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Cohort Study

Heparin for patients with coronavirus disease 2019 and hypercoagulation complications: A cohort study

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ABSTRACT

Background: Thrombotic complications of coronavirus disease 2019 (COVID-19) are a worrisome aspect of the disease due to their high incidence in critically ill patients and their poor clinical outcomes. The aim of this study was to compare the effectiveness of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) (fondaparinux) in hospitalized COVID-19 patients with hypercoagulable complications.

Material and methods: The study design used a retrospective cohort approach incorporating pre- and post-tests via secondary data extracted from the medical records of inpatients with confirmed COVID-19.

Results: Among the 98 individuals studied (52% women; 30.6% at >60 years of age), 35 patients received UFH, while the remaining 63 patients received LMWH (fondaparinux). The greatest decrease in the D-dimer value (0.01 ± 0.5 g fibrinogen equivalent units/mL) was observed in 12 (34.3%) and 15 (23.8%) patients in the UFH and LMWH (fondaparinux) groups, respectively. Most inpatients with confirmed COVID-19 were aged 50–59 years and were women.

Conclusion: There was a tendency toward increased D-dimer, normal prothrombin time, normal activated partial thromboplastin clotting time, and increased fibrinogen values in each COVID-19 patient. The results demonstrated a significant relationship between the D-dimer and prothrombin time parameter in confirmed COVID-19 inpatients.

1. Introduction

Since being notified of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on December 31, 2019, the coronavirus disease-19 (COVID-19) has been labelled a global pandemic. COVID-19 has had a disastrous effect on the global demography, causing more than 3.8 million deaths in various countries, and giving rise to the most important global health crisis after the influenza pandemic of 1918. On January 30, 2020, the World Health Organization (WHO) declared COVID-19 a "Public Health Emergency of International Concern" because of its rapid transmission and consequent casualties affecting both the public and health services worldwide [1]. The economically stable nations of the world are forecasted to encounter a GDP growth decrease of 7.8% including the USA, where the IMF has projected a decline of 5.9%. In the case of European countries, the Gross domestic product (GDP) growth rate is forecasted to decrease by 7.5% while in developing countries with emerging economies a 2% decrease is anticipated. However, the economy in China, India, Pakistan and Indonesia will reflect an increase in GDP in the final quarter of 2020. It has also been inferred that the global fiscal deficits will require a long time to recover post-COVID-19 control [2].

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Abbreviations

coronavirus disease 2019 (COVID-19)
unfractionated heparin (UFH)
low molecular weight heparin (LMWH)
prothrombin time (PT)
fibrinogen equivalent units (FEU)
activated partial thromboplastin clotting time (aPTT)
combined oral contraceptives (COC)
venous thromboembolism (VTE)

Four months after the first case in China, Indonesia announced the presence of two cases of COVID-19 on March 2, 2020; on March 6, 2020, these two cases of COVID-19 were confirmed. The addition of cases that initially only amounted to hundreds has subsequently reached far into the thousands. As of September 15, 2021, the Government of the Republic of Indonesia has reported 4,178,164 confirmed cases of COVID-19, with 139,682 COVID-19-related deaths and 3,953,519 individuals recovered from the disease [3]. Patients with confirmed COVID-19 usually present with fever, cough, and dyspnea. Other less common symptoms include myalgia, rhinorrhea, sore throat, headache, and diarrhea. On laboratory examination, we found lymphocytopenia and increased C-reactive protein, while abnormalities from other laboratory tests in cases complicated by coagulopathy included increased D-dimer, thrombocytopenia, a prolonged prothrombin time (PT), increased fibrinogen, increased lactate dehydrogenase, and increased ferritin. Typical imaging findings include bilateral ground-glass opacities, as well as bilateral multiple lobular and subsegmental areas of consolidation. In severe cases, complications include respiratory failure, septic shock, and multiple organ failure [4–8].

Thrombotic complications of COVID-19 are a worrisome aspect of the disease due to their high incidence in critically ill patients and their poor clinical outcomes. There are several reports of coagulopathy in patients with COVID-19 manifesting as either arterial or venous thrombosis. COVID-19 causes patients to enter a hypercoagulable state, but the pathophysiology behind the thrombotic complications observed in this disease is still not well understood. Several mechanisms have been proposed, such as the host immune response, which contributes to vascular endothelial cell injury, inflammation, activation of the coagulation cascade through tissue factor expression, and cessation of fibrinolysis [4–8].

Management guidelines for thromboembolism in COVID-19 have been established by the WHO. The management of adolescents and adults hospitalized with confirmed COVID-19 involves using low molecular weight heparin (LMWH) to prevent venous thromboembolism (VTE). Apart from the anticoagulant effect of heparin, LMWH has also been shown to have anti-inflammatory properties, which may be beneficial in combating the proinflammatory state caused by the coronavirus. Heparin is also known to have a suppressive effect on the expression of interleukin (IL)-6 and IL-8 in lung epithelial cells, which may help reduce the thrombotic complications associated with the host immune response to COVID-19. LMWH (fondaparinux) is an indirect factor Xa inhibitor, but LMWH (fondaparinux) does not inhibit thrombin at all, which is why LMWH (fondaparinux) is better for preventing heparin-induced thrombocytopenia [4,5,7–9]. The aim of this study was to compare the effectiveness of unfractionated heparin (UFH) and LMWH (fondaparinux) in hospitalized COVID-19 patients with hypercoagulable complications.

2. Materials and methods

2.1. Research design

This study was analytically observational. The research design used was a retrospective cohort approach of pre- and post-tests. This study used secondary data extracted from the medical records of inpatients who had a confirmed diagnosis of COVID-19 at the Islamic Hospital Jakarta Sukapura between August 2020 and August 2021, which meets the inclusion criteria and does not meet the exclusion criteria. This study was conducted according to the STROCSS criteria and has been reported with the checklist completed in https://www.researchregistry.com [10]. This research was submitted to the ethics committee of the Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, Jakarta, Indonesia (No. 186/PE/KE/FKKUMJ/X/2021) for approval of the ethical study. Written informed consent was obtained from all participants.

2.2. Statistical analysis

The collected data were edited, coded, and entered into a computer file. The data were cleaned and then categorized into five groups that focused on the D-dimer reference values attained by the chemiluminescent immunoassay method, namely, 0.036–0.708 g fibrinogen equivalent units (FEU)/mL. Next, the chi-square test was performed to compare the two variables in each group, and the independent samples T test was performed. To determine whether there was a significant difference between each group, the Kolmogorov–Smirnov normality test was carried out, which showed that the data were normally distributed. The chi-square test and the Kolmogorov–Smirnov normality test were also performed on the patient's characteristic data. For all statistical tests, a p value < 0.05 was considered significant. All calculations used IBM SPSS Statistics version 26 (IBM Corporation).

3. Results

Of the 702 confirmed inpatient COVID-19 cases, only 11 patients underwent PT and activated partial thromboplastin clotting time (aPTT) examinations before and after administration of the anticoagulants, among whom, 9 received heparin and the other 2 received LMWH (fondaparinux). Therefore, research on the effectiveness of heparin administration could not be carried out based on the PT and aPTT values due to the unequal number of populations from each group. Furthermore, as the patients who received the fibrinogen test before and after anticoagulation were not noted, it was unavailable for the study of the effectiveness of heparin administration. Finally, the effectiveness of heparin administration was compared based on the D-dimer values before and after treatment.

Tables 1–3 depict the distribution of study patients by age, sex, and D-dimer, respectively. The highest D-dimer values (1.01–5 g FEU/mL) were observed in 44 patients (44.9%), and the lowest D-dimer values (<0.708 g FEU/mL) were found in 8 patients (8.2%).

Table 4 shows the frequency comparison of the UFH (n = 35) and LMWH (fondaparinux) (n = 63) groups divided by age and sex. There

Table 1
Distribution by age of inpatients with confirmed COVID-19.

Age	Number of Patients	
	N	%
21–30	6	6.1
31–40	18	18.4
41–50	19	19.4
51–60	25	25.5
>60	30	30.6
Amount	98	100.0

Table 2
Distribution by sex of inpatients with confirmed COVID-19.

Sex	Number of Patients	
	N	%
Male	47	48
Female	51	52
Amount	98	100.0

Table 3
Distribution based on the admission D-Dimer values of inpatients with confirmed COVID-19.

Early D-Dimer	Number of Patients	
	N	%
<0.708 g FEU/mL	8	8.2
0.708–1 g FEU/mL	21	21.4
1.01–5 g FEU/mL	44	44.9
5.01–10 g FEU/mL	10	10.2
>10 g FEU/mL	15	15.3
Amount	98	100.0

Table 4
Frequency Comparison of the Age and Sex of Inpatients with Confirmed COVID-19 between the UFH and LMWH (fondaparinux) groups.

Variable	UFH (n = 35)		LMWH (fondaparinux) (n = 63)		Total		P
	N	%	N	%	N	%	
Age							p = 0.193
21–30	2	2%	4	4.1%	6	6.1%	
31–40	4	4.1%	14	14.3%	18	18.4%	
41–50	4	4.1%	15	15.3%	19	19.4%	
51–60	10	10.2%	15	15.3%	25	25.5%	
>60	15	15.3%	15	15.3%	30	30.6%	
Sex							p = 0.740
Male	16	16.3%	31	31.6%	47	48%	
Female	19	19.4%	32	32.7%	51	52%	

was no significant difference ($p > 0.05$) in the variables of age or sex between the UFH and LMWH (fondaparinux) groups.

Tables 5 and 6 illustrate the changes in D-dimer values before and after administration of UFH and LMWH (fondaparinux), respectively.

The D-dimer value after UFH administration and the D-dimer value after LMWH (fondaparinux) administration were compared (Table 7). The results obtained revealed no significant difference in the increase or decrease between the two groups ($p = 0.193$, $p > 0.05$, respectively), indicating that there was no significant relationship between the aPTT value and patient status.

4. Discussion

Several studies have shown that coagulopathic complications are common in patients with severe COVID-19 and are associated with increased mortality. COVID-19 can predispose patients to both venous and arterial thromboembolic disease due to the activation of coagulation caused by excessive inflammation, activation of platelets, endothelial dysfunction, and stasis of blood flow related to immobility. Indications of disease severity and the establishment of coagulopathy may vary; these indications include increased D-dimer, thrombocytopenia, elevated D-dimer levels, and prolonged PT and aPTT [7,8,11–13].

The hypercoagulable state can be enforced through an increased D-dimer value, where D-dimer is the result of the breakdown of fibrin clots that have cross-links in the D-domain. Consequently, D-dimer can be used as a parameter for measuring thrombus formation. An increase in the D-dimer value indicates the presence of a fibrinolysis process in these patients; thus, a negative D-dimer value can rule out a diagnosis of venous or arterial thrombosis, while an increase in the D-dimer value indicates a sign of thrombus formation [14,15].

In this study, most of the outpatients with confirmed COVID-19 and coagulopathy were >60 years of age. Similarly, a study at Tongji Hospital found a significant difference in young- and old-aged inpatients confirmed positive for COVID-2019, with an increase in the D-dimer value of up to 1 g/mL, prolonged PT, and increased fibrinogen. Moreover, research conducted at Union Hospital, Wuhan, China showed that most of the 81 inpatients confirmed positive for COVID-19 who were evaluated for VTE were aged 60–69 years, and 18 (22%) patients were in the 70-year age group [16,17].

In addition to the distribution by age, this study also had a slightly higher prevalence of females compared to males (51 [52%] vs. 47 [48%], respectively), although the difference was not significant. This result is in line with research conducted at Union Hospital, Wuhan, China, which showed that 44 (54%) of the 81 hospitalized patients who were confirmed to be positive for COVID-19 with VTE being studied were female, and 37 (46%) were male. In general, female sex is a risk factor associated with hypercoagulation disorders, but among patients with COVID-19 with native arterial occlusion is more common in men. In addition, women taking combined oral contraceptives (COC) and oestrogen replacement therapy (ERT) may have an exacerbated risk of VTE occurrence in COVID-19. COC use is associated with a two-to six-fold increase in the risk of VTE. The risk of VTE in COVID-19 can also be exacerbated in pregnancy (the risk increases by four to five times) and in postmenopausal women [8,17–19].

The admission D-dimer values in this study were found to be in the interval of 1.01–5 g FEU/mL in as many as 44 patients (44.9%), while the lowest D-dimer values were <0.708 g FEU/mL in 8 patients (8.2%). The results of this study are in accordance with research at Tongji Hospital, which showed that among 449 patients, 315 had a mean D-dimer value of 1.47 (0.78–4.16) g FEU/mL, while the remainder had a

Table 5
Comparison of D-dimer values before and after UFH was administered to inpatients with confirmed COVID-19.

		D-Dimer (post-UFH)					**Total**	P Value
		increase	0.01 ± 0.5 g FEU/mL decrease	0.501 ± 1 g FEU/mL decrease	1 ± 5 g FEU/mL decrease	>5 g FEU/mL decrease		
D-Dimer (pre-UFH)	<0.708 g FEU/mL	1	1	0	0	0	2	**p = <0.001**
	0.708–1 g FEU/mL	3	4	0	0	0	7	
	1.01–5 g FEU/mL	4	6	3	3	0	16	
	5.01–10 g FEU/mL	0	1	0	3	0	4	
	>10 g FEU/mL	0	0	0	0	6	6	
Total		8	12	3	6	6	35	
		22.9%	34.3%	8.6%	17.1%	17.1%	100%	

Table 6
Comparison of D-dimer values before and after the administration of LMWH (fondaparinux) to inpatients with confirmed COVID-19.

		D-Dimer (post- LMWH (fondaparinux))					**Total**	P Value
		increase	0.01 ± 0.5 g FEU/mL decrease	0.501 ± 1 g FEU/mL decrease	1 ± 5 g FEU/mL decrease	>5 g FEU/mL decrease		
D-Dimer (pre- LMWH (fondaparinux))	<0.708 g FEU/mL	4	2	0	0	0	6	**p = <0.001**
	0.708–1 g FEU/mL	6	6	2	0	0	14	
	1.01–5 g FEU/mL	5	7	9	7	0	28	
	5.01–10 g FEU/mL	1	0	0	4	1	6	
	>10 g FEU/mL	0	0	0	0	9	9	
Total		16	15	11	11	10	63	
%		25.4%	23.8%	17.5%	17.5%	15.9%	100%	

Table 7
Comparison of the effectiveness of UFH and LMWH (fondaparinux) in confirmed COVID-19 inpatients.

Variable	UFH (n = 35)		LMWH (fondaparinux) (n = 63)		P value
	N	%	N	%	
Post-D-dimer Value					p = 0.193
Increase	8	22.9%	16	25.4%	
decrease of 0.01–0.5 g FEU/mL	12	34.3%	15	23.8%	
0.501–1 g FEU/mL decrease	3	8.6%	11	17.5%	
1–5 g FEU/mL decrease	6	17.1%	11	17.5%	
> 5 g FEU/mL decrease	6	17.1%	10	15.9%	

mean D-dimer value of 4.70 (1.42–21.00) g FEU/mL [20,21].

In this study, 63 of the patients with hypercoagulation complications used LMWH (fondaparinux) as an anticoagulant. This LMWH (fondaparinux) group comprised the largest number of patients with a change in D-dimer value, with 16 patients (25.4%) showing an increase post-treatment. The second highest order was observed in 15 patients (23.8%) who experienced a decrease in D-dimer value (0.01 ± 0.5 g FEU/mL) post-treatment. This is consistent with a previous study in which portal vein thrombosis disappeared completely, and the target blood vessels were patent in two patients 7 days after drug administration, in four patients 14 days after drug administration, and in one patient 21 days after drug administration. The D-dimer value decreased significantly during treatment, and this decreased value showed had a predictive value for portal vein recanalization ($p = 0.018$). No side effects, such as bleeding, hypohepatia, or thrombocytopenia, occurred in any of the patients. These results indicate that the decrease in the D-dimer value is the result of fibrin formation and fibrinolysis caused by the administration of LMWH (fondaparinux) [22–25].

An increasing amount of data are reporting a high incidence of coagulopathy and VTE among hospitalized patients with COVID-19. However, little is known about the potential association between antithrombotic therapy and COVID-19 or the resulting prognosis. Thromboprophylaxis anticoagulants, including LMWH, low-dose UFH, or LMWH (fondaparinux), are recommended for acutely ill hospitalized medical patients with an increased risk for thrombosis. In this study, there was a slight difference between treatments in patients with hypercoagulable complications who were given UFH and LMWH (fondaparinux) $p = 0.193$ ($p > 0.05$). This is in line with research by Russo et al., who reported that the incidence of VTE and bleeding events, including major bleeding and clinically relevant non-major bleeding, did not significantly differ between patients with COVID-19 who were taking LMWH (fondaparinux) and those receiving UFH therapy. In addition, compared with the use of UFH, treatment with LMWH (fondaparinux) did not yield statistically significant differences in the progression of acute respiratory distress syndrome or in-hospital mortality, although the rates of both were numerically lower [26]. The limitation of this study is that the subjects of this study with secondary data obtained from medical records of inpatients confirmed with COVID-19 have incomplete data, because not all inpatients with confirmed COVID-19 undergo a complete coagulation examination before and after administration of UFH or LMWH. Anticoagulants, so the number of patients who can be the subject of this study is still limited but has met the criteria for calculating the research subject. Therefore, I hope that further research can be carried out with a larger number of research subjects in order to obtain better and more meaningful research results.

5. Conclusion

Most of the hospitalized patients with confirmed COVID-19 were >60-years of age and female. In this study, patients in both treatment groups (UFH and LMWH (fondaparinux)) showed a significant decrease in D-dimer values, suggesting that both drugs have a similar effectiveness in the treatment of coagulopathy.

Ethical approval

This research was submitted to the ethics committee of the Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, Jakarta, Indonesia (No. 186/PE/KE/FKKUMJ/X/2021) for approval of the ethical study. Written informed consent was obtained from all participants.

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Author contribution

M.F, M.H and S.N.N.A.T designed the study. M.F, M.H, S.N.N.A.T and R.D carried out the laboratory analyses. M.F, R.A, A.S, M.R.P and A. R.J reviewed the data, conducted the statistical analyses, and interpreted the results. M.F, M.H, S.N.N.A.T, R.A, M.R.P and A.F wrote the first draft of the paper, which all authors critically reviewed. All authors read and approved the final manuscript.

Consent

None.

Registration of research studies

Trial registry number.

1. Name of the registry: Research Registry
2. Unique Identifying number (UIN) or registration ID: researchregistry7813 at April 16, 2022.
3. Hyperlink to specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/register-now#home/registrationdetails/6259fe44d4fa7d00223d140a/

Guarantor

Prof. Mochammad Hatta, MD, PhD, Clin Microbiologist (Cons).

Patient consent

None.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability

All data generated or analysed during this study are included in this published article.

Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104042.

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