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NEPHROLOGY – ORIGINAL PAPER

Gabapentin versus pregabalin in improving sleep quality and depression in hemodialysis patients with peripheral neuropathy: a randomized prospective crossover trial

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Abstract
Purpose In dialysis patients, painful peripheral neuropathy (PPN) is associated with sleep disturbance and mood disorders. Our goal was to compare the effects of gabapentin and pregabalin on improving sleep quality and depression among hemodialysis patients with PPN.
Methods Fifty hemodialysis patients with PPN were randomized into 2 groups, to receive gabapentin and pregabalin, respectively. After 6 weeks of treatment, patients underwent a 2-week washout period, followed by crossover and another 6 weeks of treatment. All patients underwent electromyography (EMG) at the outset and completed the modified Short Form of McGill Pain Questionnaire (SF-MPQ), the Beck Depression Inventory (BDI) and the Pittsburgh Sleep Quality (PSQI) assessment at baseline and at the end of the study. Forty out of 50 patients completed the 14-week study period.
Results Thirty-one out of 40 patients (77.5 %) had EMG-proven PPN. Both gabapentin and pregabalin significantly improved SF-MPQ, BDI and PSQI scores at the end of the study compared with pretreatment scores ($p < 0.001$). There was no significant difference between the two drugs in any studied parameter.
Conclusions Our results showed for the first time a good and similar efficacy of both drugs on pain intensity, quality of sleep and depression in hemodialysis patients with PPN.

Keywords Depression · Gabapentin · Hemodialysis · Painful peripheral neuropathy · Pregabalin · Sleep

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Introduction

Painful peripheral neuropathy is common in patients receiving maintenance hemodialysis [1]. This may be due to comorbid conditions such as diabetes mellitus or a result of uremia per se. Whatever the underlying cause, pain is intense and interferes with daily functioning and reduces quality of life of inflicted patients [2]. Chronic pain, sleep disturbance, and affective disorders (mainly depression) often occur simultaneously [3, 4] and are purported to have multidirectional relations with each other. Approximately, 50–70 % of individuals attending chronic pain clinics report sleep impairment [5], over 20 % have major depression [6].

Apart from depression and sleep disorders related to chronic pain, hemodialysis patients have high rates

of sleep disorders and depression due to myriad of other causes [7]. Comorbid conditions such as impaired sleep and depression exacerbate pain, and in turn, pain exacerbates the comorbid conditions. Thus, treatment of one of the components of this triad necessitates adequate control of other components for a successful overall result. Concomitant drug treatments aiming at individual components may achieve this goal. However, gabaergic drugs such as gabapentin and pregabalin may address all three components simultaneously. Accumulating evidence has shown that gabaergic drugs may have direct effects on pain and improve sleep directly independent of analgesic effects [8]. These drugs may also affect sleep quality and depression in an indirect way as alleviating pain.

Despite high frequency of neuropathic pain, sleep impairment and depression in hemodialysis population, there are no data in the literature regarding effects of treatment of pain with gabaergic drugs on concomitant depression and sleep disturbance. Thus, we aimed to evaluate the effects of gabapentin and pregabalin on sleep quality and depressive symptoms in hemodialysis patients with painful peripheral neuropathy.

Materials and methods

Study design

This is a 14 weeks long, open label, prospective, randomized crossover study that was conducted at a private hemodialysis center. The study was approved by the Local Ethics Committee. The study was carried out in accordance with the principles contained in the Declaration of Helsinki. All patients gave informed consent before taking part in this study. The primary end point of the study was to compare the effects of gabapentin and pregabalin on sleep quality and depressive symptoms in hemodialysis patients with symptoms of peripheral neuropathy. Criteria for inclusion in the study were as follows: prior diagnosis of peripheral neuropathy or currently being on drug treatment for peripheral neuropathy for at least 3 months, minimum 40 mm pain score in Short Form of McGill Pain Questionnaire, hemodialysis duration of at least 6 months, achievement of dialysis adequacy ($Kt/V > 1.2$) and age > 18 years. Exclusion criteria were as follows: presence of hepatic, cardiopulmonary and uncontrolled psychiatric disease, pain syndromes other than peripheral neuropathy, abnormal blood counts (white blood cells $<2{,}500/mm^3$ and platelet count $<10 \times 10^3/mm^3$), presence of active malignancy, untreated hypothyroidism and patients with extremity amputation. Patients under gabapentin treatment before enrollment underwent washout for 6 weeks before randomization. All patients were instructed to complete Short Form of McGill Pain Questionnaire (SF-MPQ) for the assessment of pain, Beck Depression Inventory for the assessment of depression and Pittsburgh Sleep Quality for the assessment of sleep quality at baseline evaluation. The same questionnaires were repeated before and after the first and second treatment phases. In addition, all patients underwent electromyography (EMG) performed by an experienced neurologist at the outset. Patients were randomized into either gabapentin (25 patients) or pregabalin (25 patients) treatment arms using computer-generated random numbers. After 6-week treatment period, patients underwent a 2 weeks washout. Then, we performed a crossover and reversed treatment groups for another 6-week period. The flow diagram of study protocol is depicted in Fig. 1. Gabapentin (Neurontin®, Pfizer İlaçları Ltd.Şti. Istanbul-Turkey) was administered at a dose of 300 mg after each hemodialysis session (thrice weekly) and pregabalin (Lyrica®, Pfizer İlaçları Ltd. Şti. İstanbul-Turkey) at a dose of 75 mg per day. Patients were asked not to use benzodiazepines, muscle relaxants, opioid analgesics or nonsteroidal anti-inflammatory drugs, tricyclic antidepressants and antiepileptic drugs without informing their caring physicians.

Subjects

Patients enrolled in the study were recruited among maintenance hemodialysis patients who reported neuropathic pain. A total of 80 patients out of 180 screened hemodialysis patients were evaluated in terms of eligibility for the inclusion. Thirty patients were excluded for various reasons that were described in the study flowchart figure (Fig. 1). All patients have been receiving maintenance hemodialysis for at least 6 months. Hemodialysis was performed for 4 h thrice weekly via a polysulphone dialyzer using bicarbonate dialysis fluid containing 138 mmol/L Na, 1.5 mmol/L Ca and 34 mmol/L bicarbonate.

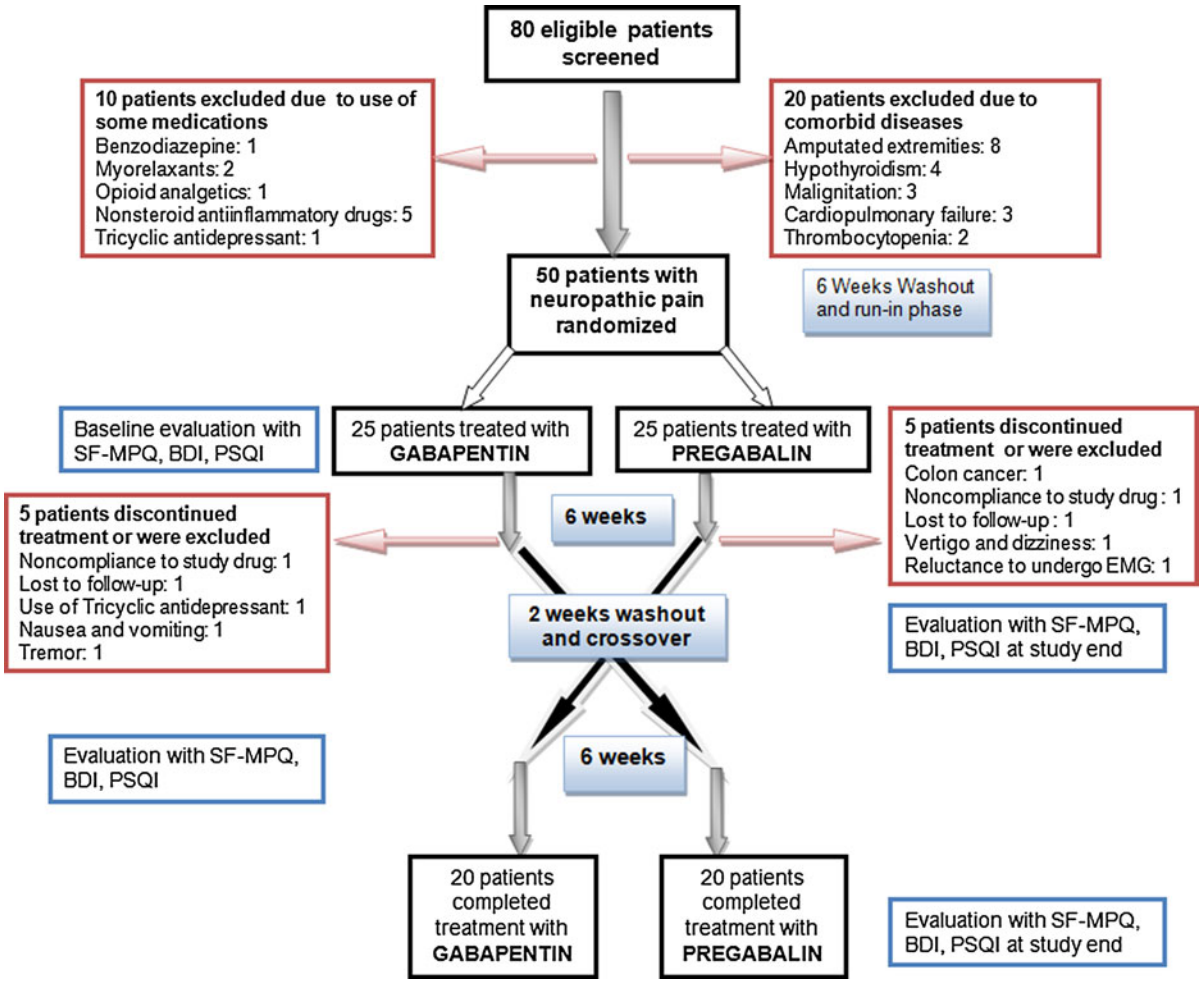

Fig. 1 Diagram of the study design

Electromyography

Nerve conduction studies were performed using a Nihon Kohden electromyography (EMG) machine (MEB-7102 K), with a filter setting of 20 Hz to 3 kHz, using an analysis time of 50 ms. For the recordings, Medtronic 9013S0401 surface recording electrodes were used. Studies were performed in a warm room, with extremity skin temperature of 32 °C or above, at the side where nerve conduction velocity measurement was done. Median motor and sensory nerve conduction velocities were performed in one upper extremity and posterior tibial, and peroneal motor conduction velocities in one lower extremity were performed by the method described by Oh [9]. Abnormality was defined as slowed velocity or absent response in at least two nerves.

Assessments of sleep quality and depression

All patients with complaints of neuropathic pain and/or previous neuropathy diagnosis were asked to complete Short Form of McGill Pain Questionnaire (SF-MPQ), Beck Depression Inventory (BDI) and Pittsburgh Sleep Quality Index (PSQI). Predialysis blood samples were drawn for hematocrit, serum calcium, phosphate, albumin and parathyroid hormone levels. The patients were monitored for drug-related adverse effects at each week's midweek hemodialysis session.

Short Form of McGill Pain Questionnaire (SF-MPQ)

SF-MPQ was used to assess the intensity of neuropathic pain. This form is made up of 3 parts: The main component of the SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) that are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors. The SF-MPQ also includes the Present Pain Intensity (PPI) index of the standard MPQ and a visual analogue scale [10]. The validity and reliability of this questionnaire have been shown in Turkish population [11].

Beck Depression Inventory (BDI)

This is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression. BDI gives more emphasis on cognitive and emotional aspects of depression than somatic aspects, namely anorexia, diminished libido and weight loss. Thus, it is an appropriate tool to evaluate the depression in patients with somatic diseases [12]. It has been validated in Turkish population [13]. Each item in the inventory can take points ranging from 0 to 3. The minimum and maximum scores of the scale are 0 and 63, respectively. The higher the score, the more severe were the signs of depression. In Turkish population, 15 points and above are accepted as an indicator of depression.

Pittsburgh Sleep Quality Index (PSQI)

This index was devised by Buysse et al. in 1989. PSQI provides a quantitative assessment of sleep which is used to define good and poor sleep [14]. Validation and reliability study was carried out by Agargün et al. in Turkish population [15]. PSQI includes a total of 24 questions, 19 of which are self-rated questions. The PSQI consists of 19 self-rated questions and five questions rated by the bed partner or roommate. The latter five questions are used for clinical information only and are not tabulated in the scoring of the PSQI. The 19 self-rated questions assess a wide variety of factors relating to sleep quality including estimates of sleep duration and latency and of the frequency and severity of specific sleep-related problems. These 19 items are grouped into seven component scores, each weighted equally on a 0–3 scale. The seven component scores are then summed to yield a global PSQI score, which has a range of 0–21; higher scores indicate worse sleep quality. Following are the components of PSQI: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction [14].

Statistical analysis

The data were evaluated using the SPSS 15 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) statistical program. Values are expressed as means ± standard deviation. For statistical analysis, the Friedman test was used for four measurements because differences among groups were not normally distributed. In cases of significant differences among measurements, the Bonferroni-adjusted Wilcoxon signed-rank test was used as post hoc analysis. Rank correlation analysis by Spearman (r) was used to define the relation between the PSQI, BDI scores and laboratory parameters. In all analyses, a p value <0.05 was accepted as statistically significant.

Results

Baseline laboratory data and socio-demographic characteristics of the entire study population are shown in Table 1. Forty out of 50 patients completed the 14-week study period. Ten patients were excluded from the study (Fig. 1). Fifteen patients (37.5 %) were diabetic. Baseline EMG showed the following results: sensorimotor neuropathy in 26 patients, motor neuropathy in 4 patients and isolated sensorial neuropathy in 1 patient. Overall, 31 out of 40 patients (77.5 %) had EMG-proven peripheral neuropathy. Changes in SF-MPQ, BDI and PSQI scores with gabapentin and pregabalin treatments in 40 patients are presented in Table 2. There was no difference between the study drugs in terms of efficacy against pain (percent difference after treatment -8.9 ± 4.1 (47.7 %) for gabapentin and -9.3 ± 4.0 (49.9 %) for pregabalin, respectively ($p = 0.576$)). Various adverse effects were observed with the use of gabapentin and pregabalin. There was no significant difference with regards to the frequency of adverse events between

Table 1 Demographic characteristics and baseline laboratory data of entire study population (mean ± standard deviation and percentage in parentheses)

Parameters	Values
Age (years)	58.2 ± 13.7
Gender	
Male (*n*)	12
Female (*n*)	28
Hemodialysis vintage (months)	55.1 ± 35.4
Duration of neuropathic pain (months)	59.2 ± 53.6
Etiology of renal failure	
Diabetes mellitus	15 (37.5 %)
Polycystic kidney disease	6 (15 %)
Hypertensive nephrosclerosis	2 (5 %)
Amyloidosis	2 (5 %)
Glomerulonephritides	1 (2.5 %)
Urologic causes	1 (2.5 %)
Other	2 (5 %)
Unknown	11 (27.5 %)
Hemoglobin (g/dL)	11.3 ± 1.4
Albumin (g/dL)	4.0 ± 0.3
Urea (mg/dL)	119 ± 23
Creatinine (mg/dL)	7.8 ± 1.9
Corrected calcium (mg/dL)	9.4 ± 0.8
Phosphorus (mg/dL)	4.6 ± 1.3
Intact parathyroid hormone (pg/mL)	282.1 ± 233.0
Ca × P product	43.8 ± 13.7
Corrected Ca × P product	44.2 ± 13.9
ALP (U/L)	116.6 ± 57.9
Kt/V	1.5 ± 0.2
Duration of diabetes mellitus (months)	249.4 ± 91.5

gabapentin and pregabalin despite more frequent observations in gabapentin treatment. PSQI and BDI scores were associated ($r = 0.664$, $p < 0.001$; Table 3). There was no relation of BDI and PSQI with age and laboratory parameters (Tables 3 and 4).

Discussion

The results of this current study showed beneficial effects of gabapentin and pregabalin on concomitant untreated depression and sleep disturbance in maintenance hemodialysis patients with painful peripheral neuropathy.

In a study that reviews nine clinical trials, pregabalin has been found to be effective in pain-related sleep disturbance [16]. Pregabalin basically exerts its beneficial effects on sleep quality through alleviation of chronic pain. However, accruing evidence showed that pregabalin has some favorable effects on sleep architecture as well. [8, 17, 18]. Pregabalin has also been found to be effective for the treatment of restless legs syndrome and improve sleep architecture and periodic limb movements [19].

Pregabalin has shown efficacy in the treatment of generalized anxiety disorder in a double-blind, placebo-controlled study [20]. Patients with PHN treated with pregabalin had greater improvement than placebo on the Zung Self-rating Depression Scale [21]. However, it is not evident from this study whether relief in depressive symptoms is due to amelioration of pain or not. In a pooled analysis of six studies, pregabalin

Table 2 Changes in Short Form of McGill Pain Questionnaire (SF-MPQ) and Beck Depression Inventory and Pittsburgh Sleep Quality Index (PSQI) with gabapentin and pregabalin treatments in patients with painful peripheral neuropathy (40 patients)

	Before GABA	After GABA	Before LYRICA	After LYRICA	*p**
SFMPQ TOTAL	18.9 ± 4.3	9.3 ± 4.3[a]	18.5 ± 3.9[b]	9.8 ± 3.6[a,c]	< 0.001
SFMPQ VAS	68.8 ± 12.8	33.0 ± 15.6[a]	67.0 ± 11.8[b]	32.9 ± 12.8[a,c]	< 0.001
SFMPQ PPI	2.8 ± 0.8	1.4 ± 0.7[a]	2.8 ± 0.8[b]	1.4 ± 0.7[a,c]	< 0.001
PSQI	8.7 ± 4.2	5.9 ± 3.0[a]	8.8 ± 4.6[b]	6.1 ± 4.2[a,c]	< 0.001
BDI	15.1 ± 7.6	10.9 ± 5.9[a]	13.61 ± 5.9[b]	10.9 ± 5.9[a,c]	<0.001

* Friedman test

Intergroup comparison performed by Bonferroni-adjusted Wilcoxon signed-ranks test:

[a] Compared with before gabapentin, $p < 0.05$

[b] Compared with after gabapentin, $p < 0.05$

[c] Compared with before pregabalin, $p < 0.05$

Table 3 Correlations of PSQI with other general and laboratory parameters of patients ($n = 40$)

Parameters	PSQI	
	r	*p*
Age	0.154	0.342
Hemoglobin	0.207	0.200
Albumin	−0.160	0.325
Kt/V	0.138	0.397
iPTH	0.232	0.150
BDI	0.664**	<0.001
SFMPQ VAS	0.260*	0.020
HD vintage	0.234	0.146

r correlation value by Spearman, *p* correlation significance, *BDI* Beck Depression Inventory, *SFMPQ* Short Form of McGill Pain Questionnaire, *VAS* visual analogue scale

* $p < 0.05$; ** $p < 0.001$

Table 4 Correlations of BDI with other general and laboratory parameters of patients ($n = 40$)

Parameters	BDI	
	r	*p*
Age	0.240	0.136
Hemodialysis vintage	0.015	0.926
Hemoglobin	0.215	0.183
Albumin	−0.065	0.690
Kt/V	0.145	0.372
iPTH	0.064	0.697
SFMPQ VAS	0.283*	0.011

r correlation value by Spearman, *p* correlation significance, *BDI* Beck Depression Inventory, *SFMPQ* Short Form of McGill Pain Questionnaire, *VAS* visual analogue scale

* $p < 0.05$; ** $p < 0.001$

demonstrated efficacy in treating depressive symptoms typically encountered in generalized anxiety disorder patients [22].

In contrast to gabapentin, efficacy and safety of pregabalin in the treatment of peripheral neuropathy in hemodialysis patients has not been assessed to date. Our results were in agreement with studies in the literature confirming beneficial effects of pregabalin treatment on comorbid sleep disturbance and depressive symptoms extending available data to hemodialysis patients with PPN.

Sleep disturbances and depression are quite frequent disorders in hemodialysis population and negatively impact quality of life [23]. Painful peripheral neuropathy is also common and closely interrelated with these disorders. It is of clinical importance to determine these prevalent disorders and treat appropriately. To date, effects of pregabalin on sleep quality and depression have not been appreciated in hemodialysis patients with painful neuropathy. This is the first study showing beneficial effects of pregabalin on concomitant untreated sleep disturbance and depression in hemodialysis patients. In our cohort, pregabalin was at least as effective as gabapentin on these derangements. With this information in mind, one can treat or at least ameliorate depressive symptoms and sleep impairment when treating polyneuropathy.

A few limitations deserve further attention. First, we did not perform a sleep study. We only assessed quality of sleep with a survey form and evaluated effect of drugs on these scores. Thus, pregabalin seems to have beneficial effects cumulatively in possibly heterogenous hemodialysis patients. Second, Beck Depression Inventory only assesses depressive symptoms but not specific diagnosis of clinical depression. Thus, benefits of pregabalin and gabapentin on clinical depression are yet to be determined in future studies. Third, this is not a blinded and placebo-controlled trial. However, we used randomized crossover design with open-label drugs instead. We did not find it ethical to leave the patients without drugs because most of the study participants underwent initial washout and discontinued their medications.

Despite its aforementioned limitations, this is the first study demonstrating beneficial effects of gabapentin and pregabalin in a well-characterized hemodialysis cohort. Neuropathic pain was well characterized and electromyographic evaluation supported our clinical diagnoses. In conclusion, pregabalin and gabapentin showed equal efficacy on depressive symptoms and sleep disturbance in a maintenance hemodialysis patient cohort. Prospective randomized studies are needed to better elucidate effects of individual gabaergic drugs on particular sleep disorders and clinical depression.

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