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RESEARCH ARTICLE

Effect of fondaparinux anticoagulants on D-dimer levels in Covid-19 patients

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Abstract

Background: Anticoagulants can prevent thromboembolic activities, improve prognosis, and reduce the mortality rate in Covid-19 patients with coagulopathy. **Objective:** To analyse the effect of Fondaparinux in decreasing D-dimer levels, and to determine the correlation between patient characteristics, disease severity, and D-dimer levels. **Methods:** This is a single-centre retrospective cohort study using the medical records of Covid-19 in-patients who were ≥ 17 years old, on Fondaparinux 2.5 mg OD and had D-dimer measurement pre-and post-five days-Fondaparinux therapy during hospitalisation at referral general hospital in Bengkulu, Indonesia between April 2020 and December 2021. The data were assessed to evaluate the differences in the pre-post D-dimer levels, the relationship between patient characteristics and disease severity, and the relationship between disease severity and D-dimer levels. **Results:** A total of thirty-six patients were included in this study, of which 52.78% were males and 44.44% were aged 46-55 years old. Furthermore, 88.89% had comorbidity, and 55.55% had moderate severity. There was a significant decrease in D-dimer levels in all disease severity ($p < 0.05$). Patient characteristics and disease severity were not associated with D-dimer depletion ($p > 0.05$). **Conclusion:** Fondaparinux reduced the D-dimer levels in all severity of Covid-19 patients.

Introduction

COVID-19 is an acute respiratory tract infection caused by SARS-CoV-2 transmitted by droplets with an incubation period of two to fourteen days (Di Gennaro *et al.*, 2020). Furthermore, its clinical manifestation affects the respiratory system, cytokine storm, and systemic hyperinflammation, which catalyse coagulation cascade and hypercoagulation activation, thereby leading to coagulopathy; particularly venous thromboembolism (VTE) (Barnes *et al.*, 2020).

Elevated D-dimer is a biomarker of coagulopathy, which is often detected in moderate to severe COVID-19 patients. Klok *et al.* revealed that 31% of infected people admitted to the ICU experienced VTE, and the majority had a pulmonary embolism, 27% of the total population (Klok *et al.*, 2020).

Anticoagulants can prevent thrombosis and improve the prognosis of COVID-19-associated coagulopathy. (William *et al.*, 2020). Current guidelines recommend Heparin (UFH), Enoxaparin (LMWH), Fondaparinux, or Direct Oral Anticoagulant (DOAC) for in-patients, except they are contraindicated, such as thrombocytopenia and active bleeding (Rosovsky *et al.*, 2020).

Dr M Yunus Bengkulu Hospital is one of the referral hospitals for COVID-19 cases in Bengkulu, Indonesia. To provide a better understanding of thromboprophylaxis of Fondaparinux in patients, this study determined its effect on D-dimer levels and assessed modes of correlation between risk factors and impact on treatment outcome.

Methods

Design

This is a single-centre analytical observational study with a retrospective cohort approach using data extracted from medical records of hospitalised COVID-19 patients in Farmawati Dr M Yunus, a referral general hospital in Bengkulu, Indonesia between April 2020 and December 2021. The inclusion criteria were in-patients aged at least 17 years old, receiving 2.5mg Fondaparinux (once daily) as an add-on of the standard COVID-19 therapy, and having D-dimer measurement pre-and post-five days of fondaparinux therapy.

Meanwhile, the exclusion criteria were 1) People with thrombocytopenic (PLT < 250000/mm³); 2) Had a history of recent bleeding; 3) Patients on ASA therapy as well as DOAC for seven days before admission; 4) Receiving statins; 5) Pro surgery patients; 6) Pregnant woman; and 7) Cancer patients. The methodology of this study was approved by the ethical committee of RSUD Dr M Yunus Bengkulu, Indonesia with Approval Number 07/KEPK-RSMY/III/2022

Assessment

The effect of fondaparinux anticoagulant on decreasing D-dimer levels was assessed using the Wilcoxon test. Furthermore, the Contingency Coefficient test was carried out to determine the correlation of age, gender, and comorbidities with disease severity. The Spearman test was used to explore the relationship between disease severity and the decline in D-dimer levels in COVID-19 patients.

Results

A total of thirty-six (36) in-patients confirmed with COVID-19 were included in the study. About 52.78% were males and 44.44% were 46-55 years old. Furthermore, 61.11% had Diabetes Mellitus (DM) as a comorbid disease, while 55.55% suffered a moderate degree of COVID-19, as shown in Table I and Figure 1.

Table I: Patient’s baseline characteristics and causal relationship between risk factors and disease severity

Baseline characteristic			Severity of Covid-19			Contingency coefficient test
			Mild	Moderate	Severe–Critical	
Gender	Male	19 (52.8)	2	12	5	$p = 0.507$ $r = 0.191$
	Female	17 (47.2)	4	8	5	
Age	17 - 25 years	1 (2.8)	1	0	0	$p = 0.416$ $r = 0.430$
	26 - 35 years	1 (2.8)	0	1	0	
	46 - 55 years	16 (44.4)	3	7	6	
	56 - 65 years	14 (38.9)	2	9	3	
	≥ 66 years	4 (11.1)	0	3	1	
Comorbidity	No Comorbid	4 (11.1)	1	3	0	$P = 0.653$ $r = 0.252$
	1 Comorbid	23 (63.9)	3	12	8	
	≥ 2 Comorbid	9 (25.0)	2	5	2	

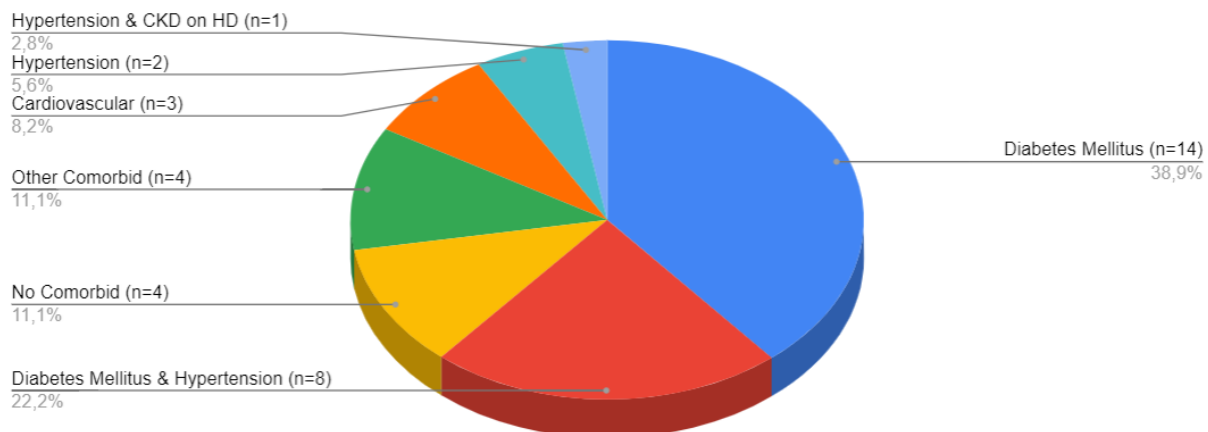


Figure 1: Types of patient comorbidities

Preliminary analysis revealed that there was a significant decrease in the patient's plasma D-dimer ($p < 0.05$). Baseline D-dimer, post-five days of fondaparinux administration and mean reduced (delta) D-dimer in the thirty-six patients were 2681.0 (715.8-9150.7) $\mu\text{g/L}$; 1024.3 (108.9-6,996.0) $\mu\text{g/L}$; and 1656.7 (82.9-8078.2) $\mu\text{g/L}$, respectively. Furthermore, the mean delta D-dimer obtained in the mild, moderate, and severe groups were 1444.7, 1317.5, and 2462.3 $\mu\text{g/L}$ respectively, as shown in Table II.

The results of the comparative hypothesis carried out using the Wilcoxon test showed a significance value (p

= 0.000 < 0.05), indicating that fondaparinux can substantially reduce D-dimer in all disease severity associated with COVID-19.

The Contingency Coefficient test results revealed that age, gender, and concomitant disorders do not correlate with the disease severity of COVID-19 ($p > 0.05$). The Spearman test showed that the level of illness does not have a significant association with the decreasing levels of D-dimer ($p = 0.890 > 0.05$), as shown in Table II.

Table II: The effect of fondaparinux and the correlation between disease severity and decreased D-dimer levels

Severity of Covid-19	Mean D-dimer levels ($\mu\text{g/L}$)		Mean delta D-dimer($\mu\text{g/L}$) (Pre – Post)	Sig. (Wilcoxon test)	Spearman test
	Pre	Post			
Mild (n= 6)	2.073.3	628.6	1.444.7	0.028 < 0.05	$p = 0.890$ $r = 0.024$
Moderate (n= 20)	2.165.2	847.7	1.317.5	0.000 < 0.05	
Severe – Critical (n =10)	4.077.4	1.615.1	2.462.3	0.005 < 0.05	

Discussion

The results showed that males were at a higher risk of COVID-19 compared to females. This finding is consistent with global data, which revealed that there were more male patients than females, and they accounted for 53.3% and 46.7% of the population respectively (Pivonello *et al.*, 2021).

This increased risk was due to their biological and behavioural characteristics (Cen *et al.*, 2020). Males have less dominant X chromosomes than females, which contain immunity-regulating genes encoding the IL, IL-4, IL-10, and IL-12 receptors (Bwire, 2020). The chromosomes also influence the oestradiol levels to promote T-cell response (Li *et al.*, 2020). Men's high testosterone and low oestradiol levels influence oestrogen receptor blockage and increase the number of ACE-2 receptors (Bwire, 2020).

Data provided by WHO in 2018 (WHO, 2019) and Riskesdas in 2018 (Kementrian RI, 2018) revealed that 70.7% and 62.9% of males in Indonesia were active smokers. The nicotine concentration in cigarettes activates ACE-2 receptors on the lung's respiratory epithelium and endothelial cells, thereby increasing access to SARS-CoV-2 and making it bind to the receptors (Ruhayat, 2021).

Smoking also promotes pro-coagulant conditions, inflammation, increased plasma fibrinogen levels, elevated factor VIII, decreased fibrinolysis, and increased blood viscosity, which can lead to VTE.

Consequently, smokers are more vulnerable to COVID-19 infection than non-smokers (Cheng *et al.*, 2013).

The result showed that most of the respondents were aged 46-55 years old, and this is inconsistent with Cen *et al.*, where people aged 65 years are 2.6 times more at risk of the disease compared to others under 65 (Cen *et al.*, 2020). The degenerative process, lower immunity, multimorbidity, less elastic lung lining, chronic inflammation, and blood thickening due to immobilization contributed to the deterioration and worsened prognosis of the elderly confirmed with COVID-19 (Elviani *et al.*, 2021).

The D-dimer concentration in healthy individuals is less than 0.4-0.5 $\mu\text{g/mL}$ or less than 500 ng/mL (Pagana *et al.*, 2019; Yao *et al.*, 2020). Huang *et al.* stated that elevated initial D-dimer levels of 1.5 $\mu\text{g/mL}$ found in patients who needed critical care assistance is a predictor of VTE (Huang *et al.*, 2020).

For the co-existent disease, Diabetes Mellitus had the highest prevalence in this study. This finding is consistent with Mishra *et al.*, that people with DM are associated with moderate severity and had significantly elevated plasma D-dimer compared to non-diabetics, namely $1509 \pm 2420 \mu\text{g/L}$ and $515 \pm 624 \mu\text{g/L}$, respectively with $p = 0.002$. Prolonged hyperglycaemia-induced endothelial dysfunction and inflammation contribute to a hypercoagulable state (Mishra *et al.*, 2020)

This result showed that plasma D-dimer significantly reduced post-fondaparinux therapy 2.5 mg q.d. for five-days in mild to critically ill hospitalised patients admitted with COVID-19. Therefore, fondaparinux was recommended as an effective thromboprophylaxis in coagulopathy associated with the disease. These findings are in line with Russo's study, where fondaparinux was safe and effective in in-patients with COVID-19 compared to enoxaparin (Russo *et al.*, 2020). Furthermore, 2.5 mg fondaparinux (once daily) has been proven to have more net clinical benefits in preventing VTE than 60 mg q.d. enoxaparin or b.i.d. in patients (Azizah *et al.*, 2022).

Fondaparinux is a synthetic pentasaccharide that specifically inhibits coagulation of factor Xa. It also has several advantages over other anticoagulants (UFH and LMWH), such as a non-porcine-based product with 100% bioavailability and a longer half-life of 17-21 hours (Donat *et al.*, 2002). Fondaparinux has a linear pharmacokinetic profile, predictable dose impact, as well as low intra- and inter-variability (Donat *et al.*, 2002).

Furthermore, it shows no cross-reactivity with heparin antibodies and is associated with a modest risk of thrombocytopenia and bleeding (Dong *et al.*, 2016).

Fondaparinux and enoxaparin (LMWH) are preferred over heparin anticoagulants (UFH) because they do not need regular activated partial thromboplastin time (aPTT) monitoring, and a once-daily administration of fondaparinux is more cost-effective and comfortable for patients (Barnes *et al.*, 2020; Becker, 2020; Azizah *et al.*, 2022).

Wolff and colleagues (2021) identified “individuals aged ≥ 65 ”, “males”, “obesity”, “multimorbidity”, “smoking history”, “immunosuppression”, “inflammation disorder”, “coagulation dysfunction”, and “hospital admission time” as major risk factors for severe COVID-19 (Wolff *et al.*, 2021). The result from this study also showed that age, gender, and coexisting diseases were insignificant to the severity of illness in patients ($p > 0.05$). This study did not find any positive correlation between disease severity and decreasing D-dimer levels in people infected with the virus ($p = 0.890 > 0.05$). The disparities in the results were related to the limitations of this study.

Limitations

This is a single-centre and a small-scale study, therefore, patients may present different conditions in other centres or globally, and they may also access standard COVID-19 therapy.

Conclusion

Thromboprophylaxis with fondaparinux therapy reduced D-dimer levels in all disease severities. Furthermore, age, gender, comorbidities, and severity levels were not associated with decreased D-dimer levels in COVID-19 patients.

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