Original article

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The effect of N-acetylcysteine on the myeloperoxidase and Tei index in patients with acute myocardial infarction

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Abstract

***Bacground*: Myeloperoxidase (MPO) is a strong oxidant and toxic to microorganisms with excess production causing tissue damage. We aimed to determine the effect of N-acetylcysteine (NAC) 600 mg orally 3 times a day for 3 consecutive days on MPO levels and left ventricle myocardial performance index (LVMPI/Tei index) in ST elevation myocardial infarction (STEMI) patients treated with fibrinolytics.**

***Methods*: Pre- and post-design, single blind experimental randomized trial, conducted on 32 patients with STEMI at Intensive Cardiovascular Care Unit (ICVCU). The subjects were divided into 2 groups: 17 patients received 600 mg t.i.d NAC for 72 hours and 15 controls. MPO levels before and after 72 hours and Tei index 72 hours after NAC therapy were measured. Statistical analysis of MPO level and Tei index were analyzed with SPSS 22. Tei index was measured using the pulsed wave Doppler (PWD) and tissue Doppler imaging (TDI).**

***Results*: NAC administration showed decrease in the marker of MPO (112.76±57.28 vs 180.40±69.03, p=0.001) and delta MPO (-50.15±46.62 vs 12.06±108.65) 72 hours after NAC therapy compared with control. NAC improved the LVMPI value compared to the control group. Tei index examination using PWD (0.39±0.11 vs 0.49±0.08, p=0.005) and that using TDI (0.41±0.08 vs 0.57±0.08, p=0.001) showed improved values for NAC administration than those with controls.**

***Conclusion*: NAC 600 mg orally 3 times a day for 3 consecutive days can reduce MPO levels and improve diastolic function by decreasing LVMPI values.**

Key words: Coronary heart disease, STEMI, MPO, left ventricle myocardial performance index.

Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide causing approximately 12.8% of all deaths. (1) Acute myocardial infarction (AMI) is triggered by systemic inflammatory process in the atherosclerotic plaques and myocardium. Among the various types of immune cells that affect the process, neutrophils play an important role in the pathogenesis of acute coronary syndrome. Ruptured atherosclerotic plaques cause arterial occlusion and life-threatening acute coronary syndrome. (2,3)

Myeloperoxidase (MPO) is the largest protein component in azurophilic granulocytes, namely polymorphonuclear leukocytes (PMN). It plays a potential role worsen the atherosclerosis process and is widely found in neutrophils, monocytes, and several macrophage tissue subtypes. It is produced when leukocytes are activated, and it plays a role in the formation of foam cells, endothelial dysfunction and apoptosis, matrix metalloproteinase (MMP) activation, and the expression of tissue factors to produce vulnerable plaque. Detection of MPO activity is useful in risk stratification and both diagnosis and identification of plaque rupture. Myeloperoxidase and its inflammatory effects reflect prognostic targets and intervention therapy in atherosclerotic cardiovascular disease. (4,5)

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Morbidity and mortality of AMI are affected by systolic and diastolic dysfunction. Parameters that combine these two components are very important in this regard. Tei index is a Doppler index that assesses systolic and diastolic function. Combination Tei index is the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) divided by ejection time (ET), and it is not affected by left ventricular geometry and heart rate. The Tei index is independent of congestive heart failure during treatment in patients with AMI. (6)

The Tei index is a reliable Doppler parameter for the evaluation and prognostic assessment of patients with myocardial infarction. The Tei index was measured using the pulse wave doppler (PWD) and tissue doppler imaging (TDI). The interval is between discontinuation and re-onset of mitral filling flow includes IVCT, ET, and IVRT. The interval b, as same as ET, is between the onset and termination of aortic ejection flow. The normal average value of Tei index is 0.39±0.05 for the left ventricle. A high Tei index value is related to pathological conditions of systolic and diastolic dysfunction. In systolic dysfunction there are prolongation of the IVCT and IVRT, but ET will be shorter, whereas in diastolic dysfunction the IVRT was the main feature. (7,8)

In this study, we aimed to determine the effect of N-acetylcysteine (NAC) 600 mg orally 3 times a day for 3 consecutive days on MPO levels and left ventricle myocardial performance index (LVMPI/Tei index) in acute myocardial infarction patients treated with fibrinolytics.

Methods

This was an experimental pre and post intervention, single blind randomized controlled trial. It was conducted in the Intensive Cardiovascular Care Unit (ICVCU) of Dr. Moewardi Hospital, Surakarta, Indonesia. The subjects consisted of 32 patients with ST elevation myocardial infarction (STEMI) undergoing treatment with fibrinolytics from June to September 2018, who have provided an informed consent and were willing to participate in the study. The patients were randomly divided into two groups, the treatment group (n=17) that received the NAC, and the control group (n=15). The treatment group received NAC effervescent therapy orally 600 mg t.i.d for 3 consecutive days, and the control group received placebo. All participants provided informed consent, and the study design was approved by the appropriate ethics review board.

The STEMI patients aged 18-75 years, with onset of symptoms less than 12 hours and treated with fibrinolysis, and those with no absolute contraindications to fibrinolytics, were included in the study according to the clinical guidelines of The European Society of Cardiology (ESC) 2017. (1) The exclusion criteria were history of previous STEMI or chronic heart failure, valvular heart disease, chronic renal failure, liver cirrhosis, chronic inflammation or malignancy, acute infection or sepsis, and acute stroke.

Parameters

The primary parameter of this study was determination of MPO. All groups underwent blood sampling. To determine MPO levels, blood samples (4 ml venous blood) were taken before administration of NAC and fibrinolytics and 72 hours after NAC therapy. MPO measurements were based on the ELISA method conducted at the Prodia Jakarta laboratory. Delta MPO was MPO levels before and after 72 hours therapy, whereas Tei index was measured using PWD and TDI. Echocardiography examination were conducted in the Echocardiography Department of Dr. Moewardi Hospital Surakarta.

Statistical analysis

Data analysis were performed with SPSS 22. MPO levels (before and after NAC administration) and Tei index were analyzed with independent t-test.

Results

The baseline characteristics of this study were showed in **Table 1**. If the distribution of quantitative variable data is normal, the difference between the 2 means was analyzed using the independent t-test. But if the distribution of data was skewed, the data were analyzed using non-parametric statistical analysis, the Mann-Whitney U test. Data normality for the quantitative variables was analyzed using the Shapiro Wilk test.

The comparison of the mean and standard deviation of the MPO levels and the results of testing differences in the NAC group and control groups before and after NAC therapy are presented in **Table 2**.

The comparison results of variable MPO before and after the NAC administration in the NAC group show a significant difference ($p = 0.001$), whereas the test results variables of MPO before and after therapy in the control group (without NAC) were not significantly different with $p=0.674$. This means that in the treatment group, administration of standard therapy plus NAC can significantly reduce MPO variables. Delta MPO

was MPO levels before and after 72 hours therapy (**Table 3**).

The Tei index had a standard range of 0.29-0.49. The mean LVMPI-PWD variable in the control group was 0.49±0.08, while that in the NAC group 0.39±0.11. The LVMPI-PWD showed a significant decrease after administration of NAC when compared to that in the controls (p=0.005). Likewise, on the LVMPI-TDI examination showed a significant difference between the mean of the LVMPI-TDI control group (0.57±0.08) and the NAC group (0.41±0.08) with p value 0.001. It can be interpreted that NAC therapy can reduce the value of Tei index or LVMPI (**Table 4**).

Discussion

This study was an experimental study conducted pre- and post-intervention, which aimed to determine the effect of NAC 600 mg orally 3 times a day for 3 days as additional therapy on MPO levels in STEMI patients who received fibrinolytic therapy. MPO is an enzyme in leukocytes, especially in neutrophils that are bound to azurophilic granules. Neutrophils play a role in the inflammatory process in STEMI. On activation, the neutrophils integrate and release MPO. MPO in STEMI plays a role in the production of oxidative stress through the halogenation cycle and peroxidase. (9)

In this study, the mean age of subjects was 56-57 years, which is the most affected age by coronary heart disease, and men have a higher predilection. Risk factors for hypertension was the most common compared to diabetes mellitus, dyslipidemia, smoking, and family history. The most common location of the infarct was the anterior wall. This study showed significant differences in MPO levels between the control group and the treatment group after administration of NAC 600 mg orally 3 times a day for 3 days. Significant differences in MPO levels were also seen in the treatment group before and after treatment, whereas a significant difference were not found in the control group. In addition, there was a significant decrease in delta MPO between the control and treatment groups. We can conclude that the administration of NAC in this study reduced MPO activity in STEMI patients treated with fibrinolytic therapy.

In the N-acetylcysteine in Acute Myocardial Infarction (NACIAM) trial conducted by Pasupathy et al in March 2010 to March 2013 that examined 132 STEMI patients treated with high doses of intravenous NAC combined with low-dose intravenous nitroglycerin, there was a decrease in infarct size in STEMI patients undergoing PCI, measured by cardiac magnetic resonance (CMR) imaging within 7 days. Myeloperoxidase, malondialdehyde (MDA), and syndecan-1 levels were also measured, and MPO was significantly correlated with the amount of myocardium that could be salvaged by administration of NAC and nitroglycerin. Myeloperoxidase and other oxidative enzymes can be used as targets in the pathogenesis of cardiovascular and inflammatory diseases. In Pasupathy's study, an analysis of MPO levels after NAC administration in the treatment and control groups revealed that MPO levels tended to decrease in patients receiving NAC. (10)

Myeloperoxidase is a bactericidal enzyme that triggers reactive oxygen species (ROS) and results in destruction of pathogens. Currently, MPO also plays a role in the mechanism of cellular homeostasis and initiation and progression of various inflammatory diseases, especially cardiovascular diseases, and is expressed mostly in immune cells, such as PMN cells, lymphocytes, monocytes, and other macrophages, and body cells. Myeloperoxidase, a major protein component in PMN is stored in the cytoplasmic membrane and binds to the azurophilic granules. The mechanism of neutrophil degranulation is considered to be related to oxidative stress. (11) Increased levels of oxidative stress by ROS stimulates release of MPO through exocytic neutrophil degranulation. Neutrophil degranulation is triggered by an increase in the intracellular calcium and is excreted into the extracellular matrix as a monomer. Factors that influence MPO levels are age, sex, smoking, and use of contraceptive pills. (12)

Oxidative and inflammatory stress play an important role in the pathogenesis of destabilization of coronary heart disease, which can cause acute coronary syndrome. Infiltration of macrophages and neutrophils results in the transformation of stable coronary plaque into unstable lesions. The role of MPO is to catalyze the conversion of chloride and hydrogen peroxide to hypochlorite, which is secreted during inflammation. Involvement of MPO in the progression of atherosclerotic plaque is well known. Enzymatically, active MPO is present in the atherosclerotic lesions with high concentration. In the advanced phase, the atheromatous plaque shows presence of MPO in the larger macrophages in the intima area when compared to that in the initial phase. (5,13)

The Tei index can potentially describe hemodynamic abnormalities in AMI patients, and it increases in infarct conditions with congestive heart

failure (Killip II-IV). Hence, the Tei index has good diagnostic and prognostic values. Biomy, et al stated that the Tei index can predict the initial dilatation of the left ventricle and early myocardial cell death in AMI. Echocardiography was performed in the first 24 hours, 1.5 days, and 90 days after AMI. The Tei index value on the first day correlated with changes in the left ventricular end diastolic volume and continued observation up to 90 days after infarction. The conclusion is Tei index is a predictor of left ventricular dilatation and cardiac death after AMI. (14)

Yesilbursa, et al in 2006 studied the effect of NAC on ventricular function of STEMI patients and showed that there were no significant differences in the variables of IVRT, E/A diastolic function, and deceleration time (15). Unlike the findings of Talasaz study (2014), there was no significant difference in the diastolic dysfunction variable (p=0.203) between the control group and the group receiving NAC. It may be because the measurement of these variables was strongly influenced by the heart rate and left ventricular geometry. (16)

Conclusion

Administration of NAC 600 mg orally 3 times a day for 72 hours can reduce MPO levels and improve diastolic function by decreasing LVMPI values. The finding of this study will provide a therapeutic option for successful management of patients with IMA.

Disclosure

The author reports no conflict of interest in this work.

Table 1. Baseline characteristics

Variables	NAC group (n=17)	Control group (n=15)	p value
Demography			
- Sex (n, %)			0.228
Male	16 (94.1)	12 (80)	
Female	1 (5.9)	3 (20)	
- Age (years)	55.24±10.19	58.27±8.07	0.363
Risk factor (n, %)			
- Hipertension	12 (70.6)	10 (66.7)	0.811
- Smoking	13 (76.5)	9 (60.0)	0.316
- Diabetes mellitus	5 (29.4)	1 (6.7)	0.100
Clinical status			
- Onset (hour)	4.82±2.63	4.8±2.65	0.980
- Systolic BP (mmHg)	136.71±24.39	132.20±28.39	0.626
- Diastolic BP (mmHg)	84.47±17.57	81±18.86	0.592
- Heart rate (beat per minute)	75.33±19.09	78.00±11.93	0.669
- Killip class (n, %)			0.583
Killip I	13 (76.65)	10 (66.7)	
Killip II-IV	4 (23.5)	5 (33.3)	
- TIMI score	4.67±2.26	3.47±1.23	
- Infarct type (n, %)			0.421
Anterior STEMI	11 (64.7)	8 (53.3)	
Non-anterior STEMI	6 (35.3)	7 (46.7)	
Laboratory parameter			
- Hemoglobin (g/dl)	13.75±1.80	13.59±1.81	
- Leucocytes ($10^3/\mu l$)	11.69±3.56	10.90±3.59	0.556
- Neutrophils (%)	72.37±14.50	72.49±22.01	0.737
- Lymphocytes (%)	18.10±11.63	15.94±8.65	0.564
- eGFR (ml/min/1.73 m^2)	64.40±26.09	72.13±29.97	0.441
- RBG (mg/dl)	161.06±62.83	136.33±31.26	0.178
- Hs troponin I (ng/l)	206.80 (33.76-8940.80)	1667.40 (5.80-5327.80)	0.895*
- LDL (mg/dl)	125.59±33.41	137.80±83.09	0.737
- Triglyseride (mg/dl)	193.88±149.46	113.47±46.69	0.055
Therapy (succesful fibrinolytic) (n, %)			0.283
- Successful	2 (11.8)	4 (26.7)	
- Failed	15 (88.2)	11 (73.3)	

Legend: NAC=N-acetylcysteine; TIMI=Thrombolysis in Myocardial Infarction; STEMI=ST elevation myocardial infarction; eGFR=estimatad glomerular filtration rate; RBG=random blood glucose; LDL=low density lipoprotein cholesterol; *=data distribution was not normal; $p<0.05$=significant at 5%; $p<0.01$=significant at 1%.

Table 2. Comparison between NAC and control group before and after NAC therapy

Variable	Control group		NAC group		Independent t-test
	Mean	SD	Mean	SD	p value
Before	168.34	79.42	162.91	79.42	0.825
After	180.40	69.03	112.76	57.28	0.001

Legend: NAC=N-acetylcysteine; SD=standard deviation; p<0.05=significant at 5%; p<0.01=significant at 1%.

Table 3. Delta MPO in NAC group and control

Variable	Control group		NAC group		t-test
	Mean	SD	Mean	SD	p value
Change (delta)	12.06	108.65	-50.15	46.62	0.022

Legend: MPO=myeloperoxidase; NAC=N-acetylcysteine; SD=standard deviation; p<0.05=significant at 5%; p<0.01=significant at 1%.

Table 4. Comparison Tei index (LVMPI-PWD and LVMPI-TDI)

Variabel	Control group		NAC group		t-test	
	Mean	SD	Mean	SD	Statistic	p value
LVMPI-PWD	0.49	0.08	0.39	0.11	Z=-2.809	0.005
LVMPI-TDI	0.57	0.08	0.41	0.08	t=5.642	0.001

Legend: LVMPI=left ventricle myocardial performance index; PWD=pulse wave doppler; TDI=tissue doppler imaging; SD=standard deviation; p<0.05=significant at 5%; p<0.01=significant at 1%.

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