Treatment of Depression and Effect of Antidepression Treatment on Nutritional Status in Chronic Hemodialysis Patients

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ABSTRACT: *Background*: Depression, which is the most common psychological complication in patients with end-stage renal disease (ESRD), has an impact on the clinical outcome and is associated with malnutrition in chronic hemodialysis patients. This study evaluated the effect of antidepression treatment on nutritional status in depressed chronic hemodialysis patients. *Methods*: Sixty-two ESRD patients who underwent dialysis for more than 6 months were interviewed and completed a Beck Depression Inventory assessment. Thirty-four patients who had scores greater than 18 on the Beck Depression Inventory score and met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for major depressive disorder were selected to receive paroxetine 10 mg/day and psychotherapy for 8 weeks. The remaining 28 patients were assigned to the control group. Change in the severity of depressive symptoms was ascertained by administering the Hamilton Depression Rating Scale. Nutritional status was evaluated by normalized protein catabolic rate, serum albumin and blood urea nitrogen level. *Results*: All patients successfully completed 8 weeks of antidepression treatment. Antidepression treatment decreased the severity of depressive symptoms (Hamilton Depression Rating Scale score: 16.6 $\pm$ 7.0 versus 15.1 $\pm$ 6.6, $P < 0.01$) and increased normalized protein catabolic rate (1.04 $\pm$ 0.24 versus 1.17 $\pm$ 0.29 g/kg/day, $P < 0.05$), serum albumin (37.3 $\pm$ 2.0 versus 38.7 $\pm$ 3.2 g/l, $P < 0.005$), and prehemodialysis blood urea nitrogen level (24.3 $\pm$ 5.6 versus 30.2 $\pm$ 7.9 mmol/L, $P < 0.001$). In the control group, no change was noted during the study period. *Conclusion*: This study suggests that antidepressant medication with supportive psychotherapy can successfully treat depression and improve nutritional status in chronic hemodialysis patients with depression. **KEY INDEXING TERMS:** Antidepressant; Depression; Hemodialysis; Malnutrition; Nutrition; ESRD. **[Am J Med Sci 2004;329(1):1–5.]**

Depression is the most commonly encountered psychological complication of chronic dialysis patients.[1,2] Its prevalence varies widely across studies, which may reflect the different criteria and methodology utilized to diagnose depression.[2,3] Depression has been shown to be associated with excess mortality in a variety of medical conditions.[4,5] Studies on maintenance dialysis patients have also showed a significant association of depression with mortality.[6–8] However, the effective treatment of depression in chronic dialysis patients presents challenging problems.[9] Antidepression treatment in hemodialysis patients is complicated by difficulty in determining the impact of chronic disease on the symptoms and the patient's response to antidepressant medication. The pharmacokinetics and safety of antidepressants also have not been extensively documented in hemodialysis patients.

Depending in part on the method used and the population studied, 40% to 70% of patients with end-stage renal disease (ESRD) are malnourished,[10,11] a complication that appears to be associated with increased mortality.[12] In our earlier study,[13] we showed that depression is closely related to nutritional status and could be an independent risk factor for malnutrition, which could partially explain the causal relation between depression and increased mortality in chronic hemodialysis patients.

The present study was undertaken to examine the feasibility of treating hemodialysis patients for depression and then to evaluate the effect of

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antidepression treatment on nutritional status in a subgroup of patients who were diagnosed with depression in our earlier study.[13]

Methods

Study Populations

Our previous study[13] investigated the relationship between depression and nutritional status in 76 ESRD patients who underwent dialysis for more than 6 months at the outpatient hemodialysis unit of Hallym University Hospital (Chunchon, South Korea). The patient characteristics, study design, measure of depression, and nutritional status have been published.[13]

Among 62 patients who completed our previous study, 34 patients with depression who had a score greater than 18 on the Beck Depression Inventory (BDI) assessment and met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) for major depressive disorder were assigned to the treatment group and received the selective serotonin reuptake inhibitor paroxetine at 10 mg/day and supportive psychotherapy conducted by independent psychiatrists for a total of 8 weeks. Patients were contacted every dialysis session during the treatment period to ascertain whether they had taken the antidepressant medication and to discuss possible side effects of paroxetine. Individual supportive psychotherapy and psychological counseling were done at intervals of 2 weeks. Group therapy was also done twice, at the start of treatment and after 4 weeks of treatment. The study was terminated after 8 weeks, but patients willing to continue treatment were offered follow-up care by a psychiatrist. The remaining 28 patients without depression were assigned to the control group of patients who received neither medication nor psychotherapy. During the course of this study, dry weight, hemodialysis session length, and dialyzer were not changed. The study protocol was approved by the Hallym University Hospital Institutional Review Board, and all patients gave informed consent.

Measure of Depression

In the treatment group, changes in the severity of depression before and after treatment were ascertained by administering the Hamilton Depression Rating Scale (HDRS) and Zung Self Rating Depression Scale (SDS) assessments. In this longitudinal study, we did not use the BDI questionnaire because some patients were reluctant to fill out the same BDI questionnaire that was administered in the previous cross-sectional study.

The HDRS is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms.[14] It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The 17 items are rated on either a five-point (0–4) or a three-point (0–2) scale. The total score ranges from 0 to 53 with normal (0–6), mild (7–17), moderate (18–24), and severe (25–53) depression. A psychiatrist who was not an investigator determined the HDRS scores.

The SDS is a 20-question self-rating assessment for depression that is much simpler than the BDI questionnaire.[15] The 20 items are answered on a four-point Likert scale with 1 representing a minimal (none or only a little of the time) and 4 a severe (most or all of the time) problem. The raw score is converted to a 100-point scale, and the total score ranges from 35 to 100, with normal (35–49), mild (50–59), moderate (60–69), and severe (70–100) depression.

Dialysis Adequacy and Biochemical Analyses

Dialysis adequacy (KT/V_{urea}, where K indicates dialyzer urea clearance, mL/minute; T, hemodialysis session length, minute; and V, volume of urea distribution, mL) and normalized protein catabolic rate (nPCR) as a marker of protein intake were calculated with a web-based variable-volume, single-pool urea kinetic calculator (Hypertension Dialysis Clinical Nephrology, http://www.hdcn.com/).[16] The contribution of residual renal function was included in the calculation. Urea, albumin, hematocrit, and bicarbonate were measured by standard techniques. Samples were taken with the subject in a nonfasting state and were collected immediately after initiation of hemodialysis.

Multifrequency Segmental Bioimpedance Analysis

It is possible by multifrequency segmental bioimpedance analysis (BIA) to distinguish total body water and extracellular fluid (ECF) by using the resistance of cell membranes to relatively low-frequency currents.[17] At high frequencies, currents flow across both intra- and extracellular spaces, but at low frequencies, currents flow mainly through extracellular space, allowing the assessment of ECF alone. Segmental BIA can measure the resistance of the trunk or each limb separately. The results of segmental BIA of the trunk and extremity are then summed up to produce whole-body BIA. It is a more appropriate approach to monitor body water during hemodialysis than whole-body BIA, because changes in local resistance can be allocated to segments with uniform geometry and resistivity.[18] Water volumes are calculated by means of a population-based regression equation using impedance index (height squared/resistance). Lean body mass that contains 73.4% of total body water is determined and fat mass can be calculated by subtracting lean body mass from body weight.

Eight stainless steel tactile electrodes were used to measure the impedance of the trunk and extremity (Inbody 2.0, Biospace Co, Seoul, South Korea), as in another study.[19] The hand electrode consisted of thumb pipe and palm cylinder electrodes, and the foot electrode consisted of frontal and rear sole plate electrodes. Impedance was measured at frequencies of 5, 50, 250, and 500 kHz. The validation of the method has been reported using a sodium bromide dilution and a deuterium oxide dilution.[17] The water volume in the trunk measured by BIA was compared with the water volume measured by dual energy x-ray absorptiometry as the reference in 171 healthy subjects, giving a correlation coefficient of 0.982 and a standard error of estimation of 0.695 L. The measurements were performed at 30 minutes after hemodialysis with the subject in standing position. BIA was done repeatedly before and after antidepression treatment.

Statistical Analysis

Data analysis was performed using a statistical software program (SPSS for Windows, version 10.0; SPSS, Chicago, IL). Data are presented as mean ± standard abbreviation (SD). Differences between groups were assessed by unpaired Student t test and χ^2 test. To compare values obtained at baseline and 8 weeks of treatment, a paired t test was used. P values less than 0.05 were considered significant.

Results

The principal clinical data of the subjects are presented in Table 1. In the treatment group, mean age and proportion of diabetic patients were higher than in the control group. Table 2 shows the baseline characteristics and the changes in the severity of depression, nutritional parameters, BIA, and other clinical variables in the treatment and control groups. Antidepression treatment decreased HDRS score and increased nPCR, serum albumin, and blood urea nitrogen concentration. Antidepression treatment also induced a slight but significant increase in intracellular fluid (ICF) volume and a decrease in ECF volume as measured by BIA. There was no significant change in KT/V_{urea}, plasma bicarbonate, hematocrit, and interdialytic weight gain

Table 1. Baseline Clinical Characteristics in the Treatment and Control Groups

Variables	Treatment Group (n = 34)	Control Group (n = 28)
Age (year)	52.5 ± 11.2[a]	44.4 ± 9.3
Male (%)	52.9	60.7
Hemodialysis duration (month)	53.8 ± 35.3	49.2 ± 29.6
Diabetes mellitus (%)	41.2%[a]	14.3%
BDI score	30.7 ± 7.9[a]	13.0 ± 6.4

BDI, Beck Depression Inventory. Values are expressed as mean ± SD unless otherwise noted.

[a] $P < 0.05$.

during antidepression treatment. In the control group, no change was noted during the course of this study.

All patients successfully completed 8 weeks of supportive psychotherapy and antidepressant medication. Paroxetine was well tolerated by study patients without evidence of major adverse events, even though four patients (8.3%) had mild central nervous symptoms (drowsiness, dizziness) during the study period.

Discussion

There is a paucity of data relating to the effectiveness of therapeutic interventions in the treatment of depression occurring in patients with ESRD.[20,21] A recent study[22] showed that only a small percentage of depressed patients (16%) were being treated for depression. Wuerth et al[9] reported that depression is treatable with antidepressant medication in a small but significant percentage of ESRD patients on chronic peritoneal dialysis. In their study, 45% (27 of 65) of the eligible patients with depression agreed to further assessment with possible treatment and 11 of 20 patients for whom antidepressant medication was prescribed completed 12 weeks of therapy. Treatment of depression is dictated by the patient's needs and acceptance for medication and psychiatric referral, as well as the nephrologist's comfort with prescribing antidepressants. In our study, all of the eligible and enrolled patients completed the antidepression treatment trial without dropout. Reasons may be ease of administration (one tablet per day), lack of side effects, combined psychosocial support, and nursing staff's effort to increase medication compliance. There may be also cultural and racial differences in patients' responses to medical recommendation. Because most of the patients enrolled in this study reside in a rural area, patients' characteristics and response to medical recommendation could be different from those of patients who undergo dialysis in urban hemodialysis units located in large cities.

Our earlier cross-sectional study[13] showed positive correlations between the severity of depressive symptoms and the degree of malnutrition in chronic hemodialysis patients. In this prospective study, antidepression treatment increased nPCR, blood urea nitrogen, and serum albumin concentrations, all of

Table 2. Baseline Values and Changes in the Severity of Depression, Nutritional Status, and Other Clinical Variables in the Treatment and Control Groups

	Treatment Group (n = 34)		Control Group (n = 28)	
	Baseline	8 Weeks	Baseline	8 Weeks
Severity of depression				
HDRS	16.6 ± 7.0	15.1 ± 6.6[a]	Not measured	Not measured
SDS	59.2 ± 10.9	56.0 ± 12.6	Not measured	Not measured
Nutritional parameters				
Serum albumin (g/L)	37.3 ± 2.0[b]	38.7 ± 3.2[a]	41.5 ± 4.1	41.6 ± 4.3
BUN (mmol/L)	24.3 ± 5.6	30.2 ± 7.9[a]	26.9 ± 5.7	28.5 ± 6.6
nPCR (g/kg/day)	1.04 ± 0.24[b]	1.17 ± 0.29[a]	1.19 ± 0.20	1.18 ± 0.22
Bioimpedance analysis				
Intracellular fluid volume (L)	19.7 ± 3.6	20.1 ± 3.6[a]	21.0 ± 4.2	21.1 ± 4.4
Extracellular fluid volume (L)	10.0 ± 1.8[b]	9.6 ± 1.6[a]	11.2 ± 2.4	11.3 ± 2.4
Lean body mass (kg)	42.9 ± 7.5	42.9 ± 7.3	45.4 ± 8.8	45.3 ± 9.2
Fat mass (kg)	8.9 ± 4.2	9.1 ± 4.1	9.6 ± 3.9	9.6 ± 4.0
Other clinical variables				
KT/V_{urea}	1.26 ± 0.26	1.29 ± 0.29	1.28 ± 0.22	1.29 ± 0.26
Bicarbonate (mmol/L)	17.7 ± 2.8	17.6 ± 2.2	17.3 ± 2.9	17.4 ± 3.3
Hematocrit (%)	26.0 ± 3.8	25.9 ± 6.2	25.8 ± 4.3	26.4 ± 5.2
Post-hemodialysis weight (kg)	53.1 ± 9.0	52.8 ± 8.6	55.5 ± 9.8	55.7 ± 9.9
Interdialytic weight gain (kg)	2.25 ± 0.97	2.29 ± 1.97	2.22 ± 1.01	2.37 ± 1.62

Values are expressed as mean ± SD unless otherwise noted.

[a] $P < 0.05$ *versus baseline values of treatment group.*

[b] $P < 0.05$ *versus control group.*

which are well-known markers of dietary protein intake and body protein stores in steady-state chronic hemodialysis patients. Antidepression treatment also significantly increased ICF volume measured by BIA. The hydration state of the ICF reflects water volume occupying the body cell mass, and the changes occur because of changes in the anabolic-catabolic state due to nutritional factors or illness.[23] Therefore, the rise in ICF volume shown in this study could reflect an increased anabolic state. Overall, these findings suggest that antidepression treatment has therapeutic potential for the management of malnutrition in chronic hemodialysis patients with depression.

There is some evidence that major depression is accompanied by activation of the inflammatory response system and that proinflammatory cytokines may play a role in the etiology of depression.[24,25] Proinflammatory cytokines, which are commonly increased in ESRD patients, are responsible for the increased protein catabolism, poor oral intake, and malnutrition in maintenance hemodialysis patients.[12] Accordingly, proinflammatory cytokine-induced chronic inflammation could be a common cause of both depression and malnutrition in chronic hemodialysis patients.

It is also known that different classes of antidepressants, including selective serotonin reuptake inhibitors, reduce the release of proinflammatory cytokines from activated macrophages and increase the release of endogenous cytokine antagonists such as interleukin-1 receptor antagonist and interleukin-10.[26–28] Therefore, antidepressants could reduce cytokine-induced protein catabolism, which will result in improvement of nutritional status in chronic hemodialysis patients. Because improvement of depressive symptoms is usually accompanied by increased oral intake, both decreased protein catabolism and increased protein intake could be possible mechanisms of the beneficial effect of antidepression treatment shown in this study. Unfortunately, indicators of inflammation such as serum high sensitivity C-reactive protein level and change in dietary habits were not measured, and the authors wish to acknowledge the speculative nature of this statement.

Paroxetine is a selective serotonin reuptake inhibitor that was chosen because of its ease of administration (once-daily dosing), absence of active metabolites, and favorable side-effect profile, including lower levels of cardiotoxicity than tricyclic antidepressants.[29] However, the initial dose of 10 mg was maintained without dose modification during the course of this study because of possible side effects and drug interactions. This relatively small dose and the short duration of treatment might be causes of insignificant change in SDS score. If higher dose and longer duration of paroxetine was used, more significant changes in the severity of depression and nutritional parameters could be expected.

This study is limited by its small sample size and lack of an appropriate control group. Our study population was recruited from the single outpatient hemodialysis unit in which all patients had intimate relationships with each other and most of the patients who were diagnosed as having depression wanted antidepression treatment. Because psychosocial support and compliance are associated with reduced mortality in chronic hemodialysis patients,[30] our antidepression treatment included supportive group psychotherapy as well as antidepressant medication. Therefore, we could not assign patients with depression to a placebo-treated control group.

Conclusion

Our study suggests that antidepressant medication with supportive psychotherapy can successfully treat depression and improve nutritional status in chronic hemodialysis patients with depression. Greater attention to the screening of depressive symptoms in chronic hemodialysis patients and the initiation of appropriate antidepression treatment may be needed. A large, controlled multicenter study to evaluate the effect of this therapeutic approach on the mortality and morbidity in chronic hemodialysis patients is required. To clarify the exact role of depression and antidepressant treatment in the pathogenesis and management of malnutrition in chronic hemodialysis patients, further confirmatory studies, including measurement of inflammatory markers and cytokine levels, are also required.

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