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The effect of N-acetylcysteine on inflammatory and oxidative markers in patients receiving hemodialysis; a single-arm clinical trial study

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ABSTRACT

Introduction: Oxidative stress is common in patients with chronic kidney disease, especially those that need hemodialysis. Due to the increased chance of oxidative stress and inflammation following dialysis, the risk of developing atherosclerosis and heart disease is higher in these patients. In the case of a chronic kidney disease and hemodialysis, highly sensitive C-reactive protein (hs-CRP) as a marker of inflammation and malondialdehyde (MDA) can be considered as an indicator for oxidative stress. N-acetyl cysteine (NAC) is a thiol antioxidant acting as a free radical scavenger. There are conflicting results regarding the effect of NAC on inflammation and oxidative stress.

Objectives: This study was designed to evaluate the effect of this drug on hs-CRP and MDA in patients undergoing hemodialysis.

Patients and Methods: This single-arm clinical trial study was performed on 26 patients receiving hemodialysis. The patients were treated with NAC 600 mg twice a day for two months. They were tested before the treatment and two months later. The data were analyzed using SPSS (version 22). Chi-square and paired T-tests were also employed for the statistical analysis of the data. Moreover, *P* value of <0.05 were considered statistically significant.

Results: In this study, 26, out of 32, participants completed the study and were included in the final analysis. The results showed that, compared to baseline, treatment with NAC significantly reduced albumin ($P=0.025$) and hs-CRP ($P=0.003$). Moreover, supplementation with NAC significantly increased hemoglobin ($P=0.005$), serum iron ($P=0.002$), transferrin saturation ($P<0.001$), and calcium ($P=0.026$). However, no significant difference was observed at the end of the study in white blood cells (WBC; $P=0.337$), platelets ($P=0.809$), ferritin ($P=0.797$), calcium-phosphorus product (Ca×P; $P=0.93$), triglycerides ($P=0.604$), total cholesterol ($P=0.411$), low-density lipoprotein (LDL; $P=0.145$), high-density lipoprotein (HDL; $P=1.00$), and malondialdehyde (MDA; $P=0.960$).

Conclusion: The present survey suggests that NAC may be an effective option in managing hemoglobin, serum iron, transferrin saturation, calcium, albumin, and hs-CRP in patients receiving hemodialysis. Further researches are needed to confirm the veracity of our findings.

Trial Registration: The trial protocol was approved in the Iranian registry of clinical trial (identifier: IRCT2016111529812N2; https://irct.behdasht.gov.ir/trial/23866, ethical code; 17/1/257428).

Implication for health policy/practice/research/medical education:
Considering the high level of inflammatory factors in end-stage renal disease (ESRD) patients who are undergoing hemodialysis and that the highest mortality rate is related to ischemic heart disease, inflammation and anemia both play a role in this mortality. In this work, taking 600 mg N-acetyl cysteine (NAC) twice daily for 8 weeks has significantly reduced inflammation and improved anemia. Hence, the administration of NAC is helpful in the treatment of resistant anemia, which is probably caused by inflammation.

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Clinical Trial

Introduction

Oxidative stress is very common in patients with chronic kidney disease, especially in those receiving hemodialysis. During hemodialysis, loss of antioxidants, interaction between blood components and the dialysis membrane, and presence of bacterial products that cross the dialysis membrane directly or indirectly stimulate the release of reactive species by neutrophils, thus leading to oxidative stress (1-5).

The patients undergoing hemodialysis are at higher risks of atherosclerosis and increased oxidative stress, which can be fatal. Malnutrition, inflammation, and atherosclerosis, known as the MIA syndrome in these patients create a vicious cycle in which malnutrition leads to atherosclerosis and vice versa (5-9). Highly sensitive C reactive protein (hs-CRP) is regarded as an inflammatory marker, and many studies have shown that it is associated with cardiovascular events (10). Malondialdehyde (MDA) is an active aldehyde produced by the oxidation of unsaturated fatty acids in the body, and it can be considered as an indicator of oxidative stress in patients receiving hemodialysis (11). N-acetyl cysteine (NAC) is a thiol antioxidant acting as a free radical scavenger. NAC, which exerts its antioxidant effect through increased glutathione levels, is utilized to treat acetaminophen toxicity, prophylaxis of contrast-induced nephropathy, and chronic obstructive pulmonary diseases (12). NAC therapy has also been used for patients receiving dialysis. However, the effects of NAC on the reduction of inflammatory factors and oxidative stress in patients undergoing hemodialysis are controversial (13-15).

Objectives

Therefore, the present study sought to evaluate the therapeutic effect of NAC intervention on patients undergoing hemodialysis.

Patients and Methods

Study design and participants

This interventional trial (single-arm clinical trial) was carried out on patients receiving hemodialysis in Shahid Sadoughi and Shahid Rahnemoon Hospitals affiliated to Shahid Sadoughi University of Medical Sciences, Yazd, Iran, from July 2016 to August 2016.

Inclusion and exclusion criteria

The inclusion criteria were; age >18 years, hemodialysis with arteriovenous vascular access, and receiving hemodialysis for more than three months (three sessions per week); no symptoms of active infection in the month before and during the study; no elevation of liver enzymes (AST and ALT); no blood transfusions during the study; no collagen vascular disease as the etiology of end-stage renal disease (ESRD); no use of corticosteroids or immunosuppressive drugs; no history of myocardial infarction or stroke in the last three months; and NAC tolerance or no allergy to NAC. The patients excluded from the study were those who underwent hemodialysis with a cuffed or uncuffed venous catheter. All the participating patients received a daily dose of folic acid 5 mg, atorvastatin 20 mg, and vitamin B groups.

Sampling

In our study, a confidence level of 95%, a power of 80%, a standard deviation of 6.1, a minimum difference of two units between the means before and after the intervention, and the minimum sample size of 20 participants were taken into account.

Blinding

This study was single-arm clinical trial study, therefore due to the lack of a control group, all participants were aware of NAC supplementation, and blinding was not possible.

Data collection

The patients were visited three times: at the beginning of the study, four weeks later, and at the end of the treatment. At the time of the visit, they were evaluated for regular medication, signs and symptoms of infection, hospitalization status, and possible side effects of the medication. The criterion for the correct use of the drug and the other information, including hospitalization status, symptoms of infection, blood transfusion, and drug side effects, were based on the patients' statements.

Intervention

After sufficient information about the study protocol was provided to the patients, informed consents were obtained from them. Finally, 32 patients were selected. They received 600 mg NAC tablets (Avicenna Laboratory Inc. Pharmaceutical Company, Isfahan, Iran), twice a day for two months.

Outcome

At first, blood samples were taken immediately prior to the initiation of hemodialysis sessions. The blood samples were divided and sent to two labs. One part was sent to the central laboratory for testing hemoglobin (Hb), white blood cells (WBC), platelet count, serum iron level, total iron binding capacity (TIBC), ferritin, total cholesterol, triglyceride, high-density lipoprotein (HDL), albumin, calcium, and phosphorus. The other part of the blood samples was encoded as baseline pre-dialysis determiners and then centrifuged in less than one hour by the researcher in another lab. The obtained serum samples were stored at -70 °C. The samples were thawed to measure highly sensitive CRP (hs-CRP) and MDA. Hs-CRP was measured by the enzyme-linked immunosorbent assay (ELISA) method using a monoband kit (Monobind Company, United States). MDA was measured using the thiobarbituric acid (TBARS) method. The total monthly

dosage of NAC was delivered to the patients to take home. During the follow-up visits, any probable adverse effect of NAC and any symptoms of infectious diseases during the previous month were asked about. Two months later, blood samples were again drawn immediately prior to the initiation of hemodialysis sessions, and sent to the Central Laboratory for testing the same blood factors as before, and the other blood samples were encoded and considered as post-dialysis determiners.

Statistical analysis

All the data were extracted from the patients' forms and analyzed using SPSS (version 22). Paired t-tests was conducted for the statistical analysis of the data. The values were expressed as mean± standard deviation (SD) or number (percentage). *P* values less than 0.05 were considered statistically significant.

Results

With respect to the inclusion and exclusion criteria, 32 individuals were selected out of 130 patients undergoing hemodialysis in Shahid Sadoughi and Shahid Rahnemoon Hospitals. During two months, six patients were excluded from the study (two patients had active infections, two had renal transplantation, and two suffered from nausea and vomiting) (Figure 1). One patient also complained of a bitter taste in the mouth and another complained of itching, which were resolved with continued treatment. General characteristics of study participants are demonstrated in Table 1. The etiology of the ESRD was diabetes mellitus in 10 patients (38.5%), and hypertension was the etiology of ESRD in 5 patients (19.2%). The ESRD etiology in various diseases is presented in Table 2.

Before the intervention, the patients' mean of Kt/V was 1.4±0.14. Two months following the intervention, this mean value was decreased to 1.38±0.16, indicating a non-significant difference ($P=0.66$). In the beginning of the study, the dosage of recombinant erythropoietin was 146.7± 0.66 (IU/kg/W), while, at the end of the research, it decreased to 136.8± 46 (IU/kg/W), indicating a non-significant difference ($P=0.312$).

Table 3 illustrates the laboratory data of the patients receiving hemodialysis in Shahid Sadoughi and Shahid Rahnemoon Hospitals before and after the NAC therapy.

Table 1. General characteristics of study participants

Variables	Value
Age, years	55.81±14.13
Gender	
Female	4 (15.4)
Male	22 (86.4)
Duration of hemodialysis, years	4.59±3.64

Table 2. Etiology of end-stage renal disease in patients receiving hemodialysis

Renal failure etiology	Values
Diabetes mellitus	10 (38.5)
Hypertension	5 (19.2)
Glomerulonephritis	3 (11.5)
ADPKD	2 (7.6)
BPH	2 (7.6)
Renal stone	1 (3.8)
Nephrectomy	1 (3.8)
Unknown	2 (7.6)

Values are reported as n (%).
Abbreviations: ADPKD, Autosomal dominant poly cystic kidney disease; BPH, Benign prostate hypertrophy.

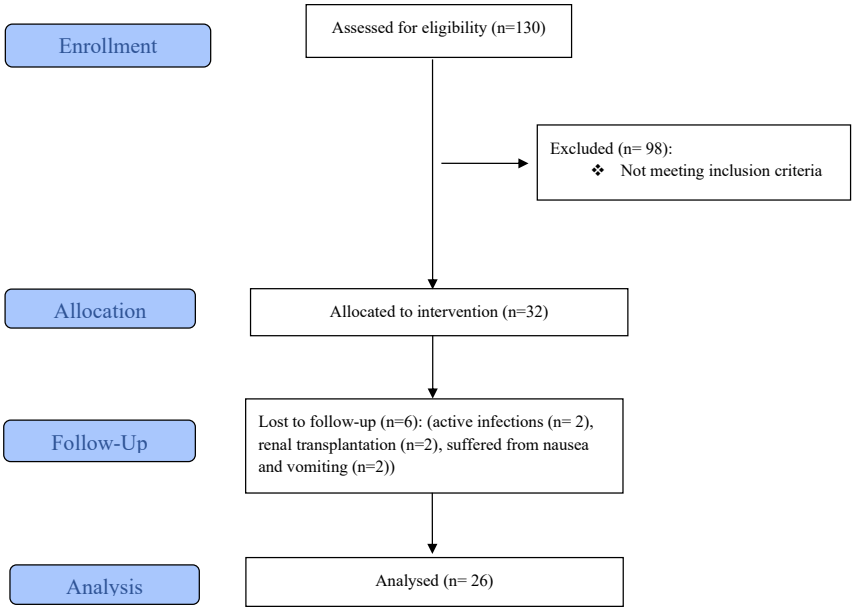

Figure 1. Summary of participant flow diagram.

Table 3. Laboratory data of the patients before and after undergoing NAC therapy

Variables	Before treatment	After treatment	Mean difference	*P* value*
WBC (/mm^3)	5534±1781	5803±1785	269±4	0.337
Hemoglobin (g/dL)	10.21±1.69	10.69±1.72	0.48±0.03	0.005
Platelet (/mm^3)	140040±52726	137366±50248	-2674±2478	0.809
Serum iron (µg/dL)	60.30±13.09	74.34 ± 17.15	14.04±4.06	0.002
Ferritin (µg/L)	374.35±364.54	356.47±256.20	-17.88±108.34	0.797
Transferrin saturation	23.56 ± 5.09	34.26 ± 11.16	10.7±6.07	<0.001
TIBC (%)	257.34± 33.28	266.65± 60.34	9.31± 27.06	0.013
Calcium (mg/dL)	8.71±.70	9.08±.77	0.37±0.07	0.026
Ca×P product (mg^2/dL^2)	44.30 ± 12.11	44.14 ±11.03	-0.16±1.08	0.930
Albumin (g/dL)	4.131±0.26	4.00±.20	-0.131±0.06	0.025
Triglyceride (mg/dL)	98.23±51.4	101.46±45.1	3.23±6.3	0.604
Cholesterol (mg/dL)	120.38±23.4	117.03±26.9	-3.35±3.5	0.411
LDL (mg/dL)	64.154±20.16	58.500±22.05	-5.654±1.89	0.145
HDL (mg/dL)	35.154±6.29	35.154±6.74	0.00±0.45	1.000
MDA (µmol/dL)	27.635±15.84	27.450±12.50	-0.185±3.34	0.960
hs-CRP (mg/l)	6.377±8.0460	3.723±5.9937	-2.654±2.0523	0.003

Values are reported as mean± SD. * *P* value was obtained by pair t-test (2-tailed).
Abbreviations: WBC, white blood cell; TIBC, Total iron binding capacity; LDL, Low density lipoprotein; HDL, high density lipoprotein; MDA, malondialdehyde; hs-CRP, high sensitive CRP; Ca×P product; calcium-phosphorus product

Discussion

The present study evaluated the effect of NAC supplementation on patients undergoing hemodialysis for eight weeks. The results demonstrated that NAC supplementation has a considerable effect on hemoglobin, serum iron, transferrin saturation, calcium, albumin, and hs-CRP levels. However, the findings of the present study do not suggest any effect of NAC supplementation on WBC, platelets, ferritin, Ca×P product, lipid profile and MDA concentrations.

In this study, the administration of NAC led to a notable decrease in hs-CRP levels, indicating a reduction in systemic inflammation. The findings suggest that NAC may have beneficial effects on inflammatory markers, which could have implications for its use in managing conditions associated with elevated hs-CRP. This reduction underscores the potential of NAC as a therapeutic agent in modulating inflammatory responses. This result is consistent with the findings of other studies (13,16). However, Larki et al observed no significant difference regarding CRP. Such conflicting results can be attributed to the older age of the patients in their study than in the present study. In that research, no significant change was observed in ferritin level, which is consistent with the present study (14).

In this study, after the use of NAC for two months, serum iron, TIBC, and transferrin saturation increased. The patients' ferritin level, however, underwent no significant change. The study showed a significant increase in the patients' hemoglobin. Although the improvement of anemia was statistically significant, it was probably not clinically significant. Indeed, the improvement of anemia may have been related to the reduction of inflammation. The lack of change in the patients' ferritin may also have been due to other factors involved in inflammation, such as dialysis itself and the dialysis filter, which are not completely controlled. Other changes, such as increased serum iron, increased TIBC, and increased transferrin saturation, can be justified regarding anemia improvement. Another noteworthy point is that the mean dose of erythropoietin was not statistically significant during the treatment. These results were consistent with some of the previous studies (17).

In some other studies, the administration of NAC had no significant effect on hematocrit (17,18). These conflicting results can be attributed to the shorter duration of those studies compared to that of the present study. In this study, no significant difference of MDA level was observed during the NAC administration. However, Najafian et al showed a significant difference in the MDA level. This difference could be due to the disparity of the two studies in terms of participants' gender, given that most of the patients in the present study were men, while there was no significant difference between the numbers of the men and women in the research by Najafian and colleagues (19). Other studies also revealed that the oxidative stress was higher in men than in women, which may be due to the role of estrogen on increasing the activation of glutathione metabolism as a powerful antioxidant in the body (20). In addition, there are a higher levels of estrogen receptors in the female body, which directly induces the expression of genes associated with the cellular response to oxidative stress, such as glutathione peroxidase (20). Like in the present study, Feldman et al, observed no

change in the two variables of nitric oxide and asymmetric dimethylarginine (ADMA) (21). Dashti-Khavidaki et al, detected no difference in the level of MDA, either (22). Moreover, aging was associated with oxidative stress such that oxidative stress increased with aging in a previous study (23). In the present study, the patients were younger than those in the study by Trimarchi et al (15). Although some studies showed no difference despite the old age of their participants (21), others like the present study revealed that the use of NAC at a younger age would make no significant difference in the MDA level (22).

In the present study, the levels of serum albumin and calcium before and after receiving NAC were significantly different such that albumin decreased. This finding contradicts other studies (13,14). In this study, serum calcium increased. This finding is consistent with the study by Larki et al (14), but not other studies (13,17,18). Considering the decrease in albumin observed in this study, the statistical significance was evident, but it does not seem to have a clinical value. Similarly, the increase in blood calcium, although statistically significant, was not considered clinically valuable.

The results of the present study revealed that NAC has not produced superior changes in improving WBC, platelet, Ca×P product, and lipid profile. In accordance with our results, Hatami et al found that WBC and platelet had not significantly reduced from baseline following six months of NAC supplementation in cirrhotic patients (24). While several studies have reported that NAC is effective in improving lipid profiles, this is not consistent with the findings of the present study (25,26). The cause of these findings is unclear; however, it could be attributed to the larger sample size, different populations, or a longer duration of intervention in these studies.

Another important point is the side effects induced by NAC administration. In the present study, two patients developed symptoms of nausea and vomiting, which led to their exclusion from the study. Two other patients, one with a bitter taste in the mouth and the other with complaints of itching, improved with continued administration of NAC. In general, in these patients, the most common complication was related to gastrointestinal problems, such as nausea, vomiting, bitter taste in the mouth, and itching. In many studies, no specific side effects were reported, which is probably due to the different pharmaceutical company of the drug employed or the underreporting of side effects in previous studies (16-19,21). One study reported mild itching (13). In another study, fatigue was common, followed by gastrointestinal complications, including nausea, vomiting, and itching. The pharmaceutical company of the drug used in the aforementioned study was the same as that in the present study (14).

Overall, the patients participating in this study had a lower mean hs-CRP than those in other studies, and the strict exclusion criteria applied to minimize confounding factors, resulted in only 32 out of 130 eligible individuals to enter the study. However, a sample size of 20 was sufficient. Improvement in hs-CRP and hemoglobin was reported after a two-month course of NAC, but no significant changes were observed in MDA. One of the strengths of this study was the simultaneous evaluation of various inflammation- related factors, which showed that, even in individuals who already had lower inflammation and better health status than in other studies, NAC could still induce significant changes in hs-CRP and anemia.

Conclusion

In this study, the use of NAC for two months caused a significant decrease in hs-CRP, but it did not change the MDA level. At the same time, it significantly increased serum iron, TIBC, and transferrin saturation. Giving at constant dose of erythropoietin also led to a statistically significant increase in the hemoglobin level, although this change was not clinically significant. In general, it seems that NAC administration can help improve the iron profile of dialysis patients through improving their inflammatory status. In this study, however, the changes in anemia were not clinically significant. Future studies with a longer duration are recommended to evaluate the probable positive effect of NAC on anemia.

Limitations of the study

The limitations of this study were the small number of the patients, the short duration of the study, and the lack of a control group.

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Authors' contribution

Conceptualization: Roya Hemayati, Rasoul Shajari, Javad Zavar Reza, Farzaneh Najafi.
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Investigation: Roya Hemayati, Rasoul Shajari, Javad Zavar Reza.
Methodology: Roya Hemayati, Rasoul Shajari, Farzaneh Najafi.
Project administration: Roya Hemayati.
Resources: Roya Hemayati, Rasoul Shajari, Javad Zavar Reza, Farzaneh Najafi.
Software: Rasoul Shajari.
Supervision: Roya Hemayati, Farzaneh Najafi.
Validation: Roya Hemayati, Javad Zavar Reza.
Visualization: Roya Hemayati, Rasoul Shajari.
Writing–original draft: Rasoul Shajari.
Writing–review & editing: Roya Hemayati, Rasoul Shajari.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Shahid Sadoughi University of Medical Sciences approved this study (Ethical code #17/1/257428). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of internal medicine residential thesis of Shahid Sadoughi and Rahnemoon hospitals at this university. The trial protocol was approved in the Iranian registry of clinical trial (identifier: IRCT2016111529812N2; https://irct.behdasht.gov.ir/trial/23866). Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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