Is Pregabalin Effective Against Acute Lumbar Radicular Pain ?

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Abstract:

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for acute lumbar radicular pain accompanying lumbar disc herniation (LDH), but their effects are minimal. The purpose of this study was to evaluate the efficacy and safety of pregabalin (PGB) as an alternative therapy for this condition.

Methods: Patients with acute lumbar radicular pain accompanying LDH were randomly administered either NSAIDs plus PGB (30 patients) or NSAIDs alone (30 patients) for up to 4 weeks. The primary outcome was leg pain at 2 and 4 weeks. Secondary outcomes were reduction in sleep disturbances and patient global impressions of change (PGIC) at 2 and 4 weeks.

Results: Four patients in the NSAIDs plus PGB group were deemed ineligible and excluded from the study. Fewer sleep disturbances were reported by patients administered NSAIDs plus PGB compared with the NSAID monotherapy group at both 2 and 4 weeks. Additionally, the NSAIDs plus PGB group showed greater improvement in pain than the NSAID monotherapy group at 4 weeks, although this difference was not significant. PGIC was also significantly better in the NSAIDs plus PGB group than in the NSAID monotherapy group at 4 weeks. The incidence of adverse events was significantly greater in the NSAIDs plus PGB group than in the NSAID monotherapy group.

Conclusions: The combination of NSAIDs plus PGB is more effective against sleep disturbance than NSAIDs alone in patients with acute LDH, although the control of sciatic pain is minimal. Patients reported satisfactory recoveries could also be obtained, and thus, this combination therapy could be a good option for the conservative treatment of acute lumbar radicular pain, including LDH.

Keywords:

lumbar disc herniation, pregabalin, randomized controlled trial, leg pain, sleep disturbance

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Introduction

Lumbar disc herniation (LDH) is a common medical condition encountered in outpatient clinics[1-3)]. It refers to the displacement of intervertebral disc materials beyond the normal margins of the disc space[1)]. Disc materials include elements of the nucleus pulposus, annulus fibrosis, or both; their displacement can compress the nerve roots and cauda equina, causing leg and/or lower back pain[1)]. Neurological symptoms improve in many patients within the first 6 weeks of onset; thus, a 6-week period of conservative care is warranted[2,4)]. In outpatient clinics, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment because a local or systemic inflammatory reaction may contribute to LDH pain. However, the control of pain and numbness by these agents seems insufficient, judging by the results of randomized NSAIDs trials in cases of sciatica[5,6)]. In LDH, inflammation as well as neuropathic pain is typically experienced by the patient, and thus, the antineuropathic pain drug pregabalin (PGB) might help relieve pain caused by LDH[7,8)].

Although PGB was developed as an antiepileptic drug, its usefulness in alleviating neuropathic pain has been reported[9,10)]. PGB binds with high affinity to the α2δ subunit-containing voltage-gated calcium channels and controls such signaling systems as those affecting Ca^{2+} channel-mediated

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Table 1. Questions Related to the Nature of the Subject's Pain.

Points	0	1	2	3	4
Q1. Do you feel a pinprick-like pain?					
	No	Slight	Moderate	Severe	Very severe
Q2. Do you feel a pain like an electric shock?					
	No	Slight	Moderate	Severe	Very severe
Q3. Do you feel a tingling or burning pain?					
	No	Slight	Moderate	Severe	Very severe
Q4. Do you feel a pain accompanied by numbness?					
	No	Slight	Moderate	Severe	Very severe
Q5. Does only slight contact with clothing or cold wind cause pain?					
	No	Slight	Moderate	Severe	Very severe
Q6. Do you have a change in sensation (decreased or increased) at the site of the pain?					
	No	Slight	Moderate	Severe	Very severe
Q7. Is there skin swelling and/or discoloration (red or purple) at the site of the pain?					
	No	Slight	Moderate	Severe	Very severe

neurotransmitter release, activation of excitatory amino acid transporters, potassium channels, and inhibition of pathways involving inflammatory mediators[9,10]. PGB increases extracellular gamma-aminobutyric acid (GABA) concentrations in the brain by producing a dose dependent increase in L-glutamic acid decarboxylase, the enzyme responsible for making GABA[9,10].

PGB has been recommended as a first-line treatment for neuropathic pain by the Neuropathic Pain Special Interest Group[11] and is reportedly effective against pain and sleep disturbances secondary to several neuropathic diseases, such as peripheral diabetic neuropathy[12,13], post-herpetic neuralgia[14], and spinal cord injury[15]. Previous reports have also described the usefulness of PGB in cases of lumbar and cervical radiculopathy[16-18]. However, some studies concluded that PGB was ineffective in reducing the intensity of sciatica[19-21]. Thus, it is unclear whether PGB is actually useful for the treatment of radiculopathy. This confusion is compounded by several methodological limitations that can be found in the literature: (1) In many studies, several different illnesses were lumped together in the same study (lumbar spinal stenosis, LDH, spondylolisthesis, and others), but the range of illnesses responsible for the pain was very wide; it is thus important to consider such illnesses individually; (2) the duration of symptoms discussed in these studies varied, and both acute and chronic pain were discussed together; (3) no distinction was made in studies of lumbar and cervical radicular pain, and the levels of pain varied; and (4) only a limited number of prospective randomized controlled trials (RCTs) exist. Furthermore, few papers have focused on the efficacy of PGB during the acute phase of LDH to clearly establish whether PGB is useful. The purpose of this study was therefore to evaluate the efficacy and safety of PGB during acute LDH via an RCT comparing an NSAID monotherapy and a combination therapy of PGB and NSAIDs.

Materials and Methods

This prospective RCT was approved by our institutional review board. Eligibility criteria included a current episode of sciatica that persisted from 2 days to 2 weeks after onset. After providing an NSAID treatment ［LOXONIN tablets (Loxonin®, Daiichi-Sankyo; 180 mg/day)］ for 2 weeks following the first visit to our outpatient clinic, we performed magnetic resonance imaging (MRI) on those patients with moderate leg pain that interfered with their daily activities. Patients displaying LDH on MRI and a positive sign during the straight leg rising test were considered for trial recruitment. Patients who had muscle weakness (manual muscle test ≦3) were excluded from the current study, but patients with various degrees of sensory disturbance were included. Sensory disturbance of the lower limbs in the patients selected was consistent with the site of disc herniation on MRI.

Inclusion criteria

Patients qualifying for inclusion in this study were required to be between 20 and 80 years old, display LDH on MRI, have taken NSAIDs ［LOXONIN tablets (Loxonin®, Daiichi-Sankyo; 180 mg/day)］ for at least 2 weeks before the study without sufficient effect, and have had visual analog scale (VAS) pain scores of ≥40 at the beginning of the study.

The Neuropathic Pain-Screening Questionnaire, developed by Ogawa et al.[22], was used for the pain survey (Table 1). Patients'answers to the seven questions were weighted and scored. The likelihood of neuropathic pain was determined based on the total score, and patients with a total score of ≥ 6 were included in the study.

Exclusion criteria

Patients were excluded from the study if they had paralysis or bowel or bladder disorders; had a history of previous spine surgeries, a fresh vertebral fracture, or a malignant tu-

Table 2. Trial Schedule.

	Pretreatment	First day of treatment	Points in time during treatment	
		day 0	at 2 weeks	at 4 weeks
Informed consent	○			
Patient demographics	○			
NPSQ		○		
VAS pain score		○	●	●
VAS sleep score		○	●	●
PGIC		○	●	●
CGIC		○		●
Assessment of adverse events		◄———	———	———►

NPSQ: neuropathic pain-screening questionnaire, VAS: visual analog scale, PGIC: patient global impression of change, CGIC: clinical global impression of change

mor; displayed comorbidities with renal dysfunction (creatinine clearance <60 mL/min); had psychiatric disorders; were pregnant or breastfeeding; or were judged by the staff to be unsuitable for the study for other reasons.

Other medications

Participants were not allowed to take gabapentin, as it may affect the results of this study. Serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors were allowed if the doses were not altered during the study. Patients taking sleeping pills were excluded from the current study before the start of the study, and the patients selected were instructed not to take sleeping pills during the study. Patients were instructed to inform us if they used such pills for any reason during the study, but no patients did so, so we assume that no one used them.

Informed consent and randomization

We obtained informed consent from each study patient. Participating patients were randomly divided into two groups: an NSAID monotherapy ［LOXONIN tablets (Loxonin®, Daiichi-Sankyo; 180 mg/day)］ group and an NSAIDs ［LOXONIN tablets (Loxonin®, Daiichi-Sankyo; 180 mg/day)］ plus PGB (150 mg/day) group in a 1:1 ratio using a computer-generated random number sequence.

Adverse events

If there was an undesirable occurrence of any kind affecting a patient during the study, this was considered an "adverse event," warranting immediate action and, if necessary, suspension of the administration of the test drugs.

Criteria for suspension of administration of the test drugs:

1. The patient refused to participate in this study.
2. The symptoms were relieved, and the medication in this study was not needed for the patient's treatment.
3. The patient's symptoms worsened, leading to the conclusion that continuation of administration was not appropriate.
4. It was difficult to continue this study because of worsening of comorbidities.
5. It was difficult to continue this study because of the occurrence of an adverse event.
6. The patient was found to be pregnant.
7. A doctor determined that this medication should be stopped for some other reason(s).

Clinical evaluation

The primary outcome was leg pain at 2 and 4 weeks. Secondary outcomes were reduction in sleep disturbances, patient global impressions of change (PGIC), and doctor's clinical global impression of change (CGIC) at 2 and 4 weeks. The items that were evaluated included VAS pain scores (scale of 0-100) at pretreatment, 2 weeks post-treatment, and 4 weeks post-treatment; VAS sleep scores (scale of 0-100) at pretreatment, 2 weeks post-treatment, and 4 weeks post-treatment; PGIC at 4 weeks post-treatment; and CGIC at 4 weeks post-treatment (Table 2).

The PGIC/CGIC system was used to determine the efficacy of treatment on a scale of 1-7: grade 1 = no change or condition has worsened; grade 2 = almost the same or hardly any change at all; grade 3 = slightly better but no really noticeable change; grade 4 = somewhat better but the change has not made any real difference in terms of quality of life; grade 5 = moderately better with a slight but noticeable change; grade 6 = better with a definite improvement that has made a real and worthwhile difference in quality of life; and grade 7 = a great deal better with a considerable improvement that has made a significant difference in quality of life.

Statistical analysis

An unpaired *t* test or Fisher's exact test was used to evaluate differences between the two groups. A P value of < 0.05 was considered significant. The statistical analysis was conducted using PRISM software, version 6 (GraphPad Software, San Diego, CA).

Results

A total of 62 LDH patients satisfied the inclusion criteria.

Table 3. Subject Background and Treatment Efficacy.

	NSAID monotherapy	NSAIDs+PGB	*P*
Cases, n	30	26	
Age, years	53.7±15.5	48.1±12.8	0.15
Sex (male/female), n	17/13	14/12	0.83
Level of LDH on MRI			
L4-5	18	14	
L5-S	12	12	0.79
Pretreatment			
NPSQ	9.1±2.2	10.3±2.6	0.07
VAS pain score	75.7±15.7	74.3±12.3	0.71
VAS sleep score	57.7±24.7	52.1±26.2	0.41
At 2 weeks			
VAS pain score	51.5±27.9	43.1±20.2	0.21
VAS sleep score	35.8±25.1	19.4±17.7	0.007*
At 4 weeks			
VAS pain score	27.7±16.1	20.5±14.3	0.08
VAS sleep score	18.1±9.4	3.4±5.6	<0.001*
PGIC	3.3±1.8	2.3±0.9	0.01*
CGIC	2.9±2.0	2.1±1.0	0.07

LDH: lumbar disc herniation, NPSQ: neuropathic pain-screening questionnaire, VAS: visual analog scale, PGIC: patient global impression of change, CGIC: clinical global impression of change, *: statistically significant

Of these patients, two patients were excluded because of comorbidities: One had renal dysfunction, and the other had a previous spine surgery. Finally, 60 patients were included in the efficacy analysis: 30 cases were in the NSAID monotherapy group, and the other 30 cases were in the NSAIDs plus PGB group.

During the trial, four patients in the NSAIDs plus PGB group dropped out of the study: three patients experienced PGB-related adverse events (two cases of severe dizziness and one case of drowsiness), and one patient had nerve root block because of his severe leg pain. There were no significant adverse events in the NSAID monotherapy group. The percentage of subjects experiencing adverse events due to drug use, resulting in cessation of the administered medication, was not significantly different between the two groups.

Finally, 30 patients from the NSAID monotherapy group and 26 patients from the NSAIDs plus PGB group were compared. The findings, shown in Table 3, were as follows:

The primary outcome

The VAS pain scores improved to a greater extent in the NSAIDs plus PGB group (20.5 ± 14.3) than in the NSAID monotherapy group (27.7 ± 16.1) at 4 weeks after treatment ($P = 0.08$), although these differences were not significant.

Secondary outcomes

1) The VAS sleep scores improved to a greater extent in the NSAIDs plus PGB group than in the NSAIDs group at both 2 and 4 weeks after treatment.

2) PGIC was significantly better in the NSAIDs plus PGB group (2.3 ± 0.9) than in the NSAID monotherapy group (3.3 ± 1.8) at 4 weeks after treatment ($P = 0.01$).

3) CGIC improved to a greater extent in the NSAIDs plus PGB group (2.1 ± 1.0) than in the NSAID monotherapy group (2.9 ± 2.0), although this difference was not significant ($P = 0.07$).

Adverse events

Mild to moderate adverse events occurred in four cases in the NSAIDs plus PGB group: two cases of nausea, one case of leg edema, and one case of mild dizziness. In the NSAID monotherapy group, one subject had a headache, although it was not clear whether this was directly related to the NSAID monotherapy. The incidence of adverse events overall was significantly greater in the NSAIDs plus PGB group than in the NSAID monotherapy group ($P = 0.026$).

Discussion

This is the first prospective RCT to investigate the efficacy of PGB for the treatment of acute LDH. This study demonstrated that the combination of NSAIDs plus PGB provided significantly better alleviation of sleep disturbances than did NSAID monotherapy. In addition, there was a trend in the direction of better relief of leg pain in cases with the NSAIDs plus PGB group, although the degree of difference was not statistically significant (p = 0.08). Although the number of adverse events was significantly higher in the NSAIDs plus PGB group, significantly higher PGIC was also achieved, probably because of better sleep and moderate pain control. On the basis of these results, the combination of NSAIDs and PGB was judged to be a more efficacious treatment for acute LDH.

Several studies have demonstrated the efficacy of PGB in the treatment of sciatica, a common type of neuropathic pain. Taguchi et al. evaluated the effectiveness of PGB for chronic lower back and lower limb pain in a prospective, noninterventional, observational study[17]. They concluded that PGB significantly alleviated pain and improved sleep function and health status. Orita et al. investigated the efficacy of PGB in cases of radicular leg pain due to lumbar spinal stenosis in a prospective observational study[18]. They found that PGB significantly improved VAS scores for pain and sleep quality, as well as overall quality of life, with only minor adverse events. Takahashi et al. also investigated the efficacy of PGB in cases of leg pain due to lumbar spinal stenosis[16]. They concluded that a combination of NSAIDs and PGB was more effective than an NSAID monotherapy for the relief of chronic, but not acute to subacute, leg symptoms.

On the other hand, there are several studies that suggest that PGB is not particularly effective in cases of spinal-disorder-related pain. Mathieson et al. conducted a double-blind, placebo-controlled RCT of PGB in patients with sciatica[19]. Their conclusions were that PGB did not significantly reduce leg pain intensity and that adverse events occurred more frequently in the PGB group. Meanwhile, Baron et al. also conducted a double-blind, placebo-controlled RCT to evaluate the efficacy of PGB in patients with chronic lumbosacral radiculopathy[21], finding no significant differences in

pain reduction.

There are no papers evaluating the efficacy of PGB in cases of acute LDH. Slightly better relief of leg pain was observed in cases with the NSAIDs plus PGB group, although the degree of difference was not statistically significant ($p = 0.08$). In the current acute LDH cases as well, PGB might be able to alleviate neuropathic pain by suppressing the secretion of pain-related mediators in the synapses via binding of Ca^{2+} channels as previously reported[9,10]. In addition, since pain is an unpleasant sensation and a serious emotional experience, PGB could reduce pain by an anxiolytic effect increasing GABA concentrations in the brain[9,10]. As to why a statistically significant difference in pain relief was not detected in the current study, several reasons could be suspected. First, the number of patients was not large enough to detect differences or a potential statistical significance. Second, because inflammation was the main cause of the pain in acute LDH, a treatment for neuropathic pain may not significantly improve such inflammatory pain. Third, the dose of PGB administered might not have been large enough to control the neuropathic pain. Samel et al[23]. reviewed the safety and efficacy of PGB based on 11 double-blind, RCTs of PGB in patients with painful diabetic peripheral neuropathy or post-herpetic neuralgia; they found that 250 mg/day of PGB (rather than 150 mg/day) was most effective in young patients, although 150 mg/day was effective in patients over 65 years of age. Thus, higher doses might be more effective for acute LDH or other illnesses.

As with other sources of neuropathic pain, patients with leg pain due to LDH suffer not only from painful disorders but also from sleep disturbances, anxiety, and mood disorders[17,24]. Sleep disturbance results not only from sciatica but also from social stress and other factors, and influences patients'activity. For these reasons, both the alleviation of sleep disturbances and pain control are needed to improve a patient's quality of life. In a prospective observational study to evaluate the efficacy of PGB in cases of radiculopathy, the effect of PGB on comorbid symptoms (sleep disturbance, depression, and anxiety) was significant[24]. In other studies[17,25], PGB significantly alleviated sleep disturbances caused by several disorders, including sciatica via an indirect analgesic effect and a direct effect on sleep mechanisms. In the current study, PGB significantly and consistently reduced patient-reported sleep disturbances across multiple conditions.

With respect to adverse events, cognition or coordination disorders are frequently observed in cases where PGB is used[26]. In a systematic review and meta-analysis of RCTs of PGB-related adverse events, higher relative risks of balance disorder, euphoria, incoordination, ataxia, edema, and dizziness were observed[26]. The percentage of subjects who experienced PGB-related adverse events necessitating discontinuation of treatment and the total percentage of subjects experiencing some kind of adverse event were 10.0% and 23.3%, respectively, in the current study, similar to the findings in Taguchi's earlier study (9.6% and 25.5%, respectively)[17]. The incidence of adverse events due to PGB appears to be dose dependent[26]. In the current study, the dose of PGB was fixed at 150 mg/day in all cases. However, Japanese people are relatively small, and so, this dose might be too high, resulting in adverse events. Reducing the number of adverse events by carefully determining the appropriate dose of PGB on an individual basis is thus warranted.

Some limitations exist in the current study. In addition to those mentioned above, this was not a double-blind study. There was no placebo control, and this might have affected the results. In addition, this study involved only a small number of subjects. In the future, a placebo-controlled, large-scale RCT is needed to conclusively determine the effects of PGB in cases of LDH. As a second, although we included patients with radiculopathy secondary to LDH diagnosed by MRI and a positive sign during the straight leg rising test, the diagnostic specificity as "LDH" was not perfect. This study might include some patients with radiculopathy due to other lumbar diseases, and for this reason, our title for this study does not refer to LDH but rather to acute lumbar radicular pain.

In conclusion, the combination of NSAIDs plus PGB is more effective against sleep disturbance than NSAIDs alone in patients with acute LDH. Although adverse events occurred more frequently in the NSAIDs plus PGB group, the percentage of such cases necessitating the discontinuation of treatment due to severe adverse events was 10%, suggesting that this combination therapy could be an acceptable option for the conservative treatment of acute LDH.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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