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Correlation between nerve conduction changes and BETA-2 microglobulin concentration in chronic kidney disease patients on hemodialysis combined with hemodiafiltration online

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Abstract

This study aimed to investigate the correlation between beta-2 microglobulin (B2M) concentration and some nerve conduction indices and evaluate the changes in some nerve conduction indices after treatment with hemodialysis (HD) combined with hemodiafiltration online in end-stage renal disease patients. From July 2021 to July 2022, a cross-sectional study was conducted on 80 end-stage renal disease patients on HD at Can Tho General Hospital, Viet Nam. All the patients had B2M testing and nerve conduction measurements. Patients with nerve conduction disorders were treated and remeasured after 6 months to evaluate the treatment results. At baseline, there was a moderate negative correlation between B2M and the tibial nerve and motor branch of the ulnar conduction velocity (V) (r = –0.305 and –0.315, $P < .05$). There was a moderate positive correlation between B2M and motor latency of the tibial and peroneal nerve (r = 0.434 and 0.440, $P < .05$). After 6 months of using the combination of HD and hemodiafiltration online, the V (31.3 ± 7.96 up to 44.88 ± 9.67 m/s) and the amplitude (A) (1.71 ± 1.16 up to 2.61 ± 1.51 mV) of the peroneal nerve increased, the motor latency decreased (8.21 ± 2.65 down to 5.23 ± 3.58 ms). With the tibial nerve, motor conduction V increased from 30.53 ± 8.05 m/s to 43.56 ± 8.99 m/s and the A increased from 5.04 ± 3.16 mV to 7.75 ± 4.45 mV. With the ulnar nerve, the A increased, and motor latency decreased after 6 months. The nerve conduction indices also improved significantly in the median nerve.

Abbreviations: A = amplitude, B2M = beta-2 microglobulin, BMI = body mass index, ESRD = end stage renal disease, HD = hemodialysis, HDF-Online = hemodiafiltration online, V = velocity.

Keywords: beta-2 microglobulin, Can Tho, end-stage kidney disease, nerve conduction, Viet Nam

1. Introduction

Patients with chronic kidney disease are at risk of many complications such as anemia, malnutrition, heart failure, renal osteodystrophy, peripheral neuropathy, etc. In particular, peripheral neuropathy occurs at a relatively high rate, especially in patients with end-stage renal disease (ESRD) on hemodialysis (HD). Many studies suggest that this problem is associated with an increase in medium-weight uremic toxins, including beta 2 microglobulin (B2M).[1] The diagnosis of peripheral neuropathy is based mostly on the measurement of nerve conduction.[2] Treatments for peripheral neuropathy in ESRD patients include adequate dialysis, vitamin supplementations, analgesics, and dialysis by hemodiafiltration (HDF).[3] In particular, HDF, especially hemodiafiltration online (HDF-online) has a good effect on the elimination of medium and large-weight uremic toxins, thereby improving symptoms in patients with peripheral neuropathy. Many recent studies around the world have demonstrated the role of HD and HDF-online in the treatment of peripheral neuropathy.[4] However, in the Mekong Delta region, Vietnam has not had many studies on the effectiveness of this measure in patients with chronic kidney disease. This study aimed to investigate the correlation between B2M concentration with the changes of some nerve conduction indices and evaluate the changes of some nerve conduction indices in ESRD patients after standard HD combined with HDF-online.

2. Methods

2.1. Patients

1.2.1. Inclusion criteria. ≥18 years old; diagnosed ESRD with glomerular filtration rate <15 mL/min/1.73 m^2 lasting more than 3 months (according to KDIGO);[5] patients were undergoing

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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dialysis with the same filtration regimen: the same bicarbonate dialysis fluid, a low ultrafiltration coefficient K_{UF} = 10 mL/hour/mm Hg; and agreed to participate in the study.

2.2.1. Exclusion criteria. Patients with diabetes, stroke, HIV/AIDS, acute medical conditions such as acute gout attack, severe infection, myocardial infarction, acute heart failure, stroke, severe gastrointestinal bleeding, etc. Patients did not cooperate in research, or were transferred to another hospital.

2.2. Study design and variables

Study design: a cross-sectional descriptive study.

Sampling method: nonprobability convenience sampling, actually selected 80 patients.

Data collection method: all 80 patients were tested for B2M concentration before the first dialysis of the week and measured nerve conduction in both limbs by only 1 doctor using Neuropack S1 EMG measuring system at Can Tho General Hospital, Viet Nam. There were 57 patients, who had nerve conduction disorders (defined as having disorders of at least 2 nerve conduction indices), were treated with a combination of HD and HDF-online once every 1.5 months (according to the protocol of the Ministry of Health of Vietnam). After 6 months, these patients had a second nerve conduction measurement to evaluate the treatment results. Because the results on the 2 sides were almost similar, we only chose the results in the left limb for analysis.

1.2.2. Research variables. - *General characteristics*: gender, age, body mass index (BMI), the concentration of urea, creatinine, Kt/V index, serum albumin.

- *Nerve conduction indices:*

+ Conduction velocity (V): motor nerve (the tibial, peroneal, ulnar, and median nerve) and sensory (the ulnar and median nerve).

+ Amplitude (A) response: motor nerves (the tibia, peroneal, ulnar, and median nerve) and sensory nerves (the ulnar and median nerve).

+ Distal latency of the peroneal, tibial, ulnar, and median nerve.

- *Find the correlation between B2M concentration and nerve conduction indices before dialysis.*

- *Compared the changes in nerve conduction indices after 6 months of treatment using the combination of HD and HDF-online.*

2.3. Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Science (SPSS) for windows, version 22.0 (IBM Corp, Armonk, NY).

Paired samples *t* test were used when comparing 2 quantitative variables over time.

Find the correlation coefficient of Pearson *r* when comparing 2 continuous variables with normal distribution, with positive *r* called positive correlation, negative *r* called negative correlation. The correlation levels:

+ Strong correlation: $|r| \geq .7$
+ Moderate correlation: $.3 \leq |r| < .7$
+ Weak correlation: $|r| < .3$.

– When $P < .05$, the difference is considered statistically significant.

2.4. Ethics approval

The council of Can Tho University of Medicine and Pharmacy approved our study, number: 692/QĐ-ĐHYDCT, on March 31, 2021. All patients gave their consent and agreed that their personal information would be kept private.

3. Results

3.1. Baseline characteristics of participants

Of 80 patients participated in the study, the majority of patients were female (52.5%) with a mean age of 54.5 ± 15.65. Nearly half of the patients were between the ages of 40 and 60. There were 45% of patients had normal BMI, with a mean of 22.38 ± 3.4 kg/m^2. The average concentration of B2M, urea, and creatinine in the blood of patient was high (24.81 ± 3.38 mg/L, 18.72 ± 5.36 mmol/L, and 810.54 ± 217.59 µmol/L, respectively). The Kt/V index of patients reached the treatment target (1.23 ± 0.09) (Table 1).

3.2. Correlation between B2M concentration with nerve conduction indices

There was a moderate inverse correlation between B2M concentration with tibial and motor branch of ulnar nerve conduction V (the correlation coefficient *r* were –0.305 and –0.315, respectively, $P < .05$, Fig. 1). There was a moderate positive correlation between B2M with tibial and peroneal nerve distal latency (*r* =

Table 1

Baseline characteristics of participants.

Characteristics		n = 80
Gender	Male [n (%)]	38 (47.5)
	Female [n (%)]	42 (52.5)
Age range (yr)	18–39 [n (%)]	15 (18.8)
	40–60 [n (%)]	37 (46.2)
	>60 [n (%)]	28 (35.0)
Mean age		54.5 ± 15.65 yr
BMI classification	Underweight [n (%)]	11 (13.8)
	Normal range [n (%)]	36 (45.0)
	Overweight [n (%)]	33 (41.2)
Mean BMI (kg/m^2)		22.38 ± 3.4
B2M (mg/L)		24.81 ± 3.38
Kt/V		1.23 ± 0.09
Urea (mmol/L)		18.72 ± 5.36
Creatinin (µmol/L)		810.54 ± 217.59
Albumin (g/L)		34.9 ± 3.26

Indices are presented as n (%) or mean ± SD.

BMI = body mass index.

0.434 and 0.440, respectively, $P < .05$, Fig. 2). The other nerve conduction indices had a weak correlation or did not correlate with B2M concentration (Table 2).

3.3. Evaluation of the changes of nerve conduction indices after treatment

In 80 patients participating in the study, 57 patients had a disorder of at least 2 nerve conduction indices when measured for the first time. Thus, these patients had standard HD combined with HDF-online treatment once every 1.5 months (according to the guideline of the Ministry of Health, Viet Nam). After 6 months, the patients had a second nerve conduction measurement to evaluate the treatment results compared to the baseline. Table 3 results showed that the nerve conduction indices of patients who had HD combined with HDF-online treatment improved significantly after 6 months.

4. Discussion

4.1. Baseline characteristics of participants

According to many domestic and foreign studies, the incidence of chronic kidney disease in men was higher than in women, especially in patients with ESRD.[4,5] In this study, the number of female patients was somewhat higher than that of males (52.5% female, 47.5% male), this might be due to the random sampling. The mean age of the patient sample was 54.5 ± 15.65 years old, the youngest was 18 years old, and the highest was 86 years old, showing that patients with ESRD on dialysis were mostly middle-aged. There were 45% of patients with normal BMI, mean BMI was 22.38 ± 3.4 kg/m^2. Our results were similar to some domestic studies.[6] However, we found that 41.2% of the patients were overweight/obese, which was a matter of concern. The reason might be that diabetes and metabolic syndrome patients were increasing, leading to a high proportion of overweight/obese patients. The average serum B2M concentration in the study was 24.8 ± 3.38 mg/L, which was much higher than the normal index (0.8–2.2 mg/L). The B2M concentration of the patients in Nguyen Thi Thu Hai study was even much higher (58.5 ± 21.6 mg/L),[7] showing that routine HD alone was not effective in removing medium molecular weight solutes, represented as B2M. Several studies had shown that every 1 mg/L increase in B2M concentration had a 1.03-fold increased risk of all-cause mortality and a 1.04-fold increased risk of cardiovascular events in dialysis patients.[8] On the other hand, we calculated that the mean of plasma urea and creatinine concentration was 18.72 ± 5.36 mmol/L and 810.54 ± 217.59 μmol/L, respectively. The urea and creatinine levels increased because the patient in the study had ESRD. This result was similar to many other domestic and foreign studies.[6,9] According to KDIGO guidelines, they recommend a minimum delivered single pool Kt/V of 1.2 per HD session for patients with dialysis.[5] In this study, the mean Kt/V index was 1.23 ± 0.92, reflecting that patients on routine HD met the minimum requirements for dialysis—good removal of urea. However, besides urea, there were many higher molecular weight solutes that also need to be removed (typically B2M) that HD treatments had not met well. The HD technique is a method of waste removal based on the diffusion mechanism mainly, the molecules move from a place of high concentration (patient's blood) to a place of low concentration through a semipermeable membrane. The filter used in HD is usually a filter with a low ultrafiltration coefficient (Kuf < 10 mL/h/mm Hg), so it only removes excess water and small molecules well. The technique of HDF is a combination of 2 principles of diffusion and enhanced convection, in order to remove small (urea, creatinine, etc) and middle (as Beta2-microglobulin) molecular weight compounds. The HDF-online method uses supplemental rehydration fluid prepared by the HD machine, the fluid is obtained directly (online) from the dialysis fluid and can be administered before or after the membrane.[10]

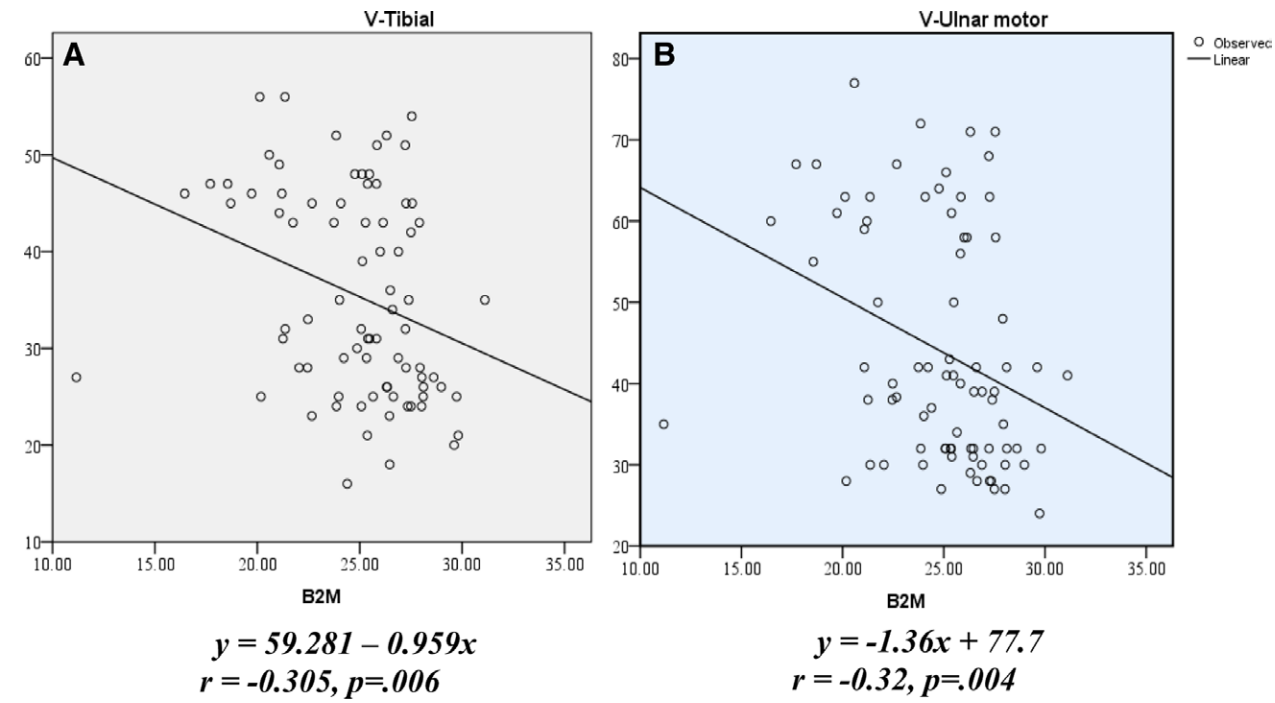

Figure 1. Correlation between B2M concentration and the tibial nerve (A) and the motor branch of ulnar nerve (B) conduction velocity. There was a moderate negative correlation between B2M concentration and the tibial nerve and the ulnar nerve conduction velocity, the correlation coefficient *r* was –0.305, *P* = .006 and –0.32, *P* = .004, respectively. B2M = beta-2 microglobulin, V = velocity.

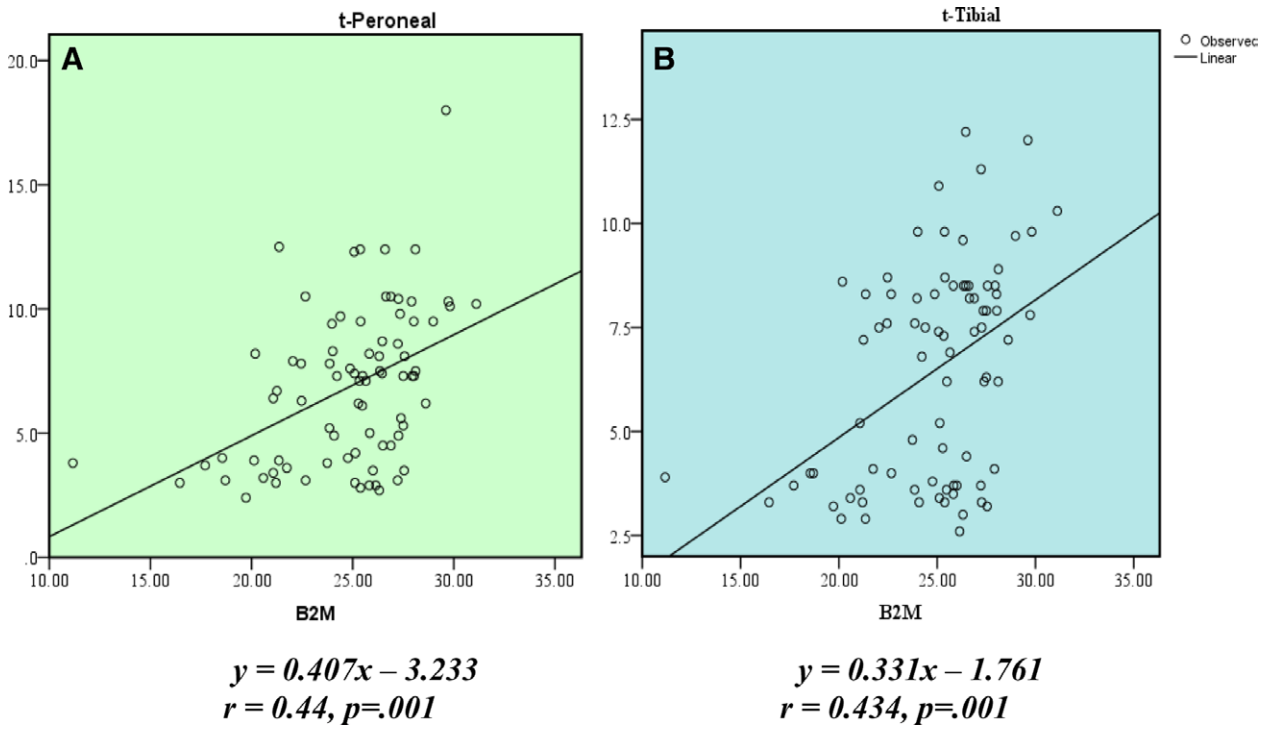

Figure 2. Correlation between B2M concentration and the peroneal nerve (A) and the tibial nerve (B) distal latency. B2M concentration was significantly and directly correlated with the peroneal nerve distal latency (r = 0.44, P = .001) and the tibial nerve distal latency (r = 0.434, P = .001). B2M = beta-2 microglobulin, t = distal latency.

Table 2

Correlation between B2M concentration with the change of some nerve conduction indices.

Nerve	Index	*r*	*P* value	Equation
Tibial	V	**–0.305**	**.006**	***y* = 59.281–0.959*x***
	A	–0.178	.114	
	dL	**0.434**	**.001**	***y* = 0.331*x*–1.761**
Peroneal	V	*–0.260*	*.02*	
	A	–0.207	.065	
	dL	**0.440**	**.001**	***y* = 0.407*x*–3.233**
Motor branch of the ulnar	V	**–0.315**	**.004**	***y* = 77.696–1.357*x***
	A	*–0.286*	*.01*	
	dL	0.218	.052	
A sensory branch of the ulnar	V	*–0.264*	*.018*	
	A	*–0.25*	*.025*	
	dL	*0.241*	*.031*	
Motor branch of the median	V	*–0.28*	*.012*	
	A	–0.192	.087	
	dL	0.156	.166	
A sensory branch of the median	V	–0.186	.098	
	A	*–0.261*	*.02*	
	dL	*0.244*	*.029*	

Bold values emphasize statistically significant differences.

A = amplitude, dL = distal latency, V = velocity.

4.2. Correlation between B2M concentration with nerve conduction indices

Patients with chronic kidney disease were affected by various factors, including the severity of the disease, the duration of the dialysis session, the concentration of substances with an average molecular weight, etc. In all of that, the average molecular weight was the one that had the highest significance. In our study, 100% of patients had elevated levels of B2M, a substance with a medium molecular weight that was characteristic of the group. Our study of the correlation between B2M concentration and nerve conduction characteristics was based on this information. The results showed that there was a moderate positive correlation between the concentration of B2M with motor latency of the peroneal (r = 0.44, P = .001), tibia (r = 0.43, P = .001), moderately negatively correlated with the V of tibial motor conduction (r = –0.305, P = .004), the ulnar nerve (r = –0.315, P = .006). The correlation between other nerve conduction indices were either absent or minimal. Additionally, Nguyen Thi Thu Hai concluded that there was a weak correlation between B2M and nerve conduction V (r = –0.41, P = .01).[7] Peripheral nerve injury might be decreased by removing medium-molecule poisons

Table 3

Comparison of the nerve conduction indices before and after 6 mo.

Nerve	Index	T0 ($\bar{X}$ ± SD)	T6 ($\bar{X}$ ± SD)	*P* value
Peroneal	Velocity (m/s)	31.3 ± 7.96	44.88 ± 9.67	**.001**
	Amplitude (mV)	1.71 ± 1.16	2.61 ± 1.51	**.001**
	Distal latency (ms)	8.21 ± 2.65	5.23 ± 3.58	**.001**
Tibial	Velocity (m/s)	30.53 ± 8.05	43.56 ± 8.99	**.001**
	Amplitude (mV)	5.04 ± 3.16	7.75 ± 4.45	**.001**
	Distal latency (ms)	7.64 ± 2.05	5.25 ± 2.3	.07
Motor branch of the ulnar	Velocity (m/s)	36.02 ± 7.68	55.07 ± 12.78	.3
	Amplitude (mV)	4.29 ± 1.39	6.42 ± 2.22	**.001**
	Distal latency (ms)	6.35 ± 1.89	3.56 ± 1.91	**.03**
A sensory branch of the ulnar	Velocity (m/s)	35.61 ± 9.85	56.23 ± 14.95	**.01**
	Amplitude (mV)	15.94 ± 6.76	25.19 ± 13.12	**.001**
	Distal latency (ms)	6.18 ± 1.83	3.45 ± 1.68	.08
Motor branch of the median	Velocity (m/s)	34.47 ± 7.94	52.18 ± 10.79	.1
	Amplitude (mV)	4.29 ± 1.76	6.52 ± 2.4	**.001**
	Distal latency (ms)	7.09 ± 1.96	4.37 ± 1.72	**.01**
A sensory branch of the median	Velocity (m/s)	32.98 ± 10.23	48.91 ± 12.07	**.001**
	Amplitude (mV)	14.35 ± 6.77	22.12 ± 10.92	**.001**
	Distal latency (ms)	6.96 ± 2.26	4.21 ± 1.67	**.003**

Bold values emphasize statistically significant differences.

like B2M, which might be done by using HDF or highly permeable membranes.

4.3. Evaluation of the change of some nerve conduction indices

When comparing the nerve conduction indices before and after 6 months, we recorded that the changes of the peroneal nerve conduction indices had statistical significance. For example, the conduction V increased from 31.3 ± 7.96 m/s up to 44.88 ± 9.67 m/s, A 1.71 ± 1.16 up to 2.61 ± 1.51 mV, the motor latency decreased from 8.21 ± 2.65 down to 5.23 ± 3.58 ms. On the tibial nerve, the conduction V (from 30.53 ± 8.05 up to 43.56 ± 8.99 m/s) and the A (from 5.04 ± 3.16 up to 7.75 ± 4.45 mV) changed significantly after 6 months. The motor latency decreased, but this difference is nonstastitic significance. Therefore, with lower limb motor nerve, most of the nerve conduction indices improved significantly after 6 months using a combination of HD and HDF-online. Nguyen Thi Thu Hai also recorded that tibial V in group 31 HD + HDF patients improved significantly after 12 months, but with the group 61 HD patients, there were not any nerve conduction indices improved statistical significance after 12 months of longitudinal study.[7]

In the motor ulnar nerve, the conduction A increased from 4.29 ± 1.39 to 6.42 ± 2.22 mV, the motor latency decreased from 6.35 ± 1.89 down to 3.56 ± 1.91 ms. In the sensory branch, the V increased considerably from 35.61 ± 9.85 to 56.23 ± 14.95 m/s, the A from 15.94 ± 6.76 to 25.19 ± 13.12 mV. These changes all had statistical significance with $P < .05$. At the time T0, a large group of patients had sensory conduction disorder, but at the time T6, the sensory ulnar nerve disorder improved clearly. Author Nguyen Thi Thu Hai[7] recorded that sensory ulnar nerve conduction V in the HDF-Online patients increased from 57.8 ± 7.6 at T0 to 60.1 ± 6.3 at T6 and 61.8 ± 7.3 at T12. These indices all increased meaningfully when we compared them with the standard HD-treated patient group. Ria Arnold et al[4] concluded that the nerve conduction indices in the patients who treated by HDF or HD using high flux dialyzer all got close to normal values than the standard HD. When analyzing the median nerve conduction indices, we realized the result was also similar to the ulnar nerve. The conduction V and A all increased after 6 months, and sensory and motor latency decreased.

Although some medium nerve conduction indices had not got the normal limit yet, all of them were higher than the baseline. Therefore, our research showed that a combination of HD with HDF-Online might improve some nerve conduction indices, as well as improved the clinical symptoms which involved in peripheral neuropathy in standard HD patients.

Nowadays, there are many studies in the world that prove the superiority of the HDF, especially HDF-OL compared with HD. However, HDF in general requires having a high ultrafiltration dialyzer, a compatible HD machine, ultrapure dialysis fluid, and well-trained medical staff, etc so the HDF cost is high, this treatment is not popular in the world, especially in Viet Nam.

Because the cause of peripheral nerve damage is chronic kidney failure, which exists permanently, a combination HDF-Online + HD just is the way to discard the continuous accumulation of toxins in chronic kidney disease patients. Therefore, we need continuous and prolonged treatment combined with many other measures in order to gain and maintain the best health status of the patient. One of the limitations of the study is that the frequency of HDF-Online in the study was only once every 1.5 months, which was low compared to many studies in the world. On the other hand, the number of patients participating in the study was low, and the follow-up period was also short. Therefore, more studies should be conducted in the future with more frequency of the combination HDF-Online + HD, larger sample size and longer follow-up time, in order to multidimensional assessment about effect as well as medical cost for ESRD patients.

5. Conclusions

This study showed that in Vietnamese chronic kidney disease patients, serum B2M concentration correlated with some nerve conduction indices such as the tibial nerve and ulnar conduction V, the tibial and peroneal nerve latency. The combination of HD and HDF-online could improve some nerve conduction indices.

Author contributions

Data curation: Viet Quoc Le, Tan Huynh Ngoc Mai.
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Methodology: Nghia Nhu Nguyen, Viet Quoc Le, Minh Van Le.
Software: Tan Huynh Ngoc Mai,
Supervision: Nghia Nhu Nguyen,

Writing – original draft: Tan Huynh Ngoc Mai, An Tuan Huynh,
Writing – review & editing: Tan Huynh Ngoc Mai, An Tuan Huynh, Nghia Nhu Nguyen, Minh Van Le.

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