The Progression of Uremic Polyneuropathy in Patients on Hemodialysis and Hemofiltration: A Two-Year Study

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Uremic polyneuropathy is one of the major complications of long-term end-stage renal disease. In the present study, we performed an electrophysiologic evaluation in 17 patients having a mean age of 49 ± 11 years. The patients were divided into two groups according to dialysis method. Group A included 9 patients who were undergoing conventional hemodialysis (mean age, 44.2 ± 12.5 years; mean duration on dialysis, 21.7 ± 4.3 months); group B included 8 patients undergoing hemofiltration (mean age, 55.2 ± 5.2 years; mean duration on treatment, 27 ± 7.6 months). Measurements of the distal latency time of the sensory fibers (median, ulnar, and sural nerves), and measurements of the distal latency time and peripheral conduction velocity of the motor fibers (median and peroneal nerves) were performed. In addition, we recorded somatosensory evoked potentials after peripheral stimulation of the median and peroneal nerves. The electrophysiologic evaluations were repeated two times at intervals of 12 months.

In group A, a statistically significant worsening of motor and sensory conductance in the upper and lower limbs was observed; in group B, a statistically significant improvement was found. These findings suggest that hemofiltration has a more beneficial effect on motor and sensory conductivity than does conventional hemodialysis.

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Key words

Uremic polyneuropathy, hemofiltration

Introduction

Uremic polyneuropathy has been recognized as a complication of end-stage renal disease (ESRD) since 1960 [1,2]. The exact pathophysiology remains unknown; however, the condition is thought to be due to secondary demyelinization of nerve fibers after primary axonal degeneration [3,4]. In various studies, the incidence of clinical polyneuropathy ranges from 10% to 63% [5]. Furthermore, electrophysiologic studies in uremic patients have shown that a reduction of conductivity exists even in patients without clinical signs [6].

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The present study compared ESRD patients undergoing either conventional hemodialysis or hemofiltration, with the aim of evaluating the possible influence of these renal replacement treatments on the progression of uremic polyneuropathy.

Material and methods

According to the presence or absence of clinical hemodynamic instability (cardiovascular disease, severe and frequent hypotensive episodes) during the first 3 months on dialysis, our ESRD patients were treated with hemofiltration (HF) or conventional hemodialysis (HD), respectively. We studied 17 patients undergoing chronic renal replacement therapies, dividing them into two groups: group A consisted of 9 patients undergoing conventional hemodialysis; group B included 8 patients undergoing hemofiltration. The criteria for patient selection were stable clinical and biochemical status for at least 2 months before the study, hematocrit > 28%, absence of residual renal function, absence of diabetes mellitus and amyloidosis or any other systemic and inflammatory disease, and absence of any medication that may have an influence on the nervous system. None of the patients had been treated with continuous ambulatory peritoneal dialysis (CAPD) before the study.

In group A, hemodialysis was performed in 4-hour sessions, 3 times per week, using bicarbonate dialysate; the ultrafiltration rate was adjusted to the clinical status of the patients. The dialyzer was a cuprophane membrane with these manufacturer's *in vitro* characteristics: 1.049 ± 0.19 m^2 surface area, vitamin B_{12} clearance of 50.88 ± 6.6 mL/min, and ultrafiltration rate of 5.51 ± 0.71 mL/min (Asahi 50H, Asahi Medical Co., Ltd., Tokyo, Japan; Terumo 12NL, Terumo Europe N.V., Leuven, Belgium).

In group B, hemofiltration was performed three times weekly using a substitution volume of 23 – 25 L per session. The length of the sessions was 4.5 ± 0.5 hours, depending on the substitution solution volume. Filters with synthetic membranes, polyacrylonitrile (PAN) or polysulfone (PS), were used. Manufacturer's *in vitro* specifications included a surface area of 1.33 ± 0.037 m^2, vitamin B_{12} clearance of 120.42 ± 18.41 mL/min, and ultrafiltration rate of 36 ± 3.82 mL/min ([PS] F60A, F60B: Fresenius Medical Care, Bad Homburg, Germany; PAN-900SF: Asahi Medical Co., Ltd.).

The patients underwent routine HD and HF treatments throughout the study period. None of the patients had any specific clinical sensorimotor disorder indicative of severe nerve malfunction. In both groups, hematocrit, hemoglobin,

and serum levels of urea, creatinine, potassium, sodium, calcium, phosphorus, alkaline phosphatase, and albumin were measured monthly [automated enzymatic methods with AU 560 analyzer (Olympus, Hamburg, Germany)]. Moreover, in each patient, serum levels of β_2-microglobulin [enzyme-linked immunosorbent assay (ELISA), AxSYM β_2-microglobulin, B3B460: Abbott Laboratories, Abbott Park, Illinois, U.S.A.] and the intact molecule of parathormone [immunoradiometric assay (IRMA), ELSA-PTH: CIS Biointernational, Gif sur Yvelle, France] were measured three times: at the beginning of the study (baseline values), and at 12 and 24 months. All the blood samples were taken before the beginning of a dialysis session.

At the same intervals on intradialytic days, the patients also underwent electrophysiologic studies that included measurements of motor conduction velocity (MCV) of the median and peroneal nerves bilaterally. These nerves were stimulated using surface electrodes. In addition, the motor distal latency time (MDL) of the median and peroneal nerves, and the sensory distal latency time (SDL) of the median, ulnar, and sural nerves were recorded.

For MCV of the peroneal nerve, the recording electrode was placed near the outer edge of the foot. The peroneal nerve was stimulated at the ankle and 2 – 3 cm above the fibula head. For MCV of the median nerve, the recording electrode was placed on the thenar muscles. The median nerve was stimulated at the wrist and at the antecubital fossa. The SDLs of the median and ulnar nerves were determined by the orthodromic method, recording at the wrist and stimulating with ring electrodes at the index and fifth finger, respectively. The SDL of the sural nerve was studied using the antidromic method. The recording electrode was placed behind and below the lateral malleolus and the stimulation electrode was placed mid calf, 14 cm proximal to the recording electrode. The somatosensory evoked potentials were studied by stimulating the peripheral nerves (median and peroneal, for upper and lower limbs, respectively) with 10 – 15 mA via a surface electrode. The latency times of the peaks, N19 for the median and P35 for the peroneal, were recorded.

A Nihon Kohden Neuropack Four Mini Evoked Potential Measuring System Model MEB-5304K (Nihon Kohden Europe Ltd., Brentford, U.K.) was used, with surface electrodes. All patients were examined at a room temperature of 21°C – 23°C, with normal skin temperature of 35°C – 36°C, and the maximum possible relaxation of the patients.

For the statistical evaluation, the Wilcoxon matched pairs test was used because the data failed the normality test owing to the small number of patients. The statistical package Statistica for Windows 5.0 (StatSoft Inc., Tulsa, Oklahoma, U.S.A.), was used. A p value less than 0.05 was considered significant.

Results

Table I presents the patients' characteristics. The biochemical data from both groups of patients did not change significantly during the study (Table II), with the exception of the β_2-microglobulin levels in group A, which increased significantly from the first to the second and from the first to the third measurements ($p < 0.008$).

According to the results of electrophysiologic examination in the patients of group A, the MDL, MCV, and SDL values appeared to continuously worsen throughout the 2-year study. This worsening was statistically significant in certain parameters at the third measurement (Table III). The changes in motor and sensory conductivities in group B moved in the opposite direction. The observed improvement of the patients in group B was statistically significant for most parameters (Table IV).

Regarding the somatosensory evoked potentials, the latency time of N19 and P35 peaks for the upper and lower limbs increased significantly in group A from the first to the last examination (Table III). The patients in group B showed an improvement of the latency time for N19 and P35 (Table IV). The observed changes in group B were statistically significant at the last examination (Table IV).

Discussion

All of the measured biochemical parameters were stable during the study, except for a statistically significant increase in serum β_2-microglobulin levels observed in group A (on conventional hemodialysis). This increase may be explained by stimulation of β_2-microglobulin production owing to poor cuprophane biocompatibility, or because of inadequate removal by diffusion (the main solute transport mechanism of conventional hemodialysis), or both [7,8].

In group B patients (on hemofiltration), a reduction in β_2-microglobulin serum levels was seen in comparison with baseline values. The reduction may be due both to high removal and to the adsorption ability of the synthetic membranes (polyacrylonitrile and polysulfone) that were used in the patients undergoing hemofiltration [9,10].

Also, the results of the electrophysiologic studies of motor and sensory conductivities and of the somatosensory evoked potentials indicate opposite changes in the two groups: deterioration in the patients on conventional hemodialysis, and improvement in the hemofiltration group.

Such a favorable effect of hemofiltration on the polyneuropathy of dialyzed patients has been also observed by Beckmann *et al.* [11], who reported improvement in the con-

TABLE I Patient characteristics.

	Group A (hemodialysis; n = 9)	*Group B (hemofiltration; n = 8)*
Age (years)	44.2±12.5	55.2±5.2 $p<0.05$
Duration of dialysis (months)	21.7±4.3	27±7.6 NS
Primary disease		
Glomerulonephritis	6	5
Polycystic disease	2	0
Unknown	1	3

TABLE II Laboratory data.

	Group A (hemodialysis; n = 9)			*Group B (hemofiltration; n = 8)*		
	Measurements			*Measurements*		
Laboratory data	*1st*	*2nd*	*3rd*	*1st*	*2nd*	*3rd*
Hematocrit (%)	32.6±3.9	32.3±4.1	32.9±5.7	31.0±3.2	30.8±2.5	31.8±3.6
Hemoglobin (g/dL)	10.8±0.4	10.7±0.4	10.9±0.6	10.2±1.3	10.2±1.1	10.5±1.4
Urea (mg/dL)	176±48	180±40	176±37	206±28	220±33	218±29
Creatinine (mg/dL)	11.6±2.1	11.9±1.9	11.3±1.2	11.7±1.7	11.6±2.1	11.0±2.4
K (mEq/L)	5.4±0.2	5.5±0.2	5.7±0.2	5.3±0.4	5.1±0.5	5.7±0.7
Na (mEq/L)	141±3.5	142±2.5	140±1.5	139±2.8	141±1.4	139±0.5
Ca (mg/dL)	8.6±0.6	8.7±0.7	8.6±0.8	9.3±1.1	8.9±0.7	9.7±1.0
P (mg/dL)	5.5±0.3	5.9±0.8	6.3±0.6	5.3±1.1	5.1±1.0	6.1±v0.8
Total proteins (g/dL)	7.4±0.6	7.6±0.2	7.7±0.5	7.8±0.6	7.3±0.4	7.4±0.7
Albumin (g/dL)	4.7±0.3	4.8±0.3	4.7±0.4	4.7±0.2	4.6±0.3	4.7±0.2
PTH (pg/mL)	381±292	339±250	409±262	197±244	181±259	197±262
β_2-microglobulin (μg/L)	29,104±7,555	35,010±8,479	41,185±7,569	31,301±11,171	29,814±9,720	28,435±8,397

PTH = intact parathormone.

TABLE III Results of electrophysiologic examinations in patients of group A (conventional hemodialysis).[a]

				Comparison between the three measurements	
	1st measurement	*2nd measurement*	*3rd measurement*	*p Value, 1st to 2nd*	*p Value, 1st to 3rd*
		Motor conductivity			
Median nerve					
MDL right (msec)	3.6±0.6	3.9±0.6	4.1±0.6	NS	0.02
MCV right (m/sec)	47.8±5.1	47.9±4.9	45.6±4.7	NS	NS
MDL left (msec)	3.5±0.4	3.8±0.5	4.1±0.7	NS	0.01
MCV left (m/sec)	48.6±4.3	48.8±5.1	46.4±4.8	NS	NS
Peroneal nerve					
MDL right (msec)	4.6±0.5	4.8±0.6	5.1±0.5	NS	NS
MCV right (m/sec)	43.4±6.6	42.2±3.4	39.5±4.1	NS	0.01
MDL left (msec)	4.5±0.9	4.5±0.9	4.8±1.0	NS	NS
MCV left (m/sec)	42.3±5.6	42.4±3.9	40.2±4.2	NS	NS
		Sensory conductivity			
Median nerve					
SDL right (msec)	3.1±0.4	3.1±0.4	3.3±0.5	NS	NS
SDL left (msec)	3.1±0.2	3.3±0.3	3.5±0.3	NS	0.01
Ulnar nerve					
SDL right (msec)	2.5±0.2	2.5±0.4	2.9±0.4	NS	0.02
SDL left (msec)	2.6±0.2	2.6±0.3	2.8±0.3	NS	0.05
Sural nerve					
SDL right (msec)	5.7±1.6	5.5±1.4	5.7±1.2	NS	NS
SDL left (msec)	6.0±1.3	5.6±1.4	5.9±1.2	NS	NS
		Somatosensory evoked potentials			
Median nerve					
Right (peak N19)	19.6±1.7	19.6±1.5	20.3±1.4	NS	0.03
Left (peak N19)	19.2±1.4	19.6±1.3	20.4±1.9	NS	0.007
Peroneal nerve					
Right (peak P35)	31.6±3.3	32.9±2.5	33.6±2.6	0.03	0.01
Left (peak P35)	31.5±3.2	32.6±2.4	33.9±2.4	NS	0.01

[a] Motor velocity values (MCVs) are given in meters per second; an increase in velocity represents conductivity improvement. The latency conductivity times (MDL, SDL) are given in milliseconds; an increase in time value represents conductivity deterioration. Changes in somatosensory evoked potential values have also the same meaning as MDL and SDL.

MDL = motor distal latency time; MCV = motor conduction velocity; SDL = sensory distal latency time.

ductivity of peripheral nerves after hemofiltration therapy for 18 – 24 months. Similarly, Streicher *et al.* [12], who evaluated 14 patients undergoing hemofiltration for 3 – 27 months, reported improvement in polyneuropathy in 6 of 7 patients.

The improved results that were observed in the hemofiltration group may be due to the different solute removal characteristics of this modality, especially in regard to substances of middle molecular weight. According to the

TABLE IV Results of electrophysiologic examinations in patients of group B (hemofiltration).[a]

	1st measurement	*2nd measurement*	*3rd measurement*	*Comparison between the three measurements* p Value, 1st to 2nd	p Value, 1st to 3rd
		Motor conductivity			
Median nerve					
MDL right (msec)	3.9±0.6	3.7±0.5	3.7±0.5	NS	NS
MCV right (m/sec)	44.7±4.9	45.6±3.1	46.3±3.1	NS	NS
MDL left (msec)	3.9±0.7	3.8±0.8	3.6±0.6	NS	0.02
MCV left (m/sec)	44.7±4.6	44.8±4.8	45.8±4.6	NS	NS
Peroneal nerve					
MDL right (msec)	4.6±0.9	4.0±0.4	3.8±0.2	0.03	0.03
MCV right (m/sec)	37.3±3.8	39.3±2.8	40.0±3.3	0.01	0.02
MDL left (msec)	4.7±0.5	4.3±0.5	4.0±0.6	0.01	0.01
MCV left (m/sec)	37.2±4.5	39.1±2.3	40.5±3.3	0.01	NS
		Sensory conductivity			
Median nerve					
SDL right (msec)	3.3±0.5	3.2±0.6	3.1±0.5	0.05	0.01
SDL left (msec)	3.3±0.6	3.3±0.7	3.2±0.6	NS	0.05
Ulnar nerve					
SDL right (msec)	2.6±0.3	2.5±0.2	2.4±0.2	NS	0.02
SDL left (msec)	2.8±0.4	2.7±0.3	2.5±0.2	0.05	0.01
Sural nerve					
SDL right (msec)	5.8±1.5	5.4±1.6	5.1±1.7	0.01	0.01
SDL left (msec)	6.1±1.7	5.7±1.8	5.3±1.9	0.01	0.01
		Somatosensory evoked potentials			
Median nerve					
Right (peak N19)	20.5±2.1	20.3±1.9	19.5±1.8	0.04	0.05
Left (peak N19)	20.8±2.6	20.1±2.3	19.5±1.9	0.01	0.01
Peroneal nerve					
Right (peak P35)	32.6±6.8	31.7±5.4	30.8±5.4	NS	0.01
Left (peak P35)	32.2±7.3	31.8±6.7	29.9±5.7	NS	0.02

[a] Motor velocity values (MCVs) are given in meters per second; an increase in velocity represents conductivity improvement. The latency conductivity times (MDL, SDL) are given in milliseconds; an increase in time value represents conductivity deterioration. Changes in somatosensory evoked potential values have also the same meaning as MDL and SDL.

MDL = motor distal latency time; MCV = motor conduction velocity; SDL = sensory distal latency time.

hypothesis of Babb *et al.* [13], the removal of such substances is determined by the surface characteristics of the hemofilter membrane. Also Bozek *et al.* [14] suggested that hemofiltration should be applied in patients who have complications owing to the accumulation of substances of middle molecular weight, as this method has proved to be efficient in the elimination of such substances. Moreover, Man *et al.* [15] have studied the fraction b4–2 and found that serum levels in healthy persons were 1 mg/L, which was increased to 4.6 ± 0.2 mg/L in uremic patients. The highest levels (13 – 19 mg/L) were observed in uremic patients with polyneuropathy. Furthermore, in experimental models, the group proved that the fraction b4–2 exhibits neurotoxic effects at high levels comparable to those found in the serum of uremic patients with polyneuropathy [15].

The lower (though nonsignificant) serum β_2-microglobulin values seen in the hemofiltration group indicate that hemofiltration, as compared with hemodialysis, is associated with increased removal of substances with larger molecular weights This observation may explain the improvement of both motor and sensory nerve conductivities in the hemofiltration patients.

Conclusion

It can be hypothesized that the unfavorable morphologic and functional changes in neural fibers may be suspended with a less uremic environment, which is achievable by hemofiltration treatment. Consequently, hemofiltration may be considered the method of choice in end-stage renal disease patients with uremic polyneuropathy. Electrophysiologic measurements may be used for diagnosis and long-term observations of uremic polyneuropathy progression.

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