IJBPAS, May, 2015, 4(5), Special Issue: 412-419

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE EFFECT OF N-ACETYL CYSTEINE ON HEMATOCRIT IN CHRONIC HEMODIALYSIS PATIENTS

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ABSTRACT

N-acetyl cysteine (NAC) is an antioxidant glutathione precursor. N-acetyl cysteine has a sulfhydryl group that possesses strong antioxidant quality and improves blood flow to the coronary arteries and peripheral arteries. Therefore, oxidative stress is a risk factor aggregating atherosclerosis and anemia followed by cardiovascular events and mortality among patients. This issue has recently been focused on.

Seventy-eight non-hospitalized patients with age range of over 18 and below 100 that were under chronic hemodialysis entered the study. They were randomly divided into an experimental group and a control one. An amount of 600 mg NAC was orally given to 39 patients twice a day over 6 weeks. The other 39 patients were given placebo with the same dose and duration. The level of hematocrit (HCT) of the patients was measured before and after the study and before hemodialysis.

The average level of HCT in the experimental group was 28.9 and 29.6 before and after prescription of NAC, respectively (P-value=0.002). The average level of HCT in the control group was 31.65 and 31.51 before and after prescription of placebo, respectively (P-value>0.05). The results of the current study indicate that NAC consumption in chronic hemodialysis patients leads to an increase in the level of HCT by reducing the level of oxidative stresses. Therefore,

oral NAC can be considered as a promising treatment to improve anemia among chronic hemodialysis patients and reduce the need to inject erythropoietin which can exert financial burden on patients.

Keywords: N-acetyl cysteine; hemodialysis; hematocrit

INTRODUCTION

Chronic kidney disease develops when kidneys lose their nephrons irreversibly. The pattern of development, prevalence, and progress of chronic kidney disease can change with demographic characteristics like gender, race, and sociocultural circumstances. Chronic kidney disease is prevalent all over the world and its prevalence is 16.8% on average [7]. The difference between men and women, in terms of prevalence and development of different renal diseases and their progress pace can be due to the difference in the number of glomeruli, hormonal response, and cytokine, and the amount of apoptosis [8-11]. Moreover, these differences can be due to the amount of synthesis and responsiveness to the amount of nitric oxide and prostaglandin, lipid oxidation, oxidative stress, collagen synthesis by mesangial cells, response to beta transforming growth factor, and alpha tumor necrosis factor [12-14]. The prevalence rate of the end stage renal disease (ESRD) is higher among men than women [15]. While prevalence of ESRD is higher among men than women, development of stage 3 and 4 chronic kidney disease is higher among women (*% for women and 5.4% for men).

Chronic kidney disease is classified into 5 stages according to the remaining performance of the kidney. Kidney performance is measured through glomerular filtration rate. Glomerular filtration rate refers to the amount of blood (in terms of cc) that is filtrated from waste toxins in one minute. Most chronic nephropathies have a progressive trend and finally lead to the loss of kidney performance at a changing pace, and need for renal replacement therapy will raise. The final phase of chronic nephropathies is called End Stage Renal Disease (ESRD). Progress of chronic kidney disease begins from the stage of reduction in renal storage performance to slight, average, and intense decrease in GFR, and finally leads to ESRD. Chronic kidney disease (CKD) is a threat to general health; however, its extent is not clear. Nowadays, 1.8 million people are about to have renal replacement therapy, these therapies generally include kidney

transplantation, hemodialysis and peritoneal dialysis [16].

Sahin et al (2007) investigated the effect of NAC on endothelial dysfunction among hemodialysis patients. They concluded that NAC obviously enhances dependent vasodilation in the flow and improve endothelial function [4].

Dashti Khavidaki et al (2008) investigated the effect of four-week therapy with oral NCA on the plasma levels of homocysteine and serum antioxidant activity among patients who had received vitamin B group from the beginning of their dialysis. They concluded that 63% of the patients had average to severe hyperhomocysteinemia. After being treated with NAC, the patients experienced a significant decrease in the level of their plasma total homocysteine. In their study, it was concluded that NAC had no effect on the plasma level of MDA and the activity of enzyme oxidants [5].

Shih-Ping Hsu et al (2009) investigated the effect of NAC on the treatment of anemia among hemodialysis in Taiwan. A remarkable increase in HCT and hemoglobin and a certain decrease in the 8-Isoprostane and oxidized LDL were observed in the NAC group. They concluded that NAC in the form of helping prescription can be a promising treatment for anemia and oxidative stress among uremic and hemodialysis patients [6].

MATERIALS AND METHODS

The present investigation was a double-blinded randomized clinical trial that was carried out in a parallel with control placebo. The participants were over 18 and under chronic hemodialysis in Imam Khomeini Hospital, Ahvaz. They were consisted of both genders.

During examining the profiles of patients of different shifts in Imam Khomeini Hospital, all of the patients were screened, which led to selection of 78 patients who qualified to enter the study, they were also provided with clear explanations, their informed consent was obtained, and moral considerations were seen to. For both NCA and placebo groups, consent was obtained provided that they did not know to which group they would be assigned. These patients were randomly assigned into an experimental group and a control one. Medication delivery and randomization of the study were carried out by someone who did not have any interference with the results. The participants were classified into two groups of 39; an experimental one and a control one. In regard with their gender, 45 patients (60%) were female and 33 patients (40%) were male;

53.3% and 66.7% of the placebo and treatment groups were female, respectively. The participants' mean age was 53.3±17.8 years. There was no significant difference between the two groups in regard with their age.

In the therapy group, three patients left the experiment because one died, one had kidney transplant, and one was noncompliant with the medication. Therefore, the final analysis of the group was carried out on 36 patients. In the placebo group, 2 patients died and one was not compliant with the medications; therefore, the final analysis was carried out on 36 patients.

HCT level of both groups was measured with the use of cell counter and Sysmex Kx21-N (manufactured by Japan) immediately before hemodialysis. Afterwards, the main group was given NCA 600 mg (produced by Zambon Company, Switzerland) twice a day with intervals of 12 hours in the form of dissolved in 50 ml of water before meals. The prescription duration of the medications was 6 weeks. In the control group, the placebo was given to the patients in the form of NAC-similar pills once every 12 hours. In regard with its shape, color, hardness, and taste, the he placebo was similar to NAC pills, which were produced in School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences. It was composed of microcrystalline cellulose, lactose, corn starch, sorbitol, and a rod (2% of the weight of the tablet). After being dissolved in 50 cc water, it has similar physical shape and taste to NAC pills.

After the experiment (6 weeks) and immediately after hemodialysis, HCT was measured in both groups again.

The collected data on the study variable, i.e. HCT before and after the study, were recorded and fed to SPSS 19.0 to be analyzed. The sample size of the present study was determined to be 78 with error percentage of 5% and capability of 80% through Med-Scale software, each group consisted of 39 patients.

RESULTS

The patients' variables investigated in the present study's two groups before and after the intervention are respectively presented in Tables 1 and 2 below. Table 1 indicates that there is no significant difference between the two groups before the investigation. According to Table 2, it can be concluded that there is a significant difference between the two group in terms of serum albumin level, ultrafiltration level, dialysis adequacy, and hematocrit.

Comparing Tables 3 and 4 indicates that the average level of HCT in the control group

before and after prescription of placebo was 31.6564 and 31.5103, respectively.

Table 1: The investigated variables of the patients in the two groups before the intervention

	Treatment (NAC)	Placebo	p-value
	Mean±SD	Mean±SD	
Dialysis Time	3.43±0.3	3.29±0.25	0.057
Albumin	3.99±0.74	4.06±0.49	0.670
Ultrafiltration	72.36±8.94	67.7±10.87	0.082
Dialysis Adequacy	1.38±0.21	1.29±0.28	0.184
Creatinine	9.15±10.76	8.08±2.94	0.615
BUN	52.7±19.42	54.86±18.45	0.667
Cholesterol	167.2±38.46	183.39±25.82	0.068
HCT	29.2±0.5	30.9±0.4	0.172

Table 2: The investigated variables after the intervention

	Treatment (NAC)	Placebo	p-value
	Mean±SD	Mean±SD	
Dialysis Time	3.43±0.3	3.29±0.25	0.057
Albumin	4.18±0.14	4.04±0.18	0.002
Ultrafiltration	74.65±7.85	69.25±9.17	0.022
Dialysis Adequacy	1.48±0.17	1.34±0.22	0.010
Creatinine	29.58±111.24	6.98±1.94	0.283
BUN	61.41±22.01	51.57±22.54	0.101
Cholesterol	159.1±35.65	173.82±16.35	0.054
HCT	30.2±1.3	30.5±1.2	0.026

Table 3: Investigating HCT level in the experimental group (treated with NAC)

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HCTafter	29.6083	36	5.06508	.84418
	HCTbefore	28.9381	36	4.87481	.81247

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HCTafter & HCTbefore	36	.971	.000

Paired Samples Test

		Paired Differences		
		Mean	Std. Deviation	Std. Error Mean
Pair 1	HCTafter - HCTbefore	.67028	1.21051	.20175

Paired Samples Test

		Paired Differences				
		95% Confidence Interval of the Difference				
		Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	HCTafter - HCTbefore	.26070	1.07986	3.322	35	.002

Table 4: Investigating HCT level n placebo (control) group

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HCTbefore	31.6564	36	5.49927	.88059
	HCTafter	31.5103	36	4.63992	.74298

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HCTbefore & HCTafter	36	.707	.000

Paired Samples Test

		Paired Differences		
		Mean	Std. Deviation	Std. Error Mean
Pair 1	HCTbefore - HCTafter	.14615	3.95906	.63396

Paired Samples Test

		Paired Differences				
		95% Confidence Interval of the Difference				
		Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	HCTbefore - HCTafter	-1.13722	1.42953	.231	35	.819

DISCUSSION AND CONCLUSION

Oxidative stress is a condition in which the balance between the produced free radical and body defense against them is disrupted and causes bio-molecular and structural changes in the cells, such as damage to RBC and creation of anemia.

Lazarove et al (2004) investigated the effect of NAC on oxidative stress and anemia by measuring the serum level of Advanced Oxidation Protein Products (AOPPs). They concluded that serum levels of AOPPs after 20 days of treatment with NAC decreased remarkably (from 82.2 mmol/li to 74.3 mmol/lit with P-value=0.039). However, it caused no significant change in anemia [2].

Trimarchi et al (2003) investigated the effect of NAC on the level of malondialdehyde (MDA) in Argentina. The observed that MDA level in hemodialysis patients compared to normal individuals increased, and that it did not decrease with hemodialysis. Moreover, they concluded that NAC reduced MDA level in an obvious way [1]. Moreover, Thaha et al (2006) studied the effect of venous NAC on reduction of serum levels of homocysteine in hemodialysis patients. In their study, NAC was given to the experimental group in the form of 4-hour intravenous infusion and the control group was given 4-hour placebo. They concluded that after hemodialysis in the placebo group the plasma level of homocysteine was 23.7% lower than its level before dialysis. However, in the patients treated with NAC, the level of homocysteine dropped 88.3% (P-value<0.008). The results of their study indicated that, every 10% reduction in plasma level of homocysteine

results in 1.45 mm Hg decrease in pulse pressure. They concluded that prescription of NAC during hemodialysis results in normalization of plasma level of homocysteine, this issue in patients with ESRD was accompanied with improvement in pulse pressure. Therefore, it can be a promising treatment to reduce cardiovascular risk among these patients [3].

The present study indicated that consumption of NAC among hemodialysis patients can be effective in improving HCT status which is one of the causes for cardiovascular and mortality factors to rise. Moreover, improvement of anemia status in these individuals and a drop in need for eprem injection can be useful for the patients in financial terms and reduce the financial pressure. According to the consumption duration and does of NAC, one can conduct more studies on the dose changes (below 600 mg twice a day) or a reduction in consumption duration (less than 6 weeks) and measure responsiveness or failure to respond to this medication in shorter time durations or lower doses.

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