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Clinical Outcomes for Severe COVID-19 Patients with Comorbid Type 2 DM through Dexamethasone Therapy at RSUP Dr. Sardjito Yogyakarta

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ABSTRACT

Background: Dexamethasone is a recommended therapy for severe COVID-19 patients who require hospital treatment. However, its use can affect blood glucose levels in patients, especially patients with diabetes mellitus comorbidity.

Objectives: This study aims to determine the clinical outcomes for type 2 diabetes mellitus (DM) patients with Severe COVID-19 comorbidity through dexamethasone as COVID-19 therapy.

Methods: This study employed the retrospective cohort an analytical observational research approach. Involving 60 patients as subjects, patients over the age of 18 received dexamethasone at RSUP Dr. Sardjito Yogyakarta between June 2021 and March 2022 and whose RT-PCR results showed severe COVID-19 with comorbidity of type 2 DM were included in the study. The blood glucose profiles derived from the patient's medical record data were the clinical outcome that already checked. The paired t-test was performed to analyze how dexamethasone affected the clinical results of the blood glucose profile.

Results: The findings of the study were identified after using dexamethasone for four days, which showed that 78.30% of patients had an increased in blood glucose. Pre and post treatment of dexamethasone for four days had a significant impact on the patient's blood glucose levels in this study, with an average change in blood glucose levels is 78.32 ± 116.77 ($p<0.05$).

Conclusion: Dexamethasone therapy demonstrates a significant effect on blood glucose levels, resulting in a statistically difference between pre and post values for four days in patients with severe COVID-19 with type 2 DM comorbidity. Consequently, special monitoring needs to be carried out in severe COVID-19 patients with type 2 DM who receive dexamethasone to avoid worsening of the patient's clinical condition.

Keywords: COVID-19; Dexamethasone; Diabetes mellitus; Clinical Outcomes.

INTRODUCTION

In December 2019, many cases of pneumonia with no known origin were reported in Wuhan. High-throughput sequencing of lower respiratory tract samples revealed the 2019 novel coronavirus (2019-nCoV), a new coronavirus.[1] The World Health Organization (WHO) announced on January 30, 2020, a Public Health Emergency of International Concern (PHEIC) or a public health emergency of international concern due to the rising number of corona virus cases. The illness is known as coronavirus disease 2019 (COVID-19), that was formally designated as severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The number of new cases

increased rapidly as more COVID-19 tests became available, and on March 11, 2020. Then, WHO declared the COVID-19 outbreak to be a global pandemic.[2]

Diabetes mellitus (DM) is one of the second highest comorbidities, namely 33.6% of COVID-19 patients in Indonesia.[3] Patients with DM have a high risk of being infected with COVID-19, and hyperglycemia can be a factor causing death, prolonging the length of hospitalization and a poor prognosis in COVID-19 patients.[4,5] The COVID-19 condition can also cause damage to pancreatic β cells and insulin resistance so that it can increase glucose and HbA1c levels, and can worsen patient DM comorbidities.[6]

Corticosteroid therapy may improve insulin resistance in patients with DM. The effect of increasing blood glucose depends on the dose of administration and can occur in patients within several hours after administration, and the effect is greater on post prandial glucose levels than fasting blood glucose levels.[7] Corticosteroid is one of the recommended therapies for COVID-19 patients, especially for COVID-19 patients who require hospital treatment with moderate to severe symptoms.[8] Corticosteroids can overcome hyperinflammation and reduce the cytokine storm that can be caused by COVID-19 infection and can reduce the death rate of COVID-19 patients, however, the use of corticosteroids in this case can worsen the condition of DM by increasing blood glucose levels, and can even cause new onset DM.[9,10] It is well known that corticosteroid therapy can trigger the emergence of new-onset type 2 DM and can worsen the condition of hyperglycemia in patients with pre-existing DM.[11]

This study aims to determine the clinical outcomes of severe COVID-19 patients with type 2 diabetes mellitus (DM) comorbidity who were given dexamethasone as COVID-19 therapy. Several previous studies have examined the administration of corticosteroids to COVID-19 patients with observed parameters, namely decreased mortality, improved clinical symptoms, reduced length of hospitalization, reduced need for mechanical ventilation, and incidence of hyperglycemia and hypoglycemia.[12–15] The difference between previous studies is in the research subjects, which was severe COVID-19 patients with comorbid type 2 DM. The observed parameters included blood glucose profiles and length of patient care in the COVID-19 ward. There has been no study that concerns at the relationship between these variables, in fact, it will be useful for practitioners to determine corticosteroid therapy in COVID-19 patients with comorbid diabetes mellitus. The results of this study provide information regarding the effect of administering dexamethasone on increasing blood glucose levels in severe COVID-19 patients with type 2 DM. Therefore, this research can increase awareness in providing dexamethasone therapy to severe COVID-19 patients with comorbid type 2 DM. Patients must be monitored regularly to avoid the risk of a bad prognosis for the patient.

METHODS

Study design

This research used an analytical observational research design, with a cohort approach with a retrospective method.

Population and samples

Population

The population or group of subjects in this study were patients confirmed positive for severe COVID-19 by RT-PCR, accompanied by the comorbidity of type 2 diabetes mellitus, who received dexamethasone therapy during the treatment period from June 2021 to March 2022, and who met the following criteria. The inclusion criteria consisted of patients aged over 18 years, confirmed severe COVID-19 cases receiving corticosteroid therapy (dexamethasone), and patients with type 2 diabetes mellitus. The exclusion criteria included patients with incomplete medical record data regarding blood glucose profiles and pregnant patients.

Samples

The sample size on this study was calculated using the formula below with a confidence level of 95%:[16]

$$n = \frac{\{Z_{1-\alpha}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_a(1-P_a)}\}^2}{(P_a - P_0)^2}$$

n = Total sample size; $Z_{1-\alpha}$= The standard value of α is obtained from the Z value of the normal curve; α = Type one error is set at 5% or 0.05, so the value of $Z_{1-\alpha}$ is 1.960; $Z_{1-\beta}$ = The standard value of β is obtained from the Z value of the normal curve; β = Type two error is set at 20% or 0.20, so the value of $Z_{1-\beta}$ is 0.84; P_0 = The proportion of COVID-19 patients with DM based on the literature is 2.6% or 0.026[17]; P_a = The anticipated proportion of events in the study is 10% or 0.10.

From the formula used, the sample size in this study can be determined with the following calculation:

$$n = \frac{\{1{,}960\sqrt{0{,}026(1-0{,}026)} + 0{,}842\sqrt{0{,}10(1-0{,}10)}\}^2}{(0{,}10-0{,}026)^2}$$

n = 58,25 ~ 59 samples

Based on the calculations above, the minimum sample size that can be used in this study is 59 patients.

Study instruments

The materials used in this research were patient medical records and worksheets. Medical record data to obtain data includes patient identity, comorbidity data, severity of COVID-19, and blood glucose profile, whereas worksheets were used to record data needed during the research. Besides medical record data and worksheets, statistical software was also used to analyze the data.

Data collection

A non-probability technique was used to collect patient data, involving a sampling technique that did not provide an equal opportunity or opportunity for each element or member of the population to be selected as a sample. Besides, it used a consecutive sampling approach. Every patient who met the research criteria was included as a subject in the research for a period of certain time, so that the number of research subjects could be fulfilled. Blood glucose data were collected during the pre-condition. On the first day of patient admission before giving dexamethasone therapy and in the post-condition on the fourth day after giving dexamethasone therapy. Patient data were secondary data taken from medical records of patients confirmed positive RT-PCR for severe COVID-19 at RSUP Dr. Sardjito Yogyakarta.

Data Analysis

Data analysis of the effect of dexamethasone administration on pre and post blood glucose level data used the paired t-test. The results of the analysis with a confidence interval (CI) of 95% stated that there is a relationship between variables if the p value is <0.05. However, if the p value is > 0.05, then there is no relationship between the two.

RESULTS AND DISCUSSION

This research was conducted at RSUP Dr. Sardjito Yogyakarta on May 2023 in the Medical Records Installation section. RSUP Dr. Sardjito Yogyakarta is the highest referral hospital for COVID-19 patients in Yogyakarta since the start of the pandemic. The subjects in the study were hospitalized patients diagnosed with RT-PCR positive COVID-19 who were diagnosed severe COVID-19 with comorbidities or a secondary diagnosis of type 2 DM who met the criteria on this study. The number of subjects who included in this study were 60 patients, the characteristics of subjects in this study can be seen in Table I.

Table I. Characteristics of Patients

Characteristics		Number of subjects (n=60)	Percentage (%)
Ages	<60 years	33	5
	≥60 years	27	45
Gender	Male	31	51.70
	Female	29	48.30
Comorbidities	CCI <4	33	55
	CCI ≥4	27	45

The age of the patients is categorized into two, namely <60 years and ≥60 years based on the previous research which examined the prevalence of COVID-19 patients in Indonesia.[18] Table I shows that there are 33 patients aged <60 years (55%), and 27 patients aged ≥60 years (45%). The results showed that the prevalence of patients' age confirmed positive for COVID-19 at Dr. Sardjito Hospital is more at the age of <60 years and is in accordance with the research conducted by Karyono and Wicaksana (2020). It states that most COVID- 19 patients in Indonesia are at the age of <60 years with the largest age range being 31-59 years.[18]

According to Karyono and Wicaksana research on 2020, the prevalence of COVID-19 patients in Indonesia is higher experienced in males than females. The recovery and mortality rates of male patients are also higher than those of female patients.[18] Then, according to the International Diabetes Federation (2015), it states that the prevalence of male DM sufferers is higher than females.[19] The results of this study are in accordance with several studies, namely the prevalence of COVID-19 patients with DM comorbidities in males is higher than in females, amounting 31 male patients (51.70%) and 29 female patients (48.30%).

The characteristics of comorbidity in this study were scored using the Charlson Comorbidity Index (CCI). This is a method for predicting the mortality rate of patients who may have various concurrent conditions (comorbidities, considering a total of 17 categories). If no comorbidities are detected, the score is zero; the greater the score, the higher the expected death rate. [20] Each patient was assessed by CCI and then categorized into two categories, namely CCI <4 and CCI ≥4. In this study, the results showed that patients with a CCI value <4 were 33 patients (55%) and a CCI value ≥4 were 27 patients (45%).

The patient's blood glucose level was obtained from medical record data using random blood glucose data. In COVID-19 patients with comorbid diabetes mellitus, a blood glucose examination was carried out at the beginning of admission before being given therapy. During treatment in the COVID-19 ward, it was carried out until before the patient leaves the hospital. It can be seen in Figure 1 of the patient's blood glucose level, which was obtained from the patient's average blood glucose per day from the 1st to the 4th treatment day. The observations blood glucose of post-condition was done until the 4th treatment day because on the 5th day and so on, several research subjects dropped out from the hospital with death or improving status so that blood glucose data was incomplete for 60 subjects. From the figure, there is an increase from day 1 (pre-condition blood glucose) until day 4 (post-condition blood glucose) following the administration of intravenous dexamethasone at a dose of 6 mg every 24 hours. Increased hepatic glycogen deposition may be observed after 3-24 hours of corticosteroid administration.[21] Meanwhile, according to another study in COVID- 19 patients without diabetes after administering dexamethasone 6 mg per day, there was an increase in blood glucose levels and the peak occurred after 7-9 hours.[22] According to other research, dexamethasone is Long-acting glucocorticoids so that the drug effect is stronger and lasts longer, with a stable hyperglycemia effect achieved within 3 hours, and lasting around 23-35 hours, followed by a temporary increase in blood glucose for 14-21 hours, and peaking after the 3rd day use.[23]

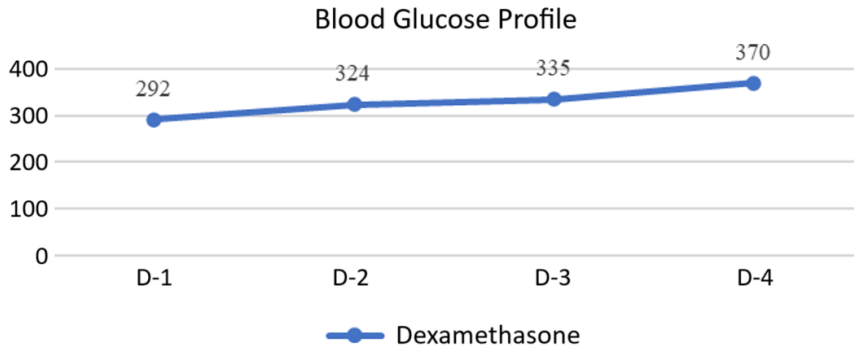

Figure 1. Blood glucose levels obtained from the average daily blood glucose results of patients on days 1 to 4 (n=60)

The blood glucose profile in this study was divided into two were increasing and decreasing. Patients with categories of increased and decreased blood glucose profiles are patients who experience changed an increase or decrease in blood glucose after administration of dexamethasone. The results of the study can be seen in Table II, that in 13 patients (21.70%), blood glucose decreased. At the same time, in 47 patients (78.30%), blood glucose increased after being given dexamethasone therapy. In 13 patients who experienced a decrease in blood glucose levels after receiving dexamethasone for four days, this could have occurred due to an increase in the insulin dose, leading to a decrease in blood glucose levels. These findings align with previous research, which indicated that COVID-19 patients who were given high doses of dexamethasone often experienced an increased need for insulin beyond the standard dose. Medications, particularly insulin therapy, are among the most common factors contributing to a decrease in blood glucose, levels.[24,25]

Table II. Percentage Change in Blood Glucose Levels After Giving Dexamethasone

Blood Glucose Profil	n (%) (N = 60)
The patient's blood glucose decreased after being given dexamethasone	13 (21,70)
The patient's blood glucose increased after being given dexamethasone	47 (78,30)

In table III, it can be seen the mean ± SD of the patient's blood glucose values, which was obtained in the pre-condition blood glucose 291.85 ± 118.65, post condition 370.17 ± 117.74, and the difference between the two is 78.32 ± 116.77. Pre-condition blood glucose was obtained from measuring the patient's blood glucose at the beginning of admission, whereas post-condition was obtained from the patient's blood glucose level on the 4th day after dexamethasone administration or on the patient's last day before leaving the hospital.[26]

The researchers carried out a normality test on pre-post blood glucose data using the Kolmogorov-Smirnov test, obtaining normally distributed data (p value> 0.05), then continued the analysis using the paired t-test. The results of pre-post statistical analysis of patient blood glucose showed a significant difference between before and after administration of corticosteroids (dexamethasone) in severe COVID-19 patients accompanied by DM comorbidity with a significant p value of 0.000 (p<0.05). According to previous research, there was an increase in the incidence of hyperglycemia in COVID-19 patients who were given high doses of dexamethasone. This significantly increased insulin requirements and there is a relationship between administration of corticosteroids and impaired blood glucose control in COVID-19 patients.[24,27,28]

Table III. Results of Analysis of the Effect of Dexamethasone on Blood Glucose Levels (Pre-Post)

	Pre N = 60 (Average ± SD)	Post N = 60 (Average ± SD)	Difference N = 60 (Average ± SD)	p value
Blood Glucose	291,85 ± 118,65	370,17 ± 117,74	78,32 ± 116,77	0,000*

Note = *there is a significant difference in blood glucose between pre and post administration of dexamethasone in severe COVID-19 patients with DM using paired T-Test.

CONCLUSION

There is a significant effect of dexamethasone therapy on blood glucose levels, with a notable difference observed between pre- and post- treatment blood glucose levels in severe COVID-19 patients with type 2 DM comorbidity. The average blood glucose difference during treatment was 78.32 ± 116.77, and the p value was 0.000 (p<0.05). This highlights the need for special monitoring of severe COVID-19 patients with type 2 DM who receiving dexamethasone therapy to avoid worsening of the patient's clinical condition.

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STATEMENT OF ETHICS

Ethical approval number on this study is KE/FK/0892/EC/2023 published by Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada and approved on 29 May 2023.

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