Analysis of *D-Dimer* Level and Prothrombin Time (PT) Activated Prothrombin Thromboplastin (APTT) on Heparin Administration to COVID-19 Patients

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Abstract

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Coronavirus is a dangerous pathogen that affects both humans and animals. Symptoms and indicators of COVID-19 infection include fever, cough, and shortness of breath, which are common in respiratory illnesses. COVID-19 has spread globally with high mortality and morbidity rates. Prothrombin Time (PT), Activated Prothrombin Thromboplastin (APTT), and *D-Dimer* parameters are blood tests to evaluate the coagulation status of COVID-19 patients, all these parameters increased in COVID-19 patients. This study aims at determining the levels of *D-Dimer*, PT, and APTT in COVID-19 patients. Clinical and laboratory records were retrospectively reviewed from 100 cases of COVID-19 admitted to hospitals. This study used a cross-sectional, descriptive, secondary data analysis design. The sample included patients from the Bhayangkara TK. I R.Said Sukanto Hospital between April-July 2021. The sample is a COVID-19 patient who was treated in the Intensive Care Unit (ICU), worsened, and given heparin. An independent variable is the administration of intravenous heparin at prophylactic doses. Dependent variables are *D-Dimer*, PT, and APTT values. The collected data is processed using Microsoft Office Excel and then being analyzed. *D-Dimer*, PT, and APTT levels in COVID-19 patients were initially high or increased after heparin administration decreased or became normal. In conclusion, there was a decrease in *D-dimer* levels, PT values, and APTT after administration of intravenous heparin at prophylactic doses.

Keywords
INTRODUCTION

Coronavirus is a dangerous pathogen that attacks humans and animals. Coronavirus comes from the subfamily Orthocoronavirinae in the family Coronaviridae and the order Nidovirales. This virus attacks the respiratory system in humans and causes several diseases such as severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus Disease 2019 (COVID-19) (3). Symptoms and signs of COVID-19 infection include respiratory symptoms such as fever, cough, and shortness of breath (3). People who have a history of co-morbidities and are elderly are at high risk of contracting COVID-19 (4).

Coronavirus disease 2019 (COVID-19), the clinical syndrome associated with infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been able to affect various worlds and scientific investigations have not occurred, previously there was a shortage of pharmacotherapy to fight the disease. The lack of treatment strategies with a variety of practice patterns already exists. Hypercoagulability in COVID-19 patients has sparked debate in clinical care regarding the use of heparin therapy (7).

The rapid spread of COVID-19 cases in various countries has put health status in a dangerous condition. The latest data from the World Health Organization reports that confirmed COVID-19 sufferers in three days on 26 April 2020 in Europe (1,341,851 patients), Asia (43,846 patients) and Africa (20,316 patients) with a global death rate of 193,710, While in Indonesia, based on data from the National Disaster Management Agency on 26 April, 2020, COVID-19 sufferers numbered 8,882 and 743 people died. The most COVID-19 sufferers are in DKI Jakarta (3,798 patients), West Java (912 patients), East Java (785 patients), Central Java (649 people) and South Sulawesi (440 patients) (4).

Laboratory parameters to identify the blood coagulation disorders occurrence in COVID-19 patients are D-Dimer, fibrin/fibrinogen, Prothrombin Time (PT/time required for blood to form clots or blood platelets) (5). D-Dimer is a fibrin degeneration product that is useful for detecting abnormal clot formation or thrombotic events and assessing the presence of a clot breaking or fibrinolytic process. Quantification of D-Dimer levels plays an important role in guiding therapy. D-Dimer level is usually elevated in patients with COVID-19 (1). Prothrombin Time (PT) is the test of time length in blood clotting based on the extrinsic and common pathways. This test is performed to determine the presence of bleeding disorders and assess the treatment taken to prevent bleeding (1). Activated Prothrombin Thromboplastin Time (APTT) is the test of time length in blood clotting
based on the basic pathway (intrinsic pathway). The APTT test is usually paneled with the PT test to determine the presence of a bleeding disorder and the possibility of profuse bleeding during surgery (2).

COVID-19 patients have not been supported by sufficient research until now, so the treatment has not been established significantly. Heparin is a drug to treat and prevent blood clots caused by certain medical conditions or procedures. Heparin works by inhibiting the work of proteins that play a role in the blood clotting process, so the blood clots formation can be prevented. However, for the time being, the use of heparin and Low Molecular Weight Heparin (LMWH), can be used. The use of low-dose heparin was associated with a significant reduction in mortality within 28 days in patient with sepsis. Other studies have shown a reduction in the risk of death at days 7 to 28 and a significant increase in the \( \text{PaO}_2/\text{FiO}_2 \) ratio in acute respiratory distress syndrome (ARDS) patients receiving high-dose LMWH therapy (6).

In a previous retrospective study, 449 patients with severe COVID-19 in China, 99 of whom received heparin (mainly LMWH) for at least 7 days, found that prothrombin time was positively correlated with 28 days. Mortality and platelet count were negatively correlated. In general, no significant difference was found in mortality between heparin users and nonusers at 28 days (30.3% vs 29.7%, \( P = 0.910 \)), but the mortality of heparin users at 28 days was lower than that of nonusers in patients with \( D-Dimer \) levels were more than six times the upper limit of normal (32.8% vs 52.4%, \( P = 0.017 \)) (18).

The primary purpose of this study was to give an analysis of \( D-Dimer \), PT, and APTT in COVID-19 patients who were used heparin. The source of data used in this study is secondary data. The data that has been collected is processed using Microsoft Office Excel and made into a graph. Data analysis included testing the frequency data for respondent characteristics based on sex, age, \( D-Dimer \) level, PT level and APTT level.

**MATERIALS AND METHODS**

**Source of patients Diagnosis criteria**

This study was conducted in the laboratory of the Bhayangkara T.K.I Raden Said Sukanto Hospital, Jakarta-Indonesia used a descriptive research type and has been approved by Bhayangkara T.K.I Raden Said Sukanto Hospital Ethical Commission with the letter of Ethical Approval Number B/2245/VII/2021. The populations in this study were all patients who confirmed positive for COVID-19 in the ICU/HCU Bhayangkara T.K.I Raden Said Sukanto Hospital between April-July 2021. A total of 100 patients, all diagnosed with COVID-19 which had confirmed a positive result of the nucleic acid test of SARS-CoV-2 by real-time fluorescence RT-PCR.
Diagnosis criteria

The sampling technique in this study was purposive sampling, which uses the criteria that have been selected by the researcher in selecting the sample. The sample selection criteria are divided into inclusion and exclusion criteria. The inclusion criteria were above 30 years old, have comorbidities such as liver disease, kidney, heart, lung, digestive tract, urinary tract, brain, and others, and COVID-19 patients who deteriorated and need ICU. Meanwhile, the exclusion criteria are abortus, hypertension, and thrombocytopenia. The tools used in this study include equipment blood sampling (syringes, citrate vacuum tubes, alcohol swabs, plasters, tourniquet, label), coagulation analyzer (Sysmex® CA-600), centrifuge, and micropipette. The ingredients used in this study include plasma citrate blood, Dade Innovin reagents, Pathrombin SL reagents, CaCl₂ reagents, OV_B reagents, and normal controls. The measurement method was used cross-sectional by looking at the decrease in the value of D-Dimer, PT, and APTT levels in the administration of heparin to COVID-19 patients.

RESULTS

The distribution of respondent characteristics based on age when giving heparin to COVID-19 patients at Bhayangkara T.K.I Raden Said Sukanto Hospital obtained as shown in the Figure 1.

Based on Figure 1, most of the respondents have an age category of 46-60 years (63.75%), followed by 31-45 years (21.25%), and > 60 years (15%). Moreover, the distribution of respondent characteristics based on gender when giving heparin to COVID-19 patients at Bhayangkara T.K.I Raden Said Sukanto Hospital is shown in Figure 2.

Based on Figure 2, most respondents were male (53.75%). Parameters of PT, APTT, and D-Dimer levels in the administration of heparin to patients with
Coronavirus Disease 2019 (COVID-19) at Bhayangkara T.K.I Raden Said Sukanto Hospital showed in Figure 3.

**Figure 3** Parameters of PT, APTT and D-Dimer Levels on Heparin

Based on Figure 3, a decrease in PT and APTT levels as well as in D-dimer levels showed after heparin administration in COVID-19 patients. Most respondents with COVID-19 had a high PT value (63.75%) before heparin administration. Meanwhile, after heparin administration, there were 53 respondents with normal PT values (66.26%) and 27 respondents with high PT values (33.75%).

Before heparin administration, most respondents with COVID-19 had high APTT (long) values (53.75%). Meanwhile, after heparin administration, there were 55 respondents with normal APPT values (68.76%) and 25 respondents with high APPT values (31.25%). Before heparin administration, most respondents with COVID-19 had high (increase) D-Dimer levels (66.25%). After heparin administration, there were 47 respondents with normal APPT values (58.75%) and 33 respondents with high APPT values (41.25%).

**DISCUSSION**

Parameters PT, APTT, and D-Dimer are blood tests to evaluate the patient's coagulation status. PT examination is to evaluate extrinsic coagulation factors, while PTT can detect the function of intrinsic coagulation factors and coagulation components. Both tests can help explain the cause of a bleeding or blood clotting disorder. APTT is part of PTT. The APTT panel is the endpoint of blood coagulation testing time that serves to assist in the diagnosis of coagulation factor deficiency in the intrinsic pathway. D-Dimer is a protein residue formed by the breakdown of blood clots. D-Dimer is a fibrin degradation product formed during the degradation of blood clots by fibrinolysis. Elevated D-Dimer in the blood is a marker of suspected thrombosis found in deep vein thrombosis, pulmonary embolism, arterial thrombosis, pregnancy, inflammation, chronic liver disease, cancer, surgery, vasculitis, and Disseminated Intravascular Coagulation (DIC) (19).

Prolonged PT, APTT, and increased D-Dimer values are often found in severe COVID-19 patients and are predictors acute respiratory distress syndrome (ARDS) occurrence, the need for care in the Intensive Care Unit (ICU), and death. Prolongation of
PT > 3 seconds or APTT > 5 seconds is a marker of coagulopathy (blood clotting disorder resulting in excessive bleeding) and a predictor of thrombotic complications in COVID-19 patients. COVID-19 patients with an increase in D-Dimer (3-4 times) need to be hospitalized even if there are no severe symptoms because it indicates there is an increase in thrombin generation and risk for thrombotic events. Efforts to prevent the occurrence of coagulopathy in these COVID-19 patients, it is necessary to provide prophylactic anticoagulants, namely Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) (20).

The results of this study are in line with coagulation parameter studies, namely Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and D-Dimer, which used a sample of 183 patients with 162 patients who survived. The study showed the average level of D-Dimer was 0.61 g/mL (normal: <0.5 g/mL), PT with a time of 13.6 seconds (normal: 11.5-14.5 seconds), and APTT with a time of 41.2 seconds (normal: 29-42 seconds) (21).

The results of this study are in line with the study of Rusdiana & Akbar (22), which showed that the levels of D-Dimer in the five patients had varied patterns. In case 1, there was an increase in D-Dimer levels >2 mg/L in the middle of treatment, while cases 2 and 3 were stable with normal D-Dimer levels <2 mg/L, but at the time of the last examination, all patients' D-Dimer levels were normal < 2 mg/L after heparin administration and on discharge. In the group of patients who died, the D-Dimer levels were both > 7 mg/L. D-Dimer is derived from the lysis of cross-linked fibrin, where an increase in its level may indicate activation of coagulation and fibrinolysis (22).

Similar studies have also shown that an increase in D-Dimer >1.0 l/mL is the strongest predictor of mortality in COVID-19 patients (23). D-Dimer >1.5 l/mL was a predictor of venous thromboembolism in COVID-19 patients with a sensitivity of 85% and specificity of 88.5% (24).

The available evidence suggests that severe COVID-19 disease can lead to coagulopathy complications in the form of Disseminated Intravascular Coagulation (DIC), which is prothrombotic with a high risk of venous thromboembolism, where PT, APTT, and D-Dimer markers can be used as a parameter for blood coagulation disorders (24). Based on this, the experts recommend
anticoagulants, reflecting the recognition of clotting dysregulation in this situation (24) because of the effectiveness of heparin therapy (especially Low Molecular Weight Heparin / LMWH) for COVID-19 treatment therapy. Before heparin administration, most respondents had high or increased levels of D-Dimer, PT values, and APTT values. Therefore, after heparin administration, D-Dimer levels, PT values, and APTT values were decreased or became normal (25). The limitations of this research were the lack of monitoring of D-Dimer, PT, and APTT levels among COVID-19 patients with heparin administration. The recommendation for future research is to add parameters for evaluating the coagulation status of COVID-19 patients, such as C-Reactive Protein (CRP), ferritin, and Lactate Dehydrogenase (LDH) levels.

CONCLUSIONS

Heparin are widely used anticoagulants by inhibitit coagulation. In COVID-19 patients, D-Dimer, PT, and APTT values before heparin administration were high or increased. Meanwhile, after heparin administration, D-Dimer, PT, and APTT values levels were decreased or became normal.

AUTHOR CONTRIBUTIONS


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CONFLICT OF INTEREST

All authors reported no conflict of interest.

REFERENCES


