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THE EFFECT OF HIGH-DOSE INTRAVENOUS N-ACETYLCYSTEINE ADMINISTRATION ON TUMOR NECROSIS FACTOR-α (TNF)

Sahrun
Faculty of Medicine, Universitas Al Azhar Mataram, Jl. Unizar No.20, Turida, Mataram, Nusa Tenggara Barat. 83237, Indonesia
cahrun.carter@gmail.com

ABSTRACT

Respiratory tract infections are among the five most common health problems worldwide, with pneumonia being a significant contributor. Pneumonia continuously increases the rates of morbidity and mortality globally. Pneumonia is classified into three categories, one of which is Community Acquired Pneumonia (CAP). The incidence of community-acquired pneumonia increases with age. The risk of death from pneumonia also increases in individuals over 65 years old and those with comorbidities.The objective of this study is to assess the impact of high-dose intravenous N-acetylcysteine on the clinical improvement of inflammatory markers (TNF-α) among hospitalized CAP patients with comorbidities.Methods: This study is a randomized controlled trial. The sample population comprises patients with respiratory diseases hospitalized at RS Patut Patuh Patju (Tripat) Gerung. The sample size was obtained through total sampling during the period from January to May 2022, ranging from 10 to 25 patients per month, with an average of 15 patients per month. The dependent variable in this study is CAP with comorbidities, while the independent variable is the clinical improvement of inflammatory markers. Data analysis between variables was performed using a t-test for two means. The aim of this study is to assess the effect of clinical improvement in inflammatory markers (TNF-α) in hospitalized CAP patients with comorbidities after the administration of high-dose intravenous N Acetylcysteine. The mean value of Tumor Necrosis Factor-α before the intervention was 77.699, and the post-test mean value was 41.137. The analysis of the paired t-test for Tumor Necrosis Factor-α showed a P value of 0.000 <α=0.05. The Mann-Whitney test used to assess the difference in Tumor Necrosis Factor-α between the Intervention and control groups after N-Acetylcysteine therapy revealed a P value of 0.000 <α=0.05. The conclusion of this study is that there is an effect of high-dose intravenous N Acetylcysteine on Tumor Necrosis Factor-α, and there is a significant difference in the change in Tumor Necrosis Factor-α between the Intervention and control groups.

Keywords: cap; N Acetylcysteine; pneumonia; tumor necrosis factor-α

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INTRODUCTION

Respiratory tract infections are among the five most common health problems worldwide, with pneumonia being a significant contributor. Pneumonia continuously increases morbidity and mortality rates globally. It is a disease caused by bacterial, viral, and fungal infections affecting the lung parenchyma. In 2015, pneumonia was the eighth leading cause of death in the United States, the fourth leading cause of death worldwide, and the leading cause of death in low-income countries. (Lank et al, 2019) According to the 2018 Basic Health Research (Riskesdas), the prevalence of pneumonia in Indonesia is 4% of the population based on diagnoses by healthcare professionals or symptoms experienced by household members. In the province of NTB, 5.98% of the population is affected by pneumonia, with West Lombok

ranking third highest after Dompu and Central Lombok. In West Lombok, in 2018, pneumonia was the 13th leading cause of death, resulting in 51 fatalities.(Riskesdas NTB, 2018) According to the World Health Organization (WHO) in 2019, pneumonia caused 14% of all deaths among children under 5 years old, totaling 740,180 fatalities. In Indonesia, the incidence of pneumonia in children under 5 years old was 278,241 cases, and in children over 5 years old, it was 163,163 cases.(Kemenkes RI, 2022).

Pneumonia is classified into three categories: Community-Acquired Pneumonia (CAP), Hospital-Acquired Pneumonia (HAP), and Ventilator-Associated Pneumonia (VAP). The incidence of community-acquired pneumonia increases with age, and the risk of death from pneumonia also increases in individuals over 65 years old and those with comorbidities(Franquet, 2018; PDPI, 2014) With Lombok being recognized as a global tourist destination, there is a need for preparedness in health resources and facilities to anticipate worsening conditions and death due to pneumonia, especially in cases where tourists contract pneumonia in Lombok. In this context, it is essential to apply advanced and scientific therapeutic approaches in line with global health developments in pneumonia management so that the latest pneumonia therapies can be implemented in Lombok. The most characteristic clinical manifestations of community-acquired pneumonia are cough, fever, and shortness of breath, with onset occurring in a community setting. The cough associated with pneumonia is acute, lasting less than 3 weeks, and is typically productive. This productive cough occurs due to hypersecretion of mucus. Physical examination may reveal crackles, while radiological examination may show consolidation, infiltrates, or ground-glass opacities (GGO). Laboratory tests may reveal increased leukocyte counts >10×10^9/L or decreased counts <4×10^9/L, with or without (Spinou & Birring, 2014).

Management of community-acquired pneumonia includes symptomatic therapy and definitive therapy. Antibiotic treatment can start with empirical therapy before pathogen culture results are available. Empirical therapy can be given based on the patient's symptoms. Mucolytics are often used as treatment for productive cough in pneumonia. In a case report/PSI published by Brodier et al., it is stated that the mucolytic effects of N-acetylcysteine (NAC) administered via bronchoscopy were proven to alleviate thick mucus obstruction in patients.(Brodier et al., 2019;Sakamoto et al., 2015) Initially, NAC was widely used as an expectorant mucolytic due to its mucolytic effects at low doses. However, in the past decade, it has increasingly been applied as an antioxidant and anti-inflammatory agent at high doses. Recently, NAC has been used as an adjunctive therapy for COVID-19 cases ranging from mild to critical, and numerous studies have been conducted to explore its effects. One such study by Ibrahim et al. in 2020 investigated the effects of intravenous NAC on severe coronavirus disease (COVID-19) and demonstrated a significant reduction in inflammatory markers following NAC administration. Adding NAC therapy for CAP patients reduces tumor necrosis factor-alpha (TNF-α), an inflammatory cytokine produced by macrophages/monocytes during acute inflammation. NAC treatment can help reduce oxidative damage and inflammation in pneumonia patients.(Ibrahim et al., 2020)

Another study by Zhang et al., (2018)t investigated the use of high-dose oral NAC for mild to moderate CAP (PSI class I-III) and found a significant reduction in the inflammatory marker TNF-α and a significant increase in total serum antioxidant levels (Rahmanto, 2021). A similar study by Li et al., (2018) targeted patients with moderate to severe CAP with comorbidities. However, there have been few studies to date on the use of high-dose intravenous NAC as an adjunctive antioxidant and anti-inflammatory therapy for CAP with comorbidities. Based on these findings and discussions, there is a clear need for further

scientific research to evaluate the effectiveness of high-dose intravenous NAC as an adjunctive therapy for CAP with comorbidities in Lombok. This research could serve as a foundation for developing additional therapeutic strategies aimed at achieving improved clinical outcomes and better oxidative stress management in the future. The objective of this study is to assess the impact of high-dose intravenous N-acetylcysteine on clinical improvement in inflammatory markers (TNF-α) among hospitalized CAP patients with comorbidities.

METHOD

This research is an experimental study utilizing a randomized controlled trial (RCT) design, where participants are divided into two groups: one group consisting of patients diagnosed with Community Acquired Pneumonia (CAP) with comorbidities in the inpatient ward receiving high-dose intravenous NAC therapy, and the other group receiving only standard CAP therapy. The study aims to evaluate the duration of clinical improvement and the impact on inflammatory markers and oxidative stress markers.

The sample population includes all lung disease patients admitted to Patut Patuh Patju (Tripat) Hospital in Gerung. The sample size is determined by total sampling for the period from January to May 2022, with a monthly average of 10-25 CAP patients, and 15 patients per month on average. Consecutive sampling is employed, encompassing all CAP patients with a Curb-65 score of 3-5 and comorbidities admitted to Tripat Hospital during the specified period. The patients are divided into two groups: the treatment group receives high-dose intravenous NAC (1200 mg-1800 mg) as an adjunctive therapy, while the control group receives only standard CAP therapy. Upon admission, routine blood tests and serum samples are collected for MDA, TNF-α, and TIOC assays. Patients then undergo standard CAP therapy along with high-dose intravenous NAC for 5 days, and are monitored for clinical and laboratory progress. At the end of the CAP recovery period, clinical evaluations, inflammatory markers, and oxidative stress markers are reassessed. Research instruments include a data collection form, intravenous NAC injection (1200 mg-1800 mg), Chest X-ray and laboratory results during treatment, and reagent kits for TNF-α, MDA, TIOC, and ELISA. The study is conducted at RSUD Tripat Gerung Lombok Barat from January 2022 to May 2022. Dependent variables: CAP with comorbidities. Independent variables: Clinical improvement, oxidative stress markers, and inflammatory markers. Numeric or categorical data will be presented in tables and figures, with results displayed according to patient characteristics and statistical test outcomes. Data analysis will be performed using an independent t-test for comparing two means.

RESULTS

According to the data in Table 1, the majority of respondents are male, comprising 72%, while females account for 27.3%. Among the patients, 68.2% had a cough, 77.3% experienced shortness of breath, 68.2% had a fever, and 63.3% had sputum. In the control group, the majority of respondents are also male, making up 77.3%, with females constituting 22.7%. In this group, 86.4% of patients had a cough, 86.4% experienced shortness of breath, 54.5% had a fever, and 81.8% had sputum.

Table 1.
Characteristics of the Respondents

Variable	Group			
	Intervention		Control	
	f	%	f	%
Sex				
Male	16	72.7	17	77.3
Female	6	27.3	5	22.7
Cough				
No	7	31.8	19	86.4
Yes	15	68.2	3	13.6
Dyspnea				
No	5	22.7	19	86.4
Yes	17	77.3	3	13.6
Fever				
No	15	68.2	12	54.5
Yes	7	31.8	10	45.5
Sputum				
Tidak	8	36.4	18	81.8
Ya	14	63.6	4	18.2

Table 2.
Tumor Necrosis Factor-α

Intervention Group					
TNF	N	Min	Max	Mean	Std. Dev
Pretest	22	10.92	137.24	77.699	26.329
Postest	22	3.14	113.43	41.137	26.853
Control Group					
TNF	N	Min	Max	Mean	Std. Dev
Pretest	22	43.9	168.2	77.181	31.8006
Postest	22	45.1	168.2	81.136	30.8863

Table 2 it is known that the mean value of Tumor Necrosis Factor-α before intervention was 77.699, and the mean value post-test became 41.137. Meanwhile, in the control group, the mean value of Tumor Necrosis Factor-α pre-test was 77.181 and experienced a change in the mean value post-test to 81.136.

The Wilcoxon Signed-Rank Test is a non-parametric method used to compare two paired samples or two related observations to determine whether the distribution of differences between these pairs is symmetric around zero. This test serves as a non-parametric alternative to the paired t-test when the normality assumption is not met(Nursalam, 2021).

Table 3.
The Influence of N-Acetylcysteine on Tumor Necrosis Factor-α in Intervention and Control Groups

Intervention Group				
TNF	N	Mean	Std. Dev	P Value
Pretest	22	77.6995	26.3294	0,000
Postest	22	41.1375	26.8538	
Control Group				
TNF	N	Mean	Std. Dev	P Value
Pretest	22	77.181	31.8006	0,078
Postest	22	81.136	30.8863	

Table 3, the results of the Paired T Test analysis for the variable Tumor Necrosis Factor-α yielded a P Value of 0.000, which is less than α=0.05. Meanwhile, in the control group, a P Value of 0.078 was obtained, which is greater than α=0.05.

DISCUSSION

The Effect of High-Dose Intravenous N-Acetylcysteine on Tumor Necrosis Factor-α

Before intervention, the mean value of Tumor Necrosis Factor-α was 77.699, and post-intervention, it decreased to 41.137. The Paired T Test analysis for the variable Tumor Necrosis Factor-α resulted in a P Value of 0.000, which is less than α=0.05, indicating an influence of high-dose intravenous N-Acetylcysteine on Tumor Necrosis Factor-α.TNF-α is produced by various types of cells, including macrophages, T lymphocytes, and endothelial cells, in response to infection or tissue damage. TNF-α functions to regulate various inflammatory processes, such as activating immune cells, inducing production of other cytokines, and initiating acute inflammatory responses. Elevated levels of TNF-α are associated with chronic inflammation and various degenerative diseases.The research by Sujana & Maulida (2021) indicates that N-acetylcysteine (NAC) affects Tumor Necrosis Factor (TNF), a proinflammatory cytokine that plays a key role in the body's immune response. TNF contributes to the inflammatory process and can trigger excessive inflammation, particularly in conditions such as COVID-19. The use of NAC has been shown to reduce levels of proinflammatory cytokines, including TNF, in severe COVID-19 patients. This suggests that NAC may help regulate overly active inflammatory responses caused by elevated TNF levels in the body. By lowering TNF levels and other proinflammatory cytokines, NAC can play a role in reducing systemic inflammation and alleviating symptoms associated with excessive inflammatory responses in COVID-19 patients.

High-dose intravenous administration of N-Acetylcysteine (NAC) has been shown to be effective in reducing oxidative stress but does not significantly affect Tumor Necrosis Factor-α (TNF-α) levels. This highlights that although NAC is a potent antioxidant, it may not be sufficient to modulate the complex inflammatory response. These findings are important to consider in the development of therapeutic strategies targeting inflammation and indicate the need for a multi-target approach in managing chronic inflammatory conditions.In line with the research by Zaka et al., (2019) NAC is known for its antioxidant and anti-inflammatory properties, which can indirectly affect TNF-α levels by modulating oxidative stress and inflammation. Studies indicate that NAC can inhibit the activation of nuclear factor-kappa B (NF-κB), a key regulator of TNF-α production, potentially reducing TNF-α levels under certain conditions. NAC's ability to replenish intracellular glutathione levels may also contribute to its anti-TNF-α effects by regulating redox signaling pathways. While NAC's direct mechanisms on TNF-α levels can vary depending on specific contexts and disease models, its overall anti-inflammatory and antioxidant properties make it a promising candidate for modulating TNF-α-mediated pathways.

NAC can inhibit the activation of nuclear factor-kappa B (NF-κB), a transcription factor involved in the regulation of TNF-α production, thereby indirectly impacting TNF-α levels. By replenishing intracellular glutathione levels, NAC can modulate redox signaling pathways involved in the regulation of TNF-α expression. The exact mechanisms by which NAC affects TNF-α levels may vary depending on the specific context, disease model, and cellular environment. Overall, NAC's antioxidant and anti-inflammatory properties make it a potential candidate for modulating TNF-α levels in various pathological conditions (Poe & Corn, 2020) According to Afriani & Maulina (2023), the impact of NAC on TNF has been a focus of several studies. NAC is known for its anti-inflammatory and antioxidant properties that can

influence TNF formation. Some studies indicate that NAC can reduce TNF production in specific inflammatory conditions by inhibiting inflammatory signaling pathways that contribute to TNF production. Furthermore, NAC can regulate immune responses by controlling the production of proinflammatory cytokines such as TNF. Therefore, NAC has the potential to decrease inflammation caused by TNF. Overall, NAC may impact the reduction of TNF production in certain inflammatory conditions through its anti-inflammatory and antioxidant properties.

According Fallah et al., (2018) Treatment with N-Acetylcysteine (NAC) in rats exposed to arsenic showed a slight increase in TNF-α levels, although the difference was not statistically significant compared to the control group. Rats that received both arsenic and NAC simultaneously showed slightly higher average levels of TNF-α, indicating a possible influence of NAC in regulating TNF-α in arsenic-exposed rats. Overall, the findings suggest that NAC may have a mild impact on TNF-α levels in arsenic-exposed rats, indicating a potential but statistically insignificant effect of NAC in modulating TNF-α in the context of arsenic-induced toxicity. Treatment with NAC in arsenic-exposed rats resulted in a slight decrease in TNF-α levels, although this decrease was not statistically significant, indicating a mild effect of NAC in modulating TNF-α. Rats that received both arsenic and NAC simultaneously showed slightly higher average levels of TNF-α, indicating a possible influence of NAC in regulating TNF-α in the context of arsenic exposure.

According Hamamsy et al., (2019) The levels of TNF-alpha (TNF-α) decreased more postoperatively in the group that received NAC compared to the control group, although this difference was not statistically significant. The reduction in TNF-α levels after surgery suggests the potential anti-inflammatory effect of NAC, as TNF-α is a marker of inflammation. However, the lack of statistical significance indicates that the effect of NAC on TNF-α levels in this study is not clinically significant. The study observed that postoperatively, TNF-α levels decreased more in the group that received NAC compared to the control group, indicating the potential effect of NAC in reducing TNF-α levels after surgery (Talasaz et al., 2013)

High-dose intravenous N-acetylcysteine (NAC) administration has shown promising effects on tumor necrosis factor-α (TNF-α) modulation. Studies have demonstrated that NAC can inhibit TNF-α-induced cell death while also acting as a pro-oxidant, promoting reactive oxygen species independent apoptosis(Sakai et al., 2023). Additionally, TNF-α blockade has been linked to reduced acute inflammatory processes and delayed wound healing in oral traumatic ulcers, indicating the significant role of TNF-α in inflammation and healing processes(Freitas et al., 2022). Furthermore, high-dose acetaminophen (AAP) with NAC has been found to inhibit M2 polarization of tumor-associated macrophages, leading to immune-mediated inhibition of tumor growth, highlighting the potential of NAC in modulating the tumor immune microenvironment and impacting TNF-α levels(Bryan et al., 2023). Moreover, a meta-analysis of randomized controlled trials has shown that NAC administration significantly reduces homocysteine levels but does not affect TNF-α levels, indicating a specific impact on certain inflammatory markers . Overall, high-dose NAC administration appears to have complex effects on TNF-α and inflammatory processes, warranting further investigation into its mechanisms and potential therapeutic applications(Neuwelt et al., 2023).
High-dose intravenous N-acetylcysteine administration effectively attenuates tumor necrosis factor-α (TNF-α) levels, as shown in the study on rat neonates with lipopolysaccharide-induced inflammation. N-acetyl-cysteine (NAC) administration, particularly via intraperitoneal (IP) route one hour after LPS injection, effectively reduced both IL-6 and

TNF-α levels in the serum(Hallajzadeh et al., 2020; Khatib et al., 2017). N-acetylcysteine (NAC) has shown promise as an anti-inflammatory agent in humans due to its antioxidant properties and ability to reduce levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β) (Tieu et al., 2022;Tenório et al., 2021). By replenishing glutathione (GSH) stores and suppressing nuclear factor kappa B (NF-κB) activity, NAC can help restore cellular redox balance and mitigate inflammation . Studies have explored NAC's potential in various conditions, including chronic respiratory diseases like chronic obstructive pulmonary disease and bronchial asthma, where its antioxidative and anti-inflammatory effects could offer therapeutic benefits. However, despite its well-established safety profile and efficacy in experimental settings, the translation of NAC's anti-inflammatory properties into consistent clinical outcomes remains a challenge, with conflicting results in different pathological conditions(Larki et al., 2019; Mokra et al., 2023)

Several studies have been conducted to evaluate the effects of NAC administration on TNF-α levels, particularly in the context of high-dose intravenous administration. The results of these studies often vary and indicate that the effect of NAC on TNF-α is not as strong as its influence on oxidative stress markers. Clinical studies assessing the impact of high-dose intravenous NAC in patients with chronic inflammatory diseases, such as sepsis or autoimmune diseases, show that although there is a reduction in oxidative stress markers, TNF-α levels do not show significant changes after NAC administration. This indicates that NAC may not directly affect the production or activity of TNF-α. Animal model research also supports these clinical findings, where NAC administration does not consistently reduce TNF-α levels, despite an increase in antioxidant capacity and a reduction in other oxidative stress markers (Hamamsy et al., 2019). NAC works primarily by increasing glutathione levels and neutralizing free radicals. However, the regulation of TNF-α involves more complex signaling pathways that are not solely dependent on the cellular redox status. The NF-κB pathway, which plays a crucial role in the regulation of TNF-α, may not be significantly affected by NAC. The production and regulation of TNF-α are influenced by various factors, including signals from pathogens, tissue damage, and interactions between immune cells. NAC may not have sufficient potential to directly modulate these complex processes.

The absence of a significant effect of NAC on TNF-α levels can be explained by several factors, including the effect of NAC is more focused on reducing oxidative stress rather than directly modulating pro-inflammatory cytokines like TNF-α. the signaling pathways that regulate TNF-α production, such as NF-κB, may not be significantly affected by the antioxidant mechanisms mediated by NAC. inflammation is a highly complex process involving various mediators and pathways. Intervention with a single antioxidant agent may not be sufficient to produce significant changes in TNF-α levels.

CONCLUSION

Based on the results of this study, we can conclude that the mean Tumor Necrosis Factor-α value before intervention was 77.699, while the mean post-intervention value was 41.137. The Paired T-Test for Tumor Necrosis Factor-α revealed a p-value of $0.000 < \alpha = 0.05$, indicating a significant effect of high-dose intravenous N-acetylcysteine on Tumor Necrosis Factor-α. Furthermore, the Mann-Whitney U test comparing Tumor Necrosis Factor-α between the Intervention and control groups after N-acetylcysteine therapy produced a p-value of $0.000 < \alpha = 0.05$, demonstrating a significant difference in the changes of Tumor Necrosis Factor-α between the Intervention and control groups.

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