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CLINICAL STUDY

The Effect of Strict Volume Control on Cognitive Functions in Chronic Hemodialysis Patients

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Cognitive dysfunction is a well-known complication of chronic renal failure that is evident in 30% of hemodialysis (HD) patients. However, the pathogenesis of this dysfunction is unknown. Left ventricular hypertrophy could develop in hypertensive HD patients without establishing normovolemia. Our aim was to evaluate the effect of strict volume control by salt restriction and ultrafiltration on cognitive functions in HD patients. This cross-sectional study was composed of 22 HD patients who were normotensive by applying a strict volume control, 24 HD patients who were normotensive by receiving anti-hypertensive drugs, and 20 healthy controls. The strict volume control was defined as managing of blood pressure control by strict salt restriction and insistent ultrafiltration. P300 recording as an indicator of cognitive disfunction was measured when blood pressures were reached at target level at the end of six-month follow-up period. In all patients, dimensions of the heart were evaluated with echocardiography on an interdialytic day. The cardiothoracic ratio and echocardiographic dimensions were significantly lower in patients with strict volume control. P300 amplitudes were significantly lower in patients on antihypertensive drugs than in patients with strict volume control (9.5 ± 5.1 versus 11.3 ± 5.4 μV). P300 latency was longer in patients on antihypertensive drugs than in the control group and patients with strict volume control (359.9 ± 39.6 versus 345.6 ± 36.7 ms). Our results suggest that hypervolemia may be one of the causal and potentially modifiable factors of cognitive dysfunction. Strict volume control may have beneficial effects on cognitive functions in hemodialysis patients.

Keywords hemodialysis, strict volume control, echocardiography, left ventricular hypertrophy, cognitive function

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INTRODUCTION

Cardiac death is up to 20 times more frequent in uremic patients than in the general population.[1] It has been accepted that volume overload is the main cause of hypertension in patients on chronic dialysis.[2,3] Hypertension is a major risk factor for cardiac diseases, including left ventricular hypertrophy (LVH), left ventricular dilatation, heart failure, and ischemic heart disease. Among these, LVH has been associated with significantly high cardiovascular mortality in hemodialysis patients. In clinical practice today, the control of hypertension in this population is usually achieved through the use of antihypertensive drugs.[4] However, reversal of hypervolemia through reduced dietary salt intake and ultrafiltration (strict volume control) can also cause a reduction in LVH in dialysis patients, even without the use of anti-hypertensive agents.[5,6]

Central nervous system dysfunction is a well-known complication of chronic renal failure.[7,8] Measurement of cognitive event-related potentials (ERPs) is an objective electrophysiological tool that has been used to investigate cognitive faculty.[9] The P300 cognitive potential obtained from auditory stimuli with oddball paradigm is a commonly used type of ERP.[10–12] Using ERPs, some studies have shown greater cognitive impairment in dialysis

patients than in controls.[13,14] A better understanding of the associations between cognitive impairment and dialysis is needed, as this may help to generate hypotheses regarding mechanisms of disease, as well as to identify potentially modifiable risk factors. Unfortunately, there are relatively few studies that have investigated the risk factors for the development and progression of cognitive impairment in the dialysis population.[15]

The aim of this cross-sectional study was to investigate the effect of strict volume control (strict salt restriction and insistent ultrafiltration) on cognitive function in hemodialysis patients.

PATIENTS AND METHODS

The study was approved by Firat University Ethics Committee. At the dialysis center in the Firat University Medical School, Elazig, Turkey, we used a regimen involving strict volume control. The need for salt restriction was emphasized, by explaining to patients and their families the implications of a salt-restricted diet and the need to avoid ready-made food.[3] Using this approach, the estimated salt intake was limited to around 4–5 g/day. Patients were allowed to drink as much as their thirst indicates, as long as salt was restricted. This approach was often found insufficient, and repeated instructions were required to get patients to change their attitudes. Our current study included 22 hemodialysis patients from our center who had normal blood pressure (BP) maintained by applying a strict volume control and who were not on any antihypertensive drugs. We used a strategy consisting of salt-restricted diet and intensive ultrafiltration to maintain pre-dialysis BP < 140/90 mmHg without any antihypertensive drugs. Until normal blood pressure and normovolemia had been reached, as evidenced by a cardiothoracic index <0.48, post-dialytic weights of patients were lowered by 0.5–1 kg under that of previous postdialysis weight. This caused no hypotensive episodes. Water intake was not restricted in these patients.

The study also included 24 hemodialysis patients from the other dialysis center who were on antihypertensive drugs and who were not following strict volume control. These patients had had normal BP (predialysis BP < 140/90 mmHg) with antihypertensive treatment over the six months prior to the study. Although salt restriction was also recommended in this other center, it was not insisted upon, as it was in our center. Pre-dialysis BP, measured manometrically, was averaged for the last three HD sessions within the week when echocardiography was performed. Twenty age-matched healthy subjects were also included as controls. Informed consent was obtained from all patients and healthy volunteers.

All patients received hemodialysis for 4 h three times weekly, using bicarbonate dialysis fluid and synthetic polysulfone membranes (Fresenius Company, Bad Hamburg, Germany) with a surface area of 1.6 m^2. The blood flow was 250–300 mL/min, and the dialysate flow was 500 mL/min. Ultrafiltration was controlled volumetrically.

Patients with any history of stroke, infection, malignancy, severe hyperparathyroidism, primary neurological and psychiatric disorder, or diabetes mellitus were excluded. In group A, primary renal diseases were glomerulonephritis (12), hypertension (6), polycystic kidney disease (2), and unknown (2). Patients were selected by matching the groups for age, duration of dialysis, and education. Patients with poorly controlled hypertension were not included in the study. Prior to dialysis, BP was measured using a sphygmomanometer, and the mean of at least three consecutive predialysis values were calculated for each patient. Blood samples for laboratory analysis were also taken before dialysis and stored at −20 °C.

Testing Procedure

P300 cognitive potential was measured on an interdialytic day in all dialysis patients. Even-related potentials were recorded with an EMG machine (Dantec key point model 4-EMG/Evoked Potential) in a silent room. P300 cognitive potential was obtained from auditory stimuli with the oddball paradigm. Event-related potentials were elicited by binaural acoustic stimuli: 200 clicks were delivered randomly by the computer. Frequent tones comprised 80% of the signal frequencies, which were set at 1 kHz, while the remaining 20% were comprised of rare tones at 2 kHz. During the examination, the subjects were asked to count the perception of the rare tones (i.e., the designed target stimuli). The recording was performed with silver disk electrodes placed on the scalp. The latency of P300 cognitive potential was measured from the onset to the peak of the largest positive-going peak. The amplitude was measured peak-to-peak for the P300 wave.

Echocardiography

All patients underwent echocardiography on an interdialytic day. Echocardiographic examination was performed using an ATL-Ultramark 9 ultrasonoscope with a 2.5–7.0 MHz transducer (Advanced Technology Laboratories, Bothell, Washington, USA), in accordance with the American Society of Echocardiography recommendations. All measurements were made by an experienced echocardiographer who was blinded to the patients. Each measured

value was averaged over three cardiac cycles. The left atrial size and the left ventricular end-systolic and end-diastolic diameters were indexed by body surface area. The left ventricular mass index (LVMI) was calculated using the following equation:[16]

$$\text{LVMI}\,(\text{g/m}^2) = 1.04 \times [(\text{IVST} + \text{LVDd} + \text{PWT})^3] - (\text{LVDd})^3 \times 0.8 + 0.6 / \text{body surface area}$$

where IVST is the interventricular septum thickness, LVDd is the left ventricular end-diastolic dimension, and PWT is the posterior wall thickness.

Statistical Analysis

Mann-Whitney U, independent samples t, and Spearman correlation tests were used for statistical analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Baseline demographic, clinical, and laboratory data for all patients and controls in the study are presented in Table 1. The number of patients on erythropoietin was similar between both groups (9/22 in patients applying strict volume control, 9/24 in patients on antihypertensive drugs), but the mean erythropoietin dose was higher in patients on antihypertensive drugs (8000 units/week vs. 4000 units/week). All patients and healthy controls had graduated from primary school; none had graduated from high school.

Thirty percent of patients on antihypertensive drugs required a combination of three anti-hypertensive drugs (calcium channel blockers, angiotensin converting enzyme inhibitors, and vasodilatators) to control their blood pressure, while the remaining 70% received two anti-hypertensive drugs (calcium channel blockers and angiotensin-converting enzyme inhibitors). In both groups, the mean BP was lower than 140/90 mmHg; however, the mean BP was significantly lower in patients applying strict volume control than in patients on antihypertensive drugs (112.7 ± 13.5/70.0 ± 12.3 mmHg, 133.7 ± 12.0/85.8 ± 12.4 mmHg, respectively, $p < 0.01$). Interdialytic weight gain was significantly higher in patients on antihypertensive drugs than in patients applying strict volume control.

The echocardiographically measured dimensions of the heart were significantly larger in patients on antihypertensive drugs, compared with patients applying strict volume control. Left atrial diameter and interventricular septum thickness were similar in both groups. Systolic function, as evidenced by ejection fraction of the left ventricle, was higher in patients applying strict volume control (see Table 2). Mean LVMI was significantly higher in patients on antihypertensive drugs than in patients applying strict volume control (144.1 ± 37.9 vs. 102.5 ± 24.0, $p < 0.001$).

The results of P300 latency and amplitudes are shown in Table 3. P300 amplitudes were significantly lower in patients on antihypertensive drugs than in the controls or in patients applying strict volume control. P300 latency

Table 1
Demographic and laboratory parameters among groups

	Control (n = 20)	Patients applying strict volume control (n = 22)	Patients on antihypertensive drugs (n = 24)	*p*
Age (y)	41.1 ± 14.2	42.0 ± 15.1	42.7 ± 12.9	
Sex (M/F)	10/10	12/10	12/12	
Dialysis duration (months)	—	52.5 ± 20.3	52.2 ± 27.2	
Systolic blood pressure (mmHg, pre-dialysis)	115 ± 14.2	112.7 ± 13.5	133.7 ± 12.0	<0.01
Diastolic blood pressure (mmHg, pre-dialysis)	72 ± 10.3	70.0 ± 12.3	85.8 ± 12.4	<0.01
Interdialytic weight gain (g)	—	1750 ± 589	2979 ± 457	<0.01
Hemoglobin (g/dL)	13.2 ± 2.2	11.2 ± 1.0	10.9 ± 0.6	
Hematocrit (%)	39.7 ± 5.9	34.3 ± 3.4	33.1 ± 2.1	
Serum albumin (g/dL)		4.1 ± 0.2	3.9 ± 0.4	
Parathormon (ng/L)		265.8 ± 159.3	209.0 ± 162.2	
Total cholesterol (mg/dL)	175.5 ± 22.2	198.0 ± 51.8	199.2 ± 38.7	
Cardiothoracic ratio (%)		43.8 ± 3.3	46.2 ± 3.7	<0.05
Kt/V_{urea}		1.5 ± 0.2	1.4 ± 0.3	

Abbreviation: P = patients applying strict volume control versus patients on antihypertensive drugs.

Table 2
Echocardiographic findings of study groups

	Patients applying strict volume control (n = 22)	Patients on antihypertensive drugs (n = 24)	*p*
IVS (mm/m^2)	11.0 ± 1.7	11.3 ± 2.3	
PWT (mm/m^2)	10.1 ± 1.3	12.0 ± 2.4	<0.005
LVMI (g/m^2)	102.5 ± 24.0	144.1 ± 37.9	<0.001
EF (%)	63.4 ± 8.9	58 ± 8.4	<0.05
LA (mm/m^2)	23.2 ± 3.4	23.6 ± 3.5	
LVDd (mm/m^2)	28.1 ± 2.6	31.6 ± 3.5	<0.001

Abbreviations: IVS = interventricular septum thickness, PWT = posterior wall thickness, LVMI = left ventricular mass index (<125 g/m^2), EF = ejection fraction, LA = left atrium diameter, LVDd = left ventricle end diastolic diameter, P = patients applying strict volume control versus patients on antihypertensive drugs.

was longer in patients on antihypertensive drugs than in the controls or in patients applying strict volume control. There was a positive correlation between P300 latency and age in patients on antihypertensive drugs (r = 0.558, $p = 0.004$).

DISCUSSION

Neuropsychological and neurophysiological tests can be used to assess cognitive function. Neurophysiological tests use electrophysiological methods (e.g., electroencephalograms and ERPs) to assess cognitive dysfunction.[17] Prolongation of P300 latency was shown to be the earliest sign of cognitive dysfunction in metabolic encephalopathies, including uremic encephalopathies.[11,12] ERP measurements provide a sensitive and useful quantitative method to assess cognitive function in chronic kidney disease.[10,18]

Cognitive decline in chronic kidney disease can be caused by various factors including uremic encephalopathy, complications of dialysis procedure, uremia per se, high prevalence of clinical and subclinical cerebrovascular disease, or a number of comorbidities (anemia, hypertension, diabetes, malnutrition, etc.) afflicting these patients.[8,19] Previous studies have generally examined the incidence and prevalence of cognitive impairment in hemodialysis patients. Sehgal et al.[20] performed a cross-sectional study of 336 hemodialysis patients. Cognitive impairment was evident in 30% of patients and was associated with more hospitalizations. Earlier studies have also reported improved cognition with dialysis.[21–23]

There are limited data regarding the risk factors on development and progression of cognitive dysfunction in dialysis patients. Kurella et al.[7] called for further studies to determine the reasons for cognitive impairment in subjects with end stage renal disease. Improved cognition has been seen with the use of erythropoietin in anemic dialysis patients.[24–26] In the present study, there was no significant correlation of hemoglobin with P300 latency. Our patients showed no severe anemia, which may explain why we did not find any correlation. However, the change in cognition is unlikely to be related to hemoglobin levels.

The relationship between volume status and cognitive function has not yet been investigated in chronic hemodialysis patients. In agreement with our previous studies,[27,28] we found that strict fluid volume control decreases BP, reduces dilated cardiac compartments, and corrects left ventricular hypertrophy. While the BP levels in patients on antihypertensive drugs were only slightly higher (not statistically significant) than those in patients applying strict volume control, the echocardiographic findings support the idea that patients on antihypertensive drugs had a persistent, discrete degree of volume expansion. While it has been reported that LVH is mostly persistent and progressive, despite anti-hypertensive drug treatment,[29] some studies have shown a remarkable reversal of LVH in ESRD patients treated by strict fluid volume control

Table 3
Electrophysiological studies in control and patient groups

	Control (n = 20)	Patients applying strict volume control (n = 22)	Patients onantihypertensive drugs (n = 24)	*p*
Age (year)	43.7 ± 8.0	42.0 ± 15.1	42.7 ± 12.9	
P300 latency (ms)	321.6 ± 28.3	345.6 ± 36.7	359.9 ± 39.6	<0.05*†, <0.001‡
P300 amplitde (μV)	12.4 ± 5.3	11.3 ± 5.4	9.5 ± 5.1	<0.05†‡

*Control vs. patients applying strict volume control.
†Patients applying strict volume control vs. patients on antihypertensive drugs.
‡Control vs. patients on antihypertensive drugs.

without drugs.[5,27,28] In the current study, we demonstrated better cognitive function in patients undergoing strict volume control who were normotensive without drugs. These beneficial effects of this normovolemic normotension may be due to the improvements in microvascular structure, tissue perfusion, inflammation, and oxidative stress. Jassal et al.[30] suggested that nocturnal hemodialysis may be associated with improved cognitive function. Although their study had not been designed to identify why cognition may improve with nocturnal hemodialysis, they suggested many hypothetical reasons, including improved toxin clearance, improved parathyroid hormone control, and changes in blood pressure or in blood pressure medications. In our study, serum parathyroid hormone levels were found similar in both groups. We found no statistical difference in the adequacy of dialysis as determined by urea kinetic modeling (Kt/V) between the two groups. Therefore, the difference in cognitive function between hemodialysis patients applying strict volume control and patients on antihypertensive drugs indicates that it is the decrease in volume that may be more important, rather than the reduction in blood pressure.

Although our results are somewhat intriguing, one should also consider the limitations of this study. The number of patients studied was relatively small. The other limitation is that we could not use more modern methods such as cardiothoracic ratio and echocardiography, in place of our clinical criteria, to assess volume status. The third limitation involves the lack of cross-sectional analysis.

In conclusion, strict volume control may have beneficial effects on cognitive function in hemodialysis patients. Hypervolemia may be one of the causal and potentially modifiable factors of cognitive dysfunction in these patients. In order to study the effect of hypervolemia on cognitive function, other potential causes of cognitive decline in dialysis patients have been excluded.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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