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Cost Effectiveness Analysis of Anticoagulants as The Therapy of Corona Virus Disease 19 (Covid-19)

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ABSTRACT

Hypercoagulation is a condition characterized by increased thrombosis and is caused by various factors, one of which is SARS-CoV-2 virus infection. Anticoagulants are the main therapeutic options such as heparin and enoxaparin. The administration of these two drugs can reduce coagulation parameters such as D-dimer, PT, and fibrinogen values. The purpose of this study was to analyze the cost-effectiveness comparison of heparin and enoxaparin as anticoagulants in severe and critical COVID-19 patients. This study is an analytical observational study with a retrospective cohort design from a provider perspective. The research subjects were severe and critical COVID-19 patients who met the inclusion and exclusion criteria at Dr. Sardjito General Hospital in the period January 2021 - January 2022. The effectiveness of anticoagulants was seen through a decrease in the D-dimer value to a value of < 500 ug/ml on day 14 in medical records, safety was assessed from the incidence of bleeding recorded in medical records, while the average direct cost data during the patient's hospitalization was studied to determine cost-effectiveness with the Incremental Cost-Effectiveness Ratio (ICER). The achievement of D-dimer value < 500 µg/ml for the heparin group was 39.5% while the enoxaparin group was 48.4%, the result showed no significant difference (p=0.293). All subjects did not experience bleeding. The average direct medical cost of the heparin group was Rp. 31,296,577 and enoxaparin was Rp. 55,205,810. The ACER calculation of heparin and enoxaparin was Rp. 79,233,841 and Rp. 114,061,591 with an ICER of Rp. 2,686,431 for a decrease in D-dimer value reaching < 500 ug/ml. This shows that enoxaparin is better at reducing D-dimer values despite having a higher cost than heparin.
Keywords: anticoagulant; cost-effectiveness; enoxaparin; heparin; COVID-19

INTRODUCTION

Severe acute respiratory syndrome covid-2 (SARS-COV-2) is a virus that causes COVID-19 that was first reported in December 2019 in Wuhan, China. Since its discovery, the virus has continued to evolve into various variants and spread rapidly as a new pandemic around the world. The rate of spread of the disease, changes in virus variants and severity of symptoms, as well as the lack of information related to this disease, are key issues around the world. Over time, the potential funds needed to deal with this pandemic have emerged, starting from management for mild to moderate patients who spend a lot of money to achieve recovery status, followed by the higher the severity of the disease, the higher the cost of treatment. Especially patients with moderate or critical severity require more comprehensive treatment with more costs, one of which is anticoagulant therapy, which is used to treat hypercoagulable conditions. This condition is experienced by around 25-53% of COVID-19 patients, as a result, in addition to requiring additional treatment costs, the patient's mortality rate also increases (Elliott et al., 2021; Henry et al., 2020; Xie et al., 2020).

Hypercoagulable conditions are caused by endothelial dysfunction mediated by angiotensin-converting enzyme (ACE) which manifests in spikes in D-dimer, fibrinogen, and prothrombin time (PT) values. Through this mechanism, all components of Virchow's triad are fulfilled, namely endothelial dysfunction, hypercoagulable status, and static blood flow which has the potential to become venous thromboembolism (VTE) in COVID-19 patients. In this case, D-dimer is a marker of thrombotic activity that is formed from the degradation of fibrin through several enzyme actions (thrombin, factor XIIIa, and plasmin), besides that it can predict the severity and length of stay (Loo et al., 2021; Maldonado et al., 2020; Tal et al., 2020).

Anticoagulant therapy such as heparin, enoxaparin, fondaparinux, and direct oral anticoagulant (DOAC) are needed to overcome these problems. Some research studies suggest that enoxaparin and fondaparinux are superior as they have minimal bleeding risk compared to heparin. The use of enoxaparin is also able to reduce patient mortality rates even though there is no significant difference in reducing pulmonary embolism, D-dimer numbers, and fibrinogen levels when compared to heparin, and does not require close monitoring, thus reducing interactions between health workers and patients infected with COVID-19. However, the administration of enoxaparin in COVID-19 patients with renal impairment is still very limited, and the price is far above heparin, making heparin one of the choices in overcoming hypercoagulable conditions in COVID-19 (Alqubbanchi & Al-Hamadani, 2021; Oliynyk et al., 2021; Pawlowski et al., 2021; Sholzberg et al., 2021).

The use of the anticoagulant which clinically and economically for hypercoagulation therapy in COVID-19 is still debatable, so the purpose of this study is to analyze the cost-effectiveness of heparin and enoxaparin which are often used as COVID-19 therapy in severe and critical degrees at Dr. Sadjito Hospital Yogyakarta. The outcomes observed are improvements in D-dimer, safety, and direct medical costs which will be used to calculate the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) using a hospital perspective. Through this study, it is hoped that effective therapy can be found at an economical cost so that it can be a reference for making rational therapeutic decisions.

METHODOLOGY

This study design was a retrospective cohort in dr. Sardjito General Hospital Yogyakarta from January 2021 to January 2022. Observations were made by evaluating the patient's D-dimer from day 1 to day 14 while the patient was receiving anticoagulants, namely heparin or enoxaparin. This study was approved by the ethics committee of the local hospital with the number LB.02.01/XI.2.2/192.2023.

Research subject

The subjects used were medical record data and cost details of adult patients with severe and critical COVID-19 at dr. Sardjito General Hospital Yogyakarta for the period January 1, 2021 - January 1, 2022, who met the inclusion criteria of male and female adult inpatients aged > 18 years who were diagnosed with severe or critical COVID-19 and one of the anticoagulant therapies, namely heparin or enoxaparin, had complete medical record data including age, BMI, platelet count, D-dimer, PT value, fibrinogen and clinical outcome parameters, and have complete cost details. The sample size calculation is as below.

$$n = \frac{\left\{ z_{1-\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1-P_2)^2}$$

Equation 1. The formula for calculating the sample size of the proportion of two populations

Through the calculation formula, the estimated sample required is 96 samples in each group.

Data source

the data used for this study was obtained through the patient's electronic medical record and patient cost report.

Research Procedure

The data obtained from data sources were subject characteristics, laboratory parameters such as D-dimer, medication, and direct cost. All of those were written in data collection sheets.

Data Analysis

The effectiveness of anticoagulant use was assessed by D-dimer reduction to normal (< 500 μg/mL) on day 14.

Descriptive analysis using chi-square was performed to analyze subject characteristics and hypercoagulation characteristics. The characteristics of the study subjects analyzed were gender, age, weight, Charlson comorbidity index, D-dimer on day 1, length of stay, and severity of COVID-19. The hypercoagulation characteristics analyzed were day 1 and day 14 D-dimer values. The safety of anticoagulant use was not analyzed because there were no side effects that occurred in all samples used.

Statistical analysis was used in analyzing the decrease in D-dimer values on day 14 during heparin or enoxaparin therapy using the independent sample t-test test if the data were normally distributed. If $p < 0.05$, there is a difference in the effectiveness of using heparin and enoxaparin as anticoagulant therapy for COVID-19. Meanwhile, cost-effectiveness was calculated by summing up all costs such as the cost of anticoagulant therapy, namely heparin or enoxaparin, other therapy costs and BMHP, medical gas costs, action costs, supporting examination costs, accommodation costs, emergency room costs, and blood flask costs and then averaged into direct medical costs for each patient. Cost differences between the two groups were analyzed using an independent t-test or Mann-Whitney test.

Cost-effectiveness analysis was calculated through total patient costs and then analyzed with the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER).

$$ACER = \frac{\Delta\ direct\ cost}{\Delta\ outcome}$$

Equation 2. ACER formula

ICER is then calculated to determine the amount of additional cost for a 1-unit change in cost-effectiveness.

$$ICER = \frac{\Delta\ direct\ cost\ enoxaparin - \Delta\ direct\ cost\ heparin}{\Delta\ outcome\ enoxaparin - \Delta\ outcome\ heparin}$$

Equation 3. ICER formula

RESULTS AND DISCUSSION

Data were collected retrospectively with a total of 177 subjects with details of 86 subjects for the heparin group and 91 subjects for the enoxaparin group. The number of subjects should have been 194 due to the number of subjects who did not meet the inclusion criteria such as subjects who did not receive anticoagulants, subjects who received dual-anticoagulants and did not have complete laboratory data.

Characteristic of Subjects

Genders are dominated by men in the enoxaparin and heparin groups, this is due to occupational factors that require interpersonal interactions as well as the high prevalence of smoking and alcohol consumption. These factors trigger the high occurrence of COVID-19 infection in men compared to women (Abate et al., 2020; Marik et al., 2021). The age variable is dominated by ages 18 - 59 years, this occurs for the same reason, namely the high level of social interaction and activity during the pandemic (Starke et al., 2021). Furthermore, the length of stay (LOS) found that COVID-19 subjects were mostly treated with a median of < 17 days with severe severity with comorbidities. Several related studies explain that the length of stay is very influential on patient comorbidities so in COVID-19 patients with comorbidities the hospitalization interval is 3 - 74 days and without comorbidities it ranges from 17 - 32 days (Fahmia et al., 2022). The body mass index (BMI) variable shows that subjects with normal BMI values are more than others, as for some possible influences on high or low BMI values in COVID-19 such as length of hospitalization, ventilator use, and the possibility of other comorbidities (Singh et al., 2022; Yang et al., 2021).The day-1 D-dimer value shows that many subjects with values > 500 µg/mL occur because, in severe and critical degrees of COVID-19, there is an increase in fibrin degradation (Sujalmo et al., 2023).

Effectiveness analysis

This study showed that the enoxaparin group was superior to the heparin group in reducing D-dimer levels, but statistically showed no significant difference among the two groups (p= 0.239

Table I. Characteristics of Subjects

Characteristics	Total subject			P value
	Total (n = 177)	Heparin (n = 86)	Enoxaparin (n = 91)	
Gender				
Man	108 (61,01%)	55 (63,95%)	53 (58,24%)	0,436[a]
Female	69 (38,99%)	31 (36,05%)	38 (41,76%)	
Age				
18 - 59 year	91 (51,41%)	43 (50%)	48 (52,75%)	0,715[a]
≥ 60 year	86 (48,59%)	43 (50%)	43 (47,25%)	
***Length of stay* (LOS)**				
≤ 17 days	91 (51,41%)	48 (55,81%)	43 (47,25%)	0,25[a]
> 17 days	86 (48,59%)	38 (44,18%)	48 (52,75%)	
***Body Mass Index* (BMI)**				
< 18,5 (underweight)	4 (2,26%)	3 (3,5%)	1 (1,1%)	
18,5 - 24,9 (normal)	85 (48,02%)	45 (52,32%)	40 (43,95%)	
25,0 - 29,9 (overweight)	53 (29,94%)	24 (27,90%)	29 (31,86%)	0,257[b]
30,0 - 34,9 (obese class 1)	28 (15,81%)	13 (7,34%)	15 (16,48%)	
35,0 - 39,9 (obese class 2)	7 (3,95%)	1 (1,16%)	6 (6,6%)	
Severity of COVID-19				
Severe	168 (94,92%)	80 (93,03%)	88 (96,70%)	0,56[a]
Critical	9 (5,08%)	6 (6,97%)	3 (3,30%)	
D-dimer day-1				
< 500 µg/mL	49 (27,7%)	19 (22,1%)	30 (33%)	0,106[a]
≥500 µg/mL	128 (72,3%)	67 (77,9%)	61 (67%)	
Charlson Comorbidity Index				
CCI < 3	150 (84,75%)	72 (83,72%)	78 (85,70)	0,712[a]
CCI > 3	27 (15,25%)	14 (16,28%)	13 (14,30%)	

[a]: *Chi-square;* [b]: *Kruskal Wallis*

Table II. Effectiveness of anticoagulants on D-dimer values of patients with COVID-19 on day 14

Anticoagulant	Dimer < 500	Dimer ≥ 500	Total	P value
Heparin	34 (39,5%)	52 (60,5%)	86	0,239[a]
Enoxaparin	44 (48,4%)	47 (51,6%)	91	

[a]: *Mann-Whitney*

(p>0.05)). These results are in line with several studies comparing enoxaparin and heparin. The result shows that enoxaparin has better bioavailability than heparin and therefore reduces D-dimer levels better, which can reduce mortality, shorten the length of hospitalization, and is associated with a better survival rate (Al Sulaiman et al., 2022; Lemos et al., 2020). In addition, the use of enoxaparin reduces the interaction between health workers and COVID-19 patients and does not require close monitoring, thus reducing the risk of COVID-19 infection (Billett et al., 2020; Oliynyk et al., 2021).

Cost analysis

Analysis of anticoagulant costs in COVID-19 used in this study is the direct medical cost of each subject. The components of direct medical costs include anticoagulants, other medication, medical devices and consumables medical materials, medical gas, medical procedures, laboratory, accommodation, emergency department, administrative, and blood flask costs. The average of all these costs was presented in the total cost of each study group.

Each cost component in Table III showed statistically significantly different results between the two groups except for administrative costs (p= >0,05). The difference occurred due to differences

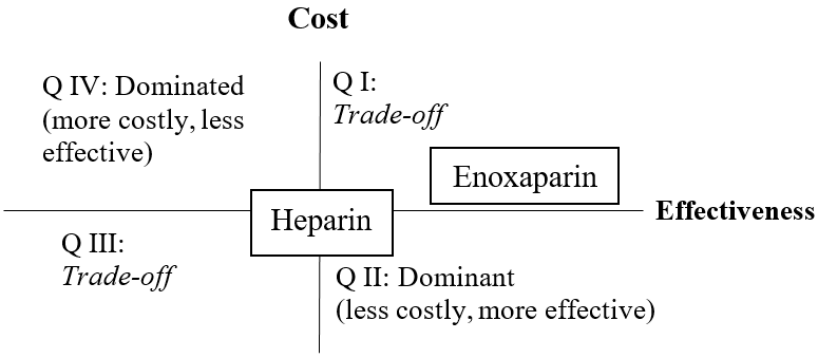

Figure 1. Cost-effectiveness plane of heparin and enoxaparin

Table III. The direct medical cost of COVID-19 subjects

Cost component	Average direct medical cost (n = 177)		P value
	Enoxaparin (Rp)	Heparin (Rp)	
Anticoagulant cost	4.766.731 ± 1.937.273	667.480 ± 260.790	0[b]
Medical devices and consumable medical materials cost	17.899.666 ± 22.369.276	7.104.130 ± 4.501.446	0[b]
Medical gas cost	2.312.725 ± 1.173.019	2.761.349 ± 993.599	0,007[a]
Medical procedures cost	11.866.104 ± 8.534.103	8.585.352 ± 9.641.998	0[b]
Laboratory cost	12.569.835 ± 6.809.412	8.014.599 ± 4.132.606	0[b]
Accommodation cost	4.123.367 ± 1.941.558	3.187.924 ± 1.267.216	0[b]
Administrative cost	36.000 ± 6.280	36.512 ± 6.820	0,125[b]
Emergency dept. cost	236.747 ± 212.365	252.169 ± 178.267	0,018[b]
Blood flask cost	1.456.344 ± 2.370.677	687.064 ± 1.461.931	0,031[b]
Total cost	55.205.810 ± 32.938.582	31.296.577 ± 17.246.349	0[b]

[a]: *Independent t-test;* [b]: *Mann-Whitney*

Table IV. ACER and ICER

Anticoagulant	Total direct cost	Outcome	ACER	ICER
Enoxaparin	Rp 55.205.810	48,40%	Rp 114.061.591	Rp 2.686.431
Heparin	Rp 31.296.577	39,50%	Rp 79.231.841	

in drug prices, length of stay, and comorbidities or different procedures in each subject. The results of the ICER and ACER calculations of the two anticoagulant groups are presented in Table IV.

Through the above calculations, it is found that the use of enoxaparin has an ICER of Rp. 2,686,431 as anticoagulant therapy in severe and critical COVID-19 patients. This puts enoxaparin in quadrant I (QI) or trade-off position because it has better effectiveness than heparin despite the higher cost.

Placed in the Q I means that despite its higher price, the efficacy of enoxaparin in reducing D-dimer levels in severe and critical COVID-19 patients is better than heparin so that the presence of lower D-dimer leads to better patient prognosis, shorter length of hospitalization and decreased patient mortality.

CONCLUSION

Enoxaparin is safe and more effective in reducing D-dimer in 14 days than heparin but the cost is higher with ICER of Rp. 2,686,431.

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