Sapporo Medical Journal
Volume 57, Issue 03, March, 2023

Efficacy of Anticoagulant Ovine Prophylaxis Therapy in COVID-19 Moderate and Mild Patients with Hypercoagulability using Enoxaparin Ovine

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Abstract—Introduction: Hypercoagulability is a hallmark of coronavirus disease (COVID-19) complications, including Pulmonary Embolism and Multiple organ failure, which are the leading causes of mortality. Anticoagulant therapy is a hallmark therapy for COVID-19 patients with hypercoagulability. In this study, we used enoxaparin ovine as the anticoagulant. **Methods:** A retrospective cohort study was conducted among 24 patients with COVID-19 admitted to Wisma Atlet Kemayoran COVID-19 Emergency Hospital between April 2022 and October 2022. D-dimer levels were determined on an I-Chroma cs2100, and X-rays were taken with a Rotanode E7239X. **Result:** Analytics were calculated using SPSS ver. 21. P value were considered statistically significant at $P < 0.05$, and there was a correlation between the decreased D-dimer group and the targeted D-dimer group levels after enoxaparin ovine treatment. ($P<0.00$). Factors including vaccination ($P=0.163$) and comorbidity ($P=0.259$) did not affect enoxaparin prophylaxis. **Conclusion:** Enoxaparin ovine prophylaxis prevents clinical deterioration in covid-19 patients. Bleeding is expected in enoxaparin ovine prophylaxis therapy, as well as in other anticoagulant therapies. Although it has an effect in decreasing D-dimer levels, we could not conclude that it did not lack efficacy because the majority of the patients were not on an oxygen device.

Keywords: Covid-19, enoxaparin, hypercoagulability, d-dimer

1. Introduction

Coronavirus disease 2019 (COVID-19) was discovered in Wuhan 2019 and has spread exponentially to over 207 countries.By March 12, 2020, the WHO had announced a global pandemic and raised concerns about its spread.[1,2] Indonesia has the second highest positive rate and mortality rate in Southeast Asia. [3] Indonesia recorded 4.289.305 positive case and 144.277 mortality case. [4,5]

COVID-19 course of the illness described close related to hypercoagulability.According to a previous study, hypercoagulability is a factor that defines the morbidity and mortality in covid-19.[6] Because hypercoagulability condition promotes thrombus formation, which can lead to multiple organ failure.One of the main causes of death in COVID-19 is acute respiratory distress syndrome (ARDS), caused by a thromboembolic event in the lung. The mortality rate caused by ARDS in COVID-19 [7,8]
Anticoagulants are the hallmark of therapy for hypercoagulability events.A study by Tang et al. showed a correlation between D-dimer levels and morbidity and mortality in patients with COVID-19. Tang observed that 183 patients infected with COVID-19 showed increased d-dmer levels in 71.4% of patients who died form DIC. Thus anticoagulant therapy has become novel therapy in covid-19 patients with hypercoagulability.[6,9]

Hypercoagulability caused by endothelial dysfunction can cause complications, such as deep vein thrombosis and pulmonary embolism. The endothelial dysfunction will activate the coagulation cascade, and inflammation caused by the virus itself will synergically be caused mortality in covid-19 patients.[10-12]

The Indonesian COVID-19 Emergency Hospital has adopted five Organization Profession guidelines including anticoagulant therapy.For patients with Moderate to mild hypercoagulability, a prophylactic anticoagulant dose is recommended. Prophylactic anticoagulant therapy is targeted to minimize clinical deterioration caused by hypercoagulability. The Indonesian COVID-19 guideline suggested prophylactic anticoagulant therapy if the patient admitted has hypercoagulation status by marked d-dimer level.[9]

Enoxaparin as one of the modalities in anticoagulant therapy, has its effect in inhibiting Factor Xa. It has a peak time of 3-4 hours after its administration.[13,14] Enoxaparin is metabolized by the liver and eliminated by the kidneys. Thus, Patients with impaired kidney function and geriatric patients need special monitoring.[15]

2. Method

2.1 Ethical Consideration

Ethical clearance was obtained and approved by the Universitas Sebelas Maretand Wisma Atlet Kemayoran COVID-19 Emergency Hospital, Kemayoran.All personally identifiable information and medical records were kept confidential.

2.2 Study Population

This study included 24 patients with confirmed COVID-19 at the Wisma Atlet Kemayoran COVID-19 Emergency Hospital between April 2022 and October 2022. Blood samples were collected prior to any medical intervention. Chest radiographs were obtained at the hospital. Medical records, including radiology and hematology test results, were analyzed using the chi-square test in SPSS ver.21. A correlation was considered significant if it was less than 0.05.

2.3 Sample Collection and Analysis

A Cohort retrospective study was conducted among 24 patients with COVID-19 admitted to Wisma Atlet Kemayoran COVID-19 Emergency Hospital between April 2022 – October 2022. D-dimer levels were determined on an I-Chroma cs2100, and X-rays were taken with a Rotanode E7239X. The D-dimer level was collected first during the preliminary blood test, and the post-therapy D-dimer test was performed after the final dose of enoxaparin ovine prophylaxis therapy was administered. D-dimer levels were grouped as more than once the normal upper limit, twice the normal upper limit, and more than three times the upper normal limit.

The decrease in D-dimer level post therapy was also grouped as under 2x normal upper limit, less than 1x upper normal limit, and the last group showed no change or even increased D-dimer level after anticoagulant prophylaxis therapy. In addition, we grouped patients with or without comorbidities and vaccination status to determine their correlation with therapy.

2.4 Ordinary TB culture

Mycobacterium tuberculosis was effectively refined out of the blue by the German Microbiologist Robert Koch in 1882. Lowenstein Jensen medium utilized for a culture of M.tuberculosisis an egg-based medium containing malachite green, potato starch, salts, and glycerol. Turnaround time for the separation of M.tuberculosis utilizing this media is 4 two months. [12] If development happens, further handling and medication powerlessness testing take a month. Different kinds of strong media utilized are Agar based media, Middlebrook 7H10 and Middlebrook 7H11 with anti-infection agents, potato based and serum-based media. Rate of development of Mycobacteria is faster in agar-based media contrasted with egg-based media. Media is clear with a huge surface territory yet there is a necessity of CO 2 for culture in agar-based media. [13] Drug powerlessness testing utilizing agar and egg-based media is awkward and held for performing in reference research centers and other well-prepared labs. This procedure takes as long as about a month and a half or more. Techniques by which medication vulnerability of M.tuberculosis should be possible are the extent strategy, total focus technique, and opposition proportion technique. [14]

2.5 Statistical Analysis

The association between d-dimer, covid-19 severity, age group, and sex was tested. A normality test was conducted using the Shapiro-Wilk test and a correlation test to determine the decrease in D-dimer level using the Wilcoxon signed t-test and chi-square test. Other contributing parameters suspected to be contributing factors were tested using the chi-square test, which was defined as statistically significant. Data editing, sorting, coding, classification, tabulation, and statistical analyses were performed using IBM SPSS. Statistical significance was set at $p < 0.05$.

3. Result

In this study, 24 patients are diagnosed with COVID-19. Among the patients, six (25%) were males, and 18 (75%) were females. The mean age of the study participants was 39±10.1 years. Of the 24 patients, only one was recognized as a severe case of COVID-19.Of the 24 patients, there are six had comorbidities.Obesity made up most of the group, with 6(25%). The characteristics and hematological profile of the patients are shown in Table I and Table II below

Table 1. Demographic population

Parameter	Frequency/Mean±std deviation
Gender	Male 6 (25%) Female 18(75%)
Age	39 ± 10.1
D dimmer	

Baseline	2208.16±1690.20
Final	1379.79±2824.61
Severity	Asymtomatic 3 (12,5%)
	Mild 13 (54.2%)
	Moderate 8(33.3%)

3.1 The efficacy of Enoxaparine Ovine

The group of the rise and d-dimer lowering of d-dimer potency had an abnormal data distribution. Our study had abnormal distributive data based on the Shapiro-Wilk test (P<0.00).

Based on this result, a correlation test was conducted using the Wilcoxon signed-rank test (P=0.00 (P<0.05). We concluded that there is a correlation between the use of enoxaparin ovine, resulting in a statistically significant decrease in D-dimer levels.

Table 2. Correlation between the rise of d-dimer level and the lowering potency of d-dimer

D-dimer raise	**Lowering Potency**			**Total**
	0	**1**	**2**	
>1x	0	2	2	4
>2x	0	0	1	1
>3x	7	4	8	19
Total	7	6	11	24

Although there was a significant decrease in the D-dimer level, we also found that eight people had a higher D-dimer level. To investigate whether it is related to comorbidity and vaccination status, we used the chi-square test to determine its correlation.

This study found no correlation between vaccination status and the lowering effect of enoxaparin ovine prophylactic therapy (P=0.163). In addition, this study found no correlation between comorbidity and the lowering effect of D-dimer. (P=0.259)

Table 3. Correlation between d-dimer lowering potency and comorbidity

	d-dimer lowering potency			**Total**
	No change	Lowered to	Lowered to	

			<2x upper normal limit	<1x upper normal limit	
comorbid	No	6	3	9	18
	Yes	2	2	2	6
Total		8	5	11	24

Table 4. Correlation between d-dimer lowering potency and vaccination status

		d-dimer lowering potency			**Total**
		No change	Lowered to <2x upper normal limit	Lowered to <1x upper normal limit	
Fully Vaccinated	No	4	1	7	12
	Yes	3	5	4	12
Total		7	6	11	24

During the study, 1 patient (4.1 %) experienced side effects while administering enoxaparin ovine prophylaxis therapy.Although there were side effects, no clinical deterioration was observed.Genitourinary bleeding in the form of gross hematuria was found on the first day of administration.The side effect procedure was selected to stop the administration of enoxaparin ovine, and the patient was switched to unfractionated heparin after the bleeding subsided on the third day.

Only one patient with oxygen supplementation was eligible for enoxaparin ovine prophylactic therapy.A nasal cannula was used at a flow rate of 4 L/min.During the administration of enoxaparin ovine on the third day, the patient showed clinical improvement to didn't need any oxygen supplementation.

4. Discussion

This study found that enoxaparin ovine significantly decreases D-dimer levels because there is a correlation between the baseline D-dimer group and the decreased D-dimer group.

This study was conducted by Tang et al.. et al.[16] Decreasing d-dimer levels below three times the normal upper limit benefits the patient from clinical deterioration, which is consistent with the findings of the present study.[16].We also observed that this study was dominated by mild covid infection; therefore, vaccination plays an important role in reducing the severity of COVID-19 infection.Decreasing the D-dimer level to less than three times the upper normal limit also benefits patients.In this study, none of the patients experienced clinical deterioration.

Although most of the population has decreased D-dimer levels, there is an increase in D-dimer levels in a few patients.Although the patient did not show an improvement in coagulation factors, those patients did not experience gross hematuria after administering enoxaparin ovine for the first day.The regimen was

stopped, and the patient was switched to unfractionated heparin.Although the IMPROVE score for bleeding risk was less than 7, the patient showed decreased kidney function (EGFR=51). The score was calculated using the Cockcroft-Gault formula. Hematuria spontaneously stopped on the third day after the termination of enoxaparin therapy. The prevalence of side effects in this study is consistent with that reported in another study. In another study by Olesan et al., the side effects of minor bleeding occurred in 3% of patients. Also, INR to address the patient's liver function was substituted by AST and ALT.[17]

5. Conclusion

Enoxaparin ovine prophylaxis therapy can decrease d-dimer levels significantly to prevent clinical deterioration in covid-19 mild and moderate patients with hypercoagulability.

Minor bleeding was the most common side effect. Enoxaparin administration must be carefully monitored in patients with impaired kidney function. Bleeding events are common during anticoagulant therapy, as observed with other therapies.

Other factors, such as comorbidity and vaccination status, did not affect the efficacy of enoxaparin ovine. Although it has an effect in decreasing D-dimer levels, we could not conclude that it did not lack efficacy because the majority of the patients were not on an oxygen device.

6. References

[1] Kementerian Dalam Negeri. 2020. Pedoman Umum Menghadapi pandemic Covid-19 Bagi pemerintah Daerah : Pencegahan, Pengendalian, Diagnosis dan Manajemen

[2] Prevention CfDCa. Interim US Guidance for Risk Assessment and Public Health Management of Persons with Potential Coronavirus Disease 2019 (COVID-19) Exposures: Geographic Risk and Contacts of Laboratory-confirmed Cases [Internet]. 2020 [updated March 7; cited 2020 March 20, 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/risk-assessment.html.

[3] World Health Organisation. The WHO Director-General's opening remarks at the media briefing on COVID-19 March 11, 2020 [Internet]. 2020 [updated March 11, 2020]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11- march-2020.

[4] World Health Organisation. Situation Report 42 [Internet]. 2020 [updated March 02; cited 2020 March 15, 2020]. Available from: https://www.who.int/docs/default-source/ coronaviruse/situation-reports/20200302-sitrep-42-covid-19. pdf?sfvrsn=224c1add_2.

[5] The importance of chest CT scans in COVID-19 [Internet]. 2020. Available from: http://www.actamedindones.org/index.php/ijim/article/download/1430/pdf

[6] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844–7.

[7] Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant HA, et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroid use: A systematic review and meta-analysis. Expert Rev Respir Med. 2020 Nov;14(11):1149–63.

[8] Dolhnikoff, Marisa, et al. "Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19." Journal of thrombosis and haemostasis: JTH 18.6 (2020): 1517-1519.

[9] Burhan E, Susanto AD, Nasution SA, Ginanjar E, Pitoyo W, Susilo A, et al. Perhimpunan Dokter Paru Indonesia (PDPI) Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI) Perhimpunan Dokter Anestesiologi dan Terapi Intensif Indonesia (PERDATIN) Ikatan Dokter Anak Indonesia (IDAI). Pedoman Tata-Laksana COVID19 Indonesia. 5th Edition.2020.

[10] Bonaventura, A., Vecchié, A., Dagna, L. et al. Endothelial dysfunction and immunothrombosis are key

pathogenic mechanisms in COVID-19. Nat Rev Immunol 21, 319–329 (2021). Available from: https://doi.org/10.1038/s41577-021-00536-9

[11] Gąsecka, A., Borovac, J.A., Guerreiro, R.A. et al. Thrombotic Complications in Patients with COVID-19: Pathophysiological Mechanisms, Diagnosis, and Treatment. Cardiovasc Drugs Ther 35, 215–229 (2021). Available from: https://doi.org/10.1007/s10557-020-07084-9

[12] Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: A retrospective case series study. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.22.20026500v1

[13] Liu J, Li J, Arnold K, Pawlinski R, Key NS. Using heparin molecules to manage COVID-19. DOI:10.1001/trh2.12353

[14] Fareed J, Hoppensteadt D, Walenga J, Iqbal O, Ma Q, Jeske W, et al. Pharmacodynamic and Pharmacokinetic Properties of Enoxaparin: Implications for Clinical Practice. Clinical Pharmacokinetics. 2003;42(12):1043–57.

[15] Antiten-A [package insert]. Bandung: PT. Biofarma. 2021

[16] Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in patients with severe coronavirus disease and coagulopathy in 2019. J Thromb Haemost 2020. DOI: 10.1111/jth.14817

[17] Olesen, JB, Lip, GY, Hansen, ML, Lindhardsen, J, Larsen, TB, Gislason, GH. Low-molecular-weight heparins versus non-heparin oral anticoagulants in the management of acute coronary syndromes: A systematic review and meta-analysis. European Heart Journal. 2018;39(6):487-495.