Impact of NAC on inflammation and nutrition in hemodialysis

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Abstract: Objective: To assess whether N-Acetylcysteine (NAC)treatment can improve inflammatory markers and nutritional status in patients undergoing Maintenance Hemodialysis (MHD). Methods: A total of 71 patients who had been on hemodialysis for more than 6 months were selected and randomly divided into an NAC treatment group (NAC 600 mg, twice daily,41 cases) and a control group (no medication,30 cases). Routine clinical data were collected, and a 3-month observation period was initiated. Inflammatory markers, including high-sensitivity C-reactive protein (h s-CRP), interleukin-6(IL-6), interleukin-10(IL-10), tumor necrosis factor (TNF), and homocysteine levels, were measured before and after treatment. Nutritional indicators, such as hemoglobin, serum albumin, and prealbumin levels, were also assessed before and after treatment. Results: After 3 months of NAC treatment in hemodialysis patients, h s-CRP and IL-6 levels significantly decreased compared to pre-treatment levels(both $P<0.01$).Homocysteine levels also significantly decreased($P<0.05$).Hemoglobin, serum albumin, and prealbumin levels significantly increased($P<0.05$ and $P<0.01$,respectively).The reduction in h s-CRP levels in female MHD patients was significantly greater than that in male patients($P<0.01$).Conclusion: NAC treatment can reduce inflammatory marker levels and improve nutritional status in hemodialysis patients, thereby benefiting these patients from anti-inflammatory therapy.

Keywords: Hemodialysis, N-Acetylcysteine, Inflammatory Markers, Nutrition

1. Introduction

Cardiovascular diseases are the leading cause of disability and mortality in patients with chronic kidney disease, with over 50%of end-stage renal disease (ESRD)patients dying from cardiovascular diseases. Their risk is 20 to 30 times higher than that of the general population[1].Traditional cardiovascular risk factors, such as gender, age, smoking, dyslipidemia, hypertension, and diabetes, cannot fully explain the high incidence and mortality of cardiovascular diseases in patients undergoing maintenance hemodialysis(MHD).ESRD patients also have other risk factors, including anemia, calcium and phosphorus metabolic disorders, elevated homocysteine levels, inflammation, malnutrition, and increased oxidative stress[2].Numerous studies have shown that inflammation and oxidative stress are important causes of the decreased quality of life and high mortality in MHD patients and are also the main reasons for various severe complications such as cardiovascular and cerebrovascular events, anemia, and malnutrition. Inflammation and oxidative stress may be involved in multiple pathological processes leading to atherosclerosis and cardiovascular events, such as elevated blood pressure [3]and endothelial dysfunction, which mediate the occurrence of cardiovascular events in ESRD patients. N-Acetylcysteine (NAC)is an antioxidant with anti-inflammatory properties. This study aims to explore the significance and value of NAC in the treatment of MHD patients by observing its effects on inflammatory markers and nutritional status.

2. Materials and Methods

2.1. Clinical data

From June 2013 to June 2015,71 patients undergoing maintenance hemodialysis (MHD) in the Department of Nephrology at the Aerospace Central Hospital were selected. here were 34 males and 37

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females, with ages ranging from 32 to 71 years, and an average age of 52.24±12.13 years. The duration of dialysis ranged from 12 to 114 months, with an average of 69.39±33.58 months. Among them, there were 25 cases of chronic glomerulonephritis,14 cases of diabetic nephropathy,10 cases of hypertensive renal damage,7 cases of drug-induced interstitial nephritis,5 cases of obstructive nephropathy,4 cases of polycystic kidney disease, and 6 cases of other causes. All patients used the Fresenius 4008B and 4008S hemodialysis machines and F7 polysulfone membrane dialyzers from Fresenius Medical Care, Germany. The dialysis modes included hemodialysis or hemodiafiltration. Hemodialysis was performed 2–3 times per week for 4 hours each time, while hemodiafiltration was performed once every 2 weeks for 4 hours each time. Arteriovenous fistulas were used as vascular access. The blood flow rate was 250–280 mL/min, and the dialysate flow rate was 500 mL/min. The calcium ion concentration in the dialysate was 1.50 mmol/L(provided by Baxter Healthcare Corporation, Guangzhou). Anticoagulation was achieved using unfractionated heparin and/or low-molecular-weight heparin. Patients with a history of smoking, malignancies, autoimmune diseases, acute or chronic infections within the past month, abnormal liver function, cardiac diseases (symptomatic or with abnormal EC G, those with a pacemaker, or after arterial stent implantation), uncontrolled diabetes, hypertension, hyperthyroidism, or those who had used lipid-lowering drugs and immunosuppressants within the past 3 months were excluded. This study was approved by the Ethics Committee of Aerospace Central Hospital, and all enrolled patients provided written informed consent. The 71 patients were randomly divided into an NAC treatment group (41 cases) and a control group (30 cases). The treatment was divided into two phases. In the first phase, lasting 4 weeks, all patients discontinued any vitamin supplements. In the second phase, lasting 3 months, the treatment group orally took NAC (provided by Hainan Zan bang Pharmaceutical Co., Ltd.) at a dose of 600 mg, twice daily. The control group did not take any medication.

2.2. Research methods

2.2.1. Clinical data

Patient demographics including age, gender, height, weight, duration of dialysis, and underlying kidney disease were recorded. On the morning of the dialysis day, fasting venous blood samples were collected from all patients to measure pre-and post-treatment levels of hemoglobin, blood urea nitrogen, creatinine, albumin, prealbumin, ferritin, serum calcium (Ca^{2+}), phosphorus(P), total cholesterol, and triglycerides. The dialysis adequacy index (Kt/V) was calculated, and serum intact parathyroid hormone levels were measured.

2.2.2. Detection of serum inflammatory markers

On the morning of the dialysis day before starting the medication and after completing 3 months of medication,5 mL of fasting venous blood was collected from all patients. The blood was centrifuged at 1500 r/min for 15 minutes, and the serum was collected and stored in a-80°C freezer. The enzyme-linked immunosorbent assay (ELISA)kits for interleukin-6 (IL-6), interleukin-10(IL-10), and high-sensitivity C-reactive protein (h s-CRP) were purchased from Abcam, UK; the ELISA kit for tumor necrosis factor-α(TNF-α) was purchased from Beijing Biolink Biotechnology Co., Ltd. The tests were performed according to the instructions provided in the kit manuals. The detection limits for IL-6, IL-10, h s-CRP, and TNF-α were 4 p g/mL,5 p g/mL,20 p g/mL, and 12 p g/mL, respectively.

2.3. Statistical analysis

Data were processed using SPSS 17.0 statistical software. Measurement data were subjected to normality tests and expressed as mean± standard deviation (x ±s). For normally distributed data with equal variances, independent samples t-tests were used for comparisons between two groups. For normally distributed data with unequal variances, t' tests were applied. Qualitative data were analyzed using chi-square(χ^2) tests. A P value of less than 0.05 was considered statistically significant.

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3. Results

3.1. Comparison of clinical data: NAC vs.Control

There were no statistically significant differences between the NAC group and the control group in terms of the composition of etiologies, age, gender, dialysis duration, inflammation, nutritional status, and Kt/V($P>0.05$). See Table 1.

Table 1 Comparison of General Clinical Data between the NAC Group and the Control Group in MHD Patients

	Age (years)	Gender (Male/Female)	Dialysis Duration (months)	Body Mass Index (kg/m²)	High-sensitivity C-reactive Protein (mg/mL)
NAC Group(n=41)	53.68±11.98	19/22	68.43±31.92	22.51±3.12	12.45±3.65
Group (n=30) Statistic	51.92±12.83	15/15	67.87±35.14	22.03±2.25	13.56±3.89
Control	t=1.431	X^2=0.019	t'=0.976	t'=0.632	t1=0.863
P	0.159	0.891	0.373	0.427	0.541
	Interleukin-6 (p g/mL)	Hemoglobin (g/L)	Albumin (g/L)	Blood Urea Nitrogen (mmol/L)	Kt/V
NAC Group(n=41)	5.03±1.25	98.79±12.51	38.58±4.63	24.68±6.69	1.48±0.21
Group (n=30) Statistic	5.22±1.41	99.26±13.33	38.96±5.17	23.70±5.17	1.51±0.32
Control	t=0.632	t'=1.04	t=1.438	t=1.384	t=0.628
P	0.365	0.304	0.151	0.173	0.531

3.2. Changes in inflammatory and nutritional indicators in NAC Group

After 3 months of treatment, the levels of serum high-sensitivity C-reactive protein (h s-CRP), interleukin-6(IL-6), and homocysteine in the NAC group were significantly reduced (all $P<0.05$), indicating statistically significant differences. The levels of serum interleukin-10(IL-10) and tumor necrosis factor-α(TNF-α) did not show statistically significant differences before and after treatment($P>0.05$). The levels of hemoglobin, serum albumin, and prealbumin were significantly increased (all $P<0.05$), indicating statistically significant differences. See Table 2.

3.3. Gender impact on inflammatory markers in NAC Group

After 3 months of NAC treatment, the decrease in serum h s-CRP levels in female patients was significantly greater than that in male patients($P<0.01$), indicating a statistically significant difference. There was no statistically significant difference in serum IL-6 levels between males and females($P>0.05$). See Table 3.

Table 2 Changes in Inflammatory Markers and Nutritional Indicators Before and After Treatment in the NAC Group

	Hemoglobin (g/L)	Albumin (g/L)	Prealbumin (mg/L)	Total Cholesterol (mmol/L)	Triglycerides (mmol/L)
Before Treatment	98.79±12.51	38.58±4.63	251±29	4.47±1.23	2.40±1.57

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After Treatment	116.34±14.36	43.15±4.57	301±34	4.37±1.46	2.29±1.25
P	0.026	0.017	0.002	0.564	0.078
	Homocysteine (mmol/L)	High-sensitivity C-reactive Protein (mg/mL)	Interleukin-10 (p g/mL)	Tumor Necrosis Factor-α (p g/mL)	Interleukin-6 (p g/mL)
Before Treatment	32±12	12.45±3.65	3.17±0.61	15.11±3.56	5.03±1.25
After Treatment	23±9	6.01±1.86	2.91±0.21	14.71±2.34	2.51±0.46
P	0.013	0.005	0.483	0.749	0

Table 3 Changes in Inflammatory Markers Before and After Treatment in the NAC Group by Gender

Inflammatory Markers	Males (n=19)			Females (n=22)		
	Before Treatment	After Treatment	Difference	Before Treatment	After Treatment	Difference
nterleukin-6	4.63±1.15	2.28±0.69	2.35±0.84	5.48±2.03	2.82±1.16	2.68±1.53
High-sensitivity C-reactive Protein	9.69±2.46	4.85±1.31	4.53±0.98	15.71±4.15	5.22±0.99a	9.96±3.75b

4. Discussion

4.1. Mechanisms and benefits of NAC treatment in hemodialysis patients

Hemodialysis is a primary treatment modality for patients with end-stage renal disease (ESRD). Approximately 30%of maintenance hemodialysis (MHD)patients exhibit a state of low-grade inflammation, referred to as the "micro-inflammatory state," which is characterized by persistent low-level inflammation in the absence of overt clinical infection. This micro-inflammatory state is associated with a high incidence of atherosclerosis in MHD patients and is an important factor contributing to poor prognosis in this population. N-acetylcysteine (NAC)is an antioxidant that interferes with the generation of free radicals, scavenges existing free radicals, modulates cellular metabolic activity, and prevents DNA damage. In addition to its antioxidant properties, NAC has been shown to inhibit the activity of angiotensin-converting enzyme in rats treated with NG-nitro-L-arginine methyl ester, thereby reducing the levels of angiotensin II, increasing nitric oxide-dependent vasodilation, improving microcirculation, and attenuating the inflammatory response [5]. Several studies have demonstrated the benefits of NAC administration in patients with chronic kidney disease [6-9].

This study demonstrates that NAC significantly reduces serum high-sensitivity C-reactive protein (h s-CRP), interleukin-6(IL-6), and homocysteine levels in MHD patients, indicating that the downregulation of the inflammatory state is associated with NAC treatment. Nascimento et al. [10] also showed that oral NAC for 8 weeks significantly reduced circulating IL-6 levels in conventional peritoneal dialysis patients. The antioxidant and anti-inflammatory effects of NAC can reduce the incidence of cardiovascular events in patients with end-stage renal disease[6].Interleukin-6 is not only an indicator of atherosclerosis but also promotes the formation of atherosclerosis through various mechanisms, including metabolism, endothelial function, and pro-coagulant effects[11-13].Pachaly et al.[14]showed that, compared with other inflammatory and oxidative stress markers,IL-6 is the strongest predictor of mortality in hemodialysis patients. The anti-inflammatory effect of NAC lies in its ability to inhibit the activation of inflammatory transcription factors, such as activator protein-1 and nuclear factor-kappa B (NF-κ B) [15], with the NF-κ B pathway playing a central role in the activation of IL-6 gene expression. Araki et al.[16]reported that

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NAC inhibits TNF-α-mediated NF-κ B activation, thereby reducing IL-6 levels. The inflammatory marker h s-CRP can also serve as an indicator for assessing cardiovascular disease risk [17-18]. In vitro studies have shown that h s-CRP activates many processes involved in the inflammatory response and can induce the expression of various adhesion molecules [19], such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin on human endothelial cells, and monocyte chemoattractant protein-1 on monocytes. Homocysteine has the effect of enhancing lipid peroxidation, is significantly correlated with the levels of inflammatory cytokines, and can predict the chronic inflammatory state in hemodialysis patients [20].

4.2. Gender differences and nutritional impact of NAC treatment

In addition, this study also found that after NAC treatment, the decrease in h s-CRP levels in female MHD patients was significantly greater than that in males, which may be related to the higher pre-treatment levels of h s-CRP in female MHD patients. Such differences have been identified in other studies [21-22]. After adjusting for body mass index and other common confounding factors, women have higher baseline serum h s-CRP levels than men, independent of race. We also observed that women, even those with end-stage renal disease, tend to have relatively higher h s-CRP levels. The reason for the higher h s-CRP levels in women is not clear, but it may be related to sex hormones [23]. The significant decrease in h s-CRP levels in women after NAC treatment suggests that female MHD patients may benefit more from NAC treatment.

This study suggests that while NAC treatment reduces the levels of inflammatory markers, it also significantly increases the levels of hemoglobin, serum albumin, and prealbumin, indicating that inflammation and malnutrition can be interrelated as cause and effect. Caglar et al. [24] found that 53%of hemodialysis patients with malnutrition had inflammation, and 72%of those with inflammation were malnourished. Malnutrition is also an important predictor of cardiovascular disease and cardiovascular event mortality in dialysis patients. Malnutrition can promote the formation of atherosclerosis by affecting endothelial function and increasing oxidative stress, while atherosclerosis can lead to malnutrition by promoting the production of inflammatory markers [25]. Therefore, the clinical management should focus on improving protein intake and factors affecting albumin synthesis in MHD patients, such as inflammation and acidosis.

5. Conclusion

In summary, NAC treatment can significantly reduce the levels of serum inflammatory markers while improving nutritional status, which may potentially lower cardiovascular mortality and improve prognosis. However, this study also has its limitations: the relatively small number of patients may introduce bias; and the lack of baseline antioxidant defense capacity testing in patients, which could influence the outcomes of the intervention.

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