Evaluation of the use of Favipiravir on the Hematology value of COVID-19 patients at Anna Bekasi Hospital in 2021

Feri Setiadi[1], Ardy Tanfil T[1*], Widyastuti[1]

[1]Pharmacy Undergraduate Study Program, Prima Indonesia College of Health Sciences
*Corresponding author email: ardytanfill@gmail.com

ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus occurred in Indonesia in early 2020. Favipiravir was used as an antiviral for the disease due to an emergency. The results of routine hematological examinations of inpatients can be used as a parameter to predict the patient's risk of severity and the effect of using favipiravir antiviral. This study aimed to determine the effect of using favipiravir on hematological values in COVID-19 patients. The method used in this research is cross-sectional. The data collection method was carried out retrospectively with the data source in the form of medical records at Anna Bekasi Selatan Hospital in 2021. The total sample that included the inclusion criteria in this study was 83 patients. The results of the study between before and after the use of favipiravir in patients without comorbidities were significant differences in the values of the Neutrophil Lymphocyte Ratio (p: 0.003), Lymphocytes (p: 0.000), Platelets (p: 0.009) while in the value of hematocrit (p: 0.185)) and hemoglobin (p:0.069) did not experience a significant difference. Patients with comorbid comorbidities using favipiravir had significant differences in hematological values, namely hemoglobin (p: 0.007), hematocrit (p: 0.004), platelets (p: 0.000) while the value of the Neutrophil Lymphocyte Ratio (p: 0.260) and lymphocytes (p: 0.234) did not experience a significant difference. Favipiravir is known to have a positive correlation with hematological values, in patients with COVID-19 infection without comorbidities using favipiravir it is known that the Neutrophil Lymphocyte Ratio value has decreased while the Lymphocyte and Platelet values have increased. However, it is known that the hemoglobin and hematocrit values did not experience a significant difference before consuming favipiravir and after consuming favipiravir.

Keywords: COVID-19, favipiravir, hematological valu

Introduction

Corona virus is a virus that has never been predicted before that it will become a virus that is very troublesome for mankind throughout the world, a virus that originally originated in Wuhan then spread throughout the world and became a major threat as a cause of respiratory problems in humans. Corona Virus, which later became better known as Corona Virus 19 (COVID-19) is a virus that can spread through liquid droplets that are produced when sufferers cough or sneeze. Humans who are infected after the incubation period of the virus will then experience several symptoms such as fever and difficulty breathing, improper handling can be dangerous and cause death(Shereen et al., 2020; Singhal, 2020).

Treatment given to sufferers of COVID-19 infection until 2021 is still in the form of out-of-label treatment considering that there is no specific drug available for COVID-19 infection. Favipiravir is one of the drugs given to patients infected with COVID-19, Favipiravir, which is known as an influenza antiviral, is used with the hypothesis that this drug can also work against infections caused by COVID-19. The safety of favipiravir is also known to be good for sufferers of mild to moderate levels of COVID-19 infection based on tests conducted in several Asian countries such as Japan, China, and Thailand(Joshi et al., 2021; Łagocka et al., 2021; Özlüşen et al., 2021; Shinkai et al., 2021).

Evaluation of Favipiravir needs to be carried out bearing in mind that drugs are chemical compounds and any administration of chemical compounds into a biological system must have a biological effect including unfavorable biological effects. Previous studies have confirmed that Favipiravir can suppress erythrocytes thereby disrupting the hematological system (Atcali et al., 2022; Yaylaci et al., 2020). Based on this background, we are interested in evaluating the effect of using favipiravir on Hematological values (Ratio of Lymphocytes, Neutrophils, Lymphocytes, Hemoglobin, Hematocrit, and Platelets) in COVID-19 Patients treated at Anna Bekasi Hospital. This research takes place in 2021.

Research Method
Materials and Materials

This study was conducted using data from laboratory test results before the patient was given Favipiravir and after the patient was given Favipiravir. Medical record data were also collected and observed, and the data was processed using SPSS software version 26.

Research Process

This research has received approval from the health research ethics committee of the Prima Indonesia High School of Health Sciences with No.107/EC/KEPK/STIKES—PI/IV/2022. The research has also received permission from Anna Hospital in South Bekasi with Number 237/EXT-DIR/RS ANNA/V/2022.

The research was carried out by collecting the names of patients diagnosed with COVID-19 and using favipiravir as the main therapy. Patient data (age, sex, co-morbidities) were obtained from the Anna Hospital Medical Records room while laboratory test results data related to hematology were obtained from the Anna Hospital Laboratory. The inclusion criteria are all patients infected with SARS COV-2 and receiving Favipiravir therapy, while the exclusion criteria set are patients infected with SARS COV-2 but not treated with Favipiravir or patients treated with Favipiravir but not infected with SARS COV-2. The data that has been collected is then processed for analysis.

Data Analysis

This study uses univariate analysis (descriptive analysis) which aims to explain or describe the characteristics of each research variable. For numerical data, the mean or average, median, and standard deviation values are used. This analysis generally only produces the frequency distribution and percentage of each variable. Furthermore, a bivariate analysis test was carried out using the t-test or Wilcoxon test. The t-test or Wilcoxon test aims to determine whether there is a significant change in the value of favipiravir before and after the use of hematological values (NLR, Lymphocytes, Hemoglobin, Hematocrit, and Platelets).

Results and Discussion

The variables that were the focus of this study were sociodemographics (age and gender, co-morbidities, and the patient's hematological scores (NLR, lymphocytes, hemoglobin, hematocrit, and platelets). This research is a cross-sectional study with data collection methods carried out retrospectively with data sources in the form of secondary data, namely medical records taken from Anna Hospital. Sampling used a non-probability sampling technique, namely a saturated sample technique that met the inclusion criteria. The population of COVID-19 patients using favipiravir was 153 patients and the samples obtained from the inclusion criteria were 83 patients. The research was carried out by collecting the names of patients diagnosed with COVID-19 and using favipiravir as the main therapy. Patient data (age, sex, co-morbidities) were obtained from the Anna Hospital Medical Records room while laboratory test results data related to hematology were obtained from the Anna Hospital Laboratory. The data that has been collected is then processed for analysis.

Table 1. Sex comparison of favipiravir use

Sex	Frequency of using favipiravir	Percentage
Male	38	45.8%
Female	45	54.2%
Total	83	100%

Table 2. Age comparison of favipiravir use

Age	Frequency of using favipiravir	Percentage
17-25	2	2.4%
26-35	8	9.6%
36-45	14	16.9%
46-55	23	27.7%
56-65	23	27.7%
66-100	13	15.7%
Total	83	100%

Table 3. Percentage of COVID-19 patients with comorbidities taking Favipiravir

Age	Frequency of using favipiravir	Percentage
No comorbid	39	47%
Hypertension	11	13.3%
Diabetes mellitus	17	20.2%
Heart abnormalities	7	8.4%
Asthma	4	4.8%
Hypertension and Diabetes Mellitus	4	4.8%
Diabetes mellitus	1	1.2%
Total	83	100%

Table 1 show the sociodemographic results of sex data obtained from a study of patients using favipiravir in COVID-19 patients at Anna Hospital in South Bekasi in 2021. The sex that consumed the drug the most was women with a total of 45 (54.2%). The number of the male sex who consumed favipiravir was 38 patients (45.8%).

The results of the research data analysis showed that the age range of COVID-19 patients using favipiravir was 46-55 years and 56-65 years with 23 patients (27.7%) each. The number of patients without comorbidities was 39 (47%) and patients with comorbidities were 44 (53%). The most common comorbid disease found in patients using favipiravir was diabetes mellitus with a total of 17 patients (20.2%) followed by hypertension with a total of 11 patients (13.3%) as can be seen in Table 3.

Based on research (Wang et al., 2020) people who have a history of diabetes mellitus have a 1,816 times greater risk of developing COVID-19 than those who do not have diabetes mellitus. People who have diabetes mellitus with COVID-19 will increase the secretion of hyperglycemic hormones such as catecholamines and glucocorticoids which results in an elevation of glucose in the blood, abnormal glucose variability, and complications of diabetes. Other studies have also stated that the comorbidities that are often found in COVID-19 patients are hypertension, diabetes mellitus, and heart disease.

Table 4. Results overview of hematology values

Hematology	Comorbid		Without Comorbid	
	Information	Frequency	Information	Frequency
Neutrophil Lympocyte Ratio	Increase	11 ± 2,3	Increase	21 ± 2,3
	Decrease	28 ±1,7	Decrease	23 ± 1,5
Lymphocytes	Increase	26 ± 2,8	Increase	24 ± 1,4
	Decrease	14 ± 1,3	Decrease	20 ± 1,3
Hematocrit	Increase	16 ± 1,2	Increase	11 ± 2,2
	Decrease	28 ± 2,9	Decrease	33 ± 1,8
Hemoglobin	Increase	14 ± 1,2	Increase	13 ± 1,3
	Decrease	30 ± 1,2	Decrease	32 ± 1,8
Platelets	Increase	29 ± 1,8	Increase	38 ± 2,2
	Decrease	10 ± 2,2	Decrease	6 ± 1,6

Our results also show that the value of the Neutrophil Lymphocyte Ratio has decreased in patients with comorbidities and patients without comorbidities. Research (Halil et al., 2022) NLR values describe an imbalance between adaptive immune responses (lymphocytes) and non-specific immune responses (neutrophils). The number of samples experienced a decrease in NLR indicating a decrease in inflammation after using favipiravir. In severe cases, higher NLR increases indicate severe dysregulation of the immune system and are unable to mitigate excessive non-specific immune responses. This exaggerated inflammatory response can lead to a cytokine storm and more extensive tissue damage.

The results of this study describe the increase in lymphocyte values in patients with comorbidities and without comorbidities. The large increase in lymphocyte values after using favipiravir indicates that there is a repair of damage to the immune system in the body. Based on research (Mus et al., 2021) a decrease in the number of lymphocytes indicates damage to the immune system.

Hematocrit is the level of red blood cells in the blood and hemoglobin is a protein in red blood that gives blood a red color and is responsible for transporting oxygen. From the results of the study it can be seen that the value of hematocrit and hemoglobin has decreased in patients with comorbidities and patients without comorbidities. In a study (Anai et al., 2021) stated that a decrease in hemoglobin values occurred several days after being diagnosed with pneumonia in COVID-19 patients with severe respiratory failure who needed respirators. Platelet values in COVID-19 patients are one of the things that need to be controlled. If there is an increase in platelet values in Covid-19 patients, it can cause coagulation or clotting and a decrease in platelet values which can eventually cause thrombocytopenia.

Statistical test results analyzed by paired t-test and Wilcoxon test showed that the values of Neutrophil Lymphocyte Ratio (p: 0.003), Lymphocytes (p: 0.000), and Platelets (p: 0.009) experienced significant differences between before and after using favipiravir. The results of this study are in line with research conducted by (Ozbas et al., 2021) with the results of research on the values of the Neutrophil Lymphocyte Ratio (p: 0.002), Lymphocytes (p: 0.001) and Platelets (p <0.001) experiencing differences between before and after use favipiravir. Statistical test results also confirmed that patients with comorbidities showed a value of Neutrophil Lymphocyte Ratio (p: 0.260) and Lymphocytes (p: 0.234), which means that there was no significant difference. The results of this study are not in line with research studies (Yaylaci et al., 2020) which stated that there were significant differences before and after using favipiravir in hemoglobin (p: 0.041), hematocrit (p: 0.026), and platelet (p: 0.005) values.

The value of Neutrophil Lymphocyte Ratio and Lymphocytes in patients with comorbidities did not experience a significant difference before and after using favipiravir. According to research, (Tawfik et al., 2022) patients with co-morbidities exacerbate COVID-19 infection. In his study, the use of favipiravir in patients with co-morbidities had a longer duration of time compared to patients without co-morbidities.

The high value of the Neutrophil Lymphocyte Ratio in COVID-19 patients is due to an imbalance between inflammation and the immune response in the body. Neutrophils are the cellular component of defense in the immune system, while lymphocytes are the main cells involved in adaptive immunity and the regulation of the inflammatory response. Patients with high NLR values are advised to be treated in an isolation room with monitoring for respiratory disorders (Kong et al., 2020). Decreased hemoglobin and hematocrit values in the study results can cause anemia. Based on research (Mintzer et al., 2009) the use of antiviral drugs can cause disorders in the hematological system. Other studies have also stated that the use of the antiviral ribavirin 41 used together with peginterferon for the treatment of hepatitis C can cause anemia (McHutchison et al., 2007).

The increase in platelet values in patients with comorbidities needs attention. SARS-CoV-2 infection can cause abnormalities in platelet hyperactivity, coagulation, thrombosis, and poor inflammatory response. Thrombosis complications often occur in COVID-19 patients who are in

critical condition and this can also increase the risk of death caused by myocardial infarction and ARDS (Acute Respiratory Distress Syndrome) (Fard et al., 2021).

Conclusion

Favipiravir is known to have a positive correlation with hematological values, in patients with COVID-19 infection without comorbidities using favipiravir it is known that the Neutrophil Lymphocyte Ratio value has decreased while the Lymphocyte and Platelet values have increased. However, it is known that the hemoglobin and hematocrit values did not experience a significant difference before consuming favipiravir and after consuming favipiravir.

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