

RESEARCH ARTICLE

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Drug utilization of N-Acetylcysteine in COVID-19 inpatients at Santa Elisabeth Hospital Purwokerto, Indonesia

Heny Ekowati *, Faradina Qorina Nadzif , Masita Wulandari Suryoputri

ABSTRACT

Background: COVID-19 is associated to an oxidant-antioxidant imbalance, which leads inflammation and tissue damage. N-Acetylcysteine (NAC), in addition to being a mucolytic, has been shown to be an effective antioxidant in the therapy of COVID-19.

Objective: The purpose of this study is to evaluate at the NAC usage profile in COVID-19 inpatients at Santa Elisabeth Hospital in Purwokerto.

Methods: A descriptive observational design was used to perform the study. Retrospective data were obtained from medical records from July 2020 to July 2021. All patients who met the inclusion criteria were sampled using the total sampling technique.

Results: NAC was usually administered to COVID-19 inpatients who have a mild illness of the disease. The most common symptoms were cough and fever. Patients with mild and moderate severity were given NAC orally (600 mg 3 times a day) and intravenously (5 gram/day), respectively. The duration of NAC administration was in the range of 8-14 days.

Conclusion: NAC was one of the therapies used at Santa Elisabeth Hospital Purwokerto for COVID-19 inpatients.

Keywords: N-Acetylcysteine (NAC), COVID-19, drug utilization

Introduction

On February 11, 2020, the World Health Organization (WHO) declared Coronavirus Disease (COVID-19), which is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. WHO reported 505,817,953 COVID-19 cases worldwide till April 17, 2022, with a death rate of 6,213,876 persons. In April 2022, Indonesia had 17,631 coronavirus positive cases. Fever, dry cough, tiredness, sore throat, and shortness of breath are common symptoms of COVID-19 infection. Hyper-inflammation associated with acute lung injury is the most common cause of death in patients with severe symptoms [2].

In the case of SARS-CoV-2 infection, N-acetylcysteine (NAC) has been used as a complement to standard treatment. The risks, benefits, and effects of glutathione synthesis, increasing immune function, and modulating the inflammatory response are all considered when using NAC for COVID-19 [3]. NAC is a mucolytic agent that also possesses antioxidant properties due to its role in glutathione (GSH) synthesis and anti-inflammatory effects [4]. In the body, GSH acts as an antioxidant and inhibits the production of proinflammatory cytokines [5]. In addition, NAC can also reduce the release of proinflammatory cytokines through inhibition of NF- κ B. As a result, NAC inhibited IL-6 expression while also substantially lowering IL-1 β and TNF- α levels. NAC also suppresses the expansion of the inflammatory cascade by regulating IL-10 [6].

In the Banyumas Regency, the Santa Elisabeth General Hospital (RSU) is one of the referral hospitals for COVID-19 patients. Santa Elisabeth Hospital has

Laboratory of Pharmacology and Clinical Pharmacy, Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, Indonesia

*Corresponding author: Jl Dr. Soeparno Karangwangkal, Purwokerto 53123, Indonesia. E-mail: heny.ekowati@unsoed.ac.id

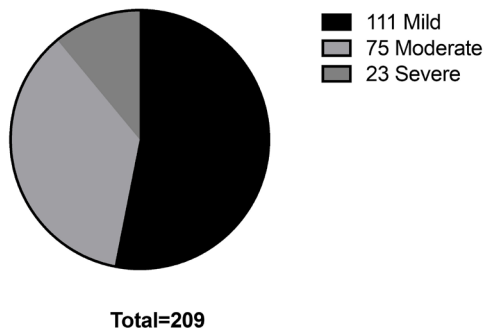


Figure 1. Characteristics of patients based on the severity of the disease

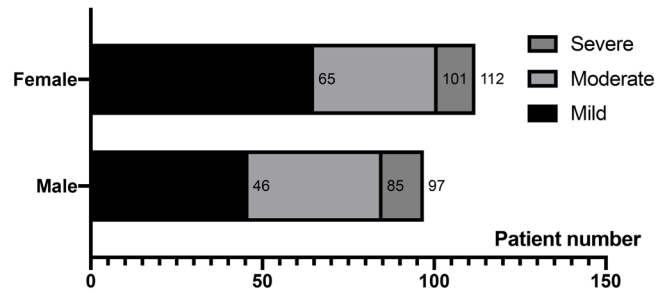


Figure 2. Patient characteristics by gender

been receiving COVID-19 patients since March 2020. Every month, the number of patients admitted with mild to severe symptoms increases. Acetylcysteine (NAC) is one of the most commonly used medications for treating COVID-19 at Santa Elisabeth General Hospital. In a COVID-19 patient with respiratory failure on day 13, administering NAC by inhalation improved substantially the patient’s condition [4]. The administration of intravenous NAC to ten severe COVID-19 patients who required a respirator significantly improved their condition [7]. There is an immediate need for research on the effectiveness of NAC as an adjuvant therapy in COVID-19. As a result, the goal of this study is to determine the pattern of NAC use at Santa Elisabeth Hospital as a predictor of therapeutic success in COVID-19 inpatients.

Methods

Research design

A descriptive observational design was used to perform the study. Medical records of COVID-19 inpatients were used to collect retrospective data from July 2020 to July 2021. Ethical clearance obtained from the Health Research Ethics Commission, Faculty of Health Sciences, UNSOED, no. 325/EC/KEPK/III/2021.

Population and sample

The population in the study was COVID-19 inpatients at Santa Elisabeth General Hospital for the period July 2020 to July 2021, with the sample consisting of patients who received NAC therapy throughout that time. The total sampling approach was used to collect data from all members of the population who met the inclusion and exclusion criteria.

Inclusion criteria: (i) hospitalized patients aged > 18 years, (ii) hospitalized patients diagnosed

with COVID-19 with or without comorbidities, (iii) hospitalized patients using NAC as a treatment for COVID-19 either orally or intravenously, (iv) patients with complete medical record data, namely: medical record number, patient identity (name, gender, age of patient), date of treatment (date of admission and discharge from hospital), diagnosis (primary and secondary), PCR swab or rapid-test results, patient subjective data (cough and shortness of breath), clinical examination (vital signs: respiratory rate, SpO₂), history of disease, history of allergies, medication history, therapy given to the patient (name of drug), type of drug preparation, the dose, route of administration, and administration frequency), and patient’s condition at the time of discharge from the hospital. Exclusion criteria: COVID-19 hospitalized patients who are pregnant.

Instrument

The Case Report Form (CRF) was employed in this study as a tool. The medical records of COVID-19 inpatients at Santa Elisabeth General Hospital were used as the primary data source in this study, and an analysis was conducted using the inclusion and exclusion criteria outlined above.

Analysis

The data were analyzed by calculating the number and demographic parameters of the patients, such as gender, age, subjective data and clinical condition, NAC administration route, and NAC use duration. The severity of the patient was classified using the Indonesian Ministry of Health’s COVID-19 Management Manual, Third Edition [8]. Prism GraphPad 8.0 software (San Diego, USA) was used to visualize the results.

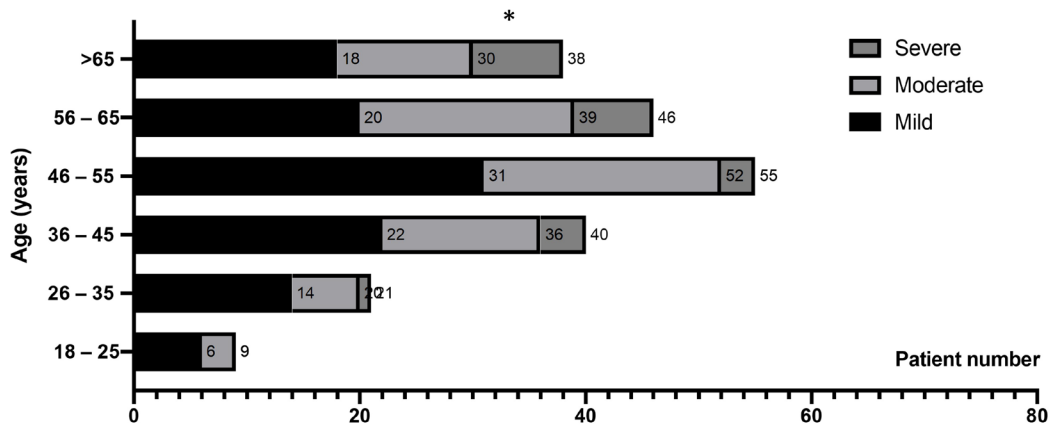


Figure 3. Patient characteristics by age range. *Patients >65 were affected the most severely, including eight patients affected

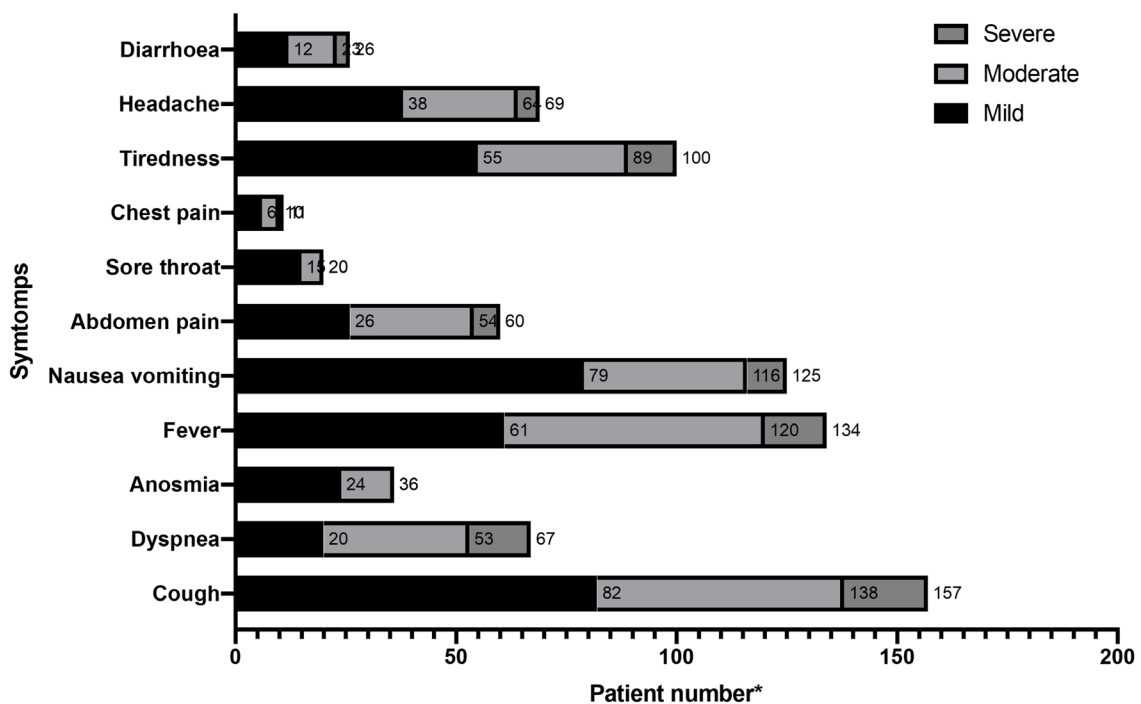


Figure 4. Symptoms in COVID-19 patients. *One patient may experience more than one symptom

Results

Characteristics of patients based on disease severity, sex, age, and symptoms

The participants in this study were inpatients at Santa Elisabeth Hospital who had been confirmed positive for COVID-19 and were receiving N-Acetylcysteine (NAC) therapy. There were 209 patients that met the inclusion criteria out of 349 who were admitted to the hospital. The subjects were characterized based on the severity of the disease, gender, age, and patient symptoms.

The majority of the 209 COVID-19 patients who received NAC therapy have mild severity (Figure 1).

Female patients dominated the number of patients with mild severity, accounting for 65 individuals (58.6%) (Figure 2). The age group most affected by COVID-19 at mild and moderate degrees was 46-55 years, with 31 patients (27.9%) and 21 patients (28.0%) respectively (Figure 3). Patients over the age of 65 were affected the most severely, including up to eight patients affected (34.8 percent).

Figure 4 shows the symptoms experienced by COVID-19 patients who were admitted to the hospital and received NAC treatment. Cough, nausea, vomiting, and fever were the most common symptoms experienced by patients in mild degrees. The most

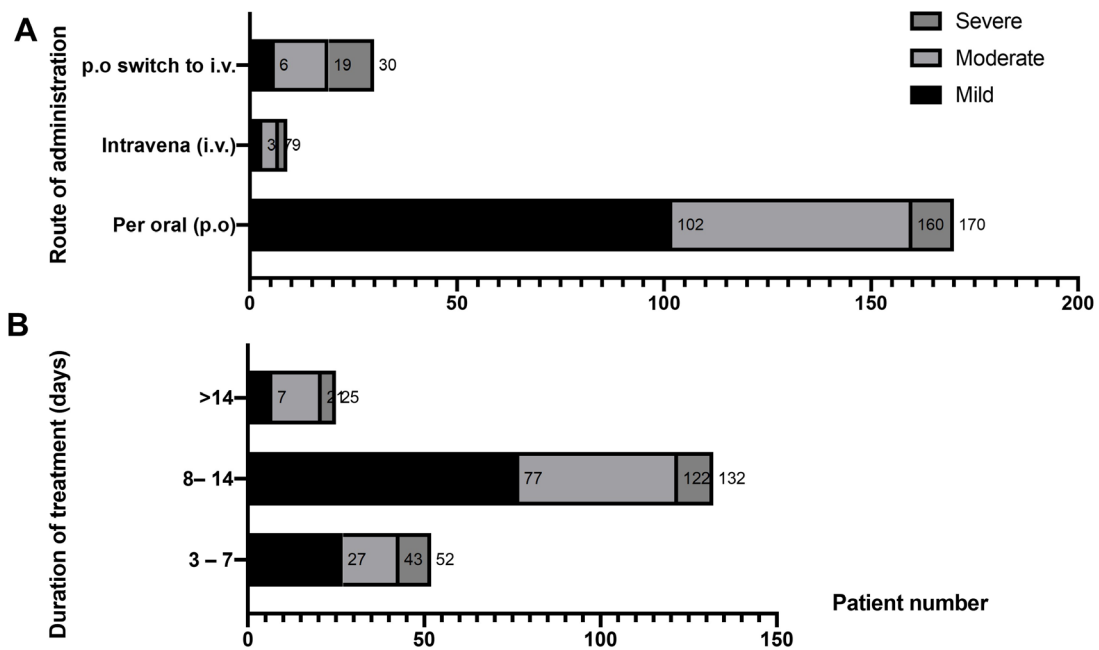


Figure 5. Profile of the use of N-Acetylcysteine in COVID-19 patients. (A) Route of administration of NAC in COVID-19 patients, (B) Duration of NAC use in COVID-19 patients

common symptoms at moderate levels were fever, cough, nausea and vomiting. Cough, shortness of breath, and fever were the most common symptoms in severe cases.

Profile of the use of N-Acetylcysteine in COVID-19 patients

N-Acetylcysteine (NAC) was given to COVID-19 patients at Santa Elisabeth Hospital orally at a dose of 600 mg three times a day and intravenously at a dose of 5000 mg once a day. The oral route was the most commonly used in patients with mild and moderate grades (Figure 5A). In severe cases, the medication was first administered orally prior to getting administered intravenously. The duration of NAC administration was determined by the length of the patient’s treatment. COVID-19 inpatients at Santa Elisabeth Hospital were usually given NAC on the first or second day. The average duration of NAC use was 8-14 days across all severity levels (Figure 5B).

Discussion

The majority of patients treated with NAC at Elisabeth General Hospital had mild illness severity. This could be because this hospital was not the first referral hospital for COVID-19 patients. Therefore, most COVID-19 patients treated were patients with mild to moderate degrees.

COVID-19 infection is equally prevalent in men and women due to a variety of risk factors. In our study, women were infected at a higher rate than men. This finding differs from those of several other studies. Men have a higher genetic expression of the ACE-2 protein than women [9]. The variety of innate immunity, steroid hormones, and variables associated to sex chromosomes all contribute to differences in immunity between men and women [10,11]. Women have more significant antibody responses than men, implying that immunological mechanisms may play a role in women’s improved recovery from COVID-19 [12]. Our findings support previous study that shows men are more likely than women to smoke and drink alcohol, both of which can exacerbate COVID-19 symptoms [11].

In our study, COVID-19 was found to affect people aged 44-55 in mild and moderate levels, whereas patients aged 65 and above were affected the most severely. This is aligned with a study, which found that older persons, particularly those in the 50-60 year age group, are more susceptible to COVID-19 [13]. Patients above the age of 60 have a higher risk of respiratory failure, require more longer treatment, and have a poorer response to treatment than those under the age of 60 [4]. Increasing age is one of the factors that decrease ACE2 levels. The imbalance between angiotensin II overactivity and angiotensin 1-7 deficiency can trigger inflammation, thrombosis, and

other adverse reactions that can exacerbate symptoms in elderly COVID-19 patients [14].

The most prevalent symptoms reported by patients were cough, shortness of breath (dyspnea), nausea and vomiting, and fever. Symptoms commonly reported in COVID-19 patients were fever, cough, dyspnea, headache, sore throat, and rhinorrhea [15]. Gastrointestinal symptoms such as nausea and diarrhea were also reported, in addition to respiratory symptoms. Fever, cough, nausea and vomiting are the most common symptoms reported by COVID-19 patients in China [16].

In patients with mild and moderate severity, oral NAC was the most usual route of administration. COVID-19 patients at Santa Elisabeth General Hospital were administered 600 mg of NAC each day. The majority of COVID-19 patients exhibit pneumonia symptoms, including an accumulation of mucus in the respiratory tract [17]. A dose of 600 mg/day is used as a mucolytic agent. NAC (600 mg/day) used orally can help to minimize the occurrence and severity of pneumonia. With about 37 percent of patients having ventilator-associated pneumonia (VAP), patients treated with NAC 600 mg had a lower incidence of pneumonia (26.6 percent vs. 46.6 percent) than patients in the placebo group [18].

NAC was given orally and later switched to intravenous in moderate and severe patients, or NAC was given solely intravenously at that condition. COVID-19 inpatients at Santa Elisabeth Hospital received a daily intravenous dose of 5 grams. The patient's condition was taken into account when switching from oral to intravenous administration. Parenteral preparations will be easier to provide to patients with moderate and severe degrees than oral preparations. At high doses (≥ 1200 mg), NAC has antioxidant and anti-inflammatory properties [19,20]. In COVID-19 patients, the purpose of NAC therapy is to work in conjunction with other anti-inflammatory and antioxidant medications.

The duration of administration of NAC depends on the length of the patient's treatment. COVID-19 inpatients at Santa Elisabeth Hospital were usually administered NAC on the first or second day. Patients with mild, moderate, and severe degrees received NAC for 8-14 days. The RI Ministry of Health's COVID-19 management guidelines, third edition, do not specify how long NAC should be used in patients [8].

Conclusion

The following is the utilization of NAC in Covid-19 inpatients at Santa Elisabeth Hospital Purwokerto: NAC was usually administered to patients who have a mild illness of the disease. The most common symptoms were cough and fever. The administration of NAC ranged from around 8 to 14 days.

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Author contributions

HE and MWS designed this study; FQN assisted with data collection; HE and FQN wrote the initial script; FQN assisted with statistical analysis; and all authors contributed to data interpretation and final approval of the manuscript.

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