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The Effects of Antidepressant Treatment on Serum Cytokines and Nutritional Status in Hemodialysis Patients

The aim of this study was to investigate the effects of antidepressant treatment on serum cytokines and nutritional status in hemodialysis patients. Twenty-eight hemodialysis patients with a depressed mood were given 20 mg of fluoxetine for 8 weeks. The degree of depressive symptoms, the serum levels of interleukin-1β, interleukin-2, interleukin-6, tumor necrosis factor-α, c-reactive protein, and markers of nutritional status were assessed at baseline and after treatment. The outcome was assessed in terms of response to treatment (>50% reduction in the score of the Hamilton depression rating scale). Antidepressant treatment decreased the serum level of interleukin-1β in both response and nonresponse groups, and increased the serum level of interleukin-6 only in the response group. At baseline, the level of interleukin-6 in the response group was lower than in the nonresponse group. Antidepressant treatment also increased fat distribution significantly in the response group which might have slightly improved the nutritional status. This study suggests that antidepressant treatment improve depressive symptoms and may affect immunological functions and nutritional status in chronic hemodialysis patients with depression.

Key Words : *Depression; Antidepressive Agents; Cytokines; Nutritional Status; Renal Dialysis*

Sang-Kyu Lee, Hong-Seock Lee†, Tae-Byeong Lee, Do-Hoon Kim, Ja-Ryong Koo*, Yong-Ku Kim‡, Bong-Ki Son

Department of Psychiatry, College of Medicine, Hallym University, Chunchon; *Division of Nephrology, Department of Internal Medicine, College of Medicine, Hallym University, Chunchon; †Department of Psychiatry, Catholic University, Daejeon St' Mary Hospital, Daejeon; ‡Department of Psychiatry, Korea University Medical Center, Seoul, Korea

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Address for correspondence
Bong-Ki Son, M.D.
Department of Psychiatry, Chunchon Sacred Heart Hospital, Hallym University, Kyo-dong, Chunchon 200-704, Korea
Tel : +82.33-252-9970, Fax : +82.33-244-0317
E-mail : bkson@hallym.ac.kr

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INTRODUCTION

Depression has been recognized as the most frequent psychological symptom in chronic dialysis patients (1). It has been also known to relate to the severity, healing, and recovering process and mortality among patients with end-stage renal disease (ESRD) who are treated with hemodialysis (HD) (1). The incident rate of depression in ESRD has been reported from 10% to 100%. Several explanations for this wide range of the incidence rate have been addressed: First, it is difficult to discriminate the depressive symptoms from the uremic symptoms; second, depending on the methods and subjects, the incidence rate might be variable (2-5). Several losses such as loss of renal function, loss of role in the workplace and family, and loss of sexual function account for the high incidence rate of depression in ESRD patients. It has been also reported that ESRD patients continue to experience a decrease in quality of life (6). The stress is maximized that they have to rely on others (doctors or family) or machines, which worsens the depression (7-9).

Recent studies have suggested that the alterations of cytokines in HD might be related to depression and altered levels of serum albumin and cholesterol (10-13). It has also been reported that acute phase, pro-inflammatory cytokines (14) such as interleukin 1 (IL-1), interleukin 6 (IL-6) and C-reactive protein (CRP) are activated in long-term HD patients (15). Experimental and clinical studies have indicated that these cytokines secreted excessively by stress might be one of the reasons for depression (16, 17). It has been known that these cytokines trigger catabolism of the body protein, which results in a negative nitrogen balance that induces malnutrition and decrease of appetite (15).

Malnutrition has been considered to relate closely to morbidity, mortality, decrease in quality of life, and delayed recovery in ESRD patients (1, 18). In consideration of the high incidence rate of depression among patients with HD, the causal relationship between depression and malnutrition among them needs to be explored (9).

Kimmel et al. (1) speculated that depression influences the immunological factors, nutritional status, and treatment

compliance. These factors can influence the survival rate of the patients, duration of hospitalization, and quality of life. Studies have also shown that although psychiatric treatments such as antidepressant and group therapy are effective to deal with depression and malnutrition, it is difficult to tell whether the improvement results only from these treatments or from interactions with other factors. Although the mechanisms of the effects of depression on survival are poorly understood, it is reasonable to hypothesize that the psychiatric treatments might improve the survival rate of the patients.

In this respect, we aimed to explore the effects of antidepressant treatment on serum cytokines and nutritional status in hemodialysis patients.

MATERIALS AND METHODS

Subjects

Forty-three patients with ESRD on HD were selected for this study. The study took place at the outpatient HD unit of Hallym University Hospital (Chunchon, Korea). Data from the subjects were collected from January 1 to June 30, 2001. Some patients were excluded because they could not complete the self-rating scale for disturbance of cognitive function. Patients were also excluded if they had experienced acute inflammation state for at least two weeks prior to the study, if they had been alcohol dependent, if they have autoimmune disease, or if they had experienced recent poor appetite and weight loss. In addition, because this study used antidepressant treatment, patients who scored less than 11 in the Beck's depression rating scale (BDI) (19) and less than 7 in the Hamilton depression rating scale (HAMD) (20) were excluded as well.

Assessment of depression

The 17-item Hamilton depression scale was administered before and after eight weeks of antidepressant treatment. We measured clinical improvement as a percent of change in HAMD score, response to treatment (defined as a $\geq$50% reduction in the score from baseline to eight weeks treatment). The subjects were divided into two groups: Response Group (RP) and Nonresponse Group (NR) that showed a less than 50% decreased rate (21).

Hemodialysis and antidepressant treatment

All of the HD subjects were treated using polymethylmethacrylate dialyzer. During the period of this study, the frequency and session length of dialysis and dry weight were maintained equally. After breakfast, the subjects took one dose of antidepressants (20 mg fluoxetine) in addition to the same amount of medications as before the experiment.

Laboratory test and measurement of cytokines

Before and after eight weeks of antidepressant treatment, 15 mL of blood was taken immediately after initiation of HD. The serum was separated and kept at -70℃. Interleukin-1 beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured by ELISA kit from Biosource Europe SA (Belgium) using a Cobra Gamma Counter (Packard, IL, U.S.A.).

Index of nutrition status

Before and after eight weeks of antidepressant treatment, a bio-electrical impedance analyzer (BIA) (Inbody 2.0, Biospace, Korea) was used to measure body weight, fat-free mass, total body water, body fat mass, fat distribution, body mass index, and arm muscle circumference.

Statistical analysis

Chi-square test and independent t-test were conducted to compare variables between the RP group and the NR group. A paired t-test was used to compare values obtained before and after antidepressant treatment. A statistical software program (SPSS for Windows version 10.0; SPSS Inc, Chicago, IL) was used to do the statistical analysis. The level of significance was set to be less than 0.05.

RESULTS

Four subjects were excluded from the analysis because they had lower scores of BDI (less than 11) and HAMD (less than 7). Four subjects with a poor medication compliance, three subjects who had transferred to other hospitals, one subject who had stopped HD because of renal transplantation, and three subjects who had died were excluded additionally. Therefore, 28 subjects were included in the analysis.

Demographic characteristics

The study subjects were 15 male and 13 female patients. The average age of the subjects was 43.6$\pm$11.3 yr. In terms of their economic status measured by annual income, 23 had a salary of less than US $10,000 per year, 4 had a salary between US $10,000 and US $30,000, and one subject earned more than US $30,000. Nineteen subjects were married, three remained single and three were divorced. The average duration of education was 10$\pm$3.5 yr. The total duration of hemodialysis was 64.4$\pm$38.5 months (range, 12 months to 156 months). As for drinking, 25 subjects stated that they did not drink and three subjects stated that they drank more than three to five times a month. All subjects responded that they did not smoke. There were no statistically significant differences in demo-

graphic characteristics between the RP group and the NR group (Table 1).

The degree of depression (Table 2)

There was no statistically significant difference in the baseline HAMD scores between the RP group and the NR group. The antidepressant treatment significantly decreased the HAMD scores in the RP group (15.36±1.75 vs. 6.36±1.22, $p<0.05$).

The serum cytokines (Table 2)

The levels of IL-2, TNF-α, and CRP were not significantly different before and after the antidepressant treatment in both NR and RP groups. Antidepressant treatment significantly decreased the IL-1β level in both groups (18.87±2.1 vs. 10.52±1.18, $p<0.05$). However, the level of IL-6 was significantly increased only in the RP group (1.66±1.66 vs. 8.85±3.39, $p<0.05$). The baseline level of IL-6 in the RP group was significantly lower in the RP group as compared to NR group (1.66±1.66 vs. 10.88±3.78, $p<0.05$).

Nutritional status (Table 2)

After eight weeks of antidepressant treatment, there was no significant difference in body weight and total body water between the two groups. However fat distribution was significantly increased in the RP group (0.815±0.012 vs. 0.823±0.012, $p<0.05$).

Table 1. The comparison of demographic data between response group and nonresponse group after antidepressant treatment (n=28)

	Response group (n=11)	Nonresponse group (n=17)
Age (yr)	42.73±3.34	44.24±2.83
Male (%)	45	65
Living with partner (%)	66	71
Economic status (low %)*	81	82
Education (yr)	10.30±1.23	9.76±0.82
Hemodialysis duration (months)	61.27±9.70	66.35±10.40

Values are expressed as mean±SE.
*Low means below US $10,000 of annual income.

DISCUSSION

The incidence rate of depression in chronic HD patients is 10-100% (1-5). In this study, 90% of the total subjects (39 subjects in 43 subjects) revealed mild depression or more severe symptoms. One reason for the high rate of depression was the use of the BDI self-rating scale. The low cut-off points (11 points for BDI and 7 points for HAMD) also contributed to the higher depression rate in this study.

Recently, selective serotonin reuptake inhibitors (SSRI) have been widely used for depression in HD patients (22, 23). Especially, fluoxetine, which is a selective serotonin reuptake inhibitor, has a little anticholinergic effect and is excreted mainly

Table 2. The comparison of severity of depression, cytokines level and nutritional status between the response group and the nonresponse group after antidepressant treatment (n=28)

	Total (n=28)		Response group (n=11)		Nonresponse group (n=17)	
	Baseline	8 Weeks	Baseline	8 Weeks	Baseline	8 Weeks
Severity of depression						
BDI	14.7±1.4		16.5±2.2		13.6±1.9	
HAMD	13.54±0.99	10.07±1.22*	15.36±1.75	6.36±1.22*	12.35±1.12	13.54±1.85
Cytokines						
IL-1β (pg/mL)	18.87±2.1	10.52±1.18*	16.20±2.55	7.69±1.48*	22.09±2.94	13.30±1.41*
IL-2 (pg/mL)	0.57±0.04	0.72±0.12	0.52±0.06	0.57±0.08	0.60±0.05	0.82±0.19
IL-6 (pg/mL)	7.26±2.51	10.58±2.37*	1.66±1.66†	8.85±3.39*	10.88±3.78	11.70±3.27
TNF-α (pg/mL)	80.67±11.4	65.37±5.97	53.15±4.67	46.60±2.88	96.45±6.88	76.39±8.30
CRP (mg/mL)	2.19±0.5	2.34±0.6	1.62±0.53	2.26±0.52	2.56±0.75	3.04±0.91
Nutritional status						
Body weight (kg)	54.74±2.08	54.92±1.98	50.71±2.35	50.61±2.33	57.64±2.97	57.99±2.73
Fat free mass (kg)	44.60±1.51	45.06±1.39	44.18±2.66	44.70±2.65	44.92±1.80	45.35±1.46
Total body water (L)	31.13±1.0	31.17±0.98	30.58±1.86	30.91±1.85	31.56±1.08	31.38±1.03
Body fat mass (kg)	10.75±1.46	10.45±1.42	8.00±0.88	7.37±1.83	12.72±2.32	12.64±2.20
Fat distribution (kg)	0.85±0.013	0.84±0.012	0.815±0.012	0.823±0.012*	0.863±0.019	0.865±0.020
Body mass index (kg/m^2)	21.52±0.74	21.40±0.69	20.94±1.09	20.85±1.03	21.99±1.02	21.83±0.95
Arm muscle Circumference (cm)	22.16±0.44	22.33±0.40	21.86±0.74	22.16±0.70	22.40±0.55	22.46±0.48

Values are expressed as mean±SE. BDI, Beck's depression rating scale; HAMD, Hamilton depression rating scale.
*$p<0.05$ versus baseline values (paired t-test), †$p<0.05$ versus baseline values in the nonresponse group (independent t-test).

by the liver. There is no influence of renal dysfunction, the rate of elimination, volume of distribution, or protein binding of fluoxetine. The plasma concentration of fluoxetine and norfluoxetine metabolites were not significantly changed by the process of hemodialysis (23).

The recommended dose of fluoxetine is 20-40 mg in the depressed patients (24). Surman (25) stated that in consideration of side effects among HD patients, two thirds of the amount for major depression is proper to HD patients. In this study, 20 mg of fluoxetine were used for the treatment of depressive symptoms. No patient showed side effects of medication. However, it was not clear whether the amount of 20 mg was enough to improve depression for all subjects.

It has been suggested that IL-1β, TNF-α, and IL-6 are pro-inflammatory cytokines, which are mainly secreted from monocytes, and function as major etiological factors of hemodialysis-related inflammatory responses (14). The blood levels of IL-1β and TNF-α were higher among HD patients than among control patients (26, 27), and these over-secretion of cytokines have been observed in amyloidosis (28), malnutrition (29, 30), and atherogenesis (31, 32). Cytokines may be secreted inappropriately due to frequent contact with bioincompatible dialyzer and uremia itself. And a correlation between over-secreted cytokines in HD patients and their depressive symptoms has also been suggested. Some studies have supported the possibility that cytokines can be overly secreted by stress and the over-secreted cytokiness can trigger depression (16). Other studies have shown that over-secreted pro-inflammatory cytokines can cause depression (33, 34). It has recently been suggested that antidepressants decrease the secretion of pro-inflammatory cytokines such as IL-1β, IL-2, and TNF-α and have negative immunoregulatory effects (35).

This study showed that after eight weeks of antidepressant treatment, while the level of IL-1β decreased significantly among all subjects, IL-6 increased significantly only in the RP group. Previous studies reported that after antidepressant treatment, IL-6 has decreased (36), however, some studies showed that after four weeks of antidepressant treatment using fluoxetine, IL-6 was significantly increased (35). The IL-6 has been considered as a cytokine with both pro- and anti-inflammatory effects. Therefore, it has been called a highly pleiotropic cytokine (37), functioning as a mediator to control secretion of other cytokines from monocytes (38). Schindler et al. (39) stated that IL-6 controls secretion of IL-1β and TNF-α. And it has been suggested that the gene expression of IL-6 is strongly controlled by cortisol, which decreases IL-6 (40-42). One of possible hypotheses from this study is as follows: Stress in HD patients activates the HPA axis to increase cortisol. While the increased cortisol keeps IL-6 at a lower level, stabilization of the HPA axis by antidepressant treatment will decrease the cortisol level, and after then these changes may increase IL-6 level paradoxically.

However, it has been suggested that there was no reverse correlation between cortisol and cytokines among endogenously depressed patients (43, 44). In this study, because the subjects were HD patients who had been exposed to stress for a while, they were different from endogenously depressed patients. Therefore, the results of this study might differ from those of studies involving endogenously depressed patients. This was supported by result from this study that at the early stage of treatment, the serum level of IL-6 in the RP group was significantly lower in the NR group. This result was consistent with the result from the study by Maes et al. (33), which showed that IL-6 was significantly high among patients who resisted antidepressant treatment. It has also been recently reported that while the level of IL-1β did not change among patients with atypical depressions, it changes in those with typical depression (45). These results suggest that the immunological pathophysiology and types of mechanism of antidepressants can be different depending on the subtype of depression (44).

Malnutrition in HD can be caused by a poor appetite, insufficient food intake, depressive symptoms, intake of various medication, bio-incompatible dialyzer, disturbance of compensating mechanisms for protein metabolism, and increased protein catabolism (46, 47). Because the malnutrition is related to morbidity and mortality (48), regular assessment of the nutritional status of the HD patient is very important.

Measurement of skinfold thickness, mid arm muscle circumference, dual energy radiograghy absorptiometry, and BIA have been suggested as methods to assess nutritional status. However, controversies exist on the precise index of measurement (49). For instance, because HD patients experience a severe change of the amount of Total Body Water measured by the method, BIA has been suggested to be an inaccurate index of measurement. In this study, even though BIA has been used to assess the nutritional status after the antidepressant treatment in all subjects, a significant change of TBW was not observed. Therefore, the comparison of nutritional status before and after the treatment was appropriate. Changes in dialysis adequacy can also influence the nutrition status. In this study, however, the influence of dialysis' change on the nutrition status was controlled by keeping the dose of dialysis constant.

Depression among HD patients can cause biological changes in the nutritional status, and the immune system, and decreased compliance to treatment. These changes can result in poorer prognosis of the disease and mortality (1). The correlation between depression and malnutrition has been reported (9). It has been stated that after antidepressant treatment, intracellular fluid, which was measured by BIA, and the amount of fat-free mass increased (50). In this study, the nutrition indices such as fat-free mass, fat distribution, and arm muscle circumference all increased in the RP group. The fat-free fat mass was calculated by combining total body water, protein, and mineral. Therefore, an increase in fat-free mass is proportional to increase of protein and mineral when total body water is not changed. Increased waist hip ratio and arm

muscle circumference which is related to anabolism, also indicate improvement of nutrition (9). Among the NR group, the indices of nutrition did not improved. These results indicate that among HD patients, depression is related to nutrition, and antidepressant treatment can improve the nutritional status.

This study has a couple of limitations. The number of the subjects was relatively small, and a placebo-controlled study was not conducted. In addition, because the dosage of the antidepressant was fixed for all subjects, the amount of antidepressant treatment might not be enough to investigate optimally the treatment effects of depression.

Considering these limitations, we need further studies on the relationship between depression and ESRD, and the role of cytokines and the hypothalamus-pituitary-adrenal axis in the pathogenesis of malnutrition in patients with chronic renal disease.

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