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Comparison between unfractionated heparin (UFH) and fondaparinux on platelets and D-dimer level in COVID-19 patients with hypercoagulation

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Abstract

Introduction: *This study aimed to compare the clinical effects between UFH and fondaparinux in COVID-19 patients with hypercoagulation.*

Material and methods: *This was a prospective cohort study. Samples were taken consecutively from hospitalized COVID-19 patients with hypercoagulation who received UFH or fondaparinux based on the standardized guidelines. A total of 71 patients met the inclusion criteria. Patients were evaluated for platelet and D-dimer values before and after administration of UFH or fondaparinux.*

Results: *Although there was no difference in D-dimer reduction between the two groups ($p = 0.44$), fondaparinux showed a greater reduction, 26% against 22% for UFH. While on platelets, there was a significant difference ($p = 0.04$) between fondaparinux and UFH. Fondaparinux showed a reduced thrombocytopenia impact, as seen by an increase in pre- and post-therapy platelets of up to 50%, compared to 16% in UFH. In regard to the incidence of Heparin-Induced Thrombocytopenia (HIT), there was no significant difference between post-UFH therapy and post-fondaparinux therapy ($p = 0.361$).*

Conclusion: *Fondaparinux did not reduce platelet levels as much as UFH, but there was no difference between the fondaparinux group compared to the UFH group in the effect of decreasing D-dimer levels and the sign of HIT.*

Key words: COVID-19; hypercoagulation; unfractionated heparin (UFH); fondaparinux; heparin-induced thrombocytopenia (HIT)

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Introduction

Diseases due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become a significant outbreak in the world since the end of 2019. Coronavirus disease 2019 (COVID-19) has a variable degree of illness, ranging from asymptomatic to severe, that causes death. Severe symptoms due to COVID-19 are known to be frequent, occurring in approximately 4–16% of patients [1, 2]. One of the determining factors for the severity of COVID-19 is hypercoagulation, which causes both arterial and venous thromboembolism. Thromboembolic cases are known to occur quite frequently in COVID-19 patients, reaching 40–70% of the total COVID-19 cases. Thromboembolic events have been reported to correlate with the patient's need for intensive care and increase the risk of death [3].

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The use of anticoagulants in COVID-19 is indicated in patients with signs of acute thrombosis or with elevated fibrinolytic markers, such as D-dimer levels. Unfractionated heparin (UFH) is often used to reduce the risk of acute thrombotic complications in COVID-19 patients [4]. However, there is a side effect of using UFH that has the potential to worsen the condition and prognosis of COVID-19 patients called heparin-induced thrombocytopenia (HIT). Thrombocytopenia can manifest either as an absolute drop in the platelet count ($< 150 \times 10^9$/L) or a relative decline of 30% to 50% from baseline platelet counts [5].

Fondaparinux is an anticoagulant that has a mechanism similar to UFH but does not cause HIT. A number of studies have shown a better clinical performance than UFH for the prevention of thromboembolism [6]. However, fondaparinux has not been widely studied for its use in COVID-19 patients who show signs of hypercoagulation. This study aimed to compare the incidence and clinical effects of HIT between fondaparinux and UFH in COVID-19 patients with hypercoagulation.

Material and methods

This research was an observational analytical study with a prospective cohort study design. Samples were taken consecutively from the population of hospitalized COVID-19 patients at Bhayangkara Hospital, Surabaya, who received anticoagulant therapy from April 2021 to September 2021.

The confirmed COVID-19 patients underwent history taking, physical examination, and laboratory examinations, such as complete blood counts and D-dimer levels. Patients with the following criteria: 1. taking anticoagulants previously; 2. history of thromboembolic and/or bleeding event in the last 30 days; 3. platelets $< 50{,}000/\mu$L; or 4. INR > 2 were excluded from the criteria for patients indicated for anticoagulant therapy.

Patients with D-dimer > 500 ng/mL and/or experiencing severe symptoms of COVID-19 were considered to have a hypercoagulable state and received anticoagulant therapy. They received either UFH or fondaparinux according to the anticoagulant management guidelines for COVID-19 from the European Society of Cardiology.

Patients were evaluated for platelet and D-dimer values before and after the administration of an anticoagulant. The impedance method of hematology analysis was used to count the platelets, whereas the enzyme-linked fluorescent assay (ELFA) method was used to measure the D-dimer levels. The evaluations of the platelet and D-dimer levels were repeated every 48 hours. The patient was followed during the treatment to observe any possible side effects of the treatment. One of the side effects that was considered was a decline in platelets. In accordance with the definition, namely a decrease in platelets below $< 150 \times 10^9$/L or a relative decline of 30% to 50% from baseline platelet counts is categorized as HIT.

Ethics for this study was provided by Bhayangkara Hospital Surabaya Ethics Committee (11/IV/2021/KEPK/RUMKIT). All patients who participated in this study understood the procedure before giving informed consent.

Data obtained from all the history taking, examinations, and repeated evaluations were analyzed using SPSS 25.0 program. The Wilcoxon test was used to compare pre- and post-anticoagulant therapy. The independence T-test was used to compare the two anticoagulant groups, and Fisher's exact test was used to compare the incidence of HIT after therapy with each anticoagulant.

Results

This study enrolled 108 patients. After going through the data exclusion process, it was found that 71 patients met the inclusion criteria. There were 35 men and 36 women, with an average age of 52 years old. Subjects were dominated by moderate symptoms, while most of them received fondaparinux therapy, as shown in Table 1.

To see the effectiveness of the therapy, measurements of platelet and D-dimer levels were carried out pre- and post-administration of drugs. Data are presented in terms of the mean (standard deviation). The analysis test showed that UFH did not give a significant difference in either platelet or D-dimer levels, while fondaparinux showed a significant difference in platelet levels, with a percentage of change reaching 50%. The percentage of change also showed fondaparinux provides a greater decrease in D-dimer levels, which is 26% compared to UFH. The P-value and mean of each variable are shown in Table 2.

The comparative test was carried out in both groups using the independence T-test. Table 3 shown that a significant difference in changes in the number of platelets between the two groups was observed. It can also be seen from the percentage of changes in Table 2, a considerable difference exists between 50% and 16%. The percentage of changes in D-dimer levels showed fondaparinux was better at reducing D-dimer levels when compared to UFH, although it did not show a significant difference in the results.

A total of 24 patients received UFH therapy, and three (11.1%) of them had decreased platelet levels. However, in the fondaparinux therapy group, two patients with thrombocytopenia were also found. Furt-

Table 1. Subject's characteristic

Variable	Frequencies (percentage)
Sex	
Female	36 (50.7%)
Male	35 (49.3%)
Severity	
Moderate	50 (70.4%)
Severe	21 (29.6%)
Medical therapy	
Fondaparinux	44 (62%)
UFH	27 (38%)

Table 2. Comparative study pre and post-therapy

Group	Variable	Mean (SD)	Percentage of difference	P-value
UFH	Platelets (10^3/μL)	Pre 258,481 (99,730)	–16%	0.115*
		Post 301,148 (151,885)		
	D-dimer (ng/mL)	Pre 6,708 (9,869)	22%	0.354*
		Post 5,197 (4,481)		
Fondaparinux	Platelets (10^3/μL)	Pre 212,159 (68,731)	–50%	0.000*
		Post 318,750 (131,344)		
	D-dimer (ng/mL)	Pre 1,154 (1,117)	26%	0.999*
		Post 844 (759)		

*Wilcoxon test

Table 3. Comparative between two groups

Variable	P value
Platelets	0.04**
D-dimer	0.44**

**Independence T-test

hermore, a comparative test analysis was carried out with Fisher's exact test, which showed no significant difference between the two therapies in regard to the incidence of HIT ($p = 0.361$) as we can see in Table 4.

Discussion

Increased inflammatory markers, such as fibrinogen, D-dimer, or C-reactive protein (CRP), in COVID-19 patients have been widely reported [7]. In addition to increased inflammatory markers, decreased platelet levels were also found in some COVID-19 patients [8]. COVID-19 infection causes a decrease in platelets through several pathways, with one of them being direct infection of marrow cells, inhibiting platelet production [9].

A decrease in the number of platelets can also be used as an auxiliary predictor to see the death rate due to COVID-19 [10]. Wool and Miller stated that low platelets were in line with severe symptoms [11]. The two groups in this study have mean platelet levels that are not too low, but the post-therapy evaluation reports significant differences between the two groups. The increase in platelets in the fondaparinux group is much higher (up to 50%), while the increase in the UFH was only 16%. This can be caused by heparin side effects, including thrombocytopenia [12]. Fondaparinux does not have a thrombocytopenic effect as severe as UFH, as it is often used as therapy for HIT [13].

Although it rarely causes thrombocytopenia, some cases have reported HIT associated with fondaparinux [14, 15]. Morangiu stated that fondaparinux had a low chance of causing HIT, but we found that two patients developed thrombocytopenia after the administration of fondaparinux [16]. In this study, three patients experienced thrombocytopenia after 6–7 days of treatment with UFH. This is in line with the study of Linkins, which states that HIT often occurs 5–10 days after receiving UFH therapy [17]. It is not possible to rule out this decrease in platelets due to the disease process or side effects of treatment, so antibody tests are required.

The D-dimer level is one of the inflammatory markers used to predict the severity and mortality in COVID-19 patients [18]. Anticoagulants have been shown to be effective in reducing inflammatory markers, such as D-dimer and fibrinogen [19]. There have not been

Table 4. Cross Tab and Fisher's Exact Test

Groups	Thrombocytopenia after therapy		P value
	No	Yes	
Fondaparinux	42 (95.5%)	2 (4.5%)	0.361*
UFH	24 (88.9%)	3 (11.1%)	

*Fisher's Exact Test ($p < 0.001$)

many studies to look at the effect of UFH on D-dimer levels, but the use of UFH can reduce the risk of death within 28 days [20]. In this study, researchers compared the D-dimer levels of patients who had received UFH and fondaparinux therapy. Both therapies with UFH and fondaparinux showed a decrease in D-dimer levels, although it was statistically insignificant. However, the fondaparinux group had a larger percentage of decrease (26%) compared to the UFH group (22%).

Limitation

In addition, the increases and decreases in other inflammatory markers still could not be excluded from the pathogenesis of the disease, so they could have caused bias in this study. The number of samples should be enlarged, so it can describe a larger population. Therefore, further research is expected to check for HIT antibodies to reinforce the diagnosis of HIT.

Conclusion

There was no difference between the two groups with regard to the effect of decreasing D-dimer levels. Fondaparinux did not show a severe thrombocytopenic effect compared to UFH. There was no difference in a sign of HIT in both groups, but it could not be ruled out from the possible pathophysiology of the disease.

Conflict of interest

None.

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