Effect of Oral N-Acetylcysteine Supplementation on the Immunity System in Patients with Acute Myocardial Infarction

Trisulo Wasyanto, Ahmad Yasa', Akhmad Jalaludinsyah

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Sebelas Maret University - Dr. Moewardi Hospital, Surakarta, Indonesia.

Corresponding Author:
Trisulo Wasyanto, MD, Ph.D. Department of Cardiology and Vascular Medicine, Faculty of Medicine, Sebelas Maret University - Dr. Moewardi Hospital, Surakarta. Jl. Kolonel Sutarto 132 Surakarta 57126, Indonesia. email: trisulo.wasyanto@gmail.com.

ABSTRAK

Latar belakang: *inflamasi, stres oksidatif dan fibrosis memegang peran penting setelah terjadinya infark miokard akut (IMA). Biomarker inflamasi yang banyak dipelajari pada penyakit kardiovaskular adalah C-reactive protein. Ada bukti bahwa myeloperoksidase (MPO) dan galectin-3 (Gal-3) memegang peran penting pada sistem imun tubuh saat terjadi IMA. Penelitian ini bertujuan untuk melihat efek pemberian terapi tambahan N-acetylcystein (NAC) secara oral 600 mg 3 kali sehari selama 3 hari terhadap sistem imun pasien IMA.* ***Metode:*** *penelitian eksperimental acak, tersamar tunggal dengan metoda pre- dan post-test. Dilakukan di Rumah Sakit Dr. Moewardi Surakarta, dari bulan Mei hingga Agustus 2018. Tiga puluh dua pasien IMA dengan elevasi segmen ST (STEMI) yang mendapat terapi fibrinolitik masuk penelitian: 17 pasien mendapat terapi standar ditambah NAC 600 mg per oral setiap 8 jam selama 3 hari dan 15 pasien mendapat terapi standar sebagai kontrol. Kadar high sensitivity C-reaktif protein (HsCRP), MPO, dan Galectin-3 dari kedua kelompok diperiksa saat masuk dan setelah 72 jam perawatan.* ***Hasil:*** *kadar HsCRP, MPO, dan Gal-3 pada kelompok NAC dan kontrol pada saat admisi tidak berbeda bermakna, sedangkan kadar antar kelompok pasca 72 jam pemberian NAC didapatkan perbedaan yang bermakna dengan nilai p untuk kadar HsCRP, MPO, dan Gal-3 sebesar 0,0001, 0,001, dan 0,017. Pada kelompok NAC saat admisi dan pasca 72 jam, didapatkan perbedaan kadar HsCRP, MPO, dan Gal-3 yang bermakna dengan nilai p secara berurutan 0,0001, 0,0001 dan 0,0001; sedangkan pada kelompok kontrol tidak didapatkan perbedaan ini. Terdapat perbedaan kadar HsCRP, MPO, dan Gal-3 yang bermakna antara kelompok NAC dan kelompok kontrol (nilai p secara berurutan adalah 0,011, 0,022 dan 0,014).* ***Kesimpulan:*** *pemberian terapi tambahan NAC 600 mg oral tiap 8 jam selama 72 jam dapat menurunkan kadar HsCRP, MPO, dan Gal-3 pada pasien IMA yang mendapatkan terapi fibrinolitik. Hasil penelitian ini akan memberikan pilihan terapi tambahan untuk pengelolaan pasien IMA yang lebih baik.*

Kata kunci: *infark miokard akut, N-acetylcystein, sistem imun.*

ABSTRACT

Background: *inflammation, oxidative stress, and fibrosis play important roles after an acute myocardial infarction (AMI) event. The most studied inflammatory biomarker in cardiovascular disease is C-reactive protein (CRP). It has been demonstrated that myeloperoxidase (MPO) and Galectin-3 (Gal-3) have some essential roles on immune system when an AMI event occurs. We aimed to determine the effect of oral N-acetylcysteine (NAC) supplementation at the dose of 600 mg 3 times daily for 3 consecutive days on the immune system of AMI patients.* ***Methods:*** *our randomized single-blinded experimental study using pre- and post-treatment evaluations was performed at Dr. Moewardi Hospital, Indonesia, from May to August 2018. Thirty-two patients with AMI and*

ST segment elevation (STEMI) who received fibrinolytic therapy were included. There were 17 patients received standard therapy plus 600 mg oral NAC supplementation every 8 h for 3 days and 15 patients received standard therapy, which served as the control group. High-sensitivity C-reactive protein (HsCRP), MPO, and Gal-3 levels of both groups were evaluated at admission and after 72 h receiving treatment. ***Results:*** *HsCRP, MPO, and Gal-3 levels between NAC and control groups at admission were not significantly different; while intergroup differences after 72 h of NAC supplementation were significant (p values of HsCRP, MPO, and Gal-3 levels were 0.0001, 0.001, and 0.017, respectively). Furthermore, in the NAC group, HsCRP, MPO, and Gal-3 levels at 72 h after treatment were significantly different from the corresponding levels at admission (p values: 0.0001, 0.0001, and 0.0001, respectively); the control group did not show these differences. There were also significant intergroup differences between the NAC and control groups regarding HsCRP, MPO, and Gal-3 levels (p values: 0.011, 0.022, and 0.014, respectively).* ***Conclusion:*** *oral supplementation of 600 mg NAC every 8 h for 72 h can reduce HsCRP, MPO, and Gal-3 levels in AMI patients receiving fibrinolytic therapy. Results of our study will provide more options for supplementation therapy to improve management of IMA patients.*

Keywords: *acute myocardial infarction, N-acetylcysteine, immune system.*

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide.[1] In the United States, the incidence of acute myocardial infarction (AMI) with ST segment elevation (STEMI) decreases; while the incidence of AMI without ST segment elevation (NSTEMI) remains constant or slightly increases.[2] In Indonesia, deaths from cardiovascular disease are increasing every year and cardiovascular disease has become the most common cause of death.[3]

Inflammation is an important factor in the development of atherosclerosis and subsequent cardiovascular events. Continuous inflammation increases the likelihood of erosion or rupture of atherosclerotic lesions. The most studied inflammatory biomarker in cardiovascular disease is C-reactive protein (CRP), an acute-phase protein, which is produced mainly by hepatocytes under the influence of cytokines such as interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α).[4] Several studies have found that serum CRP levels can predict the risk of recurrent acute cardiovascular events in hospitals[5] or 30-day or long-term mortality in cases of STEMI.[6] The pathogenesis of AMI is influenced by systemic and local process on myocardial plaque and inflammation. Various types of leukocytes play an important role in local inflammatory processes and trigger plaque rupture, one of them is known as polymorphonuclear (PMN) neutrophils.[7] PMN neutrophils play important roles in the innate and acquired immune systems. They accumulate in the inflammatory area and contribute to host endurance, regulation of the inflammatory process, and tissue injury. One important component of PMN neutrophils is myeloperoxidase (MPO).[8]

MPO is a member of a subfamily of peroxidases; it is mostly expressed in immune cells such as PMN cells, lymphocytes, monocytes, and other macrophages and cells. It is stored in the cytoplasmic membrane and binds to azurophilic granules. The mechanism of neutrophil degranulation is thought to be related to oxidative stress. MPO is involved in the production of reactive oxygen species (ROS) and other free radicals via a peroxidase or halogenation cycle. MPO is a strong oxidant, and if its levels are low and controlled, it is toxic to microorganisms and plays an important role in the immune system. However, if presents in excess and uncontrolled, MPO can cause host cell damage.[9]

Current evidence suggests that galectin plays an important role in acute and chronic inflammatory responses, as well as other diverse pathological processes.[10] Galectin-3 (Gal-3) is expressed by almost all types of immune cells and inflammation, through constitutive and induction processes. It is a lectin that binds to β-galactoside and plays a major role in the development of cardiac fibrosis in conditions of excessive pressure (pressure overload), neuro-endocrine activation, and hypertension.

However, its role in remodelling after AMI has not received enough attention.[11]

In this study, we aimed to determine the effect of oral NAC supplementation at the dose of 600 mg 3 times daily for 3 consecutive days on the immune system of AMI patients who also were treated with fibrinolytics.

METHODS

Our study was a randomized, single-blinded study involving pre- and post-treatment evaluations. The study was conducted at Dr. Moewardi General Hospital, Surakarta, from May to August 2018. This study has been approved by The Ethics Committee of Dr. Moewardi Hospital/Medical Faculty of Sebelas Maret University in Surakarta with a reference number 536/IV/HREC/2018 on May 16th, 2018.

Population and Samples

The study was conducted in 32 STEMI patients who received fibrinolytic therapy and underwent treatment at ICVCU Dr. Moewardi Surakarta, Central Java using consecutive sampling method. There were 17 patients in the N-acetylcysteine (NAC) group and 15 patients in the control group.

Study Variables

The independent variable in this study was NAC and the dependent variables were levels of high-sensitivity C-reactive protein (HsCRP), MPO, and Gal-3. The patients received effervescent NAC tablets (600 mg; Fuimucil®, Zambon Switzerland Ltd) thrice a day for 3 days.

The inclusion criteria for this study were STEMI patients with symptoms who arrived at the hospital within 12 h and received fibrinolytic drugs, patients aged 18-75 years, and patients who had no absolute contraindications for fibrinolytic drugs. The exclusion criteria were patients with a history of acute coronary syndrome (ACS) or chronic heart failure, valvular heart disease, chronic renal failure, liver cirrhosis, chronic inflammatory disease or malignancy, an acute infection or sepsis, and stroke.

Study Instrumentation

Intravenous blood (volume: 4 mL) was collected before and at 72 h after NAC administration. Levels of HsCRP, MPO, and Gal-3 were determined using ELISA by PRODIA Laboratory.

Data Analysis

Data was presented in the form of mean and standard deviation. SPSS version 22.0 for windows was used for data analysis and the significant level was set at $p < 0.05$. To determine the mean difference before and after treatment in each groups, dependent sample t-test was used if data distribution was normal and wilcoxon was used if data distribution was not. Mean difference between the two groups and mean difference between changes (delta) before and after treatment in the treatment and control groups, the independent samples t-test was performed if the data distribution was normal and Mann-Whitney test was performed if the data distribution was not normal.

RESULTS

The basic characteristics of the patients are presented in **Table 1**. Intergroup differences were not significant between the NAC and control groups.

At admission, the levels of HsCRP, MPO, and Gal-3 in the NAC and control groups were not significantly different; however, intergroup differences in the levels were significant after 72 h of NAC administration (p values: 0.0001, 0.001, and 0.017, respectively) (**Table 2**).

In the NAC group, the levels of HsCRP, MPO, and Gal-3 at 72 h after NAC treatment were significantly different from the corresponding pre-treatment levels (P values: 0.0001, 0.0001, and 0.0001, respectively). Such differences were not found in the control group (**Table 3**). In addition, there were significant intergroup differences regarding the changes in HsCRP, MPO, and Gal-3 levels (P values: 0.011, 0.022, and 0.014, respectively) (**Table 4**).

DISCUSSION

This study was an experimental study with pre- and post-treatment evaluations that aimed to determine the effect of NAC 600 mg supplementary therapy administered orally 3

Table 1. Basic characteristics

Variables	NAC group (n = 17)	Control group (n = 15)
Demographic Characteristic		
Sex, n (%)		
- Male	16 (94.1)	12 (80.0)
- Female	1 (5.9)	3 (20.0)
Age (years), mean (SD)	55.24 (10.19)	58.27 (8.07)
Risk Factors, n (%)		
- Hypertension	12 (70.6)	10 (66.7)
- Smoking	13 (76.5)	9 (60.0)
- Diabetes mellitus	5 (29.4)	1 (6.7)
Clinical Condition, mean (SD)		
- Onset (h)	4.82 (2.63)	4.80 (2.65)
- Systolic blood pressure (mmHg)	136.71 (24.39)	132.20 (28.39)
- Diastolic blood pressure (mmHg)	84.47 (17.57)	81.00 (18.68)
- Heart rate (times/ min)	75.33 (19.09)	78.00 (11.93)
- Killip I class n, (%)	13 (76.5)	10 (66.7)
- Killip II-IV class n, (%)	4 (23.5)	5 (33.3)
- Anterior STEMI n, (%)	11 (64.7)	8 (53.3)
- Non-anterior STEMI n, (%)	6 (35.3)	7 (46.7)
Laboratory Parameters, mean (SD)		
Haemoglobin (gr/dL)	13.75 (1.80)	13.59 (1.81)
eGFR (mL/min/1.73 m)	64.40 (26.09)	72.13 (29.97)
LDL (mg/dL)	125.59 (33.41)	137.80 (83.90)
Triglycerides (mg/dL)	193.88 (149.46)	113.47 (46.69)
Therapy		
Fibrinolytic therapy, n (%)		
- Success	2 (11.8)	4 (26.7)
- Failure	15 (88.2)	11 (73.3)
ACE-I/ARB n, (%)	15(88.2)	14(93.3)
Beta blocker n, (%)	12(70.6)	14(93.3)

times a day for 3 days on HsCRP, MPO, and Gal-3 levels in STEMI patients who received fibrinolytic therapy.

Effect of N-Acetylcysteine on HsCRP

Inflammation associated with CHD and AMI triggers the formation of atheroma plaques in the coronary arteries. One parameter to assess the degree of inflammation in AMI is the measurement of CRP, an acute-phase protein produced mainly by hepatocytes under the influence of proinflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor-alpha (TNF -α).[4] Several studies have shown that serum CRP levels can predict the risk of recurrent acute cardiovascular events in hospitals[5] or 30-day or long-term mortality in STEMI patients.[6]

In our study, HsCRP levels, as a marker of inflammation, were affected by oral NAC supplementation. Our finding is consistent with the theory that NAC has anti-inflammatory properties. Induction of the proinflammatory transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) is inhibited by

Table 2. Changes of biomarker levels in both groups

Parameters	NAC group	Control	P value
HsCRP, median (range)			
Admission	76.80 (10.80-270.60)	114.50 (18.10-300.00)	0.089
72 h	14.90 (3.60-266.80)	151.50 (42.50-285.20)	0.0001
MPO, mean (SD)			
Admission	162.91 (79.42)	168.34 (79.42)	0.825
72 h	112.76 (57.28)	180.40 (69.03)	0.001
Gal-3, mean (SD)			
Admission	13.92 (4.49)	12.70 (3.94)	0.427
72 h	8.40 (2.55)	11.21 (3.70)	0.017

Data are presented as mean (standard deviation), except in the case of HsCRP, which is expressed as [median (min-max)]. HsCRP: high-sensitivity C-reactive protein; MPO: myeloperoxidase; Gal-3: galectin-3.

Table 3. Changes of biomarker levels in both groups

Parameters	NAC group		
	At Admission	At 72 h	P value
HsCRP	76.80 (10.80-270.60)	14.90 (3.60-266.80)	0.0001
MPO	162.92 (57.29)	112.76 (37.50)	0.0001
Gal-3	13.92 (4.49)	8.41 (2.55)	0.0001
Parameters	**Control group**		
	At Admission	At 72 h	P value
HsCRP	114.50 (18.60-300.00)	151.50 (42.50-285.20)	0.910
MPO	168.35 (79.42)	180.41 (69.04)	0.674
Gal-3	12.71 (3.95)	11.22 (3.71)	0.310

Data are presented as mean (standard deviation), except in the case of HsCRP, which is expressed as [median (min-max)]. HsCRP: high-sensitivity C-reactive protein; MPO: myeloperoxidase; Gal-3: galectin-3.

Table 4. Comparison of changes in biomarker levels of both groups

Parameters	NAC group	Control group	P value
HsCRP	-25.10 [(-108)-(-1.80)]	-5.50 [(-77)-253]	0.011
MPO	-50.15 (46.62)	12.06 (108.65)	0.022
Gal-3	-5.51 (3.06)	-1.49 (5.49)	0.014

Data are presented as mean (standard deviation), except in the case of HsCRP, which is expressed as [median (min-max)]. HsCRP: high-sensitivity C-reactive protein; MPO: myeloperoxidase; Gal-3: galectin-3.

NAC. These transcription factors are induced in response to oxidative stress, thus supporting the argument that the anti-inflammatory properties of NAC are due to its mechanism of action as an antioxidant.[12] Various studies have also shown that NAC supplementation can inhibit various inflammatory markers such as TNF-α, IL-6, IL-3, HsCRP, and C3, and soluble intercellular adhesion molecule (sICAM). It has been proven that NAC can also reduce ischemia of reperfusion, arrhythmia injury, and expansion of infarction. Fibrinolytic agents used in AMI patients can cause reperfusion injury with marked myocardial manifestations, arrhythmias, myocardial damage, and expansion of infarct size. NAC in combination with streptokinase significantly reduces oxidative stress and improves ventricular function in patients with myocardial infarction.[13]

Effect of N-Acetylcysteine on Myeloperoxidase

Oxidative stress and inflammation play an important role in the pathogenesis of CHD, which can cause AMI. In AMI with elevation of ST segment (AMI EST), neutrophil breakdown (degradation) occurs after neutrophil activation. Neutrophils contain granules that have mediators that play a role in delivering inflammatory signals. The granules consist of vesicles, azurophilic granules, and specific granules.[7,14]

Azurophilic granules consist of MPO, which is the largest protein in neutrophils. MPO is a strong oxidant, forming reactive oxidants and other free radicals through the peroxidase cycle or through a halogenization cycle depending on the availability of the substrate. In the peroxidase cycle, MPO activation occurs through the interaction of MPO with H_2O_2 to form H_2O.[7,9] NADPH oxidase is the main enzyme in neutrophils involved in the formation of ROS. The enzyme catalyses the reaction; therefore, the reaction is called respiratory burst or oxidative burst.[14] Activation of MPO through halogenation involves halid (Cl-) and pseudohalid substrates such as thiocyanate/SCN-. This reaction causes the formation of hypochloric acid (HOCl-) and hypotonic acid (HOSCN-). The formation of reactive oxidants and other free radicals through the peroxidase cycle or through the halogenization cycle depends on the availability of the substrate.[9]

Based on the effect of MPO on the inflammatory response and oxidative stress, MPO inhibition strategies become therapeutic target. One agent that can inhibit MPO activity is NAC. This study shows MPO levels can be affected by oral NAC supplementation. NAC is a novel tripeptide that works as an antioxidant agent in various inflammatory pathways. It works optimally on hydroxyl radicals, hypochloric acid, and hydrogen peroxide. NAC inhibits the respiratory burst reaction in MPO activation, and can also reduce the formation of hypochlorous acid (HOCl) in MPO activation. It plays a role in stimulating antioxidant enzymes that reduce MPO activation.[15]

The results of our study are the same as those of the NACIAM trial conducted by Pasupathy et al.[16] in 2017, which studied a high-dose intravenous NAC supplementation combined with a low-dose intravenous nitroglycerin therapy. In the NACIAM trial, the levels of MPO, malondialdehyde (MDA), and syndecan-1 were determined. The study showed that MPO was significantly correlated to the amount of myocardium that can be saved by administering NAC and nitroglycerin therapy. Furthermore, MPO and other oxidative enzymes can be targeted in the pathogenesis of cardiovascular and inflammatory diseases. In our study, we analysed MPO levels after NAC supplementation in the treatment and control groups. There were

increased MPO levels in the treatment group. MPO levels in NAC-treated patients tend to decrease.

Effect of N-Acetylcysteine on Galectin-3

Gal-3 is secreted by activated macrophages and modulates several physiological and pathological processes, including inflammation and fibrosis. It directly induces fibroblasts to proliferate and deposit type I collagen in the extracellular matrix.[17,18] Remodelling after myocardial infarction is due to an acute loss of the myocardium, which causes structural and biomechanical changes in an effort to maintain cardiac function. Fibrosis is important in this process, including in the initial phase and after AMI.[18]

In a study by Van der Velde et al.[19] in which 247 STEMI patients underwent primary percutaneous coronary intervention (PCI), Gal-3, as a fibrosis biomarker after AMI, could be used to predict left ventricular ejection fraction and infarct area after 4 months. Since Gal-3 has an important role in the pathophysiology of adverse cardiac remodelling and could be an independent predictor of heart failure after AMI, it can be hypothesized that a therapy that can inhibit Gal-3 may affect the development of heart failure in patients with AMI.[19]

Transforming growth factor-β is an important mediator in the remodelling process.[20] Differentiation and activation of fibroblasts into myofibroblasts by inflammatory cytokines, such as TGF-β, starting with the entry of cells including macrophages, is the first step in the process of fibrogenesis. Gal-3 plays a role in this process when macrophages and TGF-β induce activation of myofibroblasts; however, recruitment of macrophages and expression of TGF-β do not depend on Gal-3.[11]

Our study findings indicate that oral NAC supplementation can affect Gal-3 levels. Results of our study are consistent with those of a study conducted by Talasaz et al.[21] evaluating the effect of NAC on cardiac remodelling based on matrix metallopeptidase (MMP)-9 and MMP-2 levels in 98 AMI patients. In the group of patients who received additional oral NAC therapy, MMP-9 and MMP-2 levels were significantly lower than the levels in the placebo group (P = 0.014 and P = 0.045, respectively). Talasaz et al.[21] aimed to determine the effects of NAC on pro-fibrotic cytokines, TGF-β and TNF-α in AMI patients. They concluded that NAC supplementation can prevent an increase in TGF-β levels compared to that in patients who were not treated with NAC and that TGF-β is strongly associated with left ventricular ejection fraction, and therefore, its antagonism may be important in preventing remodelling.

The reduction in Gal-3 levels by NAC supplementation can be explained by an indirect inhibitory mechanism through NAC's role as an antioxidant and anti-inflammatory agent. NAC, a direct antioxidant, is a ROS scavenger, but its main role as a therapeutic antioxidant agent is attributable to its role as a precursor of cysteine in the synthesis of glutathione. The role of NAC in inhibiting inflammation involves the inhibition of the induction of AP-1 and NF-κB proinflammatory transcription factors. These transcription factors are induced in response to oxidative stress.[22]

CONCLUSION

Oral NAC supplementation at the dose of 600 mg 3 times daily for 3 days can reduce levels of HsCRP, MPO, and Gal-3 in AMI patients receiving fibrinolytic therapy. The findings of this study will provide a therapeutic option for the successful management of patients with AMI.

CONFLICT OF INTERESTS

The authors report no conflicts of interest associated with this work.

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