

## Effects of Hemodialysis on Visual Pathways Assessed by Visual Evoked Potentials (VEPs)

### Hemodiyaliz Görmeye Yolları Üzerine Etkisinin Vizüel Uyandırılmış Potansiyeller (VEP) Yardımıyla İncelenmesi

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#### ABSTRACT

**Introduction:** Uremia is a metabolic disorder that affects the functions of the central nervous system (CNS). Visual evoked potentials (VEPs) can be used to demonstrate uremia-induced effects on the CNS. Data on VEPs of patients with chronic renal failure (CRF) are limited. The purpose of this study was to examine the effects of renal failure and the ultrafiltration rate (UFR) on CNS functions in patients undergoing hemodialysis (HD) using VEPs.

**Methods:** The study consisted of 30 CRF patients undergoing HD, and a control group of 28 individuals, matched in terms of age and gender. Patients with mental retardation, diabetes mellitus, demyelinating disease, stroke, use of neurotoxic drugs, and ophthalmologic diseases were excluded from the study. The pattern VEP (PVEP) parameters recorded were latencies to N75 (N1), P100 (P1) and N135 (N2) waves, and the peak-to-peak amplitude of a P100 wave. The PVEP was taken twice just before and 24 h after HD, and the PVEP parameters were compared. Additionally, the effect of the UFR on the PVEP parameters was examined.

**Results:** There was no difference between the HD group and control group in terms of gender and age (mean ages of 49.56±12.52 and 48.53±13.28 years, respectively). The average HD period was 87.53±56.34 months. The P1 latencies between the two eyes the patients with CRF were prolonged when compared to those of the controls (right eye p=0.002; left eye p=0.019). A single HD session significantly shortened the latency of the P1 waves compared to that of the baseline waves (p<0.000). Additionally, there was a positive correlation between the difference in the P1 latency before and after HD and the UFR (right eye p=0.03, r=0.525; left eye p=0.022, r=0.417, respectively).

**Conclusion:** We conclude that VEP, which is an easy, cheap, and simple electrophysiological method, can be used to determine subclinical CNS dysfunction in patients with CRF and show the effect of fluid removal during HD on the visual pathways, and to show the corrective effect of effective fluid imaging on the visual pathways.

**Keywords:** Chronic renal failure, visual evoked potentials, hemodialysis

#### ÖZ

**Amaç:** Üremi santral sinir sistemi (SSS) fonksiyonlarını etkileyen metabolik bir bozukluktur. Bu etkilenmeyi göstermek için kullanılan tanı yöntemlerinden biri de görsel uyandırılmış potansiyellerdir (visual evoked potential; VEP). Kronik Böbrek Yetmezliği (KBY) hastalarında VEP ile ilgili veriler sınırlıdır. Bu çalışmada KBY nedeni ile hemodiyaliz uygulanan hastalarda böbrek yetmezliğinin ve diyalizde çekilen sıvı miktarının (UFR) SSS fonksiyonları üzerine etkisinin VEP yardımı ile incelenmesi amaçlanmıştır.

**Yöntem:** Bu çalışmaya KBY nedeni ile hemodiyaliz tedavisi uygulanan 30 hasta ve yaş, cinsiyet bakımından benzer özelliklere sahip 28 sağlıklı kontrol alındı. Mental retardasyon, diabetes mellitus, demyelinizan hastalık, inme, nörotoksik ilaç kullanımı, oftalmolojik hastalıklar çalışma dışında bırakıldı. VEP parametrelerinden N75 (N1), P100 (P1) ve N135 (N2) latansları ile P100 dalgasının amplitüdü kayıtladı. Hemodiyalizden hemen önce ve 24 saat sonra olmak üzere 2 kez VEP çekimi yapıldı ve VEP parametreleri karşılaştırıldı. Ayrıca, diyalizde çekilen sıvı miktarının VEP parametreleri üzerine etkisi araştırıldı.

**Bulgular:** Hemodiyalize giren hastalar ile kontrol grubu arasında yaş ve cinsiyet açısından farklılık yoktu (ortalama 49,56±12,52 ve 48,53±13,28 yıl). Ortalama hemodiyaliz süresi 87,53±56,34 ay idi. KBY'li hastaların her iki göz P1 latansları kontrol grubuna göre uzamış olarak saptandı (sağ göz p=0,002, sol göz p=0,019). Tek bir hemodiyaliz seansında ilk ölçüme göre P1 latansında önemli bir azalma gözlemlendi (p<0,000). Ayrıca, hemodiyaliz öncesi ve sonrası P1 latans farkı ile diyalizde çekilen sıvı miktarı arasında da pozitif korelasyon mevcuttu (sırasıyla, sağ göz p=0,03, r=0,525; sol göz p=0,022, r=0,417).

**Sonuç:** Kolay, ucuz ve basit bir elektrofizyolojik yöntem olan VEP'in, KBY'li hastaların subklinik SSS disfonksiyonunu saptamada ve etkin sıvı çekiminin görme yolları üzerine olan düzeltici etkisini göstermede kullanılabileceği kanısındayız.

**Anahtar Kelimeler:** Kronik böbrek yetmezliği, görsel uyandırılmış potansiyeller, hemodiyaliz

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## INTRODUCTION

Chronic renal failure (CRF) is characterized by abnormal kidney function, and a progressive decline in the glomerular filtration rate for different pathological reasons (1). In cases where the glomerular filtration rate is less than 15 mL/min/1.73 m<sup>2</sup>, renal replacement treatment is administered. Hemodialysis (HD), peritoneal dialysis, and kidney transplantation are applied as renal replacement treatments. The toxins that accumulate in patients with CRF affect various systems and organs in the body, including the central nervous system (CNS), with neurological, behavioral, emotional, and cognitive disorders occurring, depending on increases in parathormone, creatinine (Cr), and urea levels and electrolyte imbalances in the blood (2–4). Analyses of electrophysiological parameters, such as VEPs can aid the diagnosis of CNS dysfunction. VEPs can be particularly useful, as they are a noninvasive electrophysiological measurement, and can be easily applied (5, 6). Various techniques can be used to determine the VEP which is a time-dependent cortical response to a result of a stimulus. A checkboard pattern with consecutive contrast changes is often used as a stimulus. This produces a so-called pattern VEP (PVEP). This response, which reflects the transmission of the action potential from the central retina to the occipital cortex, is recorded using surface electrodes and amplifiers. An abnormal VEP response is present in numerous diseases that affect the optic nerve, including rheumatologic diseases, spinocerebellar degeneration, multiple sclerosis, and migraine (7–9). Some studies have suggested that among VEP parameters, the P1 latency is prolonged in patients with CRF, but the reason has not been specified (5, 6). To the best of our knowledge, there have been no studies of the correlation between the amount of fluid removed during HD and P1 latency.

The purpose of this study was to examine the effects of renal failure and HD on the visual pathways of CRF patients undergoing HD by analyzing their VEPs. The study also aimed to investigate the effect of the fluid removed during HD on the latency of P1 waves.

## METHODS

The HD group consisted of 30 patients diagnosed with CRF who had undergone bicarbonate-based low-flux HD for 4 h/day, 3 days/week for at least 6 months at Sakarya University Training and Research Hospital Department of Nephrology, and a control group of 28 individuals matched in terms of age and gender. The approval of the local ethics committee was obtained, and all the patients signed a written informed consent form. Patients with comorbidities such as mental retardation, diabetes mellitus, demyelinating disease and stroke, and ophthalmologic diseases (cataract, glaucoma, and retinopathy), in addition to those taking neurotoxic drugs were excluded from the study. The patient's demographic data, HD period, mean arterial pressure (MAP) values before and after HD, and ultrafiltration rate (UFR) were recorded, as well as their hemoglobin (Hgb), hematocrit (Hct), platelet (Plt), sodium (NA), phosphor (P), urea, Cr, parathyroid hormone (PTH), and urea reduction rate (URR). The PVEP measurements of the CRF patients were performed in the electrophysiology laboratory just before and 24 h after HD, with the latencies to N1, P1, and N2 waves, and peak-to-peak amplitudes of a P100 wave recorded.

A 4-channel Nihon Kohden Neuropack EMG machine (Nihon Kohden Corporation, Tokyo, Japan) with an analysis time of 500 msec and sweep speed of 50 msec was used to record the PVEP measurements. The low- and high-frequency filter settings were 1.0 and 100 Hz, respectively. During the test, all the patients were seated in a semi-darkened room, and the stimulus was presented on a television monitor 100 cm away from the tested eye. The pattern stimuli appeared on a 15-inch monitor. Each frame alternating checkboard pattern with the edge of 7 mm was used as the stimulus pattern. The display illumination was 100 cd/m<sup>2</sup>, the contrast between the black and white squares was 99%, and the pattern conversion rate was 2/sec. The monitor had the appearance of a chessboard, which converted the black squares to white, and the white ones to black (pattern reversal). The patients were asked to close one eye at a time while looking at a fixed point in the middle of the monitor. The PVEP was recorded using silver cup electrodes positioned at Oz (active electrode) and Fz (reference electrode, 10/20 system) points of the scalp.

A ground electrode was placed on the right forearm. An average of 200 runs was taken. At least two tracings were recorded for each eye.

## Statistical Analysis

For the statistical analysis, the averages of the N1, P1, N2, and peak-to-peak amplitude of the P100 wave were taken. Additionally, the VEP components were determined according to their latencies: N1 was defined as a negative peak, with a latency of 60 and 90 msec, P1 was classified as a positive peak following N1, with a latency of 80 and 110 msec; and N2 was defined as a negative peak following P1 with a latency of 125 and 150 msec. The peak-to-peak amplitude of N1-P1 was measured. All the measurements were taken by the same physician. The latencies to the N1, P1, and N2 waves, and the peak-to-peak amplitudes of P100 waves obtained from the CRF patients were compared with those of the control group.

A paired t-test was used to compare the VEP parameters just before and 24 h after HD. Correlation analyses was performed to determine the impacts of the effects of UFR, MAP, Hgb, Hct, Plt, NA, P, urea, Cr, PTH, and URR on the VEP parameters.

SPSS Statistics for Windows, Version 21.0, released 2012 (IBM Corp., NY, USA.) was used for the analysis of the study data. The conformation of the data to a normal distribution was checked. For data with a normal distribution, a t-test was used to compare the data from two independent groups, and the Mann-Whitney U test was used to analyze data without a normal distribution. A paired-samples t-test was used for the comparison of parametric data among the groups. The limit for statistical significance was accepted as  $p < 0.05$ .

## RESULTS

The study included 13 female and 17 male HD patients. The average age was 49.56±12.52. The average duration of dialysis was 87.53±56.34. There was no significant between-group difference in age and gender. Statistically significant differences were detected in the Hgb, Hct, urea, Cr, and P levels of the control group compared to those of the HD group ( $p < 0.005$ ). Table 1 shows the demographic data and laboratory parameters of the HD group, and those of the control group.

**Table 1.** Demographic characteristics, clinical characteristics, and laboratory parameters of the HD group and control group

	HD group	Control group	p
<b>Gender (m/f)</b>	<b>18/12</b>	<b>17/11</b>	<b>0.791</b>
	<b>Mean±SD</b>	<b>Mean±SD</b>	
Age	49.56±12.52	48.53±13.28	0.216
Average dialysis period (month)	87.53±56.34	-	
MAP (mm/Hg) before dialysis	93.71±10.43	-	
MAP (mm/Hg) after dialysis	83.87±10	-	
UFR (lt)	2.7±1.02	-	
Hgb (gr/dL)	10.97±1.48	12.7±1.15	0.001
Hct (%)	33.25±4.51	37.8±2.6	0.003
Urea (mg/dL)	122.04±24.89	29.3±6.2	<0.001
Cr (mg/dL)	8.9±1.86	0.7±0.16	<0.001
URR (%)	0.83±0.06	-	
PTH (pg/mL)	547.91±443.57	-	
P (mEq/dL)	4.85±1.2	3.47±0.37	0.001

MAP, mean arterial pressure; UFR, ultrafiltration rate; Hgb, hemoglobin; Hct, hematocrit; Cr, creatinine; URR, urea reduction rate; PTH, parathormone; P, phosphorus.

**Table 2.** Comparison of the VEP parameters of the before HD group versus those of the control group and the VEP parameters of the before HD group versus those of the after HD group

	Before HD	Control group	p	Before HD	After HD	p
Right eye N1 latency (msec)	73.43±8.46	71.97±6.94	0.468	73.43±8.46	73.25±7.16	0.874
Left eye N1 latency (msec)	74.35±10.71	70.88±8.08	0.163	74.35±10.71	73.74±7.92	0.640
Right eye P1 latency (msec)	103.39±6.15	98.67±5.37	0.002	103.39±6.15	97.30±8.27	<0.000
Left eye P1 latency (msec)	102.95±6.38	98.86±6.78	0.019	102.95±6.38	96.53±7.49	<0.000
Right eye N2 latency (msec)	122.21±12.11	121.97±11.74	0.938	122.21±12.11	118.89±10.49	0.026
Left eye N2 latency (msec)	122.9±12.9	121.67±11.97	0.684	122.9±12.9	119.7±13.4	0.067
Right eye P100 amplitude (µV)	6.1±1.62	5.93±1.23	0.656	6.1±1.62	6.07±1.5	0.851
Left eye P100 amplitude (µV)	5.97±1.49	6±1.23	0.925	5.97±1.4	5.77±1.4	0.136

**Table 3.** Correlations of the left and right eye P1 latencies of the before HD group with biochemical parameters

		Hgb	Hct	Urea	Cr	PTH	NA	P	Plt
Right eye P1 latency	r	0.236	0.245	0.156	0.012	0.411	0.11	0.274	0.352
	p	0.205	0.192	0.411	0.949	0.024	0.561	0.143	0.056
Left eye P1 latency	r	0.263	0.258	0.115	0.257	0.503	0.036	0.269	0.165
	p	0.161	0.165	0.544	0.17	0.005	0.848	0.055	0.372

Hgb, hemoglobin; Hct, hematocrit; Cr, creatinine; PTH, parathormone; NA, sodium; P, phosphorus; Plt, platelet.

**Table 4.** Correlations between the UFR, MAP, and URR and differences in the P1 latencies and peak-to-peak amplitude of the P100 wave before and after HD

			UFR	MAP	URR
Right eye	P1 latency	r	0.525	0.128	0.117
		p	0.03	0.501	0.538
	amplitude	r	0.102	0.007	0.083
		p	0.582	0.969	0.664
Left eye	P1 latency	r	0.417	0.11	0.031
		p	0.022	0.556	0.871
	amplitude	r	0.148	0.062	0.03
		p	0.435	0.745	0.874

UFR, ultrafiltration rate; MAP, mean arterial pressure; URR, urea reduction rate.

When the P1 latency of the right eye and P1 latency of the left eye of the before HD group were compared to those of the control group, a significant difference was detected ( $p<0.005$ ). There was also a significant difference in the P1 latency of the right eye and P1 latency of the left eye in the after HD group, as compared to these parameters in the control group ( $p<0.005$ ). The comparison of the before HD group with the after HD group revealed a significant difference in right eye N2 latency ( $p=0.026$ ).

Table 2 shows the latencies to the N1, P1, and N2 waves, and the peak-to-peak amplitudes of the P100 waves of the before HD group, control group, before HD group, and after HD group. The P100 latency of three patients in the HD group was longer than normal in both eyes. In two of these patients, the P1 latencies of both eyes after HD returned to normal levels. The P1 latency of the third patient did not return to normal levels, although it shortened. After HD, the P1 latency decreased substantially in 25 of the patients. The other five patients did not experience a substantial reduction.

Table 3 shows the results of the correlations of the left and right eye P1 latencies with Hgb, Hct, urea, Cr, PTH, NA, P, and Plt values. There was a positive correlation in the before HD group between the left eye and right eye P1 latencies and PTH (right eye  $p=0.024$ ,  $r=0.411$ ; left eye  $p=0.005$ ,  $r=0.503$ ), as shown in Table 3.

There was a significant difference between the UFR and P1 latencies in the before and after HD groups ( $p=0.022$ ,  $r=0.417$ ;  $p=0.03$ ,  $r=0.525$ , respectively). There was no significant difference between the MAP and P1 latencies and peak-to-peak amplitudes of the P100 waves of both eyes, or between the URR and these parameters (Table 4).

## DISCUSSION

In this study, a number of VEP parameters, the N1 latency, P1 latency, N2 latency, and peak-to-peak amplitudes of the P100, of a HD group, and control group were evaluated. Additionally, the effect of HD on laboratory parameters, including the MAP and UFR, on VEPs were investigated. In the present study, the P1 latency of the HD group was prolonged compared to that of the control group. We found no correlation between the VEP parameters and MAP, and laboratory findings in the HD group. The P1 latency before HD was prolonged compared to that after HD. There was a positive correlation between the P1 latencies, and the UFR before and after HD.

Via the study of VEP parameters, the ultimate aim was to determine the beneficial effects of HD, and the impact of the fluid removed during HD on subclinical CNS dysfunction, and pathologies related to eyesight in CRF patients. We postulated that the fluid removed during HD not only adjusted liquid levels in the body but also improved VEP parameters.

Previous studies reported that uremic toxins that accumulated in patients with CRF by affected the CNS, and caused various problems, such as stupor, coma, speech disorders, sleeping disorders, dementia, convulsion, polyneuropathy, headaches, dizziness, irritability, cramp, concentration disorders, fatigue, and restless leg syndrome (3–10). The patients included in the present study had no neurological complaints, and the results of

neurological examinations were normal. The analysis of the VEPs of these patients was aimed at the detection of subclinical CNS function disorders. A previous VEP study group reported an N1 of 62–67 msec, P1 of 88–93 msec, and N2 of 136–149 msec (11). In the present study, the average N1 of the HD group was  $73\pm 8.4$  msec, whereas the P1 and N2 was  $103\pm 6.1$  msec and  $122\pm 12.1$  msec, respectively. In the control group, the average N1, P1, and N2 was  $71\pm 6.9$  msec,  $98\pm 5.4$  msec, and  $121\pm 11.7$  msec, respectively. Gender-comparative VEP study reported that the N1, P1, and N2 latencies were longer in men than in women (11). The gender distribution of the study groups may explain differences in recorded VEP parameters. In our study, the gender distribution of the HD group and control group was similar.

Previous studies that analyzed the VEPs of patients with CRF reported prolongation in P1 latency (5, 6, 8, 12). Similarly, in the present study, the P1 latency before HD was prolonged compared to that of the control group. In addition, the N1, N2, and peak-to-peak amplitudes of the P100 waves of the before HD group were similar to those of the control group.

Previous research demonstrated that the accumulation of neurotoxins was responsible for the prolongation of P1 latency in CRF patients undergoing HD. Lewis et al. suggested that underlying dysfunction of the neural system, together with a reduction in the cortical suppression of afferent stimulation normally exerted by the thalamic reticular system, and the basal ganglia, might account for abnormal VEP findings, such as prolonged latencies, in HD patients (12, 13).

A few studies reported that HD had a positive effect on VEP parameters in CRF patients. These studies observed a shortening in P1 latency, and an increase in the peak-to-peak amplitude of P100 waves due to HD (6, 12). In the present study, among the VPE parameters, although HD shortened the P1 latency and N2 latency of the left eye, there was no significant change in the N1 and peak-to-peak amplitudes of P100 waves. The reason for the reduction in the P1 latency is unclear. It may be due to differences in the MAP, URR, and UFR. There was a positive correlation between the UFR and the reduced P1 latencies, illustrating the beneficial effect of effective fluid removal on VEP parameters. The decrease in cerebral blood flow and pressure due to fluid removal may also explain this beneficial effect.

Previous studies found no correlation between biochemical values and VEP parameters (14). However, one study found a weak correlation between P1 latencies and PTH values (5). In the present study, the VEP parameters were not correlated with the laboratory values Hb, Hct, BUN, Cr, P, and NA. However, there was a positive correlation between PTH and P1 latency in both eyes. This can be explained by the impact of various factors, including dietary protein intake and lean body mass, on levels of serum urea and Cr, both of which are small-molecular weight nitrogenous waste products, and potentially toxic to the CNS. Furthermore, studies have shown that the retention of some middle molecular weight substances were correlated with uremic neurotoxicity. Another study highlighted the role of the toxic effects of PTH in changes in VEP values between two HD sessions (6).

One limitation of the present study is the small number of patients. Another limitation is that additional comorbid diseases were excluded according to the anamnesis information, clinical evaluation, and laboratory findings of the patient's history, clinical evaluation, and laboratory findings. Thus, some of the patients may have had underlying comorbid diseases that were not recorded.

In conclusion, VEP is a simple, cost-effective, and noninvasive method, which can be applied to illustrate the beneficial effect of fluid removal, and detect subclinical CNS dysfunction in CRF patients in the period prior to the appearance of clinical findings. The present study sheds light on the importance of volume control in CRF patients undergoing HD, and the impact that fluid control may have on CNS dysfunction in HD patients.

**Ethics Committee Approval:** Approval of the ethics committee was taken from the Ethics Committee of Sakarya University.

**Informed Consent:** Written informed consent form was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

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