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# Effect of N-acetylcysteine on Malondyaldehyde Content After Iron Treatment in Chronic Kidney Disease Stage 5D Patients

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SUPRAPTI BUDI*3) YASUHIKO TOMINO*4)

*Objective* : This study was performed to evaluate and assess the influence of N-acetylcysteine (NAC) on malondialdehyde (MDA) levels as a biomarker of oxidative stress in chronic kidney disease (CKD) stage 5D (hemodialyzed) patients after parenteral iron therapy.

*Materials and Methods* : This was a randomized, open-label, parallel-group trial comparing oxidative stress induced by intravenous (IV) administration of 100mg of iron sucrose (control group) with an additional IV administration of 5g NAC. At hemodialysis (HD) sessions pre- and post-plasma MDA levels were measued. Eighteen patients were enrolled, including 9 as controls and 9 in the treatment group.

*Results* : In the control group, plasma MDA level increased from 3.71 $\mu$M to 13.89 $\mu$M ($p=0.008$), whereas in the treatment group, the level increased from 4.48 $\mu$M to 7.89 $\mu$M ($p=0.059$). The difference between the groups was also significantly different ($p=0.015$).

*Conclusions* : It appears that NAC has the ability to decrease MDA level as a biomarker of oxidative stress caused by iron treatment in CKD patients.

*Key words* : CKD stage 5D, oxidative stress, plasma MDA, NAC, iron sucrose

## Introduction

Kidney disease is a silent epidemic and a global health problem[1)2)]. In of chronic kidney disease (CKD) stage 5, the accumulation of uremic toxins causes changes in immune function and organs, and leads to many secondary complications. Complications include fluid and electrolyte abnormalities, metabolic acidosis, anemia, secondary hyperparathyroidism, renal osteodystrophy and cardiovascular disease (CVD)[3)]. Anemia is one of the many complications that arise early in the course of kidney diseases. It is one of the non-traditional risk factors of CVD in CKD patients, where the leading cause of death is CVD. The main cause of anemia in CKD patients is a decrease in the production of erythropoietin hormone by progenitor cells in the kidney, where 90% of production occurs[3)].

Pharmacological treatment of anemia in CKD patients is chronic therapy with erythropoietic stimulating agent. In spite of to the benefits of iron therapy, the use of iron in CKD patients poses a dilemma. Iron can lead to potential toxicity in the kidneys through increased oxidative stress[4)5)]. Oxidative stress may play an important role in the pathogenesis and progression of kidney diseases. Increased oxidative stress is characterized by increased levels of MDA in plasma. MDA is the single strongest predictor of CVD prevalence in pa-

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tients undergoing HD. Therefore, antioxidant therapy is needed to prevent oxidative stress caused by iron administration.

N-acetylcysteine (NAC) is a thiol. Thiols are mucolytic agents, and precursors of L-cysteine and glutathione. This drug is a source of sulfhydryl groups in cells and a scavenger of free radicals through interaction with reactive oxygen species (ROS), such as OH- and $H_2O_2$[6]. The administration of NAC is expected to reduce the level of disability and death from CVD in patients with CKD stage 5. Based on its pharmacological effects, NAC as an antioxidant is also expected to reduce oxidative stress as a result of IV iron in CKD patients, thus decreasing the occurrence of renal tubular damage, increased glomerular permeability, and inflammation of the kidneys[1]. The purpose of this study was to evaluate the effect of IV NAC on the MDA level in CKD staged 5D patients receiving iron sucrose during HD.

## Materials and Methods

### Research Design

This study was a simple, parallel, open-label randomized clinical trial to determine the antioxidant effects NAC 5 g IV on MDA oxidative stress after IV administration of 100 mg of a iron sucrose preparation in patients with chronic kidney disease (CKD) stage 5D who received erythropoietin and were undergoing HD. This study was reviewed by the Dr. Soetomo Hospital Ethics Committee and met their requirements.

### Subjects and Sample Size

This study involved two groups, a control group and a treatment group. Total sample size was 18 patients divided into nine patients in the control group and nine in the treatment group. Both groups received 100 mg of iron sucrose at 30 minutes after HD, while the treatment group received additional 5 g of NAC intravenously. NAC was given 1 hour before HD and 1 hour after HD. Blood sample for MDA before treatment was taken 1 hour before HD for both groups, or right before the administration of NAC in the treatment group. Blood sample for MDA after the treatment was taken 1 hour after HD for both groups, or immediately after NAC administration in the treatment group. Subjects had CKD stage 5 and were undergoing HD 2 times a week in the Unit of HD Dr. Soetomo Hospital, Surabaya, Indonesia, they met the inclusion criteria.

Inclusion criteria were as follows : CKD patients with a. estimated glomerular filtration rate < 15 m*l*/min on HD ; b. Hb < 11 g/dl ; c. stable clinical condition ; d. serum ferritin concentration < 200 ng/m*l* and transferrin saturation < 20% ; and e. who have given informed consent. Exclusion criteria were as follows : patients with a. uncontrolled hypertension (diastolic pressure > 110 mmHg or systolic > 180 mmHg during screening) ; b. patients with anemia with Hb < 8 g/d*l* requiring packed red cells resuscitation therapy ; c. congestive heart failure (new york heart association III-IV) ; d. history of malignancy, liver disease, or alcoholism ; e. iron therapy in the last 3 months ; f. serum albumin < 3 g/d*l* ; g. a history of urinary tract infections ; h. history of severe hyperparathyroidism indicated by parathyroid hormone > 10 times above normal value ; i. major surgery within the last 12 weeks ; j. a history of systemic hematologic disease (sickle cell anemia, myelodisplastic syndromes, hematologic malignancies, myeloma, or hemolityc anemia) ; k. treatment using steroids or other immunosuppressants ; or antioxidant drugs (folic acid, vitamin B6, B12 or other antioxidants) ; m. known or suspected contraindications or allergies to iron sucrose and or NAC. Dropout criteria were also as follows : a. patients did not undergo HD for at least 4 hours. b. uncontrolled blood pressure during drug delivery ; and c. withdrawal from the study. MDA levels in plasma were determined using a MDA-586 spectrophotometer.

This study used the MDA-586 method, a specific method for MDA measurement, because the wavelength of 586 does provide a significant color reaction for MDA 586, when other compunds such as 4-hydroxy-2-nonenal (HNE) are present. In addition to the MDA-586 method, the most widely used method for evaluating lipid peroxidation is an examination of thiobarbituric acid-reactive substance (TBARS). Thiobarbituric acid (TBA) reacts with MDA, producing a stable chromogen. The TBARS method is easy to use but not specific beacuse aldehydes other than MDA may react with TBA to produce compounds that can give the same absorbance with MDA[7,8].

Statistical Analysis

Before determination of the differences in MDA levels before and after treatment in both the control and treatment groups, we performed data normality tests of MDA levels in each group using the Kolmogorov Smirnov test. If data distribution was normal, the paired sample t test was performed as a comparative test. If data distribution was not normal, Wilcoxon test was used. An unpaired sample t test was used to determine the difference of the effect of NAC on MDA levels in treatment group compared with the control group, if data distribution was normal. If data distribution was not normal, the Mann-Whitney test was used.

## Results

In this analysis, MDA levels before and after treatment in the control group were compared using the Wilcoxon test because one data distribution was not normal. Wilcoxon test results showed that administration of IV iron sucrose increased plasma MDA levels significantly ($p = 0.008$) (Table-1, Figure-1).

In Table-1, which shows the mean levels of MDA before and after treatment, it is evident that the administration of IV iron sucrose increased MDA levels significantly ($p = 0.008$). In Figure-1, the levels of MDA after treatment in the control group (represented by red bars) are increasing, compared with MDA before treatment (represented by blue bars). Administration of iron sucrose has been shown to trigger an increase in oxidative stress that causes lipid peroxidation. In the treatment group, increased levels of MDA were not significant ($p = 0.059$), which means that administration of NAC in the treatment group reduced MDA levels. Increased mean MDA level in the treatment group receiving NAC were lower than those in the control group (Figure-1).

To determine differences in MDA levels before and after treatment in the treatment group, we used the paired sample t test since data distribution was normal. The results obtained by the paired sample t test revealed a p value of 0.059 indicating there was no significant difference between pre-MDA and post MDA-levels (Table-2). Figure-1 shows that the average increase of MDA in the treatment group were lower than those in the control group. Comparative test results between groups used the unpaired sample t test because data distribution in the control and treatment groups was normal (Table-3). The results of

Table-1 Levels of MDA before and after treatment in the control group

| Samples | Level<br>Mean ± SD (μM)<br>(range) | Statistical test |
|---|---|---|
| Before | 3.71 ± 4.84<br>(1.45-16.56) | Wilcoxon<br>p=0.008 |
| After | 13.89 ± 7.27<br>(2.89-26.08) | |

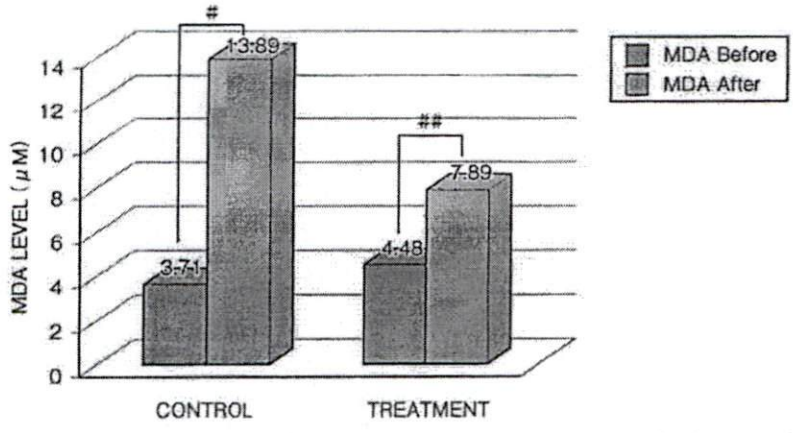


Figure-1 Comparison of MDA levels before and after treatment in the control and treatment groups

Description :
# : p = 0.008
## : p = 0.059

Table-2 Levels of MDA before and after treatment in the treatment group

| Samples | Level | Statistical test |
|---|---|---|
| | Mean ± SD (μM) (range) | |
| Before | 4.48 ± 4.51 (1.08-14.19) | Paired sample t test p = 0.059 |
| After | 7.89 ± 3.87 (1.72-14.38) | |

Table-3 Results of a comparison and statistical testing of the difference in mean MDA levels between control and treatment groups

| Groups | MDA difference | Significance (p < 0.05) |
|---|---|---|
| | Mean ± SD (range) | |
| Control group | 10.19 ± 5.81 (0.33-21.59) | 0.015 |
| Treatment group | 3.41 ± 4.67 (− 6.25-8.08) | |

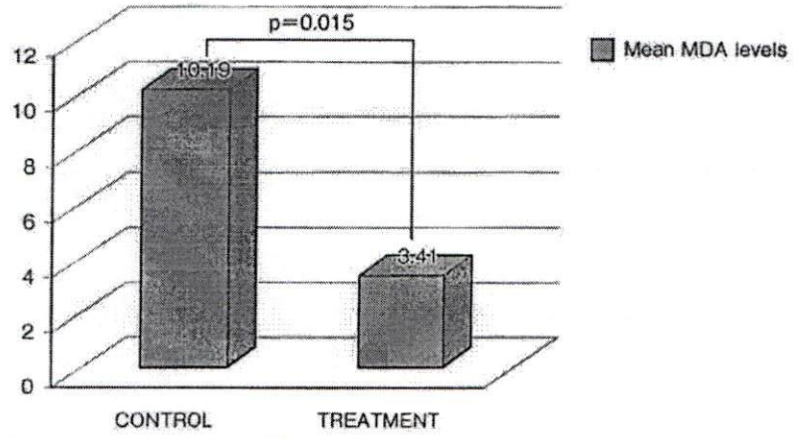


Figure-2 Comparison of differences in mean MDA levels between the control and treatment groups

the statistical analysis showed a p-value of 0.015, which means that there was a statistically significant difference in MDA levels between treated group and the control group. The difference in mean MDA levels in the treatment group was significantly less than that in the control group (Figure-2).

## Discussion

The increasing level of MDA in CKD patients after iron therapy has been reported by several studies[4)9)]. Iron sucrose significantly increase levels of MDA as a marker of oxidative stress. It reaches its peak within 30-60 minutes. In this study, the elevated levels of MDA in the control group were statistically significant. This is the first study to examine the effect of IV NAC on levels of MDA in CKD stage 5D patients receiving iron therapy.

Agarwal *et al.* suggested that levels of MDA increase rapidly when transferrin has not been completely saturated. This indicates that increased oxidative stress and renal damage can occur through the mechanism of free iron. Increased MDA levels are caused by lipid peroxidation due to acute oxidative stress due to iron. Iron plays a role in the progression of renal damage via the Haber-Weiss reaction and Fenton reaction. Strong oxidant radicals, i.e. hydroxyl radicals, are produced via both of these reactions. This can trigger a series of hazardous redox reactions. Hydroxyl radicals are capable of removing the hydrogen atoms of polyunsaturated fatty acid to initiate lipid peroxidation[10)~12)]. Therefore, the MDA oxidative stress marker increases significantly in the control group given iron sucrose.

In a comporative study, the difference in mean MDA levels between groups revealed significant differences between the treatment group receiving NAC and the control group (p = 0.015) (Table-3). Figure-2, shows a comparison of the difference in MDA levels, indicating elevated levels of MDA in the group receiving NAC but not in the control group. A variety of evidence suggests that HD

helps trigger oxidative stress, although some researchers claim that the effect of HD on oxidative stress is still controversial[13) 14)]. On the one hand, HD causes oxidative stress due to activation of inflammatory cells by the influence of a biocompatible membrane and loss of water-soluble anti-oxidants or due to the formation of free radicals[15) 16)]. On the other hand, there is reduced lipid damage and repair of proteins (cysteine, homocysteine, cysteinyl glycine, glutathione) by plasma amino thiols[17)]. A study has shown that total plasma levels of MDA increased significantly in patients with end stage kidney disease > HD > peritoneal dialysis than in the control group[13)]. Therefore, MDA levels may remain the same as a result of oxidative stress that persists in the treated group.

In this study, NAC proved significant in lowering the levels of MDA compared with control group. NAC is a precursor of L-cysteine and reduces glutathione. Glutathione (GSH) is one of the cell antioxidant defenses and is a key cellular defense against oxidative damage[6) 18)]. GSH is used by GSH peroxidases to reduce $H_2O_2$ and organic peroxides and form GSSG. It is known that superoxide and $H_2O_2$, which is formed by metabolism, generates ROS that can form organic peroxides. GSH peroxidases protect cell proteins and cell membranes against oxidation[19)].

NAC medication has direct and indirect antioxidant effects[18)]. Direct antioxidant effects of NAC inactivate hydroxyl radical (OH) due to free thiol groups that can interact with the electrophile group of ROS. Deactivation of the hydroxyl radical reaction is very rapid with a constant speed of 1.36 x $10^{10}$/M. second. These reactions produce NAC thiol radical intermediates that ultimately form NAC disulfide. NAC effect as an indirect antioxidant that induces synthesis of glutathione, because NAC is subject to metabolism *in vivo*[18)].

NAC medication undergoes rapid deacetylation by acyclase I enzymes in the intestine, and in the liver, it produces metabolites that are released into the systemic circulation. One of its main metabolites is L-cysteine, which is released in the circulation and used by cells to form glutathione. Glutathione cannot enter the cells directly and should be synthesized in situ from the precursor. The presence of the sulfhydryl group (-SH) on cysteine molecules strengthens to the glutathione antioxidant[18)].

Research evidence suggests that NAC can reduce levels of the oxidative stress marker MDA. Administration of NAC at 600mg 2x a day for 30 days reduced the MDA level significantly in CKD patients undergoing HD compared with that in the control group ($p<0.002$)[20)]. Agarwal *et al.* suggested that administration of NAC at 2 x 600mg 2x a day for a week reduced the plasma AUC MDA level significantly when compared with the control group. Similarly, administration of NAC at a dose of 2 x 600mg for 10 days reduces the formation of MDA, before and after administration of IV iron in HD patients[21)]. The evidence was strengthened by the results of this study, which showed that administration of 5g NAC i.v. significantly decreased MDA levels compared with the control group. These results indicated that the NAC is a source of sulfhydril groups, and glutathione inhibits oxidative stress after IV administration of iron in patients undergoing HD (CKD 5D) and therefore reduces the risk of CVD disease complications.

NAC is safe and well-tolerated. Administration of high doses of NAC (> 3g/day) cause adverse reactions including flushing, hives, bronchospasm, hypotension, and angioedema[22)]. During this study, no adverse reactions occured as a result of 5g i.v. of NAC and 100mg i.v. of iron sucrose[13)].

## Conclusion

The study revealed that NAC administration before and after HD could lower the increasement of MDA as oxidative stress marker caused by iron sucrose treatment.

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