk of bleeding as well as anti-bleeding for bleeding complications in COVID-19 patients.[6,7]

Thromboelastography (TEG) is a tool that is used to analyze the characteristics of viscoelastic clots, platelet function, and fibrinolysis in whole blood; providing a complete picture of the patient's coagulation status. Heparin, either low molecular weight heparin (LMWH) or unfractionated heparin (UFH), is used as an anticoagulant drug to prevent thrombosis in COVID-19 patients. Starting from prophylactic doses to therapeutic doses, heparin is used to prevent the severity of COVID-19 patient course.[6,8,9] This literature review aimed to explain the role of TEG in heparin therapy for COVID-19 patients.

Thromboelastography (TEG)

The most primary and worrying complications of COVID-19 are hypercoagulability and thrombosis resulting from coagulopathy. The degree of these complications will affect the management of patient care. The risk of thrombosis includes venous thrombosis, pulmonary embolism, ischemic stroke, and myocardial infarction. In addition to thrombotic complications, hemorrhagic complications have been reported, the most common one is gastrointestinal bleeding. Due to the variation in complications between thrombosis and bleeding, anticoagulant drugs should be considered for the potential increased risk of bleeding in COVID-19 patients.[6,10]

Thrombosis and hemorrhage are products of coagulopathy and fibrinolysis. The routine laboratory parameters used to assess coagulopathy are plasma prothrombin time (PPT) and activated partial thromboplastin time (APTT). Both will show changes when the thrombosis has expanded, hence the consumption of coagulation factors has occurred. When thrombosis still occurs in the alveolar and surrounding areas, PPT and APTT values do not show significant changes. However, PPT and APTT may predict worsening bleeding in patients with bleeding manifestations. In many cases, coagulation tests do not

appear to be clinically sensitive for detecting coagulopathy and predicting clinical outcomes, it may vary between different demographics.[6,11,12]

In contrast to PPT and APTT, D-dimer and fibrin degradation (FDP) are parameters that reflect fibrinolysis products which increased in COVID-19 patients. An increase in this parameter does not necessarily indicate the severity of the disease. The increase in D-dimer has its dynamics; it can experience an increasing trend, a decreasing trend, or experience ups and downs along the way. Despite showing a prognostic association, the D-dimer test and coagulation have not been validated in large-scale multicenter studies.[6,12]

In assessing coagulopathy, fibrinolysis processes, and platelet function in one laboratory test, viscoelastic tools (VHA) such as TEG has been used to provide comprehensive information and to characterize coagulopathy in patients with COVID-19. First used in Italy and later in other parts of Europe, with the advantages of being able to analyze the viscoelastic clot characteristics of platelet function, coagulation, and fibrinolysis in whole blood specimens, it provides a complete picture of the patient's coagulation status.[6,8,9]

Generally, TEG examination produces a graph like a sleeping glass with a glass handle showing the time it takes for the first fibrin to form, which is denoted by the parameter R time. When fibrin is formed, the velocity up to an amplitude of 20 mm is described by the K rate for the velocity, while the angle formed is described by the angle. The strength of the clot will be represented by the maximum angle (MA). The smaller the R and K values and the larger the alpha value, the greater the coagulability of the blood. When the clot has reached its maximum strength, a fibrinolysis process occurs which will be assessed for 30 minutes and is described as LY30 (Lysis 30). In addition, there is a coagulation index (CI)
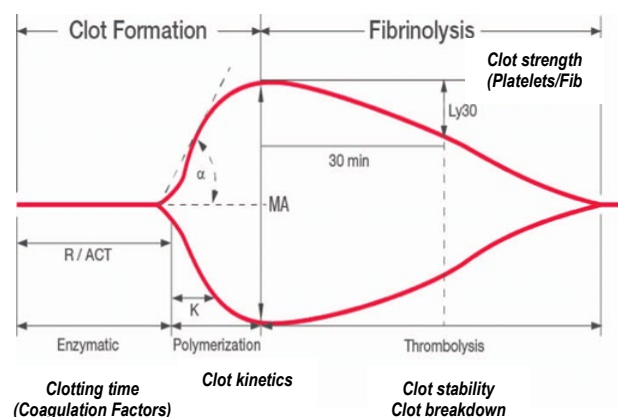

Figure 1. Schematic of TEG®5000 graph. The TEG results were quantified according to the detected clot formation time (R for reaction time), the time the specified clot firmness degree was reached (K), and the clot formation rate (alpha). Another value is the maximal amplitude (MA) which indicates the strength of the clot and also LY30.[13]

parameter which is a linear calculation between R, K, alpha, and MA which will be very useful in determining the interpretation of TEG (Figure 1). To facilitate the interpretation of TEG, the TEG analysis tree is used, which is a systematic description that describes the final result of the patient's hemostasis condition (Figure 2). The cases of TEG interpretation are shown in Figure 3.

There are 3 diagnostic areas, namely fibrinolytic, hemorrhagic, and hypercoagulable. Diagnosis of fibrinolysis concerning LY30 and MA (green box). LY30 > 7.5% with low normal to low MA, the diagnosis leads to primary fibrinolysis, i.e. lysis as primary hypocoagulable state. When high normal to high MA is found, the diagnosis leads to secondary fibrinolysis, i.e. lysis secondary to hypercoagulable state. When LY30 < 7.5%, then note the R value. When the R value is >10 min, the diagnosis leads to a hemorrhagic area (blue box). With MA values that vary from <50 to >70, they can be

categorized into factor (enzymatic) and platelet hypercoagulability when MA <50 mm, factor hypocoagulability (enzymatic) when MA is 50-70 mm, and factor hypocoagulability (enzymatic) platelet hypercoagulability when MA > 70 mm. Next, the R value <5 min, the diagnosis leads to a hypercoagulable condition (orange box). Furthermore, MA value <50 mm leads to a condition of hypercoagulability (enzymatic) platelet hypocoagulability factor. An MA value between 50-70 mm indicates factor hypercoagulability (enzymatic), and an MA value >70 mm indicates factor (enzymatic) and platelet hypercoagulability. When the R value is 5-10 min, then pay attention to the MA value because it can lead to platelet hypercoagulability when MA value is >70 mm and the platelet hypocoagulability condition when MA value is <50 mm, while MA value of 50-70 mm is normal.
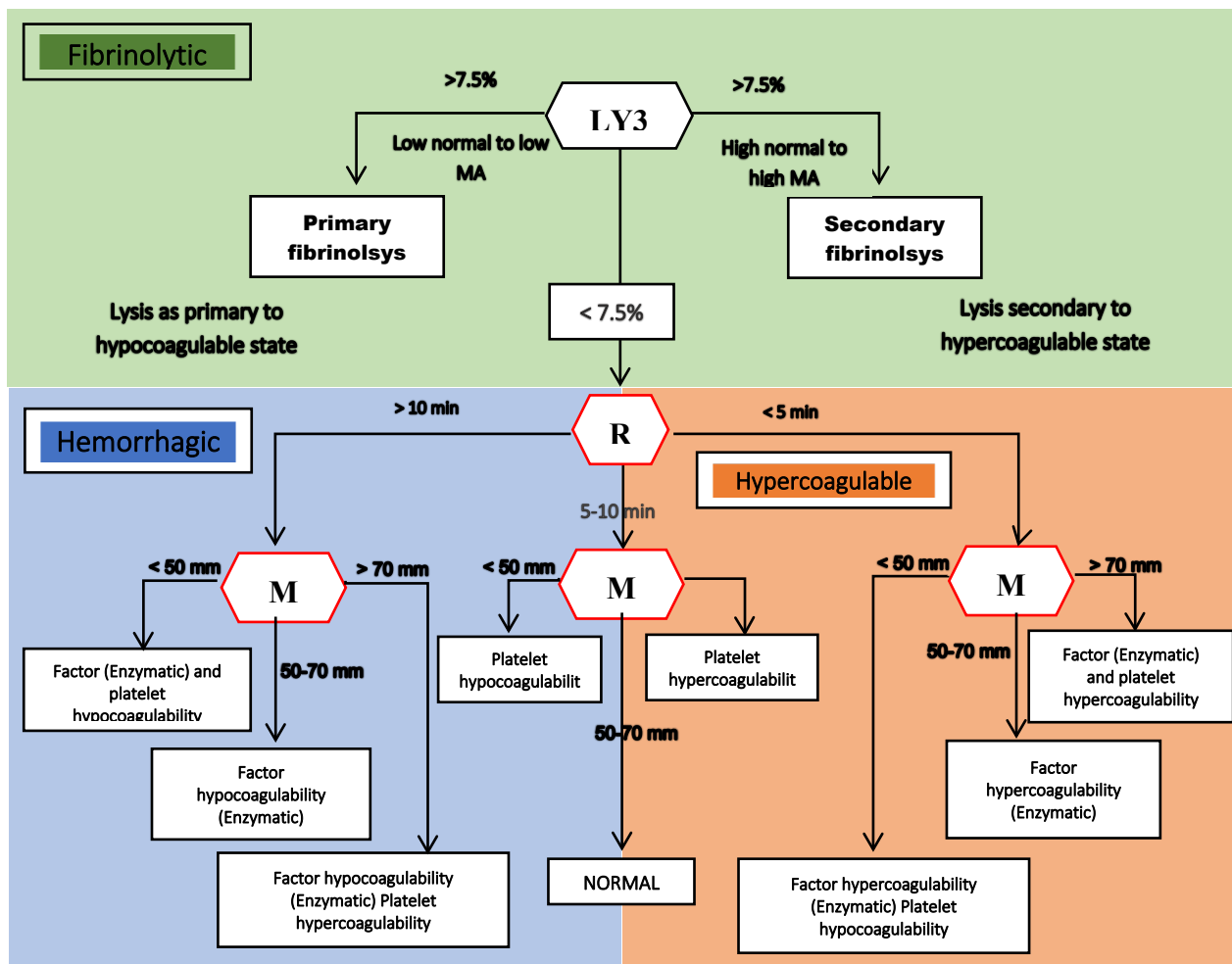

Figure 2. TEG analysis tree[14]

a.

TEG ACT	SP min 6.2	R min 6.8 5—10	K min 2.1 1—3	Angle deg 63.7 53—72	MA mm 57.2 50—70	G d/sc 6.7K 4.5K—11.0K	EPL % *1.4* 0—15	LY30 % *0.4* 0—8	A mm 57.0

b.

R min 3.2 2—8	K min 1.2 1—3	Angle deg 74.1 55—78	MA mm 70.3 51—69	PMA 0,0	G d/sc 11.8K 4,6K—10,9K	EPL % 12,2 0—15	A mm 66.6	CI 3,9 -3—3	LY30 % 12,2 1—3

c.

R min 3,3 2—8	K min 2,2 1—3	Angle deg 63,2 55—78	MA mm 53,3 51—69	PMA 0,0	G d/sc 5,7K 4,6K—10,9K	EPL % 24,2 0—15	A mm 35,7	CI 0,5 -3—3	LY30 % 24,2 1—3

d.

R min 3,7 2—8	K min 1,8 1—3	Angle deg 65,0 55—78	MA mm 51,9 51—69	PMA 0,0	G d/sc 5,4K 4,6K—10,9K	EPL % 3,4 0—15	A mm 48,0	CI 0,4 -3—3	LY30 % 3,4 1—3

e.

R min 4,9 2—8	K min 0,8 1—3	Angle deg 79,1 55—78	MA mm 76,9 51—69	PMA 0,0	G d/sc 16,6K 4,6K—10,9K	EPL % 1,7 0—15	A mm 72,5	CI 4,1 -3—3	LY30 % 1,7 1—3

f.

R min 6,8 2—8	K min 6,0 1—3	Angle deg 34,7 55—78	MA mm 40,9 51—69	PMA 1,0	G d/sc 3,5K 4,6K—10,9K	EPL % 3,5 0—15	A mm 35,4	CI -8,1 -3—3	LY30 % 3,5 1—3

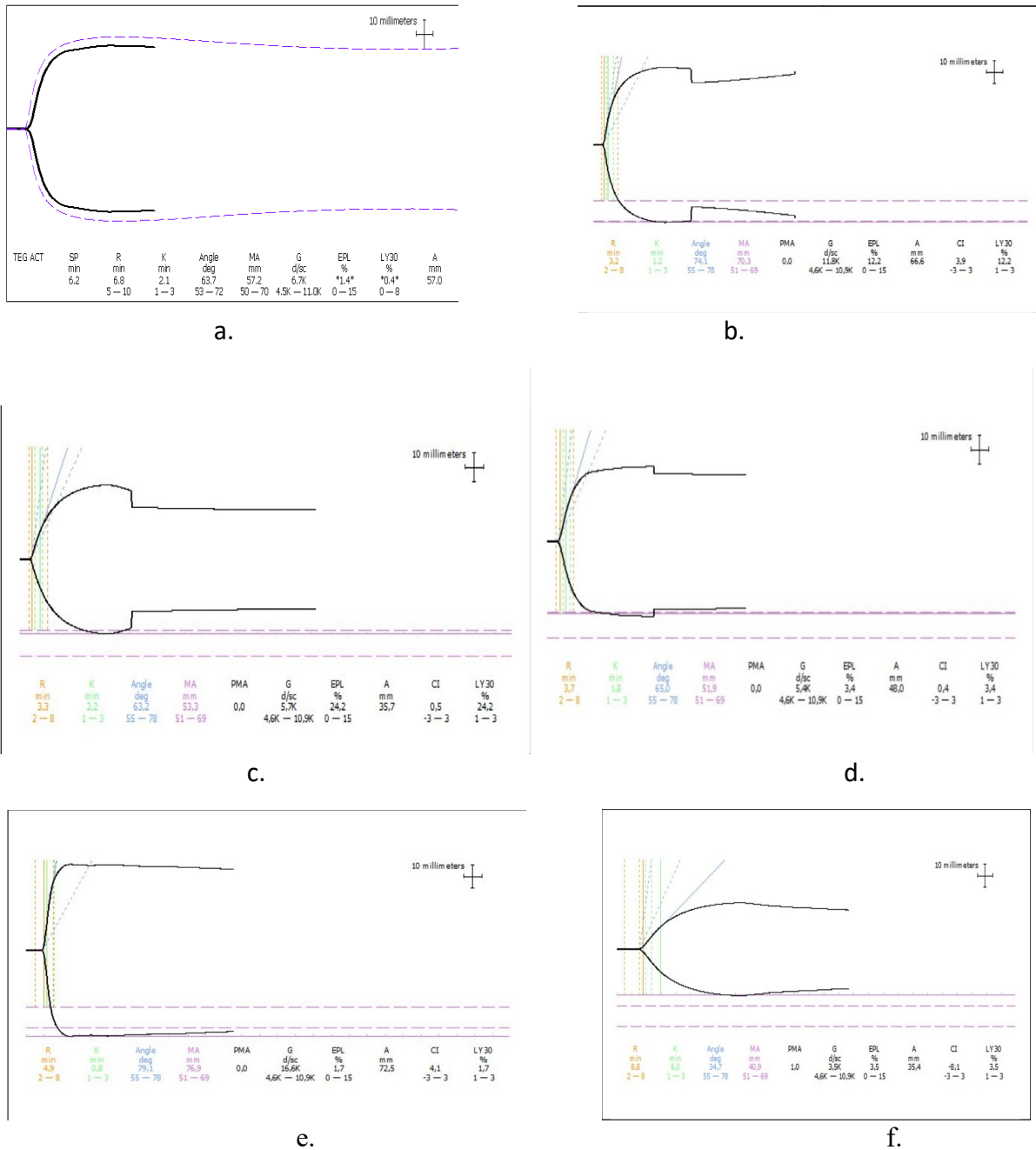**Figure 3.** (a) Normal TEG, with criteria LY30 <7.5%; R 5-10 min; MA 50-70, (b) Primary fibrinolysis, with criteria LY30 >7.5% and low normal to low MA, (c) Secondary fibrinolysis, with criteria LY30 >7.5% and high normal to high MA, (d) Factor hypercoagulablity (enzymatic), with criteria LY30 <7.5%; R <5 min; MA 50-70, (e) Factor (enzymatic) and platelet hypercoagulability, with criteria LY30 <7.5%; R <5 min; MA >70 mm, (f) Platelet hypocoagulability, with criteria LY30 <7.5%; R 5-10 min; MA <50 mm (collection of Dr. Soetomo General Hospital, Surabaya).

The hemostatic status according to TEG could be divided into 3 conditions as follows:

1. Fibrinolytic Condition

After forming a thrombus, the thrombus will be lysed by the fibrinolysis system. Fibrinolysis is a process that functions to remove clots that arise as a result of the hemostasis process to prevent uncontrolled thrombosis and embolism. The main enzyme in fibrinolysis is plasmin, a proteolytic enzyme that degrades fibrin. There are 2 types of fibrinolysis: primary fibrinolysis and secondary fibrinolysis. Primary fibrinolysis refers to fibrinolytic activity without a hypercoagulable or thrombotic state.

In contrast, secondary fibrinolysis refers to the fibrinolytic response to fibrin formation through the coagulation process. Primary fibrinolysis is often called primary fibrinogenolysis because it does not pass through the presence of fibrin.[15] Regarding its activity, there are the terms hyperfibrinolysis and hypofibrinolysis. Hyperfibrinolysis shows increased fibrinolytic system

activation which maintains the bleeding tendency. Hypofibrinolysis shows reduced fibrinolytic activity associated with thrombophilic states. Fibrinolysis shutdown was characterized by increased D-dimer and low fibrinolysis activity on TEG examination, namely LY<0.8%.[16]

2. Hypercoagulable Condition

The interpretation of hypercoagulable conditions is divided into 3 based on the parameter R time which describes the time of fibrin formation, and MA which describes the strength of the clot formed.[17] Some guidelines recommend prophylactic therapy with LMWH and UFH. LMWH has several potential advantages for prophylaxis when compared to UFH. First, various studies found that the SARS-CoV-2 Spike S1 protein receptor-binding domain interacts with LMWH. Therefore, LMWH has antiviral properties by acting as an effective inhibitor of viral attachment. Second, LMWH has anti-inflammatory and immunomodulatory effects. Third, pharmacodynamically and pharmacokinetically, LMWH works faster than UFH and has a longer half-life than UFH.[18]

Aside from the two mentioned drugs, oral anticoagulant drugs can also be considered to prevent thrombosis in COVID-19 patients. The oral drug choices often used in COVID-19 patients are warfarin, whose mechanism is a vitamin K antagonist and new oral anticoagulant (NOAC) whose mechanism is inhibitor thrombin and factor Xa. However, due to concerns about interactions with other drugs, the use of oral anticoagulants should be considered in hypercoagulable therapy in COVID-19 patients.[17]

3. Hemorrhagic Condition

Hemorrhagic conditions are interpreted by TEG device based on the R time which describes the time of fibrin formation and MA, which describes the strength of the clot formed, and the angle that describes the speed of fibrin formation and cross-linked fibrin, hence it can assess the activity of fibrinogen. This hemorrhagic condition can be caused by various possibilities, including:

a. Low fibrinogen level

Low fibrinogen level conditions can be caused by reduced fibrinogen production. Fibrinogen is synthesized in the liver, which is one of the target organs for SARS-COV-2 virus receptor, and can also be caused by excessive consumption of fibrinogen used in the hemostasis process due to damage to the endothelium. Massive blood vessels occur in COVID 19 patients. Treatment at low fibrinogen levels can be given fresh frozen plasma (FFP). It can also be given cryoprecipitate which is also part of plasma rich in fibrinogen and clotting factor.[19,20]

b. Low platelet function

Thrombocytopenia in COVID-19 patients can occur through several mechanisms, such as a cytokine storm that destroys bone marrow progenitor cells, direct inhibition of hematopoiesis by a viral infection of the bone marrow, increased autoantibodies and immune complexes leading to platelet destruction, and damage to the pulmonary endothelium leading to thrombocytopenia. Platelet aggregation and consumption of platelets result in reducing platelet number. Therapy for this condition can be given thrombocyte concentrate.[20]

c. Low clotting factor function

This can be caused by the consumption of coagulation factors caused by widespread vascular endothelial damage, hence coagulation factors are needed for the hemostasis process required due to endothelial damage. Therapy for this condition can be given cryoprecipitate rich in clotting factors.[19,20]

Heparin as Anticoagulant in COVID-19 Patients

Heparin is an anticoagulant drug which works to prevent the formation of blood clots by inhibiting the function of blood clotting factors. It works together with antithrombin III as a cofactor in inactivating thrombin and coagulation factors IX, X, XI, XII, and prevents the conversion of fibrinogen to fibrin. It is used in COVID-19 patients to prevent coagulopathy and venous thromboembolic complications. The use of heparin as an anticoagulant in COVID-19 patients was first reported from Wuhan, China. Of 449 patients with COVID-19, 350 patients did not receive heparin therapy, while 99 patients received low-dose heparin prophylaxis. Patients with increased D-dimer (6-fold) or increased coagulopathy scores due to sepsis who received prophylactic heparin had a 20% lower mortality than patients who did not receive heparin.[21]

Apart from being an anticoagulant, heparin has direct antiviral activity against SARS-CoV-2. In vitro studies have shown that heparan sulfate (a class of glycosaminoglycans of which heparin co-composes) on the cell surface is essential for entry and infectivity of coronaviruses NL63 and SARS-CoV. Heparan sulfate interacts via spike proteins as coreceptors of adhesion molecules that facilitate the interaction of SARS-CoV and the ACE2 receptor. SARS CoV-2 spike protein shows substantial and even almost irreversible binding to heparin via surface plasmon resonance.[21,22]

Heparin is known to have anti-inflammatory effects, hence it is beneficial for COVID-19 patients. The anti-inflammatory effect of heparin is through its mechanism of suppressing inflammation through interactions with inflammatory proteins, including interleukin-8, stroma-derived platelet growth factor 4 (PGF-4), stromal-derived factor 1a, neutrophil elastase, P and L selectins, CD11b/CD18, cationic eosinophil protein; and mechanisms preventing adhesion and influx of inflammatory cells into the involved area.[21,22]

Changes in TEG Due to Heparin Administration

The effect of heparin as anticoagulant to COVID-19 patients still give different results. The changes occurred depends on the amount of heparin dose used; the larger the dose, the more significant the impact on TEG result. The administration of heparin will generally affect the interpretation of the overall parameters of TEG: R time, K rate, angle, MA will change.[6]

The parameter of R time, which is significant as the time required until the formation of fibrin threads begins, is used as to indicate the enzymatic reaction parameters (coagulation factors) that will significantly affect the administration of heparin. The higher the heparin dose, the higher the R value, and no clot may form at all. Inversely proportional to the angle and MA, heparin administration will reduce the value of these two parameters.[6,23]

A study conducted by Bocci, *et al.* in Italy on 40 COVID-19 patients who were treated a full dose of enoxaparin 0.5 mg/kg body weight/2x a day or giving UFH 7500 units subcutaneously 3 times a day for 7 days in the ICU, showed TEG®6s patterns of COVID-19 patients were characterized by an increased amplification phase (MA) in the functional fibrinogen analysis and an increase in angle values in the rapid thromboelastography (rTEG). Activated clotting time (TEG-ACT) in rTEG was also reduced. While APTT shortened significantly on the 7th day of anticoagulation, TEG parameters and variables did not significantly differ at 7-day follow-up. All patients showed hypercoagulable anticoagulation, either enoxaparin or unfractionated heparin, and showed no impact on TEG patterns on the 7th day. Why did APTT commonly give changes while TEG did not, why was the result different? This was due to the different specimen. TEG uses citrate whole blood which contains platelet, coagulation plasma, and other blood cells component, while APTT uses poor plasma citrate specimen which contains coagulation factors and very low platelet.[24]

SUMMARY

TEG has an advantage over routine coagulation tests because it can simultaneously assess the activity of coagulation, fibrinogen, platelets, and the fibrinolysis system at the same time. The interpretation of coagulation status on TEG analysis tree ranged from hypercoagulable, fibrinolytic, or hemorrhagic condition. However, hypercoagulable conditions (platelet hypercoagulability, enzymatic hypercoagulability, platelet, and enzymatic hypercoagulability) were the most common coagulation condition in COVID-19 patients. There are different results from several studies about the effect of coagulation, from no impact to hypocoagulation on TEG results.

Author's Contributions
Wrote the manuscript, made figures, reviewed, and revised: YBB, YH, and NMY. All authors contributed and have approved the final version.

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