USE OF ANTICOAGULANT IN COVID-19 PATIENTS AT PKU MUHAMMADIYAH GAMPING HOSPITAL YOGYAKARTA

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🌐 https://doi.org/10.31603/pharmacy.v9i2.7038

ABSTRACT

Based on WHO data, there is about 14% average of patients who suffer from a severe level of Covid-19 disease and 5% of patients admitted to the ICU (Intensive Care Unit) are known to have symptoms of thromboembolism and coagulopathy disorders. The current management of Covid-19 therapy requires heparin. This research aims to find out the accuracy of the heparin regimen, to determine the improvement of the patient's clinical condition, the side effects of heparin based on clinical response, to analyze the relationship between the accuracy of the therapeutic regimen and the improvement of the patient's clinical condition, and also to know the incidence of side effects after heparin use. The type of this research was descriptive-analytic with a cohort design with retrospective data collection. The data were collected by taking medical records at PKU Muhammadiyah Gamping Hospital Yogyakarta. Moreover, the data were collected including heparin therapy regimens with subjective condition and patient objective during the therapy. The data obtained were analyzed by using univariate analysis technique and bivariate analysis technique. The results showed there were 61 patients who fulfilled the inclusion criteria. The evaluation of the accuracy the heparin therapy regimen obtained 95.08% correct results and 4.92% incorrect results. The analysis result of the accuracy the therapeutic regimen showed a significant relationship with clinical improvement with parameters APTT number (p=0.006; RR=0.155; CI = 0.085-0.283). Whereas, there was not found a significant relationship between the accuracy of the therapeutic regimen with the incidence of side effects (p>0.05).

Keywords: Covid-19; Anticoagulant; Heparin; Clinical improvement; APTT

1. INTRODUCTION

Coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is the etiological agent of COVID-19, which appeared in Wuhan, China, in December 2019. Since then, this disease has spread globally with more than 400,000 deaths worldwide in June 2020, and has been declared a pandemic by WHO. Confirmation cases of Covid-19 in Indonesia are still increasing. Based on the report from the Indonesian Ministry of Health, on June 4, 2021, there were 1,837,126 confirmed positive cases of COVID-19 throughout Indonesia and the Special Region of Yogyakarta with 45,233 positive confirmed cases of COVID-19 (Kemenkes RI, 2020). The results showed that patients with severe COVID-19 often experience coagulation disorders (coagulopathy) similar to other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) and microangiopathic thrombosis. Coagulation disorders in COVID-19 cause a prothrombotic state which increases the risk of thrombosis and venous and arterial thromboembolism (Levi et al., 2020). A study in the Netherlands showed that the cumulative incidence of thromboembolic events in COVID-19 patients reached 31%, with details of 27% experiencing VTE and 3.7% experiencing arterial thrombosis (Spyropoulos, 2020). Based on the results of research on COVID-19 patients experiencing thrombotic events as

indicated by changes in various blood clotting biochemical parameters such as D-Dimer, prothrombin time, and increased levels of various blood clotting factors, anticoagulant drugs can be administered for prophylaxis, intermediate or definitive therapy long term (Rusdiana & Akbar, 2020). The effectiveness of using heparin therapy in treating COVID-19 has been recommended by several experts' consensus regarding the risk of DIC (disseminated intravascular coagulation) and venous thromboembolism. The use of prophylactic therapy with heparin in more severe cases of COVID-19, or in patients with D-dimer levels more than six times above normal levels, has been shown to reduce mortality (Tang et al., 2020). The use of anticoagulants must be used with caution because they cause side effects of bleeding. The results of the study showed that the use of anticoagulants in COVID-19 patients as therapy indicated that there were major bleeding side effects in patients (Musoke et al., 2020). The objective of this research was to describe the heparin anticoagulant therapy regimen, describe the improvement in clinical conditions and side effects after using heparin anticoagulants, and the relationship between the accuracy of the heparin anticoagulant therapy regimen to the improvement in clinical condition and the incidence of side effects in COVID-19 patients at PKU Muhammadiyah Gamping Hospital, Yogyakarta.

2. METHOD

The design of this research was analytic descriptive research with a cohort design. Data collection was carried out retrospectively. The research sample was all COVID-19 patients who used the anticoagulant drug heparin during the period March 2020 – March 2021. The population taken was all patients who were confirmed to have COVID-19 at PKU Muhammadiyah Yogyakarta Hospital who were hospitalized from March 2020 – March 2021 and received heparin therapy. Samples with inclusion criteria included those with confirmed COVID-19, those receiving heparin anticoagulant therapy at PKU Muhammadiyah Yogyakarta Hospital, and patients aged more than or equal to 18 years and less than or equal to 60 years. Exclusion criteria included pregnant women with confirmed Covid-19, stroke patients, and patients with incomplete medical records.

The data collected included drug use data, and objective and subjective patient data while undergoing heparin therapy. Clinical improvements in heparin therapy based on medical records from clinical data based on laboratory data on APTT (Activated Partial Thromboplastin Time) according to the clinical interpretation manual, the accuracy of therapy based on the 3rd edition of the Covid-19 management book and identification of side effect events based on patient subjective objective data while undergoing Heparin therapy was adjusted according to the journal Meyler'S Side Effects of Drugs 15th edition. Descriptive data analysis was used to obtain the frequency and percentage (%) of each variable. Analysis to test to determine the relationship between the accuracy of the heparin therapy regimen to clinical improvement and the relationship between the accuracy of the regimen and the side effects using the Chi-square test.

This research has fulfilled the research ethics requirements and has received approval from the ethics committee of PKU Muhammadiyah Gamping Hospital Yogyakarta on July 19 2021 with No. 025/KEP-PKU/VII/2021. The number of patients who met the inclusion criteria was 61 patients

3. RESULTS AND DISCUSSION

Data collection was carried out retrospectively. The research sample was all COVID-19 patients who used the anticoagulant drug heparin during the period of March 2020 – March 2021. The sampling technique involved taking all Covid-19 patients using enoxaparin who met the inclusion criteria. This research has fulfilled the research ethics requirements and has received approval from the ethics committee of PKU Muhammadiyah Gamping Hospital Yogyakarta on July 19 2021 with No. 025/KEP-PKU/VII/2021. The number of patients who met the inclusion

criteria was 61 patients. Characteristics of Covid-19 Patients at PKU Muhammadiyah Gamping Hospital are listed in **Table 1.**

Table 1. Characteristics of Covid-19 Patients at PKU Muhammadiyah Gamping Hospital

Characteristics	Total (n= 61)	Percentage %
Age		
Adult (18-45)	24	39.34
Elderly (46-60)	37	60.65
Gender		
Male	35	57.37
Female	26	42.62
Education		
Primary School – High School	38	62.29
Diploma-Undergraduate-Postgraduate	23	37.70
Occupation		
Entrepreneur	50	81.96
Civil Servant	9	14.5
Students	2	3.2
Symptom based on Diagnose		
Moderate	57	93.44
Severe	4	5.76
Concomitant Illness		
None	45	73.77
Exist	16	26.22
Types of Concomitant Illness		
HT	2	12.5
DM	3	18.75
DM, HT	4	6.25
CKD, DM	1	6.25
CKD, HT	1	6.25
Pneumonia	1	12.5
Asthma	2	6.25
SNH	1	6.25
AKI	1	6.25
Length of Hospitalization		
< 10 days	30	49.1
≥ 10 days	31	50.81

The subject of this research based on age was categorized based on age category; Adult patients (18-45 years) and elderly patients (46-60 years). The results obtained from this age group showed that elderly patients were the age that used heparin the most compared to adult patients, with a total percentage of elderly patients (at 59.61%) and adults (at 40.38%). According to (WHO, 2021), infection with this virus generally occurs at the age of 40, so it is expected that this age range will protect oneself from COVID-19 infection. Research (Farghaly & Makboul, 2021), the age group of 40-49 years is the group most infected with SARS-CoV, with 21.3%, followed by the 50-59 years range of 20.6% while those aged ≥70 years are only 6.4%.

The results of research at the PKU Muhammadiyah Gamping Hospital, based on gender at Yogyakarta for the period of March 2020-March 2021, more male patients (57.37%) used enoxaparin during Covid-19. Based on the research results, it was found that the number of male patients suffering from Covid-19 infection shows a greater percentage than women. Research (Susilo, 2021) states that men have less attention and good knowledge in preventing COVID-19 disease than women. This was because women tend to spend more time discussing or reading related to disease prevention. According to (Kemenkes RI, 2020), in June 2020 as many as 51.5% of confirmed cases were male. This is in line with the findings of the Chinese CDC that 51.4% of the most confirmed cases occurred in men. Likewise in Italy, most cases of people with COVID-19 are men, which reach rates above 50%. Reports (Farghaly & Makboul, 2021) in his research

in Egypt, a total of 579 patients were infected, there were 311 patients (54.2%) with the male sex. The low number of cases in women could be associated with protection from sex hormones and the X chromosome which played an important role in the adaptive and innate immune system.

Based on the results of research at PKU Muhammadiyah Gamping Hospital, 57 patients (93.44%) had moderate symptoms. Moderate symptoms in Covid-19 patients, patients with clinical signs of pneumonia (fever, cough, shortness of breath, fast breathing) but no signs of severe pneumonia including SpO2 > 93% with room air (Burhan, 2020). Based on the results of the study, the highest number of Covid-19 patients with diabetes mellitus were 8 people (13.11%) and 7 people with hypertension (11.47%). According to the results of research in Bangkok Thailand, the most common comorbidities were DM (5.7%), and hypertension (4.2%) (Bruminhent et al., 2020). According to research in Nanjing China, comorbid hypertension (14.6%), DM (6.4%), and stroke (1.6%) (Liu et al., 2020). According to the results of research in Norway, risk factors for COVID-19 cases were reported, the risk factors such as male, obesity, heart failure, and diabetes (JPW, 2020). According to the results of research in Georgia USA, reported obesity (55%), hypertension (49%), and DM (33%) Meanwhile, according to research results in Teheran, Iran, many co-morbidities are due to hypertension and DM (Parohan et al., 2021). This is still relevant and in accordance with the results of research that co-morbidities that greatly affect COVID-19 cases are suffering from DM and hypertension.

Table 2. Heparin Therapy Regimen for Covid-19 Patients at PKU Muhammadiyah Gamping Hospital

Therapy Regimen	Length of Administration	Total of Patients
heparin 5000 IU/12 hours (n=58)	3	8
	4	5
	5	9
	6	11
	7	5
	8	7
	9	1
	12	1
	13	1
	16	1
	29	1
heparin 1400 IU/jam (n=2)	6	1
	29	1
heparin 1200 IU/jam (n=1)	6	1

Based on **Table 2**, research on the use of anticoagulants in Covid-19 patients at PKU Muhammadiyah Gamping Yogyakarta Hospital used heparin, namely Invlcot. From the results, the most widely administered therapeutic dose was Invlicot 5000 IU/12 hours given to 58 patients. The heparin given to the patient was prophylactic therapy at a dose of 5000 IU/12 hours subcutaneously. In patients with obese weight categories, adjustments to therapeutic doses are adjusted according to the guidelines of each health facility (Barnes et al., 2020). In patients with creatinine clearance value below 30 mL/minute or patients with acute renal impairment, it was necessary to adjust the dose of LMWH or use UFH as subcutaneous thromboprophylaxis at a dose of 5000 units every 8 to 12 hours (Miesbach & Makris, 2020). Heparin therapy was given while the patient was being treated based on the Covid-19 management guidelines (Burhan, 2020).

3.1. Accuracy of Heparin Therapy Regimen

Based on the Covid-19 management book, moderate-grade COVID-19 patients are being treated at the hospital and given prophylactic anticoagulants. The standard dose of heparin is 5000 units subcutaneously twice a day. Based on the results of the research (**Table 3**), 58 patients (95.08%) with Covid-19 received appropriate therapy. Based on the diagnosis of Covid-19 patients for moderate symptoms, it is recommended to use prophylactic anticoagulants at a dose

of 5000 units given 2 times a day. The dose given was 1400 units/hour and 1200 units/hour could be given to patients with severe or critical symptoms so giving heparin to these patients was inappropriate. Anticoagulant dosage recommendations for thrombosis prophylaxis were dynamic each institution or guideline had different dosage recommendations. The American Society of Hematology recommends giving prophylactic doses of anticoagulants over intermediate doses or therapeutic doses in COVID-19 patients with acute or critical conditions who have not been proven to have venous thromboembolism (Cuker et al., 2021).

Table 3. Accuracy of Heparin Therapy Regimen for Covid-19 Patients at PKU Muhammadiyah Gamping Hospital

Therapy Dosage	Symptom Based on Diagnosis	Correct/Incorrect
Invlicot 5000 IU/12 hours (n=58)	Moderate Symptoms	Accurate
Invlicot 1400 IU/ hours (n=2)	Moderate Symptoms	Inaccurate
Invlicot 1200 IU/ hours (n=1)	Moderate Symptoms	Inaccurate

3.2. Adverse Effects

Side effects were seen based on the patient's subjective and objective data including the patient's general condition, and laboratory data, and then studied using the literature on the COVID-19 management guidebook edition 3 and Meyler's side effects of drugs handbook edition 15 (Aronson, 2000), so the results would be obtained based on **Table 4**.

Table 4. Adverse Effects of Anti-Coagulant Therapy for Covid-19 Patients at PKU Muhammadiyah Gamping Hospital

Adverse Effect	Total (n=61)	Patients' Condition	Percentage %
Hematuria	1	Moderate Symptoms With concomitant illness	1.63
Trombositopenia	1	Moderate Symptoms No concomitant illness	1.63
Melena	1	Moderate Symptoms No concomitant illness	1.63
No Adverse Effects	58	Moderate Symptoms	95.08

Hospitalized COVID-19 patients needed regular monitoring of coagulation markers which included D-dimer, PT, platelets, and fibrinogen. If there was a worsening of coagulation markers, more aggressive critical care support was needed. If coagulation markers were stable or improving, it could be a guide for step-down therapy if supported by improved clinical conditions (Levi et al., 2020).

3.3. Clinical Improvement

Clinical improvement in Covid-19 patients included heparin therapy based on medical records from clinical data on coagulopathy reduction seen from the APTT (Activated Partial Thromboplastin Time) number (according to the normal rate of interpretation of clinical data at PKU Muhammadiyah Yogyakarta Hospital and according to the 3rd edition of the COVID-19 management manual. Parameters of coagulation disorders that could be found in COVID-19 patients included increased D-dimer concentration, prolonged prothrombin time (PT), activated partial thromboplastin time (APTT), increased fibrinogen, and thrombocytopenia. Prolonged PT >3 seconds or aPTT >5 seconds was a marker of coagulopathy and a predictor of thrombotic complications in COVID-19 patients (Levi et al., 2020). Clinical Improvement of Anti-Coagulant Therapy in Covid-19 Patients at PKU Muhammadiyah Gamping Hospital, listed in **Table 5**.

Table 5. Clinical Improvement of Anti-Coagulant Therapy in Covid-19 Patients at PKU Muhammadiyah Gamping Hospital.

Number Clinical Repair APTT	Total n=61	Mean±SD H1	APTT H3	Percentage %
Getting Better (25-40 seconds)	49	31.7±11.36303	31.1±13.39403	80.32
Not Getting Better (>40 seconds)	12			19.67

Description

  H1   : APTT number on day 1

  H3   : APTT number on the 3rd day

Based on research conducted at PKU Gamping Hospital, the heparin therapy regimen given to Covid-19 patients out of 61 patients, the number of patients improved in 49 patients (80.32%) clinical condition improved with laboratory data such as the APTT score was not prolonged. Prothrombin time (PT), PT was slightly prolonged in patients who did not survive admission (15.5 seconds [range 14.4-16.3 seconds] in patients who did not survive compared to 13.6 seconds [13.0-14.3 seconds] in patients who did) survival; normal values [11.5-14.5 seconds]). PT values were also slightly prolonged in hospitalized patients requiring intensive care compared to those who did not (12.2 seconds [range 11.2-13.4] compared to 10.7 seconds [range 9.8-12.1]) (Tang et al., 2020). PT and APTT are exogenous and endogenous coagulation system factors, which can be used for early diagnosis of DIC. PT and APTT can also be used as sensitive indicators to reflect various degrees of coagulation dysfunction. In addition, the results of this research also demonstrated a significant association between coagulation factors and disease outcome, suggesting D-dimer, PT, and APTT may be useful as diagnostic indicators for the development of 21 specific diseases. In the first PT test, two abnormalities (15 seconds) were found in 8 patients which were aggravating while 5 abnormalities (15 seconds) were found in 23 patients who died. While the second and third PT examinations found 10 and 18 abnormalities (> 15 seconds) respectively in 23 patients who died. Gradually increasing DD and PT levels show a significant correlation with disease progression. The third time the PT and APTT tests had AUCs of 0.937 and 0.856, respectively, indicating that PT and APTT have a very large value in determining disease prognosis (Long et al., 2020).

3.4. Relationship of Therapeutic Regimen with Clinical Improvement and Incidence of Adverse Effects

In this research, an analysis of the accuracy of the therapeutic regimen was based on the literature on the management guideline for COVID-19 edition 3 and the success of therapy was seen from the normal rate of APTT in patients during heparin therapy. The relationship between the therapeutic regimen and clinical improvement and the adverse effects was based on **Table 6**.

Table 6. Correlation between regimen accuracy and clinical improvement and the relationship between regimen accuracy and side effects

	Accurate	Not exactly	p-value
Adverse Effect			
With adverse effect	2	1	0.006
No Adverse effects ES	56	2	
Effectiveness			0.413
Getting Better	59	9	
Not Getting Better	3	0	

Note: *p value <0.05, there was a relationship between the regimen accuracy and the improvement in clinical conditions

In **Table 4** the regimen accuracy for clinical improvement seen from the parameters of the APTT number showed that 49 patients improved. The significant value showed that there was a relationship between correct regimen and clinical improvement (p=0.006; RR=0.155; CI=0.085-

0.283), meaning that correct heparin regimens had a 0.155 times probability of experiencing clinical improvement compared to inappropriate regimens.

In this research, an analysis of the accuracy of the therapeutic regimen based on the literature on the 3rd edition of the COVID-19 Management Manual and the results in Table IV of the relationship between the therapeutic regimen and the adverse effects showed that 3 patients experienced side effects. The significant value showed that there was no relationship between the treatment regimen and the incidence of side effects (p=0.413; RR=1.48; CI=0.650 -3.22).

4. CONCLUSION

The accuracy of the heparin therapy regimen in Covid-19 patients at PKU Muhammadiyah Gamping Hospital was found to be 95.08% correct and 4.91% incorrect. The side effects that occurred in Covid-19 patients at PKU Muhammadiyah Gamping Hospital were obtained at 4.91%, namely thrombocytopenia, melena, and hematuria. There was a relationship between the accuracy of the therapeutic regimen and clinical improvement, that the parameter APTT ($p<0.05$). However, there was no significant relationship with the adverse effects ($p>0.05$). In the future, research should be carried out on Covid-19 patients using the anticoagulants enoxaparin and fondaparinux and conduct research on the relationship between clinical improvement and co-morbidities.

5. CONFLICT OF INTEREST

The author has no conflict of interest to declare in this research.

6. ACKNOWLEDGMENT

The author would like to thank PKU Muhammadiyah Gamping Hospital for permission and for carrying out this research.

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