Crit Care Shock (2019) 22:299-306

Effects of N-acetylcysteine on high-sensitive C-reactive protein level and wall motion score index after ST-segment elevation myocardial infarction and fibrinolytic therapy: A randomized trial

Trisulo Wasyanto, Savithri Indriani, Ahmad Yasa

Abstract

***Objective*: To determine the effect of N-acetylcysteine (NAC) on the high-sensitive C-reactive protein (hsCRP) level and wall motion score index (WMSI) in patients with ST-segment elevation myocardial infarction (STEMI) treated with fibrinolytic therapy.**

***Methodology*: We performed a randomized pre-post study in consecutive patients who received fibrinolytic therapy for STEMI at Dr. Moewardi Hospital from July through August 2018. Patients were randomly allocated to receive NAC 600 mg 3 times daily for 3 days (treatment group) or no NAC (control group). Patients underwent pre- and post-treatment hsCRP measurement and echocardiographic examination with calculation of the WMSI. Pre- and post-therapy differences in clinical characteristics were analyzed within and between groups using independent sample t-, Mann-Whitney, paired t-, and Wilcoxon tests as appropriate.**

***Results*: Thirty-two patients were analyzed. The control and treatment groups included 15 (mean age 58.27±8.07 years) and 17 (mean age 55.24±10.19 years) patients, respectively. There were significant between-group differences in hsCRP levels (p=0.001) and WMSIs (p=0.005) after therapy. In the control group, the median post-therapy hsCRP and WMSI were 151.50 mg/l (range 42.50-285.20) and 1.3 (range 1.1-1.7), respectively, compared to 14.90 mg/l (range 3.60-266.80) and 1.2 (range 1.0-1.5), respectively, in the treatment group.**

***Conclusion*: Patients with STEMI who received NAC (600 mg 3 times daily for 3 days) in addition to fibrinolytic therapy had lower post-intervention hsCRP levels and WMSIs than patients who received fibrinolytic therapy alone. These findings will provide a therapeutic option for the successful management of patients with AMI.**

Key words: Myocardial infarction, C-reactive protein, N-acetylcysteine.

Introduction

Coronary heart disease (CHD) and acute myocardial infarction (AMI) are leading causes of death worldwide. (1-3) However, in Indonesia, deaths from cardiovascular disease have increased yearly, and cardiovascular disease is the most common cause of death. (4) Previously AMI was more common in developed countries, but currently, the incidence of AMI is increasing in developing countries, like in Indonesia. (4,5)

In CHD and AMI, inflammation triggers the formation of atheromatous plaques within the coronary arteries. The complex mechanism of atheroma development is thought to be initiated by inflammation that leads to endothelial dysfunction and subsequent plaque instability and rupture as well as an increase in coagulation cascade activity. (6,7) C-reactive protein (CRP), an acute phase protein produced mainly by hepatocytes under the influence of proinflammatory cytokines such as interleukin (IL) -6 and tumor necrosis factor-alpha (TNF-α), is an easily measured parameter for assessing the degree of inflammation in AMI. (8) CRP is a useful marker of vascular inflammation and predictor of cardiovascular events. (9) The

From Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Indonesia (Trisulo Wasyanto, Savithri Indriani, Ahmad Yasa).

Address for correspondence:
Trisulo Wasyanto, MD, PhD
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Indonesia
Jln. Kolonel Sutarto 132, Surakarta 57126, Indonesia
HP: +62811294225
Fax: +62271611593
Email: trisulo.wasyanto@gmail.com

high-sensitive CRP (hsCRP) examination was developed to detect CRP levels between 0.5-10.0 mg/l, and several studies have shown that serum hsCRP measurement can predict the risk of acute cardiovascular events in hospitalized patients (10) and 30-day and long-term mortality in ST-elevation acute myocardial infarction (STEMI). (11)

Studies in animals have shown that N-acetylcysteine (NAC) can improve survival and prevent inflammation, left ventricular remodeling and dysfunction, and interstitial fibrosis. The use of thrombolytic agents in patients with AMI can cause reperfusion injury with myocardial stunning, arrhythmias, and expansion of the infarct. NAC, in combination with streptokinase, can significantly reduce oxidative stress and improve ventricular function in patients with myocardial infarction. (12)

In patients with STEMI treated with fibrinolytic, NAC administration reduced the levels of matrix metalloproteinases (MMP) 9 and 2 which contribute to post-infarct cardiac remodeling and the incidence of major adverse cardiac events (MACE) in the first year of follow-up. (13) Further, in patients receiving primary percutaneous coronary intervention (PCI) for STEMI, NAC administration led to a significant reduction in infarct size. (14)

AMI can cause regional wall motion abnormalities, and the specific myocardial region affected is associated with the distribution of the coronary arteries. Regional wall abnormalities are most frequently assessed using the wall motion score index (WMSI). The WMSI is based on the 16-segment model recommended by the American Society of Echocardiography (ASE) and calculated as the sum of the scores of the visualized segments. (15) Large myocardial infarctions are associated with a high WMSI because the index reflects abnormal wall movements, i.e., the WMSI correlates with the area of myocardial asynergy. (16)

In this study, we aimed to determine the effect of NAC on the serum hsCRP and WMSI in patients with STEMI who received fibrinolytic therapy.

Methodology

We performed a randomized pre-post study in consecutive patients who received fibrinolytic therapy for STEMI at Dr. Moewardi Hospital (Surakarta, Indonesia) in the Intensive Cardiovascular Care Unit (ICVCU) from July through August 2018. This study was approved by the Ethical Review Committee from Universitas Sebelas Maret/Dr. Moewardi Hospital and informed consent was obtained from the patients or their legal representatives. The patients were randomly allocated to receive NAC (Fluimucil®, 600 mg effervescent tablets; Zambon Switzerland Ltd., Cadempino, Switzerland) every 8 hours for 3 days (treatment group) or no NAC (control group).

Eligible patients were those treated for their first episode of STEMI. We diagnosed STEMI according to the practice guidelines developed by the American College of Cardiology Foundation/American Heart Association Task Force. (17) We excluded patients with a previous myocardial infarction, chronic heart failure, renal failure, or inflammation, valve dysfunction, liver, thyroid, or autoimmune disease, malignancy, acute or chronic infection, sepsis, acute stroke, or a history of surgery in the past 3 months. Patients who received treatment with anti-inflammatory drugs, supplements, or antioxidants and those who died within 72 hours of treatment were also excluded.

We evaluated patient's hsCRP levels upon emergency department (ED) admission and 72 hours after admission. We recorded patient's age, sex, medical history, hemodynamic parameters at admission, and risk factors for cardiac events, drug history, and electrocardiogram (ECG) results. All patients were monitored and received daily evaluations while hospitalized. Echocardiographic evaluation was carried out in all patients during their hospitalization.

In the treatment group, NAC was administered before fibrinolytic therapy and continued for 72 hours. Fibrinolysis was performed in both groups using 1.5 million units of streptokinase diluted in 100 cc of sodium chloride delivered intravenously over 30-60 minutes. We assessed serum hsCRP 72 hours after fibrinolysis was performed using an enzyme immunoassay (Roche Diagnostics, Rotkreuz, Switzerland). We defined delta-hsCRP as the difference between the hsCRP level at admission and 72 hours after fibrinolysis.

Patients then underwent a two-dimensional echocardiographic examination (Vivid S6 ultrasound machine, GE Healthcare, Chicago, IL, US). Three longitudinal cross-sectional views (parasternal long axis, short axis, and 4-chamber) were obtained to assess the 16 segments described by the ASE. The contractility of each segment was scored as follows: normal, 1; hypokinetic, 2; akinetic, 3; dyskinetic, 4; and aneurysm, 5. The segment scores were summed to obtain the wall motion score, and the WMSI was calculated by dividing the wall motion score by 16.

Statistical analysis

We assessed patient age, sex, risk factors for hy-

pertension, smoking status, diabetes status, clinical conditions of onset, systolic and diastolic blood pressure, heart rate, Killip class, STEMI type, laboratory parameters (hemoglobin, estimated glomerular filtration rate [eGFR], low-density lipoprotein [LDL], triglycerides), ejection fraction (Simpson), fibrinolysis outcome, and medication administration (angiotensin-converting enzyme [ACE] inhibitor, β-blocker) for normality and then analyzed these variables in both groups. Pre- and post-therapy differences within the treatment and control groups were assessed using independent sample t- and Mann-Whitney tests for normally and non-normally distributed data, respectively. Between-group differences were analyzed using paired t- and Wilcoxon signed-rank tests for normally and non-normally distributed data, respectively. Data are presented as means±SD. All analyses were performed using SPSS 22.0 Statistics for Windows (IBM Corp., Armonk, NY, US). We considered a p value <0.05 statistically significant.

Results

We evaluated 35 patients for participation in the study. Three of these were excluded because they died within 72 hours of hospitalization. The remaining 32 patients were randomized into the control (n=15) and treatment (n=17) groups. There were no significant between-group differences in baseline characteristics (**Table 1**).

The treatment and control groups showed no significant difference in serum hsCRP level at the time of admission (p=0.089). However, after 72 hours of therapy, hsCRP levels were significantly lower in patients treated with NAC than they were in the control group (p=0.0001, **Table 2**).

Further, while the treatment group showed a significant decrease in hsCRP levels after 72 hours of therapy (p=0.0001), a similar difference in pre- and post-therapy hsCRP was not found in the control group (p=0.910, **Table 3**).

In addition, we found a significant difference in the delta hsCRP level between the control and treatment groups (p=0.011, **Table 4**).

The post-therapy WMSIs in the control and the treatment groups also differed significantly (p=0.011, **Table 5**).

Discussion

In this experimental pre-post study, we found that NAC 600 mg administered 3 times daily for 3 days reduced hsCRP levels and affected WMSIs in patients with STEMI who were treated with fibrinolytic therapy.

According to a theory, the initial hsCRP value reflects low-grade inflammation. However, Makrygiannis et al, 2013, found that the initial hsCRP value was an independent predictor of cardiac death and new non-fatal myocardial infarction in patients with STEMI treated with fibrinolytic. (11)

We also found that hsCRP decreased significantly in our treatment group 72 hours after fibrinolysis, while in the control group, hsCRP showed an insignificant increase during the same interval. In the control group, the peak hsCRP level occurred 72 hours after fibrinolysis. This is supported by several studies conducted by Makrygianiss et al. (11) We found that the delta-hsCRP after treatment was significantly larger decrease (about 25.10) in the treatment group than it was in the control group.

This is consistent with the theory that NAC has anti-inflammatory properties. (18) NAC inhibits induction of the pro-inflammatory transcription factors activator protein-1 and nuclear factor-κβ (NF-kβ). These transcription factors are induced in response to oxidative stress, which supports the argument that NAC acts as an anti-inflammatory through its antioxidant properties. (19,20) Various studies have also shown that administration of NAC can inhibit various markers of inflammation such as tumor necrosis factor alpha (TNF-α), interleukin (IL) -6, IL-3, hsCRP, complement 3 (C3), and soluble intercellular adhesion molecule (sICAM). Concurrent administration of NAC and reperfusion therapy in patients with myocardial infarction significantly reduced oxidative stress by decreasing plasma hydroperoxide concentration. (21)

NAC has been shown to affect oxygen derived from free radicals and oxidants and repair reperfusion injuries in animal models. Sochman et al studied the cardioprotective effect of NAC in dogs and concluded that NAC was effective in reducing infarct size and significantly reducing the incidence of reperfusion ventricular arrhythmias. (22) Studies conducted by Forman et al showed that administration of NAC before reperfusion could reduce myocardial stunning but does not reduce myocyte mortality after reperfusion. (23) Reduced infarct size and maintenance of left ventricular function have been reported in patients with STEMI after NAC infusion during fibrinolysis and primary percutaneous coronary intervention. (14) This is consistent with our finding that the WMSI was significantly lower in the treatment group than it was in the control group. Several clinical studies have also shown that intravenous infusion of NAC during thrombolysis is associated with a decrease in infarct size and improved left ventricular function. (22,24)

NAC is a potent antioxidant that can directly elim-

inate hydroxyl radicals. NAC acts on vascular cell adhesion molecule-1 and adhesives mediated by the endothelium, thereby mitigating the detrimental effects of oxidative stress. Moreover, NAC reduces oxidative damage in the target tissue, allowing sufficient oxygen consumption and increasing overall oxygenation. (13) Finally, through its action as an anti-inflammatory, NAC decreases hsCRP. The benefits of decreasing inflammation through the use of NAC, including reduced ischemia-reperfusion injury, arrhythmia incidence, myocardial damage, and infarct expansion, were reflected by the lower WMSIs we found in our treatment group compared to the control group. (12,13) Additionally, decreased inflammation in patients with AMI can reduce the extent of adverse cardiac remodeling, thereby reducing the incidence of heart failure due to AMI. (25)

Conclusion

NAC 600 mg administered three times daily for 3 days reduced hsCRP levels in patients with STEMI treated with fibrinolytic. Further, patients receiving NAC had lower WMSIs than those who did not. These findings will provide a therapeutic option for the successful management of patients with AMI.

Disclosure

The authors report no conflicts of interest in this work.

Table 1. Baseline characteristics in patients treated for ST-elevation myocardial infarction

Variable	Treatment group (n=17)	Control group (n=15)	p value
Demographics			
- Sex			
Male, n (%)	16 (94.1)	12 (80.0)	0.228
Female, n (%)	1 (5.9)	3 (20.0)	
- Age	55.24±10.19	58.27±8.07	0.363
Risk factors			
- Hypertension, n (%)	12 (70.6)	10 (66.7)	0.811
- Smoking, n (%)	13 (76.5)	9 (60.0)	0.316
- Diabetes mellitus, n (%)	5 (29.4)	1 (6.7)	0.100
Clinical factors			
- Onset (hour)	4.82±2.63	4.80±2.65	0.980
- Systolic blood pressure (mmHg)	136.71±24.39	132.20±28.39	0.626
- Diastolic blood pressure (mmHg)	84.47±17.57	81.00±18.68	0.592
- Heart rate (beats per min)	75.33±19.09	78.00±11.93	0.669
- Killip class I, n (%)	13 (76.5)	10 (66.7)	0.538
- Killip class II-IV, n (%)	4 (23.5)	5 (33.3)	
- Anterior STEMI, n (%)	11 (64.7)	8 (53.3)	0.421
- Non-anterior STEMI, n (%)	6 (35.3)	7 (46.7)	
Laboratory results			
- Hemoglobin (g/dl)	13.75±1.80	13.59±1.81	0.796
- eGFR (ml/min/1.73 m^2)	64.40±26.09	72.13±29.97	0.441
- LDL (mg/dl)	125.59±33.41	137.80±83.90	0.737
- Triglycerides (mg/dl)	193.88±149.46	113.47±46.69	0.055
Therapy			
- Fibrinolysis			
Successful, n (%)	2 (11.8)	4 (26.7)	0.283
Unsuccessful, n (%)	15 (88.2)	11 (73.3)	
- ACE-I/ARB, n (%)	15 (88.2)	14 (93.3)	0.927
- β-blocker, n (%)	12 (70.6)	14 (93.3)	0.100

Legend: STEMI=ST-elevation myocardial infarction; eGFR=estimated glomerular filtration rate; LDL=low-density lipoprotein; ACE-I/ARB=angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

Table 2. Comparison of high-sensitive C-reactive protein levels in groups treated with and without N-acetylcysteine

	Treatment group	Control group	p value
Admission	76.80 (10.80-270.60)	114.50 (18.10-300.00)	0.089
72 hours	14.90 (3.60-266.80)	151.50 (42.50-285.20)	0.0001

Legend: Data are presented as median (minimum-maximum).

Table 3. Changes in high-sensitive C-reactive protein levels in groups treated with and without N-acetylcysteine

	Admission	72 hours	p value
Treatment group	76.80 (10.80-270.60)	14.90 (3.60-266.80)	0.0001
Control group	114.50 (18.10-300.00)	151.50 (42.50-285.20)	0.910

Legend: Data are presented as median (minimum-maximum).

Table 4. Comparison of delta high-sensitive C-reactive protein in the control group and patients treated with N-acetylcystein

Variable	Median (minimum-maximum)	Mean rank	p value
Control (n=15)	-5.50 [(-77)-253]	20.97	0.011
Treatment (n=17)	-25.10 [(-108)-(-1.80)]	12.56	

Legend: Delta hsCRP is the difference between hsCRP level at admission and 72 hours after fibrinolysis.

Table 5. Comparison of wall motion score index in the control group and patients treated with N-acetylcysteine

Variable	Median (minimum-maximum)	Mean rank	p value
Control (n=15)	1.3 (1.1-1.7)	20.03	0.005
Treatment (n=17)	1.2 (1.0-1.5)	13.38	

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