



Gabapentin vs. Pregabalin for the Treatment of Neuropathic Pain in Patients with Spinal Cord Injury: A Crossover Study

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Abstract

Objective: Neuropathic pain is a frequent complication of spinal cord injury. Almost 70% of patients with spinal cord injury (SCI) experience pain, and nearly one-third of these patients describe their pain as severe. Gabapentin and pregabalin are considered as first-line treatment for post-SCI neuropathic pain. However, there is no study comparing the effects of gabapentin and pregabalin in the management of neuropathic pain in patients with SCI. In this prospective, randomized, crossover clinical trial, we aimed to compare the efficacy of gabapentin and pregabalin in the treatment of neuropathic pain associated with SCI.

Material and Methods: Thirty patients with spinal cord injury experiencing neuropathic pain were recruited for the study. Patients took medications for 8 weeks. After a 2-week washout period, medications were switched in a crossover design. The outcome measures for this study were visual analogue scale (VAS) for pain, VAS for sleep, Short Form Beck Depression Inventory, and the pain disability index.

Results: Twenty-one patients completed the study. Seven patients who did not want to change their medication while they were using the first drug (4 patients were using gabapentin and 3 patients were using pregabalin) and 2 patients who experienced dizziness and nausea (both were in the pregabalin group) were dropped off. There was no difference between both drugs in terms of their efficacy for pain, anxiety, and sleep ($p<0.05$).

Conclusion: There was no statistically significant difference between gabapentin and pregabalin in terms of study parameters for the treatment of neuropathic pain in patients with SCI.

Keywords: Spinal cord injury, neuropathic pain, gabapentin, pregabalin

Introduction

Neuropathic pain is a frequent complication of spinal cord injury (SCI). Almost 70% of patients with SCI experience pain, and nearly one-third of those patients describe their pain as severe (1). Therefore, pain interferes with SCI patients' daily activities, social participation, and quality of life (2). The majority of patients complaining of chronic pain report pain onset within the first 6 months of their injury, irrespective of the type of pain

(3). For neuropathic pain observed after SCI, antiepileptics and antidepressant drugs are reported to be commonly used (4).

Mechanisms of neuropathic pain following SCI are not totally clear. However, there are many anatomical, neurochemical, excitotoxic, and inflammatory alterations from peripheral sites to the brain that could lead to a change in spinal neuron function and then to pain (5). Because elimination of the cause of pain may not generally be possible, the focus of treatment then becomes symptomatic relief or helping the patient to manage pain.

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There are a large number of treatments that are used for symptomatic relief, often with little evidence of efficacy. Even when controlled clinical trials have been performed, satisfactory relief (as defined by a 50% reduction in pain) is at best obtained in about one-third of patients (6).

Gabapentinoids, which are now considered to be first-line treatment for post-SCI neuropathic pain, mimic the neurotransmitter GABA and show indirect interaction with the GABA receptor. Interaction with voltage gated N-type calcium ion channels at the $\alpha_2\delta$ subunit and also indirect interaction with the NMDA receptor could increase the activity of inhibitory neurons, causing a decrease in the transmission of nociceptive signals (4,7).

Ahn et al. (8) conducted a before-and-after trial of SCI patients with pain, in which they found that gabapentin was effective in decreasing neuropathic pain refractory to conventional analgesics. Siddall et al. (9) reported that patients in the treatment group receiving 150 to 600 mg daily of pregabalin experienced a significantly greater improvement in pain and sleep than those in the control group. Vranken et al. (10) found that subjects in the pregabalin treatment group reported a significant decrease in pain and improvements in visual analogue scale (VAS) and SF-36. Levendoglu et al. (11) conducted a crossover study involving 20 subjects with neuropathic pain for more than 6 months, in which they found that gabapentin was more effective than placebo in reducing neuropathic pain. To et al. (12) studied the impact of gabapentin in SCI patients with neuropathic pain and reported a significant decrease in pain. Rintala et al. (13) compared the effects of gabapentin, amitriptyline, and an active control (diphenhydramine) on pain intensity after SCI in patients with neuropathic pain. Gabapentin, when compared with amitriptyline or diphenhydramine, was not more effective in reducing pain intensity.

To the best of our knowledge, there is no study comparing the effects of gabapentin and pregabalin in the management of neuropathic pain in patients with SCI. The aim of this study was to compare the effectiveness of gabapentin and pregabalin in SCI patients with neuropathic pain.

Material and Methods

The study was designed as a prospective, crossover, randomized clinical trial. The study protocol was approved by the local ethics committee, and written informed consent was provided by each patient.

The 18-week study period included 8 weeks for gabapentin or pregabalin use and a 2-week washout period between the use of two medications. After the washout period, drugs were switched in a crossover design.

Inclusion criteria for this study were as follows: SCI patients with pain below the level of injury in areas without normal sensation (14), age between 14 and 75 years, and a Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) score above 12. Exclusion criteria were as follows: concomitant brain injury, cognitive impairment, seizure disorder,

the use of antiepileptics and antidepressants, and hypersensitivity history to gabapentin and pregabalin. The use of other analgesic medications was stopped at least 15 days before the study, and patients were informed not to use other analgesics during the study. Laboratory testing was performed at weekly intervals during the study.

Patients completed the LANNS Scale, pain VAS, sleep VAS, Short Form Beck Depression Inventory (Harcourt Brace & Co., San Antonio, TX), and the pain disability index before and after each treatment period (15,16).

The LANNS Scale is a 7-item self-report scale that was developed to identify pain of predominantly neuropathic origin (17). A score exceeding 12 on the LANNS Scale, representing neuropathic pain, was required for inclusion in the study. Turkish version of S-LANNS is a reliable and valid differential diagnostic measure of neuropathic pain (18). The VAS has proven to be a reliable and a valid measure of pain intensity and unpleasantness (19).

The baseline pain level and the effect of pain on sleep was recorded once a day for the last week using a 10-point VAS scale before initiating medication. Additionally, subjective intensity and frequency of pain, disability due to pain, and quality of sleep were assessed using 10-point scales. During the study period (18 weeks), patients were asked to document pain levels on the VAS and the effect of pain on sleep every night in their daily diaries, in which the morning and afternoon pain levels were recorded on the same day, as well as the previous day's nighttime pain level was documented. The evaluation of these scores was conducted at baseline times (weeks 0, 8, 10, and 18); Short Form Beck Depression Inventory and the pain disability index were also documented at baseline times (weeks 0, 8, 10, and 18).

Patients were initially randomized into a gabapentin treatment group (group A) or a pregabalin treatment group (group B). During the first 2 weeks of the use of each medicine, patients received gradually titrated dosages. Gabapentin was administered orally 3 times a day; however, pregabalin was administered 2 times a day. Before increasing the dose at each interval, the subject was observed by a blinded physician to document any side effects. If no significant side effects were noted, the dose was increased. Adverse effects of medicines were monitored and recorded. All patients' dosages were titrated to tolerability up to 1800 mg/day for gabapentin and 300 mg/day for pregabalin during 2 weeks, regardless of any efficacy achieved at lower dosages.

Statistical Analysis

StatsDirect Statistical software was used for crossover analysis of pain and sleep VAS, Beck Depression assessment, and pain disability index scores within and between the groups. The significance level was set at $p < 0.05$.

Results

Thirty patients with spinal cord injury experiencing neuropathic pain were recruited for the study. Twenty-five of them

Table 1. Raw data obtained from both groups

	First period				Second period			
	Pregabalin group		Gabapentin group		Pregabalin group		Gabapentin group	
	Beginning	End	Beginning	End	Beginning	End	Beginning	End
Pain VAS	7.05±1.92	3.83±3.40	7.02±1.63	4.77±2.77	7.42±1.66	2.53±1.98	8.60±1.34	5.00±1.41
Sleep VAS	4.92±3.94	3.23±4.13	5.14±3.84	1.72±2.79	5.00±4.5	0.81±1.64	5.40±5.07	1.25±2.5
BDI	17.42±10.94	14.23±11.79	10.64±5.31	10.5±5.0	12.12±3.64	10.85±3.80	13.80±13.31	6.5±2.64
PDI	18.50±16.44	15.69±15.65	23.28±22.24	14.92±20.83	15.37±20.98	8.0±11.83	16.80±7.82	17.5±9.98

VAS: visual analog scale; PDI: pain disability index; BDI: Beck depression inventory

Table 2. Crossover analysis of the results

	Test for relative effectiveness of 2 drugs		Test for treatment effect		Test for period effect		Test for treatment-period interaction	
	t	p	t	p	t	p	t	p
Pain	-1.97	0.06	-1.98	0.06	-1.07	0.3	-0.76	0.45
PDI	-0.69	0.50	-0.70	0.49	-1.38	0.18	-0.74	0.47
BDI	0.61	0.55	0.61	0.55	-1.04	0.31	-1.63	0.12
Sleep	0.48	0.64	0.47	0.64	-0.74	0.47	-0.36	0.72

PDI: pain disability index; BDI: Beck depression inventory

were male (83.3%), and 5 of them were female (16.7%), with age ranging from 14 to 63 years (mean age, 32.93±11.87). The mean time since injury was 31.48±61.08 months (range, 1-276 months). The mean motor score was 52±19.52, and the mean sensory score was 142.80±49.35.

Seven patients who did not want to change their medication while they were using the first drug (4 patients were using gabapentin and 3 patients were using pregabalin) and 2 patients who experienced the side effects of dizziness and nausea (both were in the pregabalin group) were dropped off. Finally, 21 patients completed the study (female: male, 2:19). The mean age was 33.7±11.8 years (range, 20-63 years). The mean time since injury was 30.3±65.9 months (range, 1-276 months).

The raw data of evaluations are presented in Table 1. Crossover analysis of the results revealed that there was no difference between both drugs in terms of all assessments of neuropathic pain (pain and sleep VAS, Beck depression inventory, and the pain disability index) outcome measures (p>0.05) (Table 2).

Discussion

The results of this study revealed that pregabalin was as effective as gabapentin in the treatment of neuropathic pain in patients with SCI. We also found that both gabapentin and pregabalin were effective in improving sleep and anxiety. This may reflect an improvement in daily functioning and ability to participate in life activities, which may be interpreted as an improvement in quality of life. There was no statistically significant difference between these 2 agents in terms of pain,

sleep, anxiety, daily functioning, and ability to participate in life activities.

Neuropathic pain is a common problem after SCI. Many studies have provided evidence that SCI-related pain leads to decreased function and quality of life (1). However, the present literature demonstrates a substantial need for comparative studies of pharmacologic therapies for neuropathic pain (20).

There is strong evidence supporting the use of gabapentin and pregabalin in the treatment of pain after SCI, particularly central or neuropathic pain (4). Gabapentin (8,11,12) and pregabalin (9,10) have both been shown to be effective in reducing such pain after SCI. They have been shown to be first-line therapy with tricyclic antidepressants in the most recent literature (19,21).

In a crossover study (11) involving 20 subjects with neuropathic pain for more than 6 months, it was found that gabapentin was more effective (p<0.05) than placebo in reducing neuropathic pain. Pain relief was observed with gabapentin use from the beginning of the study; however, statistically significant pain relief started from the second week, and this corresponded to a dose of 1800 mg/day. Therefore, we titrated the dosages up to 1800 mg/day for gabapentin as an optimum dosage in our study. A randomized trial of pregabalin in patients with neuropathic pain due to SCI showed strong evidence that 150-600 mg/day pregabalin was effective in reducing duration-adjusted average change in pain compared with baseline (22). In current study, we observed significant pain relief with 300 mg/day pregabalin.

Adverse effects of gabapentin and pregabalin have been reported to be minor and well tolerated, consisting primarily of somnolence, dizziness, weakness, edema, vertigo, and headache. These drugs also have the benefit of limited interactions with other medications and the lack of organ toxicity (11). In our study, 2 patients in the pregabalin group experienced side effects. These side effects led to discontinuation of treatment (dizziness and nausea) and were similar to the literature (4,9).

One important issue to be considered during crossover analysis is carryover or residual effects. Carryover effects occur when the effect of treatment given in the first period persists into the second period and changes the effect of the second treatment. The absence of a statistically significant period effect or treatment-period interaction in our study revealed that there was no carryover effect.

The limitations of our study were a small sample size and the lack of quality of life assessment. In this study, the results revealed that the efficacy of pregabalin for pain was superior to the efficacy of gabapentin, although it was not statistically significant ($p=0.06$). A larger sample size may clarify this potential trend toward significance. Further studies should compare the effects of gabapentinoids on daily functioning and quality of life in patients with SCI.

Conclusion

According to the results of our study, both gabapentin and pregabalin can be added to the list of first-line medications for the treatment of neuropathic pain in patients with SCI.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gülhane Military Medical Academy.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author contributions: Concept - B.Y.; Design - B.Y.,E.Y.; Supervision - A.S.G., A.K.T.; Resource - E.Y., Ö.K.O.; Materials - E.Y., Ö.K.O.; Data Collection and/or Processing -B.Y., E.Y., Ö.K.O.; Analysis and/or Interpretation - B.Y., A.S.G.; Literature Search - B.Y., Ö.K.O.; Writing - B.Y., E.Y., A.S.G.; Critical Reviews - E.Y., A.K.T.

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