

COVID-19 Pharmacological Treatment at the Udayana University Hospital in April-May 2020

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Since the COVID-19 pandemic in Indonesia, pharmacological therapy for COVID-19 cases to date are recurrently based on clinician's assessments of drugs, or what drug combinations might work in managing COVID-19 cases, and not yet based on empirical evidence from clinical trial studies, which also limited available in the early of pandemic. This study aims to provide data on drugs utilized during the treatment of the COVID-19 cases and the rationalization of their use. This research is a cross-sectional descriptive study conducted at the Udayana University Hospital in April-May 2020. Demographic and treatment data were obtained through inpatient medical records, and research sample was selected by total sampling method. 95 cases of COVID-19 hospitalized during April-May 2020 were included in the study. The standard COVID-19 drugs given were vitamin C (100%), chloroquine phosphate (61.1%), azithromycin (34.7%) or levofloxacin (5.3%), and oseltamivir (37.9%) or lopinavir-ritonavir (3.2%). Other drugs given were low molecular weight heparin (2.1%), alprazolam (1.1%), amlodipine (3.2%), clobazam (9.5%), meropenem (2.1%), and metformin (3.2%). Administration of high doses intravenous vitamin C was found to be beneficial, while chloroquine phosphate, antibiotics, and antivirals need to be reconsidered based on their risks and benefits in COVID-19 management.

Keywords: Azithromycin; Chloroquine Phosphate; COVID-19; Favipiravir; Oseltamivir; Vitamin C.

The first case of COVID-19 in Indonesia was reported in March 2020, since then the numbers of cases are increasing until today. Antiviral therapy that has proven efficacy against SARS-CoV-2 has yet to be found, as well as evidence-based guidelines or management protocols for COVID-19.¹ The main pharmacological management of COVID-19 cases to date is still based on clinician's assessment regarding drugs, or what drugs combination might

work in the COVID-19 case, and not yet based on empirical evidence from clinical trial studies.¹ There are not many data regarding the drugs that are effective for COVID-19 based on Randomized Controlled Trial (RCT) especially in the early of pandemic. Until now, The Indonesian Ministry of Health has published the third edition of the COVID-19 management protocol in December 2020.² The first edition of the protocol released by

the Indonesian Ministry of Health recommends several drug options for COVID-19 cases, ranging from cases with no symptoms to severe symptoms.³ However, it is not certain how the recommended pharmacological therapy options work and can help patients with COVID-19.

Apart from these problems, this protocol has become a guideline for specialized health facilities that treat COVID-19 in several regions in Indonesia. Udayana University Hospital is one of referral hospital for COVID-19 treatment in Bali, Indonesia. Even though the management protocol has been established, evidence-based medicine still needs to be applied in the treatment of COVID-19 patients. There is not much data on the drugs used in COVID-19 patients in Indonesia. Descriptive preliminary data can be a first step for the application of evidence-based medical science related to drugs in COVID-19, particularly in Indonesia.

Considering the need for evidence-based practice and data publication, this study aims to collect data on pharmacological treatment given in COVID-19 patients at the Udayana University Hospital, and discuss the rationalism of its use, to provide an overview of the COVID-19 treatment development in Indonesia.

MATERIALS AND METHODS

This study was a descriptive cross-sectional study conducted in September 2020. All data on hospitalized COVID-19 patients at Udayana University Hospital in April-May 2020 were used in this study. Data on age, sex, drugs name, drugs dose, and duration of treatment were obtained from medical records. Univariate analysis was used to present the frequency and percentage of categorical data, as well as mean and standard deviation for normally distributed numerical

Table 1. Pharmacological treatment administered during treatment

Drug	Dose	N (%)
Vitamin C	Mild: 500 mg tid-qid, orally, for 14 days	95 (100)
Chloroquine Phosphate	Moderate-severe: 400 mg tid, intravenously Mild: 500 mg bid, orally, for 12 days Moderate: 500 mg bid, orally, for 5-7 days Weight: 500 mg bid, orally (days 1-3), followed by 250 mg every 12 hours, orally (days 4-10)	58 (61.1)
Antibiotics		38 (40)
Azithromycin	Mild: 500 mg uid, orally, for 5 days Moderate: 500 mg uid, intravenously or orally, for 5-7 days Weight: 500 mg each uid, intravenously, for 5 days	33 (34.7)
Levofloxacin	Mild: 750 mg uid, orally, for 5 days Moderate: 750 mg uid, intravenously or orally, for 5-7 days Weight: 750 mg uid, intravenously, for 5 days	5 (5,3)
Antivirus		39 (41.1)
Oseltamivir	Mild: 75 mg bid, orally Moderate-severe: 75 mg bid, orally	36 (37.9)
Lopinavir-Ritonavir	400 mg/100 mg bid, orally, for 14 days	3 (3,2)
Anticoagulants		
Low Molecular Weight Heparin	1 mg/kgBW bid	2 (2,1)
Other Drugs		
Alprazolam	0.25-0.5 mg tid	1 (1,1)
Amlodipine	5-10 mg uid	3 (3,2)
Clobazam	20-30 mg uid	9 (9,5)
Meropenem	1 g tid	2 (2,1)
Metformin	500 mg tid	3 (3,2)

data, otherwise median and interquartile range were used. Statistical analyses were performed using SPSS version 17 for windows. The research protocol was approved by the Institutional Review Board.

RESULTS AND DISCUSSION

Positive COVID-19 hospitalized cases in April-May 2020 were 95 cases. The age range of cases was 20-73 years, with a median of 32 years (interquartile range/IQR = 18 years). Males are more dominant (72.6%) than the females (27.4%). The median length of treatment was 12 days (IQR = 11 days), with the fastest length of treatment was 5 days and the longest was 57 days. Referring to the first edition of the COVID-19 management protocol from the Indonesian Ministry of Health, the pharmacological treatment given during treatment is summarized in Table 1. Median duration of treatment for cases is presented in Table 2.

Vitamin C

In this study, all cases received vitamin C. Vitamin C was known to be a potent antioxidant with anti-inflammatory and immuno-supportive properties.^{4,5} The role of vitamin C in viral infections is to decrease the pro-inflammatory response, improve epithelial barrier function, clear alveolar fluid, prevent sepsis-related coagulation problems, and as an essential factor in the production of type I interferon as long as the immune system responds to the virus.^{6,7} Vitamin C has been found

to be effective in the treatment of pneumonia and infections due to its direct inhibitory effect on pathogens, protects the respiratory tract mucosa, and helps improve complaints of upper respiratory tract infections.^{8,9} In relation to the severity of COVID-19 disease, vitamin C was found to reduce the mortality of complications such as ARDS and shock in COVID-19 patients, as well as shorten the length of treatment in the Intensive Care Unit (ICU).^{10,11}

The benefits given by vitamin C depend on the dosage. The plasma level required to achieve maximum function of vitamin C as an antioxidant is estimated to be >175 mg/L (1000 μmol/L), ten times higher than the normal physiological levels.¹² Oral administration results in lower plasma concentrations due to sodium-dependent vitamin C transporter-1 (SVCT1) regulation, making intravenous administration more desirable.¹² Oral administration of 3 grams of vitamin C supplementation is safe and effective in dealing with respiratory or systemic infections, but if consumed every 4 hours it will only produce a plasma concentration of around 220 μmol/L.^{13,14} For therapeutic purposes, intravenous vitamin C doses of 10-16 grams per day result in plasma levels >1000 μmol/L and provide maximum benefits from vitamin C.¹⁵ Based on our data in Table 1, the intravenous dose of vitamin C given was low, thus the benefits of vitamin C may not be as expected.

High doses of vitamin C are reported to have minimal side effects. Some studies reported that patients with pneumonia and sepsis, doses as high as 100 grams/day did not cause diarrhea and other side effects.^{16,17} In this study we found that 3 patients (3.2%) received metformin. It should be noted that high doses of vitamin C can affect the measurement of blood glucose with a glucometer, therefore blood glucose tests should be done in a central laboratory.¹⁸

Chloroquine

Chloroquine was given because of its role as an immunomodulator and antiviral. As an immunosuppressant, chloroquine accumulates in lysosomes and influences lysosomal and autophagosome activity in lymphocytes, causing inhibition of lymphocyte function in the immune system, therefore immune system activation does not occur.¹⁹⁻²³ Chloroquine also prevents toll-like receptor activation and inhibits cytokine production

Table 2. Median length of treatment by drug

Drug	Length of Treatment (days) (median (IQR))
Vitamin C	12 (11)
Chloroquine Phosphate	
Yes	11 (15)
No	15 (8)
Antibiotics	
Azithromycin	15 (19)
Levofloxacin	15 (16)
No	11 (8)
Antivirus	
Oseltamivir	10 (7)
Lopinavir-Ritonavir	(-)
No	14 (10)

by mononuclear cells.^{24,25} As an antiviral, previous in vitro studies of chloroquine on SARS-CoV found that chloroquine interferes with ACE2 terminal glycosylation, decreasing ACE2 and SARS-CoV S protein binding affinity, thereby inhibiting SARS-CoV infection.²⁶ However, these findings indicate that chloroquine is more appropriate in the early stages of infection, before SARS-CoV-2 decreases ACE2 expression and activity.²⁷ In addition, chloroquine can inhibit replication of the viruses by interfering the entry of viruses that are mediated by endosomes.²⁸

Although its mechanism of action has been studied, the latest publication of the World Health Organization (WHO) solidarity trial states that hydroxychloroquine has minimal or no effect in hospitalized COVID-19 patients.²⁹ Apart from that, the side effects are quite alarming, including retinopathy, neuromyopathy, and cardiomyopathy. Chloroquine also is excreted slowly from our body and has long half-life. Based on these data and finding, the risks and benefits to patients must be taken into account when prescribing chloroquine for COVID-19 cases.³⁰

The chloroquine dosage for COVID-19 cases is still inconclusive. China recommends a dose of 500 mg twice daily for 7 days for person who has bodyweight more than 50 kg, while for less than 50 kg, the recommendation dose is 500 mg twice daily on the first day followed by 500 mg once daily until day 7. This Chinese recommendation yields a total dosage of 4-7 grams of chloroquine.³¹ Indonesian protocol recommends chloroquine with longer duration, ranging from 5-15 days.³

Due to the large volume of distribution and the long half-life of chloroquine (32-50 days), the duration of administration is not recommended to exceed 5 days to avoid accumulation in plasma and tissue.³² Administration of high doses is also avoided in severe or critical COVID-19 patients, especially those receiving azithromycin and oseltamivir.³³

Antibiotics

The administration of azithromycin and levofloxacin in the management protocol made them became of a standard treatment rather than based on the evidence of a bacterial infection.³ Until recently, the use of azithromycin has been widely reported in the literature, and is recommended

in several COVID-19 management guidelines in various countries.^{3,27,34-36} Apart from having antibacterial activity, azithromycin was found to have antiviral and immunomodulatory effects which made this drug a concern in the COVID-19 pandemic.³⁵

As an immunomodulator, azithromycin acts on the inflammatory cascade and signaling processes of cells. Azithromycin was found to decrease mucus hyper secretion and induce relaxation of contracted airway smooth muscle, as well as reduced hyper secretion of pro inflammatory like cytokines and chemokines.^{35,37} The antiviral effect of azithromycin is beneficial for various viral infections (zika, ebola, and influenza) in vitro. However, the results of studies on SARS-CoV-2 are still inconclusive.³⁵

The optimal dose of azithromycin for SARS-CoV-2 infection is unknown, but its use is reported to be safe with minimal risk of severe side effects. Side effects of concern include prolonged QT interval, torsade de pointes, ventricular tachycardia, and sudden cardiac death.³⁵

Despite the benefits, the One Health organization sees the prolonged use of antibiotics contributes to antibiotic resistance.³⁸ Within WHO interim guidance, even antibiotics are not recommended as either treatment or prophylaxis, unless there is clinical sign of bacterial coinfection.³⁹ In Indonesia, azithromycin and levofloxacin are still included in the December 2020 edition of the COVID-19 patient management protocol.²

Antiviral

The antiviral recommended in Indonesia is oseltamivir or favipiravir. Like antibiotics, this drugs administration is also a standard treatment in Indonesia.³ While the administration of both drugs is not recommended by WHO other than for clinical trials, the Indonesian COVID-19 management protocol until the latest edition still includes the administration of oseltamivir or favipiravir.^{2,39}

Oseltamivir works by inhibiting neuraminidase, unlike other viruses (such as influenza A and B), SARS-CoV-2 does not have neuraminidase.⁴⁰ The study in Wuhan even reported that oseltamivir had no role and positive outcome for COVID-19 patients.⁴¹ Guan *et al.* found oseltamivir did not reduce ICU admission rates, need for ventilators, and mortality rates for COVID-19 patients.⁴² On the other hand,

favipiravir increased the degree of relieve, decrease the duration of fever, cough, and viral clearance (median 4 days).^{43,44}

The lopinavir-ritonavir combination (Aluvia) works specifically by inhibiting proteases, particularly the HIV-1 protease. The results of the latest randomized clinical trial showed that lopinavir-ritonavir 400 mg/100 mg administration had no benefit in hospitalized COVID-19 patients. Additionally, side effects of diarrhea, nausea, and weakness were frequently reported in patients receiving this regimen.^{45,46}

Clobazam

In addition to the standard COVID-19 drugs, during treatment, 9 patients (9.5%) experienced anxiety disorders that required pharmacological treatment. In this condition, clobazam was given. The interaction between clobazam and chloroquine phosphate should be noted. Clobazam affects the hepatic metabolism of chloroquine phosphate by inhibiting the CYP2D6 enzyme. The consequence of this interaction is prolonged the chloroquine phosphate's half-life, which may increase the risk of chloroquine toxicity.⁴⁷

CONCLUSION

The COVID-19 pharmacological treatment given during treatment at the Udayana University Hospital is in accordance with the COVID-19 management protocol by the Indonesian Ministry of Health. Administration of chloroquine phosphate, antibiotics, and antivirals during treatment needs to be reconsidered by weighing the benefits and risks, thereby reducing the cost burden and unnecessary drug consumption.

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Conflict of Interest

The authors declare no conflict of interests.

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