Effect of N-Acetylcysteine on Inflammatory and Biochemical Markers of Hemodialysis Patients: A Randomized Controlled Trial

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Abstract- The oxidative stress results in atherosclerosis and cardiovascular diseases in patients receiving hemodialysis. *N*-acetylcysteine is a well-known antioxidant agent. There are little studies about the effect of *N*-acetylcysteine on patients receiving hemodialysis, and, if any, their results are inconsistent. This study, as a double-blind, randomized clinical trial, was conducted on 44 hemodialysis patients in Shahid Beheshti Hospital, Yasuj, Iran in 2015. Patients were randomly allocated into two groups, in the intervention group, N-acetylcysteine 600 mg every 12 hours for eight weeks was administered and the second group received placebo during this period every 12 hours. Blood samples were taken to measure C-reactive protein, interleukin-6 and other biochemical markers such as ferritin, albumin, and creatinine at baseline and at the end of treatment. 40 patients completed the study (21 on N-acetylcysteine, 19 on placebo), with a mean age of 60.72±17.60. There was not any significant difference between intervention and control groups in interleukin-6 (8.85±6.9 vs. 10.32±8.68, 95% CI, -3.52 to 6.46; *P*=0.55) and C - reactive protein (0.85±0.29 vs. 0.9±0.31, 95% CI, -.14 to .24; *P*=0.60). In addition, there was no significant relationship between the two groups in other biochemical markers. In this study, administering *N*-acetylcysteine was safe and caused a reduction in some inflammatory markers, but these changes were not significant in comparison with placebo.

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Introduction

The mortality rate in end-stage renal disease (ESRD) patients is significantly higher than the general population, due to cardiovascular diseases. In other words, cardiovascular diseases cause more than 50% of deaths in patients receiving dialysis (1). In ESRD patients, there are classic risk factors for cardiovascular diseases, such as high blood pressure, diabetes mellitus, smoking and hyperlipidemia. Furthermore, patients with chronic renal failure have some cardiovascular risk factors caused by uremia, including volume overload, anemia, calcium and phosphorus metabolism disorder, hyperhomocysteinemia, micro-inflammatory state, and oxidant stress (1,2).

N-acetylcysteine is a thiol-containing compound, which is used as an antioxidant. It seems that treatment with N-acetylcysteine may cause an increase in glutathione level. Glutathione is the most important antioxidant in the body. It has an extremely important role in neutralizing some toxic substances, including peroxide compounds and other free radical generating molecules (3,4,5). *N*-acetylcysteine is applied in the treatment of acetaminophen overdose, prevention of renal damage caused by radio-contrast agents in imaging procedures, and as a mucolytic (6,7,8).

Through decreasing the oxidative stress, *N*-acetylcysteine has led to improvement in the prognosis of deceased-donor kidney transplantation. The oxidative stress is caused by an imbalance between oxidants and antioxidants. Glutathione is the most common intracellular free thiol, reduction of which may lead to a reduction in cellular antioxidant capacity. *N*-acetylcysteine, which is the precursor of l-cysteine and reduced glutathione, acts as an antioxidant agent (9,10).

The oxidative stress results in atherosclerosis and

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cardiovascular diseases in patients receiving dialysis. *N*-acetylcysteine is a well-known antioxidant agent. Given the fact that *N*-acetylcysteine is a cheap and harmless agent, and that there are little studies about the effect of *N*-acetylcysteine on patients receiving dialysis, and, if any, their results are inconsistent, our purpose in this study was to show the effect of N-acetylcysteine on inflammatory and biochemical markers of hemodialysis patients, hoping that we would be able to take a step towards reducing cardiovascular diseases and mortality rate in these patients.

Materials and Methods

This study, as a double-blind clinical trial, was conducted on 44 patients who were on hemodialysis in Shahid Beheshti Hospital, Yasuj, Iran, in 2015. This study had been approved by ethics' committee of Yasuj University of Medical Sciences (ethics code YUMS.REC.1394.7). All patients have written an informed consent form before entering the trial. Assumed ethical consideration included confidentiality of information, no imposing any cost to patients, and allocating a code to each patient.

Inclusion criteria were as follows: (a) age more than 18-year-old, (b) receiving hemodialysis at least twice a week, for about three months, (c) negative history of taking medication influencing the inflammatory markers such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), in a recent month (d) absence of active infectious disease, malignancy, rheumatic diseases and other obvious inflammatory diseases. Exclusion criteria were as follows: (a) patient's displeasure to continue participation in the study, (b) taking the medicines influencing the inflammatory process during the study, (c) hypersensitivity to NAC (d) developing the active infectious disease, and malignancy during the study and need to kidney transplantation. First of all, the project and its purposes were explained to patients. After obtaining informed written consent, patients were randomly (with a ratio of 1:1) assigned into 2 groups. Random Permuted Blocks was used for randomization with blocks of the size of 4 that after every 4 patients there was an equal number assigned to each treatment. For each block, one of the arrangements (CCII, CICI, ICCI, IICC, ICIC, CIIC) was randomly chosen(C= Control, I= Intervention).

Both groups were interviewed, and the necessary medical history was taken, and physical examinations (such as measuring blood pressure, temperature, and weight) were performed. Demographic characteristics and all consumed drugs were recorded. Then, 5 mL blood samples were taken (when dialysis catheter was attached to the patient, blood sampling was done from the same route) in order to measure C-reactive protein (CRP) and interleukin-6 (IL-6). Blood samples were transferred to a laboratory to be tested using the same and fixed procedure and kit (IL-6 and CRP were tested using enzyme-linked immunosorbent assay (ELISA) method). In addition, ESR (erythrocyte sedimentation rate), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), cholesterol, triglyceride (TG) , serum iron, total iron binding capacity (TIBC), ferritin, hemoglobin, blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), bilirubin, and blood sugar (BS) were measured for patients before and after treatment.

Then, patients were treated double-blindly with *N*-acetylcysteine. Neither patients nor physicians that prescribed the drugs were informed of group assignment. Pill bottles were coded by blue and green color that only researcher knew the code and the code-breaking was readily available only for a researcher in case of a medical emergency. The intervention group was treated with a 600 mg dose of *N*-acetylcysteine every 12 hours for eight weeks. The dose of N-acetylcysteine was determined by previous studies (1,11). The control group was also treated with a placebo every 12 hours for the same duration (drug and placebo were products of Avicenna Laboratories Inc. pharmaceutical company, Iran). The placebo had the same form and the same pharmaceutical flavoring agent, but with the different active ingredient. In order to be sure that patients have taken their medication, they were asked to bring with them the empty drug shells in the next visit. At that time, in addition to a checkup, the patient's drug box was controlled for the presence of confounding medications, such as corticosteroids or NSAIDs. The patients were included were interviewed, monitored, and examined for detecting of drug side effects such as vomiting, nausea, dyspnea, anaphylactic reaction, flushing, urticaria, hypotension, chest tightness, and other reactions, based on the dialysis frequency of at least twice a week.

In this study, the Numerical Rating Scale (NRS) was used to measure and assess the complications, such as nausea, vomiting, pruritus, and fatigue. In this method, the patient was asked to express the severity of his/her complication based on a 10 centimeters ruler; on which 0 was equal to no complication, and 10 was equal to the most severe complications.

A sample size of 22 patients was calculated using

comparing two mean formulas. It was estimated to yield 80% power (type II or beta error of 0.20%) to detect a difference of 13.3 or more between two groups in IL6 (mean difference$_1$= -1.94=IL6 in NAC group, mean difference$_2$= 1.19= IL6 in placebo group, S_1=3= standard deviation of IL6 in NAC group, S_2=2= standard deviation of IL6 in placebo group [12]), allowing 5% of type I error. With considering 50% attrition rate in each group, a total sample size of 44 was assumed.

Statistical analysis

Data analyses were performed using SPSS$_{21}$ (SPSS, Chicago, IL, USA) software. Continuous variables with normal distribution were presented as mean± standard deviation, and were compared by independent samples T-test and paired T-test. Nominal variables were taken as counts (or frequencies) and were compared by chi-square test. Mann-Whitney U was used for continuous variables without normal distribution. All statistical tests were based on two-tailed probability. P<0.05 was considered statistically significant (α= 0.05 and power 80%).

Results

The mean age of subjects was 60.72±17.60 years. Of 44 patients, 40 patients completed the study (21 on NAC, 19 on placebo). During the study, one patient from each group left the study because of displeasure. Also, two people from the control group left the study due to kidney transplantation. So, this study continued with 21 patients in the intervention group (12 women, 9 men) and 19 persons in the control group (7 women, 12 men) (Figure 1).

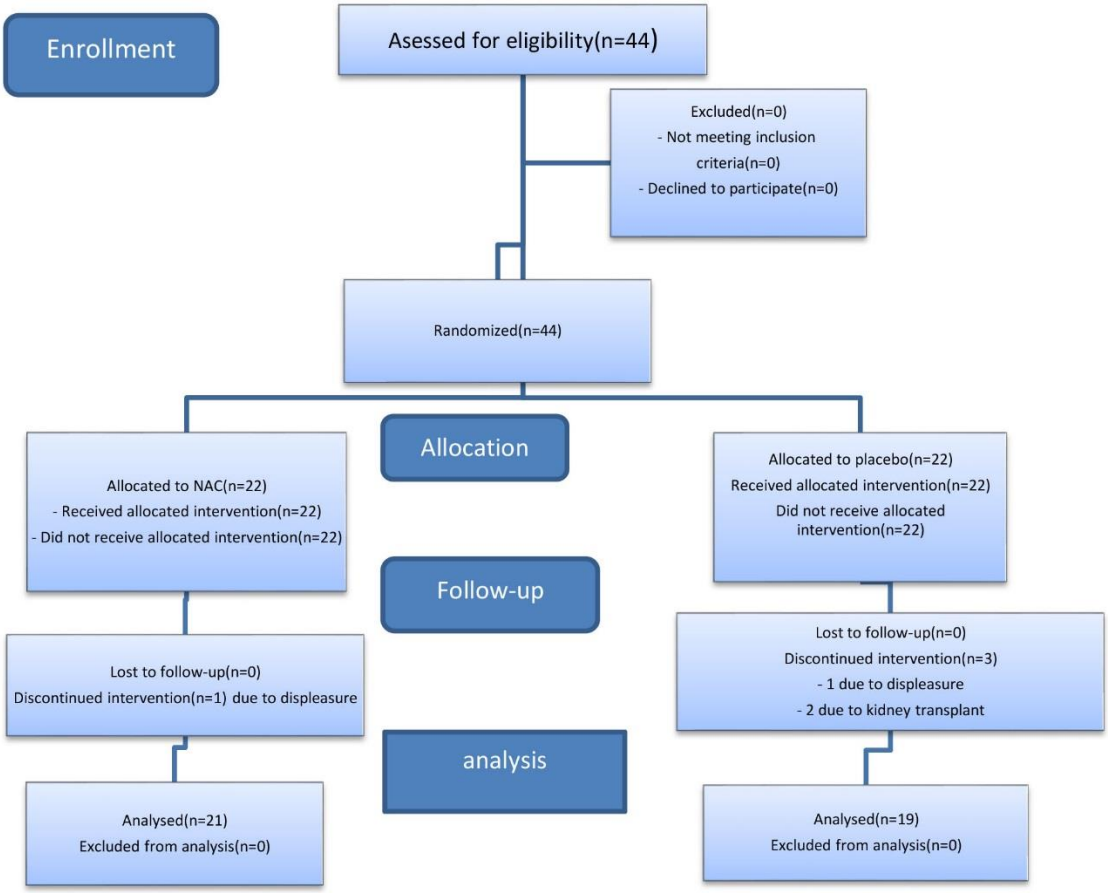

Figure 1. Schematic flow diagram of a randomized controlled trial to compare the effect of NAC and placebo in hemodialysis patients

The cause of renal failure was unknown in 5 patients (12.5%). Its causes were diabetes in 11 patients (27.5%), high blood pressure in 18 patients (45%), and polycystic disease of kidneys in 6 patients (15%).

Differences between the NAC and placebo groups were not statistically different for any variable (including drug history such as erythropoietin, atorvastatin, vitamins, and other drugs.). Demographic characteristics of participants are shown in table 1.

Table 1. Characteristics of the N-acetylcysteine and placebo groups

Variable		Total	Intervention		*P**
			NAC	Placebo	
Age (years) Mean±SD		60.72± 17.60	60.61± 16.61	61.05± 19.09	0.9
Gender	**Men**	21 (52.5%)	9 (42.8%)	12 (63.1%)	0.1
	Women	19 (47.5%)	12 (57.2%)	7 (36.9%)	
The cause of renal failure	**Unknown**	5 (12.5%)	1 (4.8%)	4 (21.1%)	0.1
	Other	35 (87.5%)	20 (95.2%)	15 (78.9%)	
Taking anti-hypertensive medicine	**Yes**	36 (90%)	20 (95.2%)	16 (84.2%)	0.3
	No	4 (10%)	1 (4.8%)	3 (15.8%)	
Duration of dialysis(years) Mean±SD		2.61 ± 2.42	2.56 ± 2.96	2.67 ± 1.73	0.8

* Independent-samples t-test was used for comparing the age and duration of dialysis, *Chi*-square test for comparing gender and Fisher Exact test for comparing the cause of renal failure and status of taking antihypertensive medicine. **SD: Standard Deviation

As shown in table 2, there was not any significant difference between intervention and control group in IL-6 (8.85±6.9 vs. 10.32±8.68, 95% CI, -3.52 to 6.46; *P*=0.55), CRP (0.85±0.29 vs. 0.9±0.31, 95% CI, -.14 to .24; *P*=0.60) and other biochemical markers (Table 2).

Table 2. Change in inflammatory and biochemical markers in hemodialysis patients before and after intervention in comparison with the placebo group

Variable	Before intervention (mean ± SD)		*P*	After intervention (mean ± SD)		*P*	P_{in} NAC	P_{in} placebo
	NAC	Placebo		NAC	Placebo			
IL-6(mcg/dl)	35.93 ± 16.02	37.16 ± 25.21	0.85	8.85 ± 6.9	10.32 ± 8.68	0.55	0.0001	0.0001
CRP(mcg/dl)	1.73 ± 0.96	2.26 ± 1.29	0.14	0.85 ± 0.29	0.9 ± 0.31	0.60	0.0001	0.0001
Albumin(gr/dl)	3.80 ± 0.35	3.76 ± 0.56	0.80	3.83 ± 0.44	3.77 ± 0.38	0.65	0.54	0.87
Ca(mg/dl)	9.38 ± 0.96	9.46 ± 1.70	0.84	10.12 ± 1.77	9.38 ± 1.43	0.15	0.01	0.85
P(mg/dl)	4.47 ± 1.36	5.03 ± 1.65	0.24	4.47 ± 0.65	4.61 ± 0.65	0.52	0.98	0.28
PTH(mcg/dl)	115.36 ± 70.53	143.42 ± 106.80	0.32	155.19 ± 128.61	165.73 ± 95.18	0.77	0.11	0.17
TG(mg/dl)	110.71 ± 73.17	101.94 ± 53.23	0.67	121.42 ± 86.27	198.26 ± 57.45	0.57	0.33	0.44
Cholesterol(mg/dl)	119.47 ± 25.10	126 ± 28.08	0.44	141.42 ± 43.67	145.78 ± 32.95	0.72	0.005	0.002
Ferritin(mcg/dl)	669 ± 433.08	823.68 ± 784.19	0.43	498.85 ± 343.97	616.10 ± 540.77	0.41	0.01	0.23
Serum iron(mcg/dl)	67.28 ± 25.77	83.15 ± 37.19	0.12	68.33 ± 31.35	78.63 ± 24.01	0.25	0.89	0.58
TIBC(mcg/dl)	181.28 ± 34.35	172.57 ± 32.38	0.41	175.28 ± 40.29	169.10 ± 52.40	0.67	0.22	0.61
hemoglobin(gr/dl)	11.07 ± 1.57	11.32 ± 1.80	0.63	11.36 ± 1.44	11.25 ± 2.03	0.84	0.30	0.86
BUN(mg/dl)	44.33 ± 13.72	47.42 ± 15.09	0.5	39.83 ± 18.76	50.31 ± 20.33	0.09	0.26	0.23
creatinine(mg/dl)	6.11 ± 2.44	7.98 ± 2.93	0.03	7.36 ± 0.365	7.45 ± 0.380	0.86	0.21	0.54
Na(mEq/L)	141.28 ± 4.34	139.68 ± 5.11	0.29	137.57 ± 4.06	136.31 ± 2.31	0.23	0.003	0.007
K (mEq/L)	5 ± 0.68	5.27 ± 1.01	0.32	4.72 ± 0.48	4.99 ± 0.73	0.17	0.08	0.11
BS(mg/dl)	86.47 ± 12.49	83.73 ± 7.62	0.41	94.23 ± 19.16	92.57 ± 17.52	0.77	0.02	0.03
ALT(Iu/L)	18.76 ± 9.62	15.63 ± 9.76	0.31	19.90 ± 13.14	12.26 ± 7.24	0.261	0.69	0.10
AST(Iu/L)	18.04 ± 8.13	17.42 ± 7.25	0.79	23.09 ± 13.53	17.21 ± 5.56	0.07	0.10	0.86
ALP (Iu/L)	269.85 ± 81.94	273.84 ± 100.44	0.89	324.14 ± 116.46	311.42 ± 145.17	0.76	0.01	0.02
Bilirubin T(mg/dl)	1.41 ± 0.48	1.27 ± 0.39	0.32	1.37 ± 0.39	1.44 ± 0.35	0.58	0.68	0.08
Bilirubin D(mg/dl)	0.29 ± 0.12	0.26 ± 0.11	0.43	0.29 ± 0.12	0.32 ± 0.11	0.41	0.91	0.002
ESR (mm/hr.)	12.76±5.79	14.45±6.32	0.38	20.85±13.64	20.57±15.88	0.95	0.03	0.06
PLT(1000×mm3)	177.19±54.65	149.89±60.70	0.14	158.33±53.42	141.68±51.63	0.32	0.12	0.55

*All variables followed the normal distribution. Independent Sample t-test was used for comparison. NAC: N-acetylcysteine, CI: confidence interval, SD: standard deviation, IL-6: Interleukin-6, CRP: C-reactive protein, Ca: calcium, P: phosphorus, PTH: parathyroid hormone, TG: triglyceride, TIBC: total iron binding capacity, BUN: blood urea nitrogen, Na: sodium, K: potassium, BS: blood sugar, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, ESR: Estimated Sedimentation Rate, PLT: Platelet, Cr: Creatinine.

Mean±SDs of systolic blood pressure before and after the intervention was 136.19±21.78 vs. 138.09±22.27 and diastolic blood pressure was 85.47±10.72 vs. 85.8±6.90 (*P*=0.32 and *P*=.35 respectively).

Side effects of NAC and placebo (based on NRS) are shown in Table 3.

Table 3. Comparison of the Side effects of NAC and placebo in hemodialysis patients

Side effects	NAC (Mean Rank)	Placebo (Mean Rank)	*P*
Nausea	22.14	18.68	0.36
Vomiting	21.76	19.11	0.48
Pruritus	20.69	20.29	0.91
Fatigue	24.29	16.32	0.03

- Mann-Whitney u was used for analyzes(variables didn't have a normal distribution)

Discussion

The previous studies have shown that the oxidative stress and inflammatory markers are increased in patients receiving dialysis, and these patients are at more risk of death than the general population, especially because of cardiovascular diseases (1). Given the antioxidant and anti-inflammatory properties of *N*-acetylcysteine, and the fact that it can decrease oxidative stress and pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNFα) and interleukin-1 (IL-1), and is a drug with low complications, (12) it is expected that this drug would be useful in patients receiving hemodialysis.

In our study, in the intervention group the level of IL-6, CRP, and ferritin (as a positive phase reactant) was decreased, but these changes were not significant in comparison with the placebo group. The level of albumin, as a negative phase reactant, had no significant change. Thus, given the fact that some inflammatory factors are decreased after administering *N*-acetylcysteine and some of them did not change and taking into account that these changes were not significant in comparison with the placebo group, it could be concluded that *N*-acetylcysteine is not effective in reducing inflammation in hemodialysis patients. In this study, also we had significant reductions in the levels of IL-6, CRP, and ferritin in patients who receive a placebo. These findings emphasized the fact that having control group and randomization is important in clinical trials.

In a study by Nascimento and others, on 22 patients receiving peritoneal dialysis, that support our result, administering *N*-acetylcysteine had no significant effect on CRP, TNFα, pentraxin 3, and oxidative stress markers (pentosidine, advanced oxidation protein products, homocysteine, glutathione, asymmetric dimethylarginine, and free sulfhydryl), but unlike our results, *N*-acetylcysteine caused a significant reduction in IL-6 level (11).

Sadadi and others, in their study on 24 hemodialysis patients concluded that administering *N*-acetylcysteine led to reductions in CRP and IL-6 levels, but that study was not of placebo-control type. Also in their study, the levels of calcium and PTH had decreased after receiving *N*-acetylcysteine (1). Our study showed that there was no significant difference between the levels of Ca, PTH, and the other biochemical markers, such as phosphorus, cholesterol, TG, serum iron, TIBC, hemoglobin, serum Na, serum K, AST, ALT, ALP, bilirubin, and BS, before and after intervention in both groups. In contrast to study by Sadadi and others, (1) in the present study we had a larger sample size (40 vs. 24), and also we had a placebo group for comparison.

In a study by Marcin Renke and others, that support our result, 20 non-diabetic patients with albuminuria (GFR= 61-163), were treated with a 1200 mg daily dose of *N*-acetylcysteine for eight weeks. The results showed that *N*-acetylcysteine had no influence on blood pressure, albuminuria, and plasma level of homocysteine (13). Our results indicated that there is no significant difference between systolic and diastolic blood pressures before and after intervention in both groups.

Helosia M. and others, in their study on rats, found that *N*-acetylcysteine had been effective in preventing from nephrosclerosis and reduction of kidneys functions in rats with chronic renal failure (14). In a study by Moist L. and others, on 30 patients with chronic kidney disease stages 3 and 4, after administering a single dose of *N*-acetylcysteine, the serum levels of creatinine and cystatin-c had not been decreased (15). In our study, also there was no any change in BUN and serum creatinine levels in *N*-acetylcysteine receiving subjects in comparison with the placebo group. In contrast, to study by Helosia M. and others, our trial was performed on ESRD patient who were on hemodialysis, and we did not expect significant changes in serum levels of BUN and creatinine because when hemodialysis was initiated the

kidneys are almost incapacitated and this may neutralize the useful and anti-inflammatory effects of *N*-acetylcysteine.

In previous studies, *N*-acetylcysteine had been mentioned as a drug without any complication (10,11,16). In this study, *N*-acetylcysteine also had no considerable complications, though we noticed increased fatigue in patients receiving this drug. Our study also has limitations such as small sample size and also we did not measure serum level of *N*-acetylcysteine in patients.

In future studies, it is far better to use larger sample size and administer *N*-acetylcysteine before ESRD stage and before initiating dialysis, because by initiating ESRD and dialysis, the kidneys are almost incapacitated and this may neutralize the useful and anti-inflammatory effects of *N*-acetylcysteine.

In summary, administering *N*-acetylcysteine in patients receiving hemodialysis has no considerable complications. Although its administration had caused a reduction in some inflammatory markers, these changes were not significant in comparison with placebo.

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