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Original Article

The Effect of Pregabalin on the Quality of Life in Patients with Central Post-Stroke Pain

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ABSTRACT

Objective: Pregabalin is an off-label drug used to reduce central neuropathy pain that often accompanies and affects the quality of life in central post-stroke pain (CPSP). This study was conducted to determine the effect of pregabalin on CPSP. **Methods:** Patients with CPSP who were prescribed pregabalin 75 mg/day for treatment were included in this study. The severity of pain (worst, least, average, and right now) and the quality of life were assessed with a Brief Pain Inventory (short form) (BPI-sf) questionnaire. The assessment was conducted before treatment, in week 4, and at the end of treatment (week 12). The Friedman test and, subsequently, the Wilcoxon post-hoc test was conducted to compare the severity of pain and the quality of life before and after therapy. **Results:** A total of 36 patients with CPSP (21 male and 15 female) were included. The study found a reduction in the severity of pain after four weeks of treatment and after 12 weeks of treatment (CI 95%, $p<0.05$). A minor change of the quality of life significantly improved in week 4 in all sub-items of the BPI-sf questionnaire (general activity, mood, walking ability, work, relations with others, sleep, enjoyment of life) (CI 95%, $p<0.05$). After 12 weeks of treatment, the quality of life demonstrated a mild change in all sub-items. The major adverse event shown in this study was somnolence (13.89%). **Conclusion:** Pregabalin is safe and effective in reducing the severity of pain as well as improving the quality of life in Indonesian patients with CPSP.

Key words: Pregabalin, Central post-stroke pain, Quality of life, Pain.
Key messages: Central post-stroke pain can decrease the quality of life. Pregabalin is effective in improving the quality of life of CPSP patients.

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INTRODUCTION

Pregabalin is part of a new generation of anticonvulsants. Like other anticonvulsants, pregabalin has an analgesic effect, especially on neuropathic pain. Several studies of the use of pregabalin for peripheral neuropathic pain have been conducted, such as pregabalin for diabetic neuropathic pain, post-herpetic neuralgia, neuropathic cancer pain, and fibromyalgia.[1-5] Pregabalin is a first-line therapy in any neuropathic pain, such as post-herpetic neuralgia, post-amputation pain, neuropathic cancer pain, and central pain.[6]

There is still a lack of evidence on the use of pregabalin in central neuropathic pain. Central post-stroke pain (CPSP) is a form of central neuropathic pain. The pain in CPSP patients significantly affects their quality of life. Almost all aspects of quality of life decrease, particularly sleep quality, cognitive function, mobility, emotion, fatigue, and physical activity.[7] A study by Vrenken *et al.* revealed a positive result at a dose of 125–600 mg/day after four weeks of therapy in patients with central neuropathic pain (CPSP and spinal cord injury).[8] Another study was conducted by Kim *et al.*, where pregabalin at a dose of 150–600 mg/day was administered to 219 CPSP patients, who were observed for 13 weeks. There was no significant difference between pregabalin and placebo regarding pain reduction, but pregabalin was shown to affect the utility of CPSP patients.[9]

A recent study of pregabalin was also conducted by Onouchi *et al.* in CPSP patients in Japan. The dose was 150–600 mg/day, and the patients were observed for 53 weeks. Pregabalin use showed an effect within 53 weeks of therapy and was well tolerated. However, the use of pregabalin for CPSP still requires further research.[10]

Pregabalin in the United States is registered for diabetic neuropathy pain therapy, spinal cord injury, post-herpetic neuralgia, and adjunctive therapy for adult partial seizure. In Europe, pregabalin is indicated for the treatment of central and peripheral neuropathic pain, epilepsy, and generalized anxiety disorder.[5,11] In Indonesia, the use of pregabalin is registered for peripheral neuropathic pain and as adjunctive therapy for partial seizures with or without secondary generalization. Therefore, the use of pregabalin for CPSP is still classified as off-label drug use in Indonesia. This study aims to examine the effect of pregabalin on the quality of life of CPSP patients.

METHODS

Study design and setting

This is a prospective, multicenter, observational study conducted in Yogyakarta, Indonesia. Two outpatient clinics from a private hospital and a general government hospital participated in this study.

Subjects

The inclusion criteria were patients with CPSP (aged >18 years) who were receiving pregabalin at 75 mg/day, communicable, and willing to participate in this study. Patients with epilepsy, using other analgesics,

with a history of renal insufficiency, and who were pregnant, or breast-feeding were excluded.

Procedure

Outpatients who met the inclusion criteria were asked to sign an informed consent form. The patient's data (gender, education level, age, history of the disease, and medication history) were recorded, and the patient was then assisted to fill out the Brief Pain Inventory (short form) (BPI-sf) questionnaire.

The BPI-sf was used to evaluate the effectiveness and safety of pregabalin. The effects of pregabalin were assessed from the four categories of pain severity (worst, least, average, and right now), while pain-induced quality of life was evaluated from seven categories (general activity, mood, walking ability, work, relations with others, sleep, and enjoyment of life). The BPI-sf used was the BPI in the Indonesian language that has been tested for validity (r = 0.625) and reliability (Cronbach's alpha value = 0.899).

The BPI-sf was performed before therapy, at week 4 of treatment, and at the end of treatment (week 12). The alteration of BPI-sf score indicates the patient's response. A change of 0–25% is considered no difference or minor, 25–50% mild, 50–75% moderate, and greater than 75% extreme. An alteration of > 50% change of the baseline score is considered as an improvement in the quality of life.

Statistical analysis

The Friedman test followed by the Wilcoxon post-hoc test was used to compare the severity of pain before and after treatment as well as to compare the quality of life before and after treatment (weeks 4 and 12).

RESULTS

Forty-five patients met the inclusion criteria and signed the informed consent form. Nine patients (20%) were excluded because they discontinued pregabalin therapy due to pregabalin side effects. Thirty-six patients remained until completion of the study (21 male and 15 female). The patients' ages were between 40 and 76 years (mean 57.11 ± 7.51 years).

Changes in the severity of the pain category can be seen in Figure 1. Changes in the quality of life can be seen in Figure 2. Table 1 shows the distribution of patients (%) in the change of the quality of life (minor, mild, moderate, and extreme). The Friedman test followed by the Wilcoxon post-hoc test resulted in a p-value <0.05, which indicates a significant difference in the severity of pain (in all the sub-items) and quality of life (in all the sub-items) before therapy, at week 4 of treatment, and at the end of treatment.

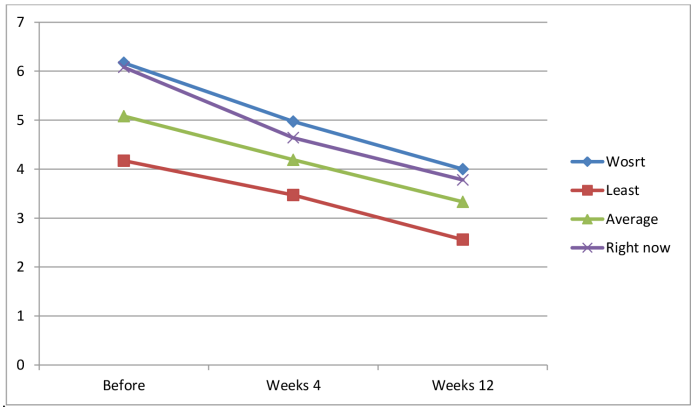

Figure 1: Changes in the mean scores of BPI-sf pains intensity before treatment, after weeks 4, and at the end of treatment. There is a significant difference between baseline and after treatment (CI 95%, p<0.05).

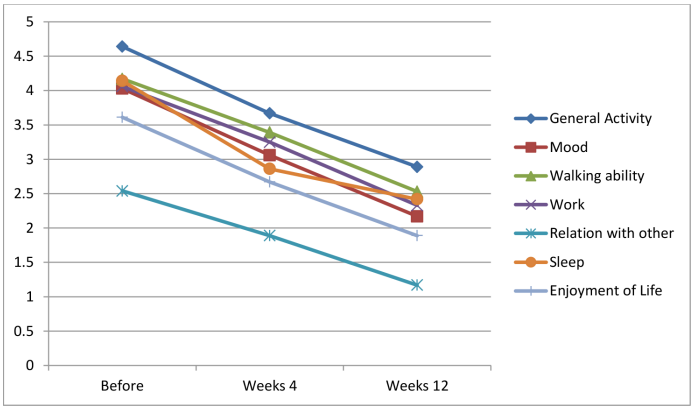

Figure 2: Changes in the mean scores of BPI-sf qualities of life before treatment, after weeks 4, and at the end of treatment. There is a significant difference between before treatment and after treatment in all sub items scores (CI 95%, p<0.05).

DISCUSSION

Patients with CPSP are often psychologically affected, involving deterioration in sleep quality and daily activities. Up to a 40% decrease in the quality of life was mentioned to be mainly related to physical activity disturbance due to CPSP. Chronic pain in CPSP is also known to potentially cause depression.[12]

Pregabalin (3-isobutyl-γ amino butyric acid) is a GABA analogue with a mechanism of action like gabapentin. It has analgesic, anticonvulsant, and anxiolytic effects. Pharmacology pregabalin-related bonding results in the presynaptic alpha-2-delta (A2D) subunit of Ca2+ channels (binding to calcium channels and modulating calcium influx). Therefore, pregabalin reduces the electron excitability of neuronal damage.[4,13,14]

In this multicenter study, pregabalin was found to be effective in reducing pain and improving the quality of life of CPSP patients. In the first month, there was a decrease in the intensity of pain in all sub-items of the BPI-sf (worst, least, average, right now). This reduction is classified mostly as a minor change (70.83±3.58%) (Table 1). However, there was a significant difference before and after treatment (CI 95%, p<0.05) (Figure 1). In the third month, the decrease in pain intensity still occurred and the change shifted towards mild change (55.55±8.78%). In CPSP patients, neurons in the central nervous system are damaged because of stroke. The damage begins with a thalamic lesion but is now also associated with an extra-thalamic lesion. The neuronal damage results in spontaneous pain, evoked pain, or both. The characteristics of the pain are burning, aching, pricking, lacerating, shooting, squeezing, throbbing, sharp, stabbing, painful pins and needles, dull, and cramping. Hyperalgesia, dysesthesia, and allodynia are common in CPSP patients. The Multidisciplinary on Neuropathic Pain recommends pregabalin as the first line of CPSP therapy. Pregabalin has been shown to be useful in a variety of peripheral neuropathic pains, reduces pain, and improves the health quality of patients with CPSP.[16]

The reduction in the severity of pain will affect the quality of life of CPSP patients. Patients' quality of life after the first month of therapy involved mostly minor changes (56.74±6.59%). Minor changes were seen mainly in the aspect of relationship with others (63.89%), where reduction in pain will help in building relationships with others. Meanwhile, enjoyment of life was the aspect seen most in the mild changes (44.44%). It is possible for patients to enjoy life with less pain. In the third month of treatment, the changes shifted towards mild change (53.17±9%) mostly related to general activity (63.88%). There was a significant difference in the quality

Table 1: The distribution of the patients (%) according to grading the change in pain intensity and quality of life at the baseline, after weeks 4 and at the end of treatment (n=36)

Grading BPI-sf	Distribution of patients (%) Weeks 4				Distribution of patients (%) Weeks 12			
	No Change or minor (0-25%)	Mild (26-50%)	Moderate (51-75%)	Extreme (>75%)	No Change or minor (0-25%)	Mild (26-50%)	Moderate (51-75%)	Extreme (>75%)
Pain Intensity								
Worst	75	22.22	0	2.78	25	66,67	5.55	2.78
Least	69.44	27.78	0	2,78	19.44	58.33	11.11	11.11
Average	72.22	25	0	2.78	36.11	60	11.11	2.78
Right now	66.67	22.22	11.11	0	30.55	47.22	22.22	0
Mean±SD	70.83±3.58	24.30±2.67	2.78±5.55	2.08±1,39	27.78±7.17	55.55±8.78	12.49±7.00	4.17±4,81
Quality of Life								
General activity	61.11	36.11	2.78	0	22.22	63.88	2.78	11.11
Mood	55.55	33.33	8.33	2.78	22.22	41.67	8.33	27.78
Walking ability	61.11	33.33	2.78	2.78	27.78	41.67	11.11	19.44
Work	58.33	38.89	0	2.78	22.22	55.55	8.33	13.89
Relation with other	63.89	22.22	5.55	8.33	19.44	50	5.55	25
Sleep	52.78	36.11	2.78	8.33	25	58.33	8.33	8.33
Enjoyment of Life	44.44	44.44	5.55	5.55	11.11	61.11	11.11	16.67
Mean ±SD	56.74±6.59	34.92±6.78	3.86±2.78	4.17±3.40	21.42±5.25	53.17±9.00	7.93±2.97	17.46±7.12

of life before and after treatment (weeks 4 and 12) (CI 95%, $p<0.05$). This result suggests that pregabalin affects the severity of pain and quality of life of the patient from the first month of therapy. CPSP patients often experience fatigue, which affects the quality of life, especially work and daily activities. Other conditions often experienced by CPSP patients are sleep disorders, decreased fitness, and mood.[17] A study suggests that patients with neuropathic pain will experience disruption in mental aspects. This condition has the potential to degrade the quality of life, especially regarding mood, relations with others, and enjoyment of life.[18] Therefore, therapy is needed to help improve the quality of life.

This study reported three side effects that occurred in 36 patients who completed the therapy. As many as five patients (13.89%) experienced somnolence, one patient had a tremor, and another patient suffered from dry mouth. These side effects were minor and did not affect the patients in completing the therapy course. A study of the adverse effects of pregabalin mentions that the side effects include somnolence, dizziness, peripheral oedema, and dry mouth. Somnolence occurred in at least 10% of patients, while dry mouth had a smaller incidence. These side effects are dose-dependent.[19,20]

This study had no control group; hence, it cannot study the placebo effect on the parameters. The 75 mg/day dose of pregabalin was considered safe for Indonesians, while the recommended dosage from previous studies was 125–600 mg/day. However, this study suggests that pregabalin in small doses and limited populations affects CPSP and is well tolerated by Indonesians. Further research is still needed.

CONCLUSION

Pregabalin is safe and effective in reducing the severity of pain as well as improving the quality of life in Indonesian patients with CPSP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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