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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Pregabalin for the Treatment of Neuropathic Pain in Patients Undergoing Hemodialysis

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Abstract

Objective Pregabalin is a gamma aminobutyric acid derivative administered for neuropathic pain. It binds to α2δ subunits of voltage-dependent calcium channels, and inhibits calcium inflow of synapses and the release of excitatory neurotransmitters. This study investigated the efficacy and safety of pregabalin in patients with peripheral neuropathic pain undergoing maintenance hemodialysis.

Methods This study was a prospective, open-label, single-arm, multi-center trial. Patients were treated with an initial dose of pregabalin at 25 mg; this was then increased up to a maximum of 150 mg depending on the patient during a 12-week study period. Visual Analog Scale, Eight-Item Short Form Health Survey (SF-8), and laboratory data were collected at baseline and the end of the study.

Results A total of 45 patients with peripheral neuropathic pain were included, of whom 35 patients were analyzed. The final mean dose of pregabalin was 50.7 mg daily. Mean Visual Analog Scale scores significantly decreased from 52.4 mm at baseline to 34.1 mm at the end of the study ($p < 0.0001$). Scores for all eight categories of the SF-8 significantly increased compared with baseline ($p < 0.05$). Both physical and mental component summary scores of the SF-8 also significantly increased ($p < 0.05$). Ten patients were withdrawn from the study because of drowsiness, dizziness, and invalidity; however, no serious adverse drug reactions were recorded.

Conclusions If adverse effects are carefully monitored and the administered dosage prudently determined, pregabalin can be an effective treatment for peripheral neuropathic pain in patients undergoing hemodialysis.

Trial Registration: UMIN000023117.

Key Points

Visual Analog Scale and Eight-Item Short Form Health Survey scores were improved by pregabalin treatment in hemodialysis patients with peripheral neuropathic pain.

If adverse effects are carefully monitored and the administered doses are prudently determined, pregabalin can be efficient in the treatment of peripheral neuropathic pain in patients undergoing hemodialysis.

1 Introduction

Chronic pain is classified clinically as either nociceptive pain, neuropathic pain, or psychogenic pain [1–4]. Neuropathic pain can be divided into peripheral neuropathic pain and central neuropathic pain. Typical diseases presenting with peripheral neuropathic pain include diabetic peripheral neuropathy, post-herpetic neuralgia, chronic postoperative pain, phantom limb pain, and carpal tunnel syndrome caused from dialysis-related amyloidosis, especially in dialysis patients. Counterparts of central

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neuropathic pain comprise pain after stroke and spinal cord injury.

The Japanese Society for Dialysis Therapy recently reported that the leading cause of dialysis initiation in Japan is diabetic nephropathy [5, 6]. Many patients experience diabetic peripheral neuropathy or other peripheral neuropathic pain such as dialysis-related amyloidosis because the pain is not sufficiently alleviated by non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have been predominantly administered to treat pain in patients undergoing dialysis; however, there are numerous types of pain that are not sufficiently alleviated by NSAIDs, such as neuropathic pain. Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."

Pregabalin was recommended as one of the first-line treatment options for neuropathic pain in neuropathic pain guidelines, alongside tricyclic antidepressants, serotonin-noradrenalin reuptake inhibitors, and gabapentin [7–10]. The pregabalin dosage is initially 75 mg twice daily or 50 mg three times daily, and is increased to 300 mg daily within 1–2 weeks in patients with normal kidney function; the maximum daily dose is 600 mg. For hemodialysis patients, the pregabalin induction dose is 25 or 50 mg daily, the maintenance dose is 50 or 75 mg daily, and the maximum dose is 100 or 150 mg daily [11]. This is because the half-life duration can increase up to five fold and the frequency of adverse reactions may increase depending on the dosage in patients with end-stage kidney disease [11]. Pregabalin relieves pain by inhibiting calcium channels and can be expected to reduce the pain in cases when NSAIDs are ineffective; however, there are few data on the efficacy and safety of pregabalin in hemodialysis patients. Therefore, this study investigated the efficacy and safety of pregabalin in patients with peripheral neuropathic pain undergoing maintenance hemodialysis.

2 Patients and Methods

2.1 Study Design

This study was a prospective, open-label, single-arm, multi-center trial. The study design is shown in Fig. 1. Patients received oral pregabalin at a dose of 25 mg daily; if any adverse events occurred, the patient was withdrawn from the study, if not, the dose of 25 mg was maintained. If the patient response was insufficient, the dose was increased up to 50 mg daily after 2 weeks of pregabalin treatment. If adverse events did not occur and the efficacy was insufficient, the dose of pregabalin was increased once every 2 weeks, up to a maximum of 150 mg daily. Patients were monitored for 12 weeks. The study protocol was approved by the Ethics Committee of Keiai Hospital, and all patients provided written informed consent (Clinical Trials Registration: UMIN000023117). The study protocol was designed in accordance with the Declaration of Helsinki. All patients were treated with hemodialysis or hemodiafiltration therapy three times per week in 4-h sessions at three Japanese blood purification centers. This prospective study was conducted between June 2014 and December 2015.

Enrollment criteria for the study were as follows: (1) age $\geq$20 years and $\leq$ 85 years, (2) hemodialysis duration >6 months at enrollment, (3) patients who could make a decision, and (4) patients who were diagnosed with peripheral neuropathic pain by a neurologist. Exclusion criteria comprised the following: (1) a history of severe heart failure, angina, myocardial infarction, or stroke

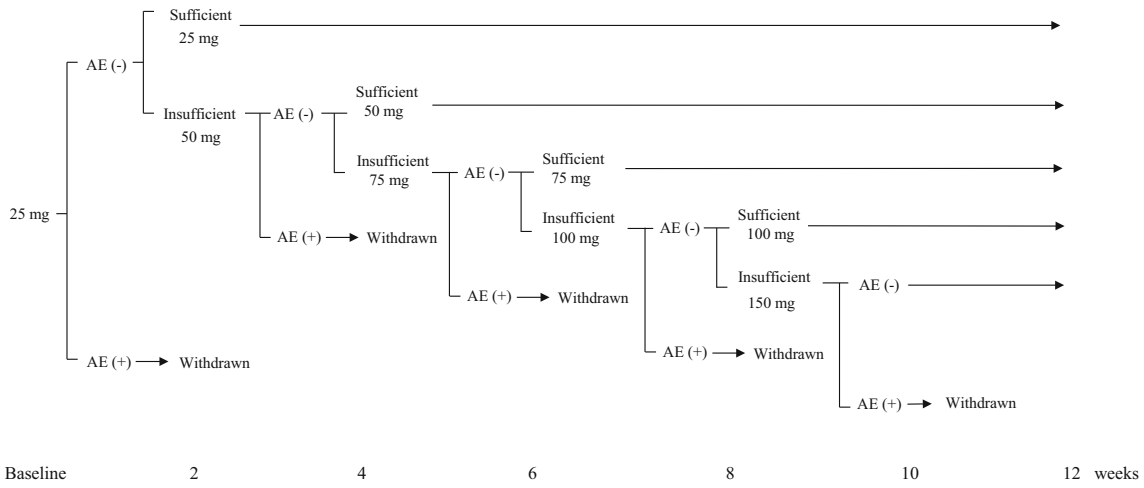

Fig. 1 Study design. *AE* adverse events

within the past 6 months, (2) the presence of infectious disease, thyroid disease, malignant tumors, or treatment with corticosteroids or immunosuppressants, (3) current hospitalization, (4) a history of angioedema, (5) a history of hypersensitivity to pregabalin, and (5) dementia with difficulty in making decisions. During the study period, patients continued their regular medications, such as NSAIDs, anti-hypertensive agents, erythropoiesis-stimulating agents, phosphate binders, and lipid-lowering agents. All patients received the same erythropoiesis-stimulating agent, namely, recombinant human erythropoietin (epoetin alfa). The dosages of analgesic medications at baseline were unchanged and other analgesic agents were not administered throughout the study. However, in cases of intolerable pain, acetaminophen was administered as needed and this was recorded.

2.2 Study Evaluations

The primary efficacy endpoint was the comparison of Visual Analog Scale (VAS) scores before and after the administration of pregabalin. The secondary endpoints comprised the changes in the eight items of the Short Form Health Survey (SF-8) from baseline to the end of the study and pregabalin safety.

The SF-8 was developed as an abridged version of the SF-36 that is used commonly to measure health-related quality of life [12, 13]. Scores are given based on eight items (Physical functioning: SF8PF, Role physical: SF8RP, Bodily pain: SF8BP, General health: SF8GH, Vitality: SF8VT, Social functioning: SF8SF, Role emotional: SF8RM, and Mental health: SF8MH). The physical component summary (PCS) and the mental component summary (MCS) were calculated using the formulae as described previously [12].

The safety and tolerability of pregabalin treatment were assessed by monitoring and recording all adverse events, in addition to monitoring clinical laboratory test results and physical assessment findings. Adherence to oral pregabalin treatment was evaluated based on a pill count once every 2 weeks. Patients with poor adherence, defined as <80 % by pill count, were withdrawn from the study. Patients could be withdrawn in the event of allergy/intolerance to the drug, following an event that, in the investigator's opinion, might have posed a risk to the patient or confounded the results of the study. At each visit, subjects were questioned with regard to study compliance (diet and medications), concomitant medications, and adverse events. Safety assessments were performed throughout the study. Adverse events were graded by intensity: mild, moderate, or severe. Serious adverse events were defined as medical events that resulted in death, hospitalization, or significant disability or incapacity.

Blood cell counts and levels of serum creatinine, serum urea nitrogen, total protein, albumin, electrolytes, total cholesterol, low-density lipoprotein cholesterol, triglyceride, serum iron, transferrin saturation, and serum ferritin were measured by routine clinical chemistry procedures using commercial kits. High-sensitivity C-reactive protein and serum β_2-microglobulin were measured by latex agglutination. Intact parathyroid hormone was measured by radioimmunoassay. Kt/V was measured based on pre-dialysis and immediate post-dialysis blood urea nitrogen levels using a formal single-compartment model of hemodialysis urea kinetics. All these parameters were measured every 4 weeks and blood samples were obtained before the start of a hemodialysis session. Pre-dialysis systolic and diastolic blood pressure values were recorded at each hemodialysis session. The cardiothoracic ratio was measured by assessing a chest X-ray every 4 weeks. These variables were evaluated, and compared at baseline and 12 weeks (at the end of the study).

2.3 Hemodialysis Procedure

In all patients, the hemodialysis procedure was performed using dialyzers containing high-flux membranes (such as polysulfone, polyacrylonitrile, or cellulose triacetate) at a blood flow rate of 200–250 mL/min and at a dialysate flow rate of 500 mL/min. Hemodiafiltration was performed using the post-dilution method with sterile replacement fluid (Sublood-BSG®; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) at a volume of 8–10 L/session. The surface area of the dialyzer membrane was selected according to the patient's body weight. The glucose concentration of the dialysate and replacement fluid was 100 mg/dL. Heparin was administered at 2600–5000 U per 4-h hemodialysis session for anticoagulation. The volume of ultrafiltration was maintained on the basis of clinical dry weight during each session.

2.4 Statistical Analysis

Data were expressed as mean ± standard deviation or median [interquartile range] as appropriate. Changes in parameters were analyzed using the paired t test. To determine the size effect, Cohen's d was calculated. Statistical significance was set at $P < 0.05$. All analyses were performed using the JMP ver. 11 software (SAS Institute Ltd., Cary, NC, USA).

3 Results

3.1 Baseline Demographic and Clinical Data

This trial screened 257 patients, of whom 45 eligible hemodialysis patients were enrolled and treated with pregabalin (Fig. 2). Overall, ten patients did not complete the

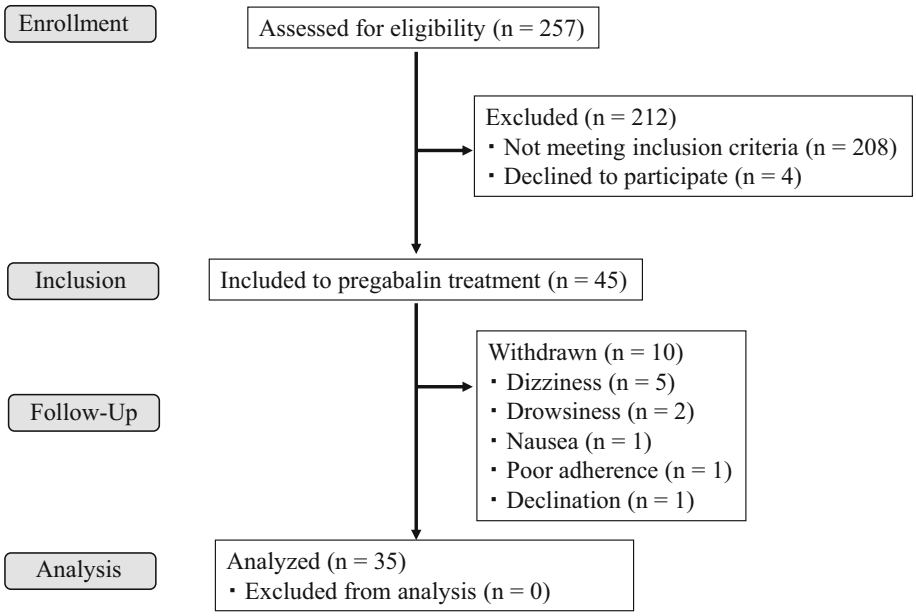

Fig. 2 Patient disposition

assessment or treatment. The other 35 patients were included in the final analysis (Table 1). During the study period, the dose of NSAIDs, anti-hypertensive agents, erythropoiesis-stimulating agents, phosphate binders, active vitamin D, and lipid-lowering agents remained unchanged in all patients. None of the patients required acetaminophen or received intravenous iron therapy. The distribution of the final dosage of pregabalin was 25 mg ($n = 8$), 50 mg ($n = 19$), 75 mg ($n = 7$), and 100 mg ($n = 1$). The final mean (±standard deviation) dose of pregabalin was 50.7 ± 18.6 mg daily.

3.2 Efficacy

The change in the VAS score from baseline to the end of the study is shown in Fig. 3. Mean VAS score significantly decreased from 52.4 ± 18.7 mm at baseline to 34.1 ± 18.3 mm at the end of the study ($p < 0.0001$). The changes in SF-8 scores are shown in Table 2. In all SF-8 items, the score significantly increased. As shown in Fig. 4, MCS and PCS also significantly increased after pregabalin treatment. Table 3 shows the clinical variables of the patients who completed the trial at baseline and at the end of the study. There were no significant differences in serum urea nitrogen, albumin, electrolytes, lipid profiles, or C-reactive protein levels during the study period.

3.3 Tolerability and Safety

During treatment, ten patients were excluded from the study. Six patients (60 %) withdrew within 2 weeks of

Table 1 Baseline patient characteristics and medications

Variables	Values
N (men/women)	35 (23/12)
Age, years	72 [68–76]
Duration of dialysis, months	56 [49–82]
BMI, kg/m^2	22.5 ± 1.7
Cause of ESKD	
Diabetic nephropathy	14 (40.0)
Glomerulonephritis	10 (28.6)
Nephrosclerosis	9 (25.7)
Other	2 (5.7)
Dialysis mode	
Hemodialysis	30 (85.7)
Hemodiafiltration	5 (14.3)
Vascular access	
Arteriovenous fistula	31 (88.6)
Arteriovenous graft	4 (11.4)
Cardiovascular comorbidity	
Ischemic heart disease	3 (8.6)
Cerebrovascular disease	1 (2.9)
Peripheral artery disease	1 (2.9)
Analgesic medication	
NSAIDs	7 (20.0)
PGE1	3 (8.6)
Vitamin B_{12}	3 (8.6)

Values are mean ± standard deviation, median [interquartile range], or numbers (%)

BMI body mass index, *ESKD* end-stage kidney disease, *NSAIDs* non-steroidal anti-inflammatory drugs, *PGE1* prostaglandin E1

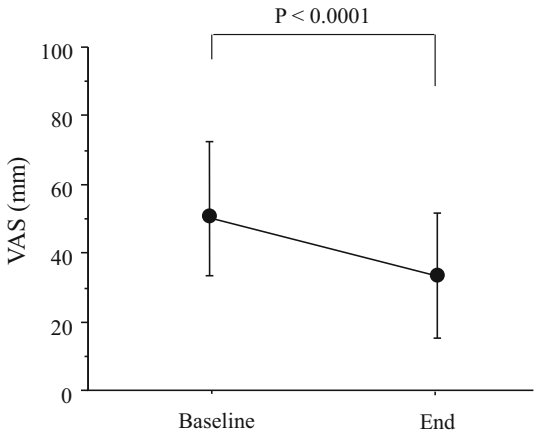

Fig. 3 Changes in VAS before and after treatment of pregabalin. Cohen's $d = 0.99$. *VAS* visual analog scale

pregabalin treatment because of nausea ($n = 1$), drowsiness ($n = 2$), and dizziness ($n = 3$); these were suspected to be associated with pregabalin treatment. After 4 weeks, pregabalin treatment was discontinued in some patients because of dizziness ($n = 2$) and poor adherence ($n = 1$). After 6 weeks, one patient withdrew from the study because pregabalin was insufficient.

Of the patients who completed the study, one patient experienced dizziness the following day after the start of pregabalin treatment; however, this patient was not excluded from the study because the symptom diminished after 3 days. Peripheral edema as an adverse effect was not detected in any patient.

4 Discussion

The mechanism of peripheral neuropathic pain has been gradually clarified and the administration of medication for neuropathic pain has recently become more widespread. Medication guidelines for peripheral neuropathic pain have been issued in USA and in European countries [7–10]. Furthermore, the greater efficacy of pregabalin at relieving post-herpetic neuralgia than other conventional medicines, and its efficacy in the alleviation of diabetic neuropathy and other peripheral neuropathic pain have been reported [14–23]. In a European report, 37 % of chronic lumbago

Table 2 Changes in scores of SF-8 items before and after pregabalin treatment

SF-8 items		Baseline	End	Cohen's *d*	*P* value
1	General health	43.1 ± 8.8	47.8 ± 8.1	0.56	0.0155
2	Physical function	37.8 ± 12.6	42.7 ± 8.0	0.47	0.0233
3	Role–physical	36.7 ± 12.9	44.1 ± 9.0	0.67	0.0002
4	Bodily pain	39.8 ± 7.1	44.7 ± 8.2	0.64	0.0002
5	Vitality	43.0 ± 8.0	48.3 ± 7.6	0.68	0.0007
6	Social functioning	40.5 ± 11.9	44.8 ± 11.3	0.37	0.0031
7	Mental health	44.8 ± 8.1	48.6 ± 7.4	0.49	0.0019
8	Role–emotional	45.3 ± 7.9	48.5 ± 6.5	0.44	0.0036

Values are mean ± standard deviation

SF-8 Eight-Item Short Form Health Survey

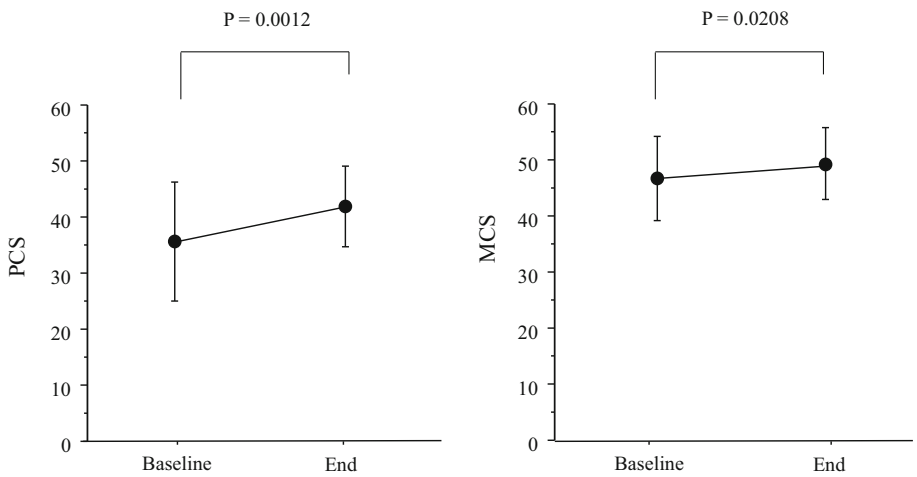

Fig. 4 Changes in MCS and PCS before and after treatment of pregabalin. Cohen's $d = 0.70$ for PSC and 0.38 for MCS. *MCS* mental component summary, *PCS* physical component summary

Table 3 Vital signs and clinical parameters before and after pregabalin treatment

Variables	Baseline	End	*P* value
Systolic blood pressure, mmHg	147 ± 18	146 ± 19	0.814
Diastolic blood pressure, mmHg	81 ± 9	81 ± 8	0.924
Heart rate, bpm	75 ± 10	75 ± 9	0.599
Cardiothoracic ratio, %	49.5 ± 4.7	49.1 ± 4.0	0.557
Kt/V	1.36 [1.30–1.39]	1.36 [1.30–1.39]	0.769
Hemoglobin, g/dL	10.9 ± 0.8	10.9 ± 0.7	0.944
Serum urea nitrogen, mg/dL	56.6 ± 9.6	57.3 ± 9.2	0.211
Creatinine, mg/dL	9.0 ± 2.6	9.0 ± 2.5	0.363
Total protein, g/dL	6.7 ± 0.5	6.7 ± 0.4	0.611
Serum albumin, g/dL	3.8 ± 0.3	3.8 ± 0.3	0.331
Total cholesterol, mg/dL	150 ± 25	150 ± 21	0.625
LDL-cholesterol, mg/dL	86 ± 21	86 ± 18	0.966
Triglyceride, mg/dL	107 ± 45	106 ± 45	0.889
Calcium, mg/dL	8.9 ± 0.6	8.9 ± 0.6	0.894
Phosphate, mg/dL	5.5 ± 1.2	5.5 ± 1.0	0.899
Intact PTH, pg/mL	114 [73–187]	129 [72–176]	0.519
β_2-Microgloblin, mg/L	25.5 ± 6.1	25.7 ± 5.5	0.571
Hs C-reactive protein, mg/dL	0.148 ± 0.08	0.142 ± 0.07	0.127
Iron, μg/dL	57 ± 19	59 ± 19	0.470
TSAT, %	27 ± 9	26 ± 8	0.385
Ferritin, ng/mL	124 ± 72	114 ± 74	0.459

Values are mean ± standard deviation or median [interquartile range]

Hs high-sensitivity, *LDL* low-density lipoprotein, *PTH* parathyroid hormone, *TSAT* transferrin saturation

cases involve neuropathic pain [24]. In addition to postherpetic neuralgia, the prevalence of neuropathic pain is also high, for example, 30–40 % after thoracotomy, 20–30 % after breast cancer surgery, and 10 % after inguinal hernia surgery [25]. To our knowledge, this study was the first clinical study to investigate the efficacy of pregabalin for neuropathic pain in a dialysis patient population.

The SF-8 is a commonly used, health-related quality-of-life scale. In this study, SF-8 scores did not worsen for any item examined after pregabalin treatment. PCS and MCS significantly increased after pregabalin treatment. Pregabalin is a gamma aminobutyric acid derivative for neuropathic pain that binds to α2δ subunits of voltage-dependent calcium channels, inhibits calcium inflow of synapses and the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P, and controls pain [26]. Recently, the potential effect of pregabalin on spinal α2-adrenergic receptors and its analgesic effect through the enhancement of the descending pain inhibitory system has been highlighted. In the present study, high-sensitivity C-reactive protein was measured to confirm that pregabalin did not relieve pain through anti-inflammatory effects. There was no significant change in high-sensitivity C-reactive protein during this study.

The frequency of adverse reactions such as somnolence, dizziness, and peripheral edema increases with the dose. Even in patients with normal kidney function, the frequency of adverse reactions is higher in older people [27], thus sufficient attention should be paid to the correct dosage. The dosage of pregabalin is determined based on the creatinine clearance rate. Because pregabalin does not bind to plasma proteins and is highly dialyzed, the administration of an additional supplement is recommended after hemodialysis [11]. Therefore, the dosage is initially 25 or 50 mg daily and is increased gradually based on tolerability. It is necessary to start with a lower dose based on tolerability and then monitor adverse effects. The half-life of pregabalin is 6.7 h; it is not metabolized by hepatic cytochrome P450 and is excreted unchanged mostly by the kidneys [28]. Therefore, it is unlikely to be affected by pharmacokinetic interactions; however, dose adjustments are required in patients with impaired kidney function.

In this study, ten patients were withdrawn because of adverse effects including drowsiness and dizziness, or because of insufficient effects, although peripheral edema was not observed. Of note, 60 % of these patients were withdrawn after 2 weeks of pregabalin treatment. Therefore, it is recommended that pregabalin should be initiated at a lower dose and the dosage adjusted based on

tolerability with potential adverse effects monitored closely. However, this trial was conducted as a single-arm study. The efficacy of the pregabalin was shown by the reduction in VAS and SF-8 scores from the baseline. A few clinical studies have shown that pregabalin treatment can be effective for neuropathic pain in a dialysis population based on VAS and SF-8 scores. One study reported that pregabalin was effective for treating uremic pruritus based on the VAS score [29]. The severity of pruritus measured by the VAS reduced significantly in the pregabalin group ($n = 62$) compared with the placebo group ($n = 60$). Although the mean VAS in the pregabalin group was significantly reduced from 80 mm at baseline to 14 mm at 12 weeks, the change was not significant compared with that in the placebo group, from 77.3 mm at baseline to 57 mm at 12 weeks. Although there have been two reports of SF-36 scores improving after pregabalin treatment in patients with normal kidney function [30, 31], few studies have investigated SF-8 in a dialysis population. Therefore, further studies with larger sample sizes may be required to demonstrate the effect of pregabalin on neuropathic pain in dialysis patients.

There are some limitations to this study. In particular, it was conducted at just three centers, thus it might not reflect the clinical management of hemodialysis patients throughout Japan. In addition, the results may not be generalizable to non-Japanese patients. Because this trial did not have a double-blind design, the absence of masking may have introduced a bias. Therefore, randomized crossover or parallel studies are needed because the evidence relating to the efficacy and safety of pregabalin in dialysis patients is still lacking. Finally, the number of the patients was small; therefore, larger studies may be required to confirm the efficacy of pregabalin in this population.

5 Conclusion

If side effects are carefully monitored and the administered doses are prudently determined, pregabalin can be efficient in the treatment of peripheral neuropathic pain in patients undergoing hemodialysis.

Compliance with Ethical Standards

Funding No sources of funding were received for the preparation of this study.

Conflict of interest MA has received honoraria from Kyowa Hakko Kirin, Daiichi Sankyo, and Otsuka Pharmaceutical. The other authors declare that they have no relevant financial interests.

Ethical approval All procedures in this study were in accordance with the 1964 Helsinki Declaration, and the ethical committees of our hospitals approved the study.

Informed consent Written informed consent was obtained from all patients.

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