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Original Research

The Effectiveness of High-dose N-acetylcysteine in Severe COVID-19 Patients

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Abstract—*The study's objective was to describe the effect of using high doses of N-acetylcysteine on severe COVID-19 patients. N-acetyl cysteine, known as a mucolytic agent, in high doses (>1200 mg/day) is also known as glutathione boosting treatment, that may reduce proinflammatory cytokine so it may beneficial reduce the risk of severity. This study was an observational descriptive, evaluated from the length of stay of all patients with severe COVID-19 (clinical signs of pneumonia plus severe respiratory distress) and by monitoring the drug use data, laboratory data, and clinical data at Bhayangkara H.S Samsoeri Mertojoso Hospital Surabaya. The data was collected retrospectively from patients' Health Medical Records who got high dose N-acetylcysteine in October 2020 – February 2021, with standard therapy: antivirus (Remdesivir), antibiotics, vitamins, symptomatic and comorbid therapy, anticoagulant, and corticosteroids (Dexamethasone) as inclusion criteria, then described descriptively. The observation result confirmed that the use of a high dose of N-acetylcysteine (NAC) [1 x 1200 – 5000 mg] po/iv had effective and beneficial results as seen from the patients' length of stay, which was 12 days for patients without comorbid and 14 days for patients with comorbid like diabetes and/or hypertension. The use of high dose NAC showed improvement in the patients' clinical condition that is evaluated from improved oxygen saturation by 37%. In addition, the laboratory results are shown an improvement in thorax X-ray by 69% and inflammatory markers like CRP and d-dimer by 100%. Further research that uses a prospective method is needed to get a better result on the use of high-dose NAC in patients with severe COVID-19.*

Keywords: *high dose, n-acetylcysteine, severe Covid-19 patient*

Abstrak—Tujuan dari penelitian ini adalah untuk mendeskripsikan efek penggunaan N-acetylcysteine dalam dosis tinggi (>1200mg/hari) pada pasien COVID-19 yang parah (dengan gejala klinis pneumonia disertai dengan distress pernafasan berat) , dinilai dari lama rawat dan dengan pemantauan data penggunaan obat, data laboratorium, dan data klinis di RS Bhayangkara H.S Samsoeri Mertojoso Surabaya. Data dikumpulkan secara retrospektif dari Rekam Medis Kesehatan pasien yang mendapat N-asetilsistein dosis tinggi pada Oktober 2020 – Februari 2021, dengan terapi standar: antivirus (Remdesivir), antibiotik, vitamin, terapi simtomatik dan komorbiditas, antikoagulan, dan kortikosteroid (Dexametason) sebagai kriteria inklusi, kemudian dideskripsikan secara deskriptif. Hasil observasi menegaskan bahwa penggunaan N-acetylcystein (NAC) dosis tinggi [1 x 1200 – 5000 mg] po/iv memiliki hasil yang efektif dan memberi benefit dilihat dari lama rawat pasien yaitu 12 hari untuk pasien tanpa penyakit penyerta dan 14 hari untuk pasien dengan penyakit penyerta seperti diabetes dan/atau hipertensi. Penggunaan NAC dosis tinggi menunjukkan perbaikan kondisi klinis pasien yang dinilai dari peningkatan saturasi oksigen sebesar 37%. Selain itu, hasil laboratorium menunjukkan peningkatan seperti pada rontgen toraks sebesar 69%, dan penanda inflamasi seperti CRP dan d-dimer sebesar 100%. Diperlukan penelitian lebih lanjut yang menggunakan metode prospektif untuk mendapatkan hasil yang lebih baik pada penggunaan NAC dosis tinggi pada pasien COVID-19 berat.

Kata kunci: *dosis tinggi, pasien Covid-19 parah, n-asetilsistein*

INTRODUCTION

Coronavirus Disease (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (Levani et al., 2021; Organization, 2020; Susilo et al., 2020). This disease was first reported on December 31, 2019, in Wuhan, China, as pneumonia of unknown cause (Liskova et al., 2021; RI, 2020). Then it quickly spread throughout the world. WHO, on March 11, 2020, declared COVID-19 a pandemic (Dos & Wagner, 2020)

The increase in the number of cases is relatively fast and has spread to various countries worldwide. Globally, as of early December 2020, there were 65,257,767 million confirmed cases and 1.5 million deaths, with the highest number of cases in America, Europe, and Southeast Asia.

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(Khaira, 2010; Moradi and Hadi, 2021; Organization, 2020). In Southeast Asia, there were 11,023,450 cases with a death toll of 167,782. Indonesia as the largest contributor to cases, since January 3, 2020, confirmed 563,680 cases of COVID-19 with 17,479 deaths. (Khaira, 2010; Moradi & Hadi, 2021; Organization, 2020).

COVID-19 is grouped based on the severity of cases into asymptomatic, mild, moderate, severe, and critical cases (Alfhad et al., 2020; Lai et al., 2020; Suryadinata, 2018). The criteria for mild COVID-19 are patients with symptoms without evidence of viral pneumonia or hypoxia (Roorda, 2016). Common symptoms include fever, cough, fatigue, shortness of breath, muscle aches. In addition, patients also experience sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia), or loss of taste (ageusia) (Davies, 2002; Djalante et al., 2020). In moderate grade patients, the patient showed clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia, including oxygen saturation (SpO2),≥93%. The criteria for rapid breathing at the age of <2 months is ≥60x/minute, age 2-11 months is ≥50x/minute, age 1-5 years is ≥40x/minute, age >5 years is ≥30x/minute. In severe cases, patients show clinical signs of pneumonia plus one respiratory rate >30/min, severe respiratory distress (rapid breathing, grunting, very heavy chest indrawing), or SpO2 <93% on room air (central cyanosis). Critical patients are those with ARDS, sepsis, and septic shock (Burhan et al., 2018; Tian et al., 2020; Zhou et al., 2020).

Management for COVID-19 patients is given non-pharmacological and pharmacological therapy. Pharmacological therapy in asymptomatic COVID-19 patients includes administering vitamin C, vitamin D, and drugs with antioxidant properties (Rusdi, 2021; Sujana & Maulida, 2021; Vivianni & Farhanah, 2016). In mild grade patients, patients are given multivitamins like asymptomatic patients and are also given antibiotics (Azithromycin), antivirals (Oseltamivir, Favipirapir). In moderate-grade patients, patients are given multivitamins, antibiotics (Azithromycin or Levofloxacin), antivirals (Favipirapir or Remdesivir), Low Molecular Weight Heparin (LMWH) / Unfractionated Heparin (UFH) anticoagulants. In severe or critically ill patients, oxygen therapy is given if the oxygen saturation SpO2 is <93%, then multivitamins, antibiotics (Azithromycin or Levofloxacin), antivirals (Favipiravir or Remdesivir), LMWH/UFH anticoagulants, dexamethasone are given. Other therapies or additional measures that can be given to COVID-19 patients are Anti-IL-6 (Tocilizumab), Anti IL-1 (anakinra), stem cells, intravenous immunoglobulin (IVIg), convalescent plasma therapy, vaccination, N-acetylcysteine, colchicine, spironolactone, bronchoscopy, and therapeutic plasma exchange (TPE) (Burhan et al., 2018; Mazzaro et al., 1993; Sari et al., 2017).

In this study, we focused on N-acetylcysteine (NAC) because most COVID-19 patients had severe pneumonia with excess mucus in the respiratory tract (Ochs et al., 2012; Sari et al., 2015; Yuliana, 2020). The usual dose of NAC in pneumonia is (3x200 mg) po, used as a mucolytic agent. Still, NAC also has antioxidant and anti-inflammatory effects when used in high doses (600 – 2400 mg/day) po, iv, inhalation (De Flora et al., 2020; Djalante et al., 2020). Based on the COVID-19 Management Manual by the Indonesian Lung Doctors Association (PDPI), the dose of NAC used is above or equal to 1200 mg per day orally or intravenously with 2-3 times, especially for severe COVID-19. N-Acetylcysteine is used at Bhayangkara Hospital Surabaya based on the COVID-19 Management Manual by PDPI. It is also supported by evidence-based medicine research journals, which in practice at the hospital is used N-Acetylcysteine at a dose of 5 grams per day intravenously given in 500 ml PZ infusion over 6-8 hours. In addition, in the COVID-19 Hospital Clinical Practice Guidebook, Dr. Soetomo Surabaya, high dose of N-Acetylcysteine (NAC) 5 grams per day given in 500 ml NaCl 0.9% or Dextrose 5% intravenous drip 4 hours (Damayanti & Ryusuke, 2017; Sari et al., 2015, 2017).

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SARS-CoV-2 infection is associated with an imbalance of oxidants and antioxidants, resulting in inflammation and tissue damage (Damayanti and Ryusuke, 2017). Glutathione is an antioxidant widely found in the body and plays a role in protecting cells from oxidative stress (Burhan et al., 2018). Giving NAC as a "glutathione-boosting treatment" can reduce pro-inflammatory cytokines to reduce the risk of the severity of COVID-19 caused by cytokine storms in the body (Medicine, 2020; Nasi et al., 2020; Spearow & Copeland, 2020).

Liu (Liu, 2020) treated a 64-year-old male COVID-19 patient who experienced respiratory failure on the thirteenth day after hospital admission, despite being given an antibiotic, antiviral, and respiratory support therapy. Simultaneously with the therapy that has been carried out, the patient is given a bronchoscopy rinse method therapy with high doses of inhaled NAC solution (10-15 g) to clear the airways given for 11 days at one or two-day intervals, 10 to 15 g of NAC solution is infused into each patient. Bronchus alternately left, and right, the solution is maintained for two to three minutes, and then cleared by sucking using negative pressure. This therapy provides significant results in critically ill patients. The patient was discharged from the hospital after 26 days of mechanical ventilation and 46 days of hospitalization.

Ibrahim et al. (2020) also conducted a study of administering NAC to 9 patients with severe COVID-19, who depended on a respirator, aged 38-71 years. In nine COVID-19 patients, NAC was given with details of one patient (2 x 10 g) iv and eight patients (2 x 600 mg) iv. NAC administration significantly reduced inflammatory mediators such as C-reactive Protein (CRP) (the mean value of CRP levels before NAC was 160±97 mg/dL and after NAC therapy was 31±24 mg/dL) and the mean ferritin before administration. NAC therapy was 3630 ng/mL, and after therapy, it was 1543 ng/mL. In addition, it also improves lung function. Then out of ten COVID-19 patients, eight patients were discharged from the hospital, and two patients showed improvement in their condition even though they had not been discharged from the hospital.

Research from Sari et al. (Sari et al., 2015) related the effectiveness of high doses of N-Acetylcysteine in severe COVID-19 patients with oxygen saturation less than 94% or an average respiratory rate higher than 24 breaths per minute. Patients were randomly assigned to NAC 21 g for 20 hours, or 5% dextrose to the placebo group. The results were observed from the need for mechanical ventilation, mortality rate, number of ICU admissions, length of stay in the ICU, and length of hospital stay. They showed no significant difference between the two groups.

Based on the description above, it is necessary to research the use of high doses of N-acetylcysteine (NAC) in COVID-19 patients to confirm whether or not the therapy has an impact.

METODE

This observational research was conducted at Bhayangkara Hospitals. Samsoeri Mertojoso Surabaya from February-March 2021. The study population was all COVID-19 patients at Bhayangkara H.S. Hospitals. Samsoeri Mertojoso Surabaya for the period October 2020 to February 2021. All of the severe COVID-19 patients (diagnosed by pulmonologist based on Management Guideline by PDPI 2020) and receiving high-dose N-acetylcysteine therapy (greater than or equal 1200mg by any route) that hospitalized at Bhayangkara Hospital Samsoeri Mertojoso Surabaya for the period October 2020 to February 2021 were included as a sample. The research sample was selected with two criteria. First, the patient was diagnosed with severe COVID-19 (pneumonia, with respiratory distress, respiratory rate >30x/mnt, saturation <93%, and ratio PaO2/FiO2<30) and received high-dose N-acetylcysteine therapy (≥ 1200 mg/day by oral or intravenous). Second, the patient received the same standard COVID-19 protocol therapy according to the COVID-19 Guideline Management Manual by PDPI 2020. After tracing the medical record data of COVID-19 patients during the period October 2020 - February 2021, from 156

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patients with severe COVID-19 hospitalized, it was found that patients who met the inclusion criteria were 60 people.

The research material is Health Medical Record data of patients diagnosed with severe COVID-19 at Bhayangkara H.S. Hospital. Samsoeri Mertojoso Surabaya and based on the daily observation sheets on patients in October 2020 - December 2021. The instruments of this research are Data Collection Sheets, master tables, clinical datasheets, and laboratory data of the patients. Data were obtained from medical records of severe COVID-19 patients who received high-dose N-acetylcysteine therapy at Bhayangkara H.S. Hospital. Samsoeri Mertojoso Surabaya.

The collected data were analyzed quantitatively in percentage to describe: (1) The patient demographics (gender and age), duration of administration of N-Acetylcysteine, and length of patient care. Data is presented in the form of tables, diagrams, and descriptions; (2) the identification of drug dosing, frequency, duration of administration, and time to start high-dose N-acetylcysteine therapy in COVID-19 patients; (3) The binding of laboratory data such as inflammatory mediators (CRP, ferritin, d-dimer, fibrinogen), RT-PCR, complete blood count, chest X-ray; clinical data such as oxygen saturation; with the results of therapy (outcomes) in patients (whether the patient is still experiencing symptoms such as shortness of breath, cough) which is presented in the form of tables and descriptions; and (4) The side effects of N-Acetylcysteine in patients and drug interactions with other drugs.

The outcome assessment was clinical recovery with laboratory and chest x-ray parameters. Inflammatory markers evaluated were CRP, d-dimer, IL-6, and/or fibrinogen (not all of these must be included, because not all of these markers were monitored, or so that only one or two inflammatory markers could be shown before and after therapy). In addition, a serial chest x-ray was performed to assess clinical improvement.

FINDING AND DISCUSSION

Patient Demographics

In research from Medicine (Medicine, 2020), More cases of COVID-19 are in the male sex. In this study, male patients were 72% (n=43), and female patients were 28% (n=17), as listed in Table V.1. From Bwire's (2020) study, looking at genetics, the analysis shows that men have higher ACE-2 protein expression than women. Then, immunologically, as explained by Elgendy and Pepine (2020), the differences in immunity between men and women are caused by sex hormones and the X chromosome, as shown by experiments with mice when female mice were subjected to estrogen receptor inhibition and mortality due to SARS-CoV infection increased, so it was concluded that the estrogen receptor has a role in blocking some viral infections. In terms of habits, men tend to have smoking habits and alcohol consumption (Elgendy and Pepine, 2020). This can increase oxidative stress and cause reduced antioxidant protection, increased oxidative stress due to several mechanisms, namely direct damage due to radical species and inflammatory responses (Kamceva et al., 2016).

The above results reflect the agreement with the study results by Zheng et al. (2020), which showed that men over 65 years of age and smoking habits had a greater risk of experiencing a fatal and critical condition if they contracted COVID-19.

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Table 1
Number and Percentage of Age Distribution of Severe COVID-19 Patients Hospitalized

Age Range	Number of Patients
21 – 30	3 (5%)
31 – 40	6 (10%)
41 – 50	15 (25%)
51 – 60	**27 (45%)**
61 – 70	7 (11%)
71 – 80	1 (2%)
81 – 90	1 (2%)

From Table 1, the highest age of patients with severe COVID-19 hospitalized was in the 51-60 age range, which is 45% (*n*=27). It is increasingly supported by the results of research from Robert (2020), which also states that the older adult group is easier to experience severe illness due to COVID-19 with an increased risk at the age above 50-60 years because, at this age, the immune system is less reactive (immune senescence). Symptoms of COVID-19 are non-specific, such as fever (which is the immune system's response to an infection), so these symptoms may be weaker or absent in old age, leading to delayed treatment.

Table 2
Number and Percentage of Comorbid Distribution in COVID-19 Patients

Comorbid	Number of Patients
With Comorbid	**40 (67%)**
No Comorbid	20 (33%)

Table 3
Comorbidities in Severe COVID-19 Patients

Comorbid (Comorbid Disease)	Number of Patients *
Diabetes mellitus	**26 (65%)**
Hypertension	23 (58%)
Heart disease	2 (5%)
Dyslipidemia	1 (3%)

*__Note__: Patients can experience more than 1 type of comorbidity

Table 2 shows the presence or absence of comorbidities in severe COVID-19 patients. It is known that 67% (*n*=40) had comorbid and 33% without comorbidity (*n*=20). Of the 40 patients who had comorbidities (comorbidities), the most common comorbidities experienced were diabetes mellitus, with 26 patients listed in Table 3. This is following the research that states that comorbid conditions such as hypertension, diabetes, cardiovascular disease also increase the risk of COVID-19 (Zheng et al., 2020). COVID-19 patients with comorbid diabetes mellitus show a dysregulation of glucose metabolism in the body, an increase in inflammation, and a decrease in the immune system. Conditions like this can cause oxidative stress in the body and increase cytokine production, allowing organ damage (Lim et al., 2020).

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Table 4 shows the initial symptoms experienced by severe COVID-19 patients, and it was found that cough was the most common symptom experienced by patients, which was 85% (n=51 patients). From the results of the diagnosis, it was found that 95% (n=57 patients) had bilateral pneumonia, ARDS (Acute Respiratory Distress Syndrome) was 17% (n=10 patients), and bronchitis was 3% (n=2 patients). This is following the classification of COVID-19 described in the COVID-19 Management Manual by PDPI 2020, namely severe COVID-19 in adult patients showing clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one of the signs of respiratory frequency. >30x/minute, severe respiratory distress, or SpO2 < 93% in room air; and is critical if you have ARDS, sepsis, and septic shock.

Table 4
Symptoms Experienced by Severe COVID-19 Patients

Symptom	Number of Patients *
Cough	51 (85%)
Faver	39 (65%)
Dyspnea	32 (53%)
Nauseous vomit	21 (35%)
Malaise	13 (22%)
Flu like symptoms	12 (20%)
Anosmia	7 (12%)
Headache	4 (7%)
Diarrhea	4 (7%)
Heartburn	2 (3%)
Sore throat	2 (3%)
Muscle pain (myalgia)	1 (2%)
Chest pain	1 (2%)
Stomach pain	1 (2%)

High-dose NAC Usage Profile

This study found that the most widely used was iv NAC (1x5000 mg) in 48% of patients (*n*=29). The route of using NAC that patients with severe COVID-19 widely use is the intravenous route by 65% (*n*=46). Administration by the oral route was 35% (*n*=24), with a note that one patient could receive more than one route of administration. As many as 23% (*n*=14 patients) received a switch dose, and this was due to the smaller dose being used for the maintenance dose. Changing the route of use from intravenous to oral is also done because the use of other drugs by the intravenous route is no longer given. Details of the use of NAC can be seen in Table 5. The study results are following the literature, namely the dose of NAC is given 5 grams per day in 500 ml NaCl 0.9% or Dextrose 5% intravenous drip 4 hours for three days. On the fourth day followed by maintenance 600 mg every 8-13 hours orally or by intravenous drip 2 hours in 100 ml of 0.9% NaCl or 5% Dextrose. As in the NAC literature, it is given until there is clinical improvement, improvement of chest X-ray, reduction of CRP (<10 mg/dL), or improvement of hyper inflammation (Suprabawati, 2020).

In patients without comorbidities, the use of NAC dose (1x1800 mg) iv provided the shortest treatment period of 11 days. Doses (1x1200 mg) iv and (3x400 mg) po indicate the

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treatment period for 12 days. The length of treatment is calculated from MRS (hospital admission) to KRS (hospital discharge) in a state of recovery or improvement, not those who are forced to go home or die.

In patients with comorbid diabetes mellitus, NAC's most widely used dose is (1x5000 mg) iv. This dose has an average length of treatment of 16 days, and this is because there are patients who have a worse clinical condition (as inpatient number 31 in the Master Table) than four patients who were given a dose of NAC (3x400 mg) po.

Table 5
Dosage and Frequency of High-Dose NAC Received by Severe COVID-19 Patients

Medicine name	Dosage and Frequency	Number of patients
NAC	(1 x 5000 mg) iv	29 (48%)
	(1 x 2500 mg) iv	1 (2%)
	(1 x 1800 mg) iv	1 (2%)
	(1 x 1200 mg) iv	2 (3%)
	(3 x 400 mg) po	13 (22%)
	(1 x 5000 mg) iv → (1 x 1200 mg) iv	1 (2%)
	(1 x 5000 mg) iv → (3 x 400 mg) po	5 (8%)
	(3 x 400 mg) po → (1 x 5000 mg) iv	2 (3%)
	(1 x 1200 mg) iv → (1 x 5000 mg) iv	1 (2%)
	(1 x 1800 mg) iv → (1 x 5000 mg) iv → (1 x 1800 mg) iv	1 (2%)
	(3 x 400 mg) po → (3 x 600 mg) po	1 (2%)
	(3 x 400 mg) po → (1x 5000 mg) iv → (3 x 400 mg) po	1 (2%)
	(2 x 2500 mg) iv → (1 x 2500 mg) iv → (3 x 400 mg) po	1 (2%)
	(1 x 5000 mg) iv → (3 x 400 mg) po → (1 x 5000 mg) iv + (3 x 400 mg) po → (1 x 5000 mg) iv	1 (2%)

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Table 6

Dosage and Frequency of High Dose NAC for Severe COVID-19 Patients and Average Length of Stay (avLOS)

Dosis NAC	Patients wihout comorbid		Patients with Comorbid Diabetes Melitus		Patients with Comorbid Hypertensioni		Patients with Comorbid cardiovascular event		Patients with Comorbid Diabetes Melitus + Hypertension		Patients with Comorbid Dislipidemia	
	Number of px	avLOS	Number of px	avLOS	Number of px	avLOS	Number of px	avLOS	Number of px	avLOS	Number of px	avLOS
(1 x 5000 mg) iv	11 px	13 days	8 px	16 days	3 px	12 days	1 px	12 days	5 px	11 days	1 px	12days
(1 x 2500 mg) iv	0	0	1 px	12 days	0	0	0	0	0	0	0	0
(1 x 1800 mg) iv	1 px	11 days	0	0	0	0	0	0	0	0	0	0
(1 x 1200 mg) iv	1 px	12 days	0	0	0	0	1 pasien	14 days	0	0	0	0
(3 x 400 mg) po	4 px	12 days	4 px	10 days	3 px	10 days	0	0	2 px	13 days	0	0
(1 x 5000 mg) iv → (1 x 1200 mg) iv	0	0	0	0	0	0	0	0	1px	18 days	0	0
(1 x 5000 mg) iv → (3 x 400 mg) po	2 px	12 days	1 px	20 days	1 px	9 days	0	0	1 px	10days	0	0
(3 x 400 mg) po → (1 x 5000 mg) iv	0	0	0	0	1 px	15 days	0	0	0	0	0	0
(1 x 1200 mg) iv → (1 x 5000 mg) iv	1 px	14 days	0	0	1 px	16 days	0	0	0	0	0	0
(1 x 1800 mg) iv → (1 x 5000 mg) iv → (1 x 1800 mg) iv	0	0	0	0	0	0	0	0	1 px	24days	0	0
(3 x 400 mg) po → (3 x 600 mg) po	0	0	0	0	0	0	0	0	1 px	17days	0	0
(3 x 400 mg) po → (1x 5000 mg) iv → (3 x 400 mg) po	0	0	0	0	1 px	13 days	0	0	0	0	0	0

In patients with comorbid hypertension, the number of patients given NAC dose (1x5000 mg) iv was the same as the dose (3x400 mg) po, namely three patients. In addition, the switch dose is also widely used in comorbid hypertension, which is five patients. The switch dose from doses (1x5000 mg) iv to (3x400 mg) po indicates the shortest treatment period, which is nine days. In patients with cardiac comorbidities, administering a dose of NAC (1x5000 mg) iv showed a shorter treatment period of 12 days.

Then the dose (3x400 mg) po, which is 14 days. Patients with comorbid dyslipidemia were also given a NAC (1x5000 mg) iv dose with a 12-day treatment period.

Patients with comorbid diabetes mellitus and hypertension were given the most doses of NAC (1x5000 mg), indicating an average length of stay of 11 days. A total of one patient who was given a switch dose (1x5000 mg) iv to (3x400 mg) po had a treatment duration of 10 days. One of the cases of comorbid diabetes mellitus and hypertension patients with a treatment period of 24 days of treatment is Mr. DH (patient number 8 in the Parent Table) aged 46 years who were given a dose of NAC (1 x 1800 mg) iv (1 x 5000 mg) iv. The patient came with complaints of cough, shortness of breath, and fever. The patient has comorbid hypertension and diabetes mellitus, history of drug use is Amlodipine (1x5 mg) po and Glucophage (1x500 mg) po. The patient was diagnosed with COVID-19, bilateral pneumonia, diabetes mellitus, hypertensive heart disease (HHD), and ARDS. NAC (1 x 1800 mg) iv reconstituted in 100 ccs of PZ infusion solution was started on the second day of treatment until the eighth day, then its use was replaced with NAC (1 x 5000 mg) iv on days 9 to 13. Then from the 14th to the 16th day, NAC (1 x1800 mg) is given again. From the 17th day until the KRS day (24th day), high doses of NAC were not given anymore. Laboratory results in quantitative CRP value on the second day was 51.5 mg/L (reference value < 5.0 mg/L),

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then increased on the third day to 64.9 mg/L and decreased on the fifth day to 16.6 mg/L, there was no further follow-up for quantitative CRP.

The d-dimer value on the second day of examination showed a value of 118 ng/mL (reference value <500 ng/mL) which then on the third day of the d-dimer examination showed a value of 166 ng/mL (normal). Then, on the fourth day, it showed a value of 117 ng /mL (normal). On day six, the d-dimer rose to 400 ng/mL (normal). Finally, on day 22 it rose to 499 ng/mL (high). On Mr. DH, blood gas analysis was performed on the first day, and the measured pO2 value showed 137 mmHg (high) and pCO2 was 37 (normal). On the second day, pO2 dropped to 23 mmHg (low), and pCO2 dropped to 31.3 mmHg (low). On the third day, pO2 rose to 77 mmHg (low), which was still below normal, and pCO2 rose to 28.1 (low) mmHg, which was still below normal. On the fourth day, pO2 rose to 116 mmHg (high) but pCO2 slightly decreased to 27.1 mmHg (low). On the fifth day, pO2 and pCO2 showed normal values, namely 92 mmHg and 36.5 mmHg, respectively. On day 7, pO2 rose to 123 (high), and pCO2 fell to 29.2 (low). On day 9, the pO2 value remained as before, namely 123 mmHg (high), while pCO2 decreased to 23.1 mmHg (low). Furthermore, no follow-up was carried out for pO2 and pCO2. The chest X-ray on the second day of treatment showed pneumonia and cardiomegaly. On the 5th day, a chest CT scan was performed and showed bilateral pneumonia with ground-glass opacity. On the 7th day, the chest X-ray showed pneumonia results relatively the same as the 2nd-day photo. On the 10th day of examination, bilateral pneumonia improved from the 7th day. On the 15th day of examination, the results of bilateral pneumonia were relatively the same as the 10th day. Furthermore, on the last day of the treatment period (24th day), a chest CT scan was performed again, showing the results of bilateral pneumonia seen from ground-glass opacity in both lungs. Furthermore, for the RT-PCR results on the 2nd and 7th days, the RT-PCR results still showed positive results, and negative results were obtained on the 21st day of the treatment period. The patient received oxygenation therapy during the first day, nasal O2 at four lpm, and then from the second day to the tenth day. He received non-rebreathing mask oxygenation therapy of 8-10 lpm. KRS patient on the 24th day of treatment.

In this study, therapeutic outcome parameters, inflammatory markers evaluated were CRP, d-dimer, IL-6, and/or fibrinogen as much as 100% (*n*=60) showed improved results. Still, in each patient, not all of these markers were monitored, or Follow-up was performed so that only one or two inflammatory markers could be shown before and after therapy. In the literature, it is stated that NAC is given until there is clinical improvement, improvement of chest x-ray, decrease in CRP (<10 mg/dL), or improvement of hyper inflammation (Suprabawati, 2020). NAC has a mechanism of action as a "glutathione-boosting treatment" that can increase the immune response and decrease pro-inflammatory cytokines to reduce the risk of the severity of COVID-19 caused by cytokine storms in the body (Spearow, 2020). Glutathione is an antioxidant that plays a role in protecting cells from oxidative stress and is widely found in the body (Burhan et al., 2018). In addition, NAC inhibits lipopolysaccharide-mediated neurogenic inflammation by counteracting the release of Na, K-ATPase (NKA), a marker of cell necrosis, which may explain the decrease in IL-6, as well as normalizing C-reactive protein (CRP) levels with the use of NAC (Calzetta et al., 2018).

The results of the RT-PCR test, which at the end of the treatment period still showed positive results (17.5%; n=10), this was because there were still virus fragments that were still detected by RT-PCR even though the virus was no longer active (Burhan et al., 2018). Chest X-rays as much as 69% (*n*=42) showed improved results from the previous results, and as many as 39% (*n*=14) gave relatively the same results as the first chest X-ray. Chest radiographs of patients showed 95% (n=57) had bilateral pneumonia and 3% (*n*=2) had bronchitis.

Clinical data on oxygen saturation in patients with severe COVID-19 showed a saturation value of 95%. Still, only 37% (*n*=22) patients did not use oxygen on the day of KRS, while 63% (*n*=38

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patients) received oxygen. The day of KRS is still assisted by oxygenation therapy which can be an O2 nasal, O2 simple mask, or O2 Non-rebreathing mask. Oxygen therapy is recommended by WHO and the Centers for Disease Control and Prevention (CDC) as first-line therapy to treat respiratory disorders and hypoxia due to COVID-19 with various administration methods determined by the severity of the disease (Whittle et al., 2020). Other clinical data, such as body temperature, blood pressure, cough, and pulse for all patients (*n*=60), showed improved results after treatment therapy.

In addition to being an antioxidant, N-acetylcysteine (NAC) is a mucolytic agent that has a working mechanism, namely its free sulfhydryl (SH) group, which can reduce disulfide bonds, so it can be used to reduce the viscosity and elasticity of mucus (Santus et al., 2014). In this study, due to limited data in medical records, it was not possible to evaluate how NAC works as a mucolytic agent. Still, again it was only evaluated from other clinical data.

The interaction between NAC and other drugs was not found or not written in the health medical record document, so a literature study carried out an analysis related to DRP (Drug Related Problem). NAC can interact with several metals such as iron (Fe) and copper (Cu), rubber, and oxygen and oxidizing compounds. Some antibiotics such as amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are also physically incompatible with NAC or may become inactive (Sweetman, 2009). The NAC solution will change color and release hydrogen sulfide when iron, copper, rubber, and autoclaved. NAC does not react with plastic, glass, aluminum, silver, and stainless steel. The presence of light purple color in oral preparations and inhalation solutions also does not affect the drug's potency too much. Still, it is better to prevent it by using unreacted plastic and glass containers and using metal tools such as stainless steel when nebulized. The presence of a pink to light purple color in the injection preparation also does not affect the quality of the product (Mc Evoy, 2012). In COVID-19 patients, multivitamins and supplements were given, but from the results of this study, none of the multivitamins and supplements used contained iron (Fe), so no drug interactions occurred.

Based on the description above, it can be seen that the use of high doses of NAC, namely [1 x 1200 - 5000 mg] po/iv in patients with severe COVID-19 at Bhayangkara Hospital Surabaya, resulted in improved conditions in patients without comorbidities with a length of treatment of 12 days or with comorbid with 14 days of treatment. The length of treatment is influenced by NAC and is also influenced by the patient's condition and other drugs used. Data on therapeutic outcome parameters such as chest X-ray, inflammatory markers (CRP, d-dimer, IL-6) are not all followed up by hospitals, and this can be caused because COVID-19 is a complex disease, so that the parameters that determine the criteria for recovery patients viewed from many comprehensive aspects.

CONCLUSION AND SUGGESTION

Based on the study results of the Effectiveness of High-dose N-acetylcysteine in Patients with Severe COVID-19 at Bhayangkara H.S. Hospital. Samsoeri Mertojoso Surabaya in the period October 2020 to February 2021, it was concluded that the administration of N-Acetylcysteine (NAC) [1 x 1200 - 5000 mg] po/iv showed an improvement in condition in patients without comorbidities with a length of stay of 12 days or with comorbidities with a length of treatment 14 days. In addition, the administration of NAC [1 x 1200 - 5000 mg] po/iv showed an improved clinical condition, free oxygen saturation $\geq$95% as much as 37%; 69% improvement in chest x-ray and improved inflammation, observed from CRP and d-dimer as much as 100%.

The implication of research results on practice, administration of high dose N-acetylcysteine can be considered because it provides evidence of clinical benefit for patients with Severe COVID-19.

Based on the limitations of this study, it is necessary to conduct further research on the effectiveness of high-dose NAC in patients with severe COVID-19, such as with prospective research methods and with the control group using certain dosage or control group without NAC therapy, to see the effectiveness of NAC more accurately.

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