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Effectiveness of Dexamethasone, Methylprednisolone and Hydrocortisone Administration on LDH, CRP, D-and PaO2/FiO2 Ratio

Study on Patients with Confirmed Critical Degree of COVID-19 at ULIN Hospital Banjarmasin Period January-June 2021

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Abstract:

Steroids are the standard recommended therapy for COVID-19, especially in critically ill patients. Previous studies have shown that steroids are beneficial for inflammatory markers such as C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH) and D-dimer as well as the value of the PaO2/FiO2 ratio. This study aims to determine the differences in the effects of the steroid's dexamethasone, methylprednisolone and hydrocortisone on inflammatory markers. This research is a retrospective cohort study. The samples were all COVID-19 patients with critical degrees from January to June 2021. The independent variables were dexamethasone, methylprednisolone and hydrocortisone. The dependent variables are CRP, LDH, D-dimer and the ratio of PaO2/FiO2. The statistical test used was the Kolmogorov-Smirnov test and continued with the Kruskal-Wallis test and the Mann-Whitney U test. A total of 148 subjects with a total sample of dexamethasone 60, methylprednisolone 55 and hydrocortisone 33. The statistical test results showed a significant difference in the effect of the steroid dexamethasone, methylprednisolone and hydrocortisone on the value of the PaO2/FiO2 ratio (p=0.04). Administration of hydrocortisone and dexamethasone was statistically superior to methylprednisolone for increasing the PaO2/FiO2 ratio.

Keywords: COVID-19; Dexamethasone; Methylprednisolone; Hydrocortisone; CRP; LDH; D-dimer; PaO2/FiO2 ratio

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first discovered in Hubei Province, China, precisely in the city of Wuhan on December 31, 2019. Since February 11, 2020, the World Health Organization (WHO) has given the latest name, Coronavirus Disease 19. (COVID-19) caused by the SARS-CoV-2 virus. The status of the pandemic related to the SARS-CoV-2 virus was officially announced by WHO on March 12, 2020.[1]

As of December 11, 2021, according to WHO, there are 227 countries affected by COVID-19. Data in Indonesia there are 4,258,980 positive cases, 4,109,865 recovered cases and 143,929 deaths as of December 11, 2021. Data in South Kalimantan Province, a total of 69,936 positive patients with 2391 deaths and 67,532 the patient recovered. Specifically at Ulin Hospital Banjarmasin, which is the main COVID-19 referral hospital in South Kalimantan, a study was conducted on 108 COVID-19 patients who died who met the research criteria, showing that 88% of these patients were critically ill COVID-19 accompanied by severe ARDS.[2,3]

Critical degrees of COVID-19 are associated with a cytokine storm that causes overproduction of inflammatory mediators. The inflammatory response that occurs as a result of COVID-19 infection will increase several inflammatory markers such as C-Reactive Protein (CRP), Lactic Acid Dehydrogenase (LDH), and D-dimer. This inflammatory response results in lung injury which is characterized by a decrease in the PaO2/FiO2 ratio and multisystemic organ dysfunction can occur.[4,5]

Cytokine storms that occur at critical levels are a challenge in the treatment of COVID-19 and one of the therapeutic agents of concern is corticosteroids. Corticosteroids are reported to provide benefit in critically ill COVID-19 conditions. Corticosteroids have been shown to be beneficial in reducing LDH, CRP, D-dimer and PaO2/FiO2 ratio. According to The Recovery Study, it was found that corticosteroid administration can reduce mortality within 28 days of treatment in patients requiring oxygen support. In the study of Rana et al., it was found that corticosteroid therapy is effective for controlling inflammatory markers, especially dexamethasone which is effective in increasing the PaO2/FiO2 ratio in COVID-19 patients. In this study, there was also a decrease in the CRP value of COVID-19 patients with the administration of dexamethasone or methylprednisolone on day eight.[6]

From the various studies that have been published, there are still few studies showing which types of corticosteroids are the most beneficial for COVID-19, especially in Indonesia, which is the country with the most Covid cases in the world and especially in Banjarmasin, which is a city with black zone status and the Enforcement of Restrictions on Community Activities (PPKM) and the longest level 4 in Indonesia. Based on this, it is necessary to study the effectiveness of giving dexamethasone, methylprednisolone and hydrocortisone to critically ill COVID-19 patients with LDH, CRP, D-Dimer and PaO2/FiO2 ratios at Ulin Hospital Banjarmasin.

Research Method

This study is a retrospective cohort study using medical record data. The subjects were COVID-19 critical degrees confirmed by PCR and examined for LDH, CRP, D-Dimer and the PaO2/FiO2 ratio and treated in the Mawar isolation room at Ulin Hospital Banjarmasin for the period January - June 2021. Inclusion criteria (1) Patients aged over 18 year. (2) Patients who received dexamethasone, methylprednisolone and hydrocortisone therapy for at least 7 days from the start of the patient were treated in the Mawar isolation room at Ulin Hospital Banjarmasin. (3) Patients who were examined for CRP, LDH, D-dimer, PaO2/FiO2 ratio at the time of initial hospitalization and evaluation between the 7 and 10 days thereafter.

While the exclusion criteria: (1) Patients with incomplete medical record data. (2)

Patients with diabetes, hypertension and chronic kidney failure.

The research samples were then grouped based on the steroid therapy given, namely dexamethasone 6 mg/24 hours, methylprednisolone 62.5 mg/8 hours (tapping of) and hydrocortisone 100 mg/12 hours. Each group was taken the value of LDH, CRP, D-dimer and PaO2/FiO2 ratio at the beginning of admission and 7-10 days after steroid administration. The data were then performed statistical tests to assess the effectiveness of each steroid against inflammatory markers

Results

Characteristics of research subjects

In this study, sample of 148 patients with the highest steroid use was dexamethasone as many as 60 samples followed by methylprednisolone 55 samples and hydrocortisone 33 samples. In terms of age, the average age of the sample was 55.97 ± 11.9 years. Based on gender, the study sample was dominated by 99 men (66.89%). The overall mortality rate was 40 samples (27.03%). There was a decrease in the value of CRP, LDH, D-Dimer and an increase in the value of the PaO2/FiO2 ratio after steroid administration and can be seen in detail in table 1.

Table 2. Shows the results of the Kruskal-Wallis test that the steroids dexamethasone, methylprednisolone and hydrocortisone gave significantly different results in increasing the PaO2/FiO2 ratio.

Table 3 shows the Pos Hoc test with U Mann-Whitney that hydrocortisone and dexamethasone have the same strong and statistically dominant effectiveness compared to methylprednisolone in increasing the value of the PaO2/FiO2 ratio.

Discussion

Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus Disease 19 (COVID-19) and was designated a pandemic by WHO on March 12, 2020. Symptoms that appear vary widely from asymptomatic to critical and can lead to serious complications on death. In critical cases, there is an excessive inflammatory response condition that has a negative impact on the patient. This inflammatory process is characterized by changes in various inflammatory markers such as C-Reactive Protein (CRP), Lactic Acid Dehydrogenase (LDH), and D-dimer as well as a decrease in the value of the PaO2/FiO2 ratio.[6,7]

Cytokine storms that occur must be controlled immediately to reduce the mortality rate of critically ill COVID-19 patients. Giving steroids is believed to be the right step to deal with the problem of the cytokine storm. Dexamethasone is the preferred steroid of choice in critically ill COVID-19 patients. However, the administration of other types of steroids also provides benefits against these cytokine storm conditions. Commonly used steroids are dexamethasone, methylprednisolone and hydrocortisone. The three types of steroids have their respective advantages and become a challenge for clinicians in choosing the right steroid to treat critically ill COVID-19 patients individually according to clinical and patient comorbidities.[7,8]

Characteristics of the study sample

Several studies have shown that men are more susceptible to COVID-19 infection and are symptomatic. Research in Pakistan and Italy in 2020 found that men were more dominantly infected with COVID-19, which was around 72%. This is associated with more male activities outside the home so that they are more at risk of being exposed to COVID-19 than women. The results of this study are in line with the results of this study, from 148 research subjects it was found that the majority were male with 99 patients (66.89%) while 49 patients (33.11%) were female. If it was reviewed based on the steroid group, it was also found that males were more

Tabel 1. Characteristics of research subjects

Variabel	Total	Dexamethasone	Methylprednisolone	Hydrocortisone
Sample	148	60	55	33
Age (Years) mean ± SD	55,97 ± 11,9	55.08 ± 12.03	55.2 ± 11.22	58.87 ± 12.64
Gender (%)				
Male	99 (66,89%)	42 (70%)	19 (34,54%)	20 (60,6%)
Female	49 (33,11%)	18 (30%)	36 (65,45%)	13 (39,4%)
Mortality (%)				
Non Survive	40 (27,03%)	14 (23,34%)	16 (29,09%)	10 (30,3%)
Survive	108 (72,97%)	46 (76,66%)	39 (70,91%)	23 (69,7%)
CRP (mg/dl)				
Pre Steroid mean ± SD	109,69 ± 78,33	112.38 ± 71.78	108.06 ± 83.13	108.29± 82.56
Post Steroid mean ± SD	30,48 ± 73.4	43.14 ± 116.1	23.7 ± 40.55	25.56 ± 37.29
LDH (U/L)				
Pre Steroid mean ± SD	825,25 ± 483,2	804.1 ± 458.27	883.32 ± 581.49	766.9± 323.41
Post Steroid mean ± SD	479,92 ± 455,19	446.58 ± 415.39	549.87 ± 578.38	423.96 ± 235.44
D-dimer (mg/L)				
Pre Steroid mean ± SD	5,34,05 ± 10,41	8.73 ± 14.63	3.68 ± 5.11	3.41± 8.75
Post Steroid mean ± SD	2,95 ± 5,18	3.4 ± 6.17	2.68 ± 4.62	2.77 ± 4.81
Rasio PaO2/FiO2 (mmHg)				
Pre Steroid mean ± SD	135.07 ± 83,36	141.42 ± 86.6	111.6 ± 66.21	162.15± 94.19
Post Steroid mean ± SD	182,14 ± 99.63	172.62 ± 93.1	190.18 ± 100.7	186.12 ± 110.69

dominant with the percentage in the dexamethasone and hydrocortisone groups (42 (70%) and 20 (60.6%), only in the methylprednisolone group the dominant females was 36 (65.45%). A meta-analysis study by Abate et.al., stated that men are more likely to experience symptomatic COVID-19 infection ranging from mild to critical symptoms compared to women. This result is due to men's habits of smoking and drinking alcohol which can affect the immune system and men tend to interact more often with the outside environment, the activity of taking off masks when eating and drinking is associated with the number of viruses exposed than women who are at home. In men also have higher ACE2 expression than women. In women with XX chromosomes are thought to have a better immune system than XY chromosomes in males, although this theory still needs further investigation. Some of these theories support the results of this study because this study took the subject in the form

Tabel 2. The significance value of CRP, LDH, D-dimer and the ratio of PaO2/FiO2 in the Kruskal-Wallis test

Dependent Variable	Asymp. Sig.
CRP	p=0,982
LDH	p=0,926
D-dimer	p=0,227
Rasio PaO2/FiO2	p=0,041*

Tabel 3. Mann-Whitney U test on the PaO2/FiO2 . ratio group

Steroid	Asymp. Sig.
Hydrocortisone to Dexamethasone	0,552
Hydrocortisone to Methylprednisolone	0,027*
Dexamethasone to Methylprednisolone	0,43*

of critical grade cases, in theory males are indeed more at risk of developing severe-critical degrees than women so that the dominant sample is male.[9-12]

In this study, the median age of each steroid was dexamethasone (55.08 + 12.03), methylprednisolone (55.2 + 11.22) and hydrocortisone (58.87 + 12.64). All of these data are patients with critical degrees. This result is in line with the research of Lim et.al., it was found that those aged over 50 years had a high risk of experiencing severe symptoms if infected with COVID-19. The main cause of the increased risk of severity at the age of over 50 years is the immune system begins to decline and the emergence of degenerative and metabolic diseases. In addition, the study of Bunyavanich et al., found that examination of the expression of the ACE2 gene taken from the nasal epithelium showed differences between adolescents and older adults, in older adults the expression of the ACE2 gene was more dominant, thus significantly increasing the risk of infection and more severe symptoms. [13,14]

The mortality rate in this study was 27.03%. And based on the steroid group, the mortality rates were dexamethasone 14 (23.34%), methylprednisolone 16 (29.09%) and hydrocortisone 10 (30.3%). The study of Vlachos et al., stated that the mortality rate at critical levels was more than 20% and increased drastically, especially in cases of ICU care, the mortality rate reached 34%. This result is also in line with the research of Shang et al., which found that the mortality rate at a critical level reached 49% even though they had received maximum therapy. Based on the research of Hajjar et al., the mortality rate within 28 days of treatment can be higher in critical cases who do not receive steroids so that steroid administration should be given immediately with various clinical considerations.[15-17]

Effectiveness of Administration of Dexamethasone, Methylprednisolone and Hydrocortisone on CRP

C-reactive protein (CRP) is a non-specific inflammatory protein, occurs in the acute phase and exhibits an enhanced response to tissue damage, inflammation and infection. CRP values increase for 24 to 72 hours after exposure to the stimulus and decrease exponentially for 18-20 hours after resolution of exposure. In the case of COVID-19, inflammatory stimuli occur continuously, especially in severe and critical cases, so that the CRP value will continue to increase in line with the occurrence of a cytokine storm. Administration of steroids can reduce the process of tissue damage by suppressing the release of pro-inflammatory cytokines, one of which is through the mechanism of suppression of Angiotensin II activity and ADAM17 expression so that viral S protein binding with ACE2 receptors is disrupted and prevents the production of pro-inflammatory cytokines, oxidative stress (ROS), fibrosis, vasoconstriction which can cause CRP values to increase.[17]

Based on the results of the Kruskal-Wallis test, it was found that the administration of the steroid dexamethasone, methylprednisolone and hydrocortisone gave different changes in the CRP value but there was no significant difference between the three. Several studies support the results of this study, such as the study of Yang SS et al., stating that these three steroids can significantly reduce CRP values in critical cases. Cui et al.'s study also found a decrease in CRP values to 50% within 72 hours after the initiation of the corticosteroid. Research by Rana MA et al., in 2 groups given dexamethasone for 8 days and metiprednisolone for 8 days, in group 1 the mean initial CRP was 110.34 mg/dl which decreased to 19.45 mg/dl after dexamethasone administration, CRP in group 2 was 108.65 mg/dl which decreased to 43.82 mg/dl after administration of methylprednisolone for eight days. Research by Lian J et al., administration of methylprednisolone in critical cases has been

shown to improve the value of inflammatory variables including CRP.[18-21]

Effectiveness of Administration of Dexamethasone, Methylprednisolone and Hydrocortisone on LDH

Lactate dehydrogenase (LDH) is an intracellular enzyme found in cells of almost all organ systems that catalyzes the interconversion of pyruvate and lactate with the interconversion of NADH and NAD+. This enzyme is formed by 2 main subunits and is expressed in humans in 5 separate isozymes (LDH-1 in cardiomyocytes, LDH-2 in the reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in the kidney and pancreas and LDH-5 in the liver and pancreas). stria muscle. An increase in LDH value may indicate the result of multiple organ injury and decreased oxygen value with upregulation of the glycolytic pathway. In the case of COVID-19, multiple organ damage and oxygenation disturbances often occur, thus affecting LDH values. The glycolytic pathway is believed to play a role in this condition, in COVID-19 infection can also cause disruption of the glucocorticoid system so that the administration of natural or synthetic glucocorticoids can improve LDH values.[22]

Based on the results of the Kruskal-Wallis test, it was found that the steroids dexamethasone, methylprednisolone and hydrocortisone gave different D-dimer values but there was no significant difference between the three. This is in line with the study of Lopez Z et al., which stated that corticosteroid administration would significantly reduce the value of inflammatory markers such as IL-6, CRP, D-dimer, ferritin, LDH and mortality. Pinzon et al., stated that methylprednisolone, dexamethasone and hydrocortisone were significantly useful for reducing LDH values in severe-critical COVID-19 cases, especially in patients on ventilators. Research by Li Y et al., also supports that administration of corticosteroid methylprednisolone for 7 days can reduce LDH levels. [22-24]

Effectiveness of Administration of Dexamethasone, Methylprednisolone and Hydrocortisone on CRP D-dimer

D-dimer is the end product of the degeneration of cross-linked fibrin by the action of plasmin in the fibrinolytic system. COVID-19 infection causes the release of inflammatory cytokines that activate epithelial cells, monocytes and macrophages. Direct infection of endothelial cells via the ACE2 receptor also causes endothelial activation and dysfunction, tissue factor (TF) expression, and platelet activation and increased levels of Von Willebrand factor (VWF) and FVIII, all of which contribute to thrombin formation and fibrin clot formation. With the formation of fibrin, it also directly increases the value of D-dimer. Administration of glucocorticoids can minimize endothelial damage and prevent lymphocyte apoptosis which functions to increase immunity in eliminating the COVID-19 virus. The main therapy for coagulation disorders in COVID-19 is prophylactic or therapeutic anticoagulation.[24,25]

Based on the results of the Kruskal-Wallis test, it was found that the steroids dexamethasone, methylprednisolone and hydrocortisone gave different D-dimer values but there was no significant difference between the three. Research by Lopez Z et al., found that giving methylprednisolone and dexamethasone can reduce the value of D-dimer. Research by Soni M et al., said that the D-dimer value > 2.01 mg/L significantly increased the risk of disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT) and pulmonary embolism. Administration of methylprednisolone, prednisone, dexamethasone, and hydrocortisone can improve d-dimer values and reduce the risk of coagulation disorders.[24,25]

Effectiveness of Administration of Dexamethasone, Methylprednisolone and Hydrocortisone on Pao2/FiO2 Ratio

The PaO2/FiO2 ratio can predict the fraction of intrapulmonary shunts. The value of

PaO2 is used to determine the degree of hypoxaemia in patients with acute lung injury. The PaO2/FiO2 ratio is widely used as an indicator that provides information regarding arterial oxygenation and the severity of lung injury. In critical cases of COVID-19, there will be a cytokine storm that causes vasodilation, increased capillary permeability and leukocyte migration. This condition also occurs in the alveoli, namely the loss of alveolar-capillary barrier function due to vasodilation and impaired permeability resulting in the accumulation of edema fluid including leukocytes in the alveolus. Corticosteroids play a role in this mechanism to reduce vasodilation disorders, increase capillary permeability and leukocyte migration, especially in the alveoli which will be related to the value of the PaO2/FiO2 ratio. [26-28]

Based on the results of the Kruskal-Wallis test, it was found that the steroids dexamethasone, methylprednisolone and hydrocortisone gave different values of the PaO2/FiO2 ratio and a statistically significant difference was obtained with p=0.041. Many studies state that the administration of steroids can increase the value of the Pao2/FiO2 ratio. Research by Narhi F et al., stated that administration of steroids dexamethasone, methylprednisolone, prednisolone and hydrocortisone has been shown to increase oxygen saturation and reduce ventilator requirements. Research by Hyun JH et al., also showed that administration of hydrocortisone and dexamethasone significantly improved CRP, ferritin and procalcitonin values, as well as the value of the Pao2/Fio2 ratio. Research conducted by Rana MA et al., also found that dexamethasone administration could improve the PaO2/FiO2 ratio. In this study, it was found that hydrocortisone and dexamethasone were more potent than methylprednisolone in increasing the value of the PaO2/FiO2 ratio. In ARDS conditions that cause a decrease in the PaO2/FiO2 ratio, vasodilation occurs, increased capillary permeability and migration of inflammatory cells into the alveoli, administration of hydrocortisone can cause non-catecholamine vasoconstrictors and reduce recruitment of inflammatory cells so that the process of fluid accumulation in the alveoli can be inhibited. Dexamethasone is a strong steroid and has a long half-life so it has a stronger potency than methylprednisolone.[6,18,29,30]

Some of the shortcomings in this study are the limited number of samples and also the inhomogeneous distribution of data, confounding factors that cannot be fully controlled such as treatment given other than steroids, comorbidities and the onset of the overall course of the disease that can affect statistical tests and research results.

Conclusions

The administration of hydrocortisone and dexamethasone was more dominant to increase the value of the PaO2/FiO2 ratio in critically ill COVID-19 patients in the Mawar room of the Ulin Hospital Banjarmasin for the period January-June 2021.

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