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[Original Article]

THERAPEUTIC EFFICACY OF PREGABALIN IN PATIENTS WITH LEG SYMPTOMS DUE TO LUMBAR SPINAL STENOSIS

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Abstract : The purpose of this study was to evaluate the therapeutic efficacy of pregabalin in patients with leg symptoms due to lumbar spinal stenosis. Study subjects were classified into two groups according to their pharmacotherapy : the pregabalin group, treated with nonsteroidal anti-inflammatory drug and pregabalin combination therapy, and the control group, treated with nonsteroidal anti-inflammatory drug monotherapy. The two groups were compared in terms of the duration of pain after the onset of leg symptoms and the type of neurogenic intermittent claudication, whether radicular-, caudal-, or mixed-type. Numerical rating scale and Roland-Morris Disability Questionnaire scores were evaluated before and 3 months after treatment. After 3 months of treatment, there were significant differences in the numerical rating scale for radicular- and mixed-types, but not for caudal-type, between the two groups in the subjects with leg symptoms for greater than 3 months. There were significant differences between the two groups in Roland-Morris Disability Questionnaire scores for mixed-type, but not for radicular- and caudal-types, in the subjects with leg symptoms for less than 3 months and for radicular- and mixed-types, but not for caudal-type, in the subjects with leg symptoms for greater than 3 months. Nonsteroidal anti-inflammatory drug and pregabalin combination therapy may be more effective than nonsteroidal anti-inflammatory drug monotherapy for the relief of leg symptoms due to lumbar spinal stenosis, preventing aggravation of subjective symptoms and improving quality of life for patients with radicular- and mixed-types in subjects with leg symptoms for greater than 3 months, although it may be necessary to consider alternative therapy for patients with caudal-type.

Key words : Lumbar spinal stenosis, Neurogenic intermittent claudication, Pregabalin, Neuropathic pain, Therapeutic efficacy

INTRODUCTION

A neuropathic pain mechanism is generally implicated in the genesis of leg pain in patients with lumbar spinal stenosis (LSS), resulting in poor quality of life and increased costs[1-3]. In clinical situations, LSS patients often receive suboptimal treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide and are widely used for LSS patients. However, in actual practice, NSAIDs are not specific remedies for the neuropathic pain associated with LSS. Although several therapies are available for neuropathic pain, including opioids, tramadol, antidepressants, and antiepileptic drugs, gabapentin (an anti-epileptic gamma-aminobutyric acid (GABA) analog) and pregabalin have been recommended as first-line pharmacotherapies for peripheral pain due to the balance between their efficacy and tolerability[4]. Additionally, antiepileptic drugs

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and antidepressants have the advantage of acting not only on pain, but also on the associated symptoms of depression[4]. Therefore, pharmacotherapy with anticonvulsants and antidepressants may optimize treatment effectiveness and reduce the occurrence of adverse events[5].

The pathomechanisms of leg symptoms due to LSS comprise nociceptive, inflammatory, and neuropathic pain components. One of the most characteristic symptoms in LSS patients is neurogenic intermittent claudication (NIC). Verbiest defined the pathomorphologic changes of LSS, specifically encroachment of the canal by hypertrophied articular processes, and called attention to the characteristic clinical manifestations of the condition, including NIC[6–8]. Patients with NIC due to LSS have various symptoms induced by walking, such as pain, numbness, burning, a feeling of residual urine, constipation, etc. It is generally believed that leg pain is induced by nerve root impairment, while the other symptoms are due to cauda equina impairment[9–12].

If conservative therapies fail for 3 to 6 months, surgical therapy is usually considered[13]. Therefore, it may be important to know how to select conservative pharmacotherapy as primary care for patients with leg symptoms due to LSS, especially in those who are at high risk for surgical therapy.

It was reported that pregabalin was effective in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy[14]. However, little is known about the therapeutic efficacy of pregabalin for each pathomechanism of the leg symptoms of LSS. This study aimed to evaluate the therapeutic efficacy of pregabalin in patients with leg symptoms due to LSS 3 months after the start of their primary medical care.

PATIENTS AND METHODS

This study received institutional review board approval from our hospital.

Study subjects were classified into two groups according to the pharmacotherapy they received : the pregabalin group that was treated with combination NSAID and pregabalin therapy, and the control group that was treated with NSAID monotherapy. The 64 subjects (30 males, 34 females) of the pregabalin group were extracted from a total of 126 cases that were newly diagnosed patients with LSS at our hospital from August 2010 to October 2011 and who satisfied the inclusion criteria, never satisfied the exclusion criteria, and agreed with the therapeutic approach of this study. The practice of prescribing pregabalin for patients with neuropathic pain was adopted in Japan only in August 2010. The 60 control group subjects (30 males, 30 females) were extracted according to priority of medical examination from cases that were newly diagnosed patients with LSS at our hospital from January 2009, who satisfied the inclusion criteria, never satisfied the exclusion criteria, and agreed with the therapeutic approach of this study.

The inclusion criteria for subjects enrolled in this study were : 1) a diagnosis of lumbar spondylosis and degenerative spondylolisthesis ; 2) pain and/or numbness in the lumbar dermatomal distribution ; 3) motor or sensory neurological signs (hypoesthesia, hyperesthesia, allodynia, and dysesthesia) in the affected dermatomes ; 4) cognitive capability to complete the pain questionnaires ; and 5) no previous history of treatment for symptoms of LSS (Table 1).

Exclusion criteria in this study were : 1) a diagnosis of lumbar degenerative disease without LSS ; 2) patients with mostly axial spinal pain ; 3) significant motor deficits (Manual Motor Testing <3) and/or bowel or bladder dysfunction ; 4) patients with rheumatoid arthritis ; 5) patients with known diabetes, congestive heart failure, cardiac conduction abnormalities and/or thrombocytopenia ; 6) patients with known peripheral neuropathy ; 7) history of spinal surgery ; 8) workmen's compensation or disability issues ; 9) patients with chronic depression on antidepressant medication ; 10) renal dysfunction (creatinine clearance (CCr) <60 mL/min) ; 11) patients who had been diagnosed to absolutely require surgical treatment because of tertiary paralysis, NIC, and bladder dysfunction ; and 12) patients with an ankle brachial pressure index (ABI) <0.9 (Table 1). Additional exclusion criteria for the pregabalin group were : 1) patients previously using gabapentin ; 2) history of angioedema with pregabalin use ; 3) known hypersensitivity to pregabalin use (hives, blisters, rash, dyspnea, and wheezing) ; and 4) patients who had to drive a motor vehicle extensively (Table 1).

NIC is classified into three types according to the leg symptoms caused by LSS[9–12, 15]. The first type of NIC presents as unilateral radicular pain (radicular type), with symptoms of pain, burning, numbness, and paresthesia in the distribution of one or more specific dermatomes. The fifth lumbar nerve root associated with L5 stenosis is most commonly involved. The second type of LSS has symptoms with less dermatomal-specific neurogenic claudication, with nerve roots below L5 being most

Table 1. Inclusion and exclusion criteria for study subjects

Inclusion criteria
1) Lumbar spondylosis and degenerative spondylolisthesis
2) Pain and/or numbness in the dermatomal distribution of the lumbar region
3) Presence of motor or sensory neurological signs (hypoesthesia, hyperesthesia, allodynia, and dysesthesia) in the affected dermatomes
4) Cognitive capability of completing the pain questionnaires
5) No previous history of treatment for symptoms of lumbar spinal stenosis
Exclusion criteria
1) Lumbar degenerative disease without lumbar spinal stenosis
2) Mostly axial spinal pain
3) Presence of significant motor deficits (Manual Motor Testing <3) and/or bowel and/or bladder dysfunction
4) Rheumatoid arthritis
5) Known renal insufficiency, diabetes, congestive heart failure, cardiac conduction abnormalities, and/or thrombocytopenia
6) Known peripheral neuropathy
7) History of spinal surgery
8) Workmen's compensation or disability issues
9) Chronic depression on antidepressants
10) Renal dysfunction (creatinine clearance (CCr) < 60 mL/min)
11) Absolutely require surgical treatment because of tertiary paralysis, neurogenic intermittent claudication, and bladder dysfunction
12) Ankle brachial pressure index (ABI) <0.9
Additional exclusion criteria for the pregabalin group
1) Using gabapentin or with a history of failure to respond to previous gabapentin use
2) History of angioedema with pregabalin use
3) Known hypersensitivity to pregabalin use (hives, blisters, rash, dyspnea, and wheezing)
4) Driver of a motor vehicle

commonly involved (caudal type). Typically, patients present with complaints of bilateral aching, cramping, or a burning sensation in the legs. Occasionally, numbness, bladder dysfunction, and sexual difficulties also occur. The third type of LSS has both radicular and caudal type symptoms (mixed type). A previous study described a neurologic evaluation based on the gait-loading test and a functional diagnosis based on selective nerve root blocks to determine the spinal level responsible for lumbosacral symptoms[16]. The aim of the gait-loading test is to obtain information on changes induced by exercise in the symptoms and neurogenic condition of patients with NIC. The responsible spinal level affected by LSS is diagnosed exactly at the limit of walking, but not at rest. Since the therapeutic regimens for each of the three different pathomechanisms of the leg symptoms of LSS are different, they need to be clinically differentiated into the three types : radicular, caudal, and mixed types.

All study subjects who had never been treated for LSS before continued the prescribed treatment and follow-up at our hospital for more than 3 months. An independent radiologist assessed the MRIs for evidence of lumbar canal stenosis, which included all severities of degenerative spondylolisthesis. The ABI was also checked in all patients to distinguish the NIC from vascular intermittent claudication (ABI<0.9). Two subjects in the pregabalin group dropped out due to side effects of pregabalin, accounting for 1.6% of the 126 cases that were newly diagnosed with LSS from August 2010 to October 2011.

The pregabalin group finally included 62 (29 males, 33 females) subjects. The side effects of pregabalin were mainly unsteadiness while walking, dizziness, and drowsiness. Patients were asked to discontinue pregabalin therapy if such symptoms appeared. Hence, patients who could not avoid extensive operation of motor vehicles could not take part in this study. Pregabalin therapy was started after patients' renal function was assessed to ensure that their creatinine clearance was greater than 60 mL/min. All patients were observed for the appearance of heart disease and/or intestinal hemorrhage, as well as disorders of internal organs such as the liver and kidneys, while receiving NSAIDs.

When obtaining informed consent, patients

were informed about the proven superiority of surgery over conservative management for LSS[13], and also that our therapeutic approach was to first use pharmacotherapy, surgical and/or other therapies being reserved for cases in which pharmacotherapy had insufficient effect during the 3 months after its start. The first assessment of the therapeutic effect of pharmacotherapy was done 3 months after its start. None of the patients reported wanting surgical or other therapies, such as epidural block or root block during this period.

In the pregabalin group, which included 38 radicular, 10 caudal, and 14 mixed type NIC cases, the median age was 68 years (range 36–85 years), distances causing NIC were <100 m (n=15), 100–500 m (n=41), and >500 m (n=6), and the causes of LSS were lumbar spondylosis (n=49) and degenerative spondylolisthesis (n=13) (Table 2). Patients in the pregabalin group were prescribed only NSAIDs, in the form of loxoprofen sodium hydrate (n=35), celecoxib (n=25), or lornoxicam (n=2), for the first 2 weeks, with pregabalin added from the third week onwards. Pregabalin was started at a dose of 25 or 50 mg/day, and this dose was maintained if therapeutic efficacy was sufficient (n=14). If this dose did not produce sufficient pain relief within the first week, it was increased to 150 mg/day (n=42), and then to 300 mg/day (n=6), if the previous dose was insufficient after the first and second weeks, respectively (Fig. 1). On the other hand, in the control group, with 32 radicular, 14 caudal, and 14 mixed type NIC patients, the median patient age was 68 years old (range 46–84 years), distances causing NIC were <100 m (n=13), 100–500 m (n=38), and >500 m (n = 9), and the causes of LSS were lumbar spondylosis (n=36) and degenerative spondylolisthesis (n=24) (Table 2). Patients in the control group received only NSAIDs, as loxoprofen sodium hydrate (n=41), celecoxib (n=16), or lornoxicam (n=3) (Fig. 1).

The numerical rating scale (NRS) score and Roland–Morris Disability Questionnaire (RDQ) score were used to assess therapeutic efficacy. The NRS was used by the patients themselves for self-evaluation of their pain. Both the NRS and RDQ scores were examined before and after 3 months of pharmacotherapy. The two groups were compared in terms of : a) the duration of leg symptoms, i.e., less or greater than 3 months after the onset of leg symptoms ; b) the type of NIC ; and c) the NRS and RDQ scores before and 3 months after pharmacotherapy.

Statistical analyses were performed using Mann–Whitney's U test. P values less than 0.05 were considered significant. All statistical analyses were performed using StatView 5.0 statistical software (SAS Inc., Cary, NC, USA).

RESULTS

The clinical characteristics and demographics of the patients in the two groups are shown in Table 2. The pregabalin and control groups were not significantly different, except for the ratio of cases with

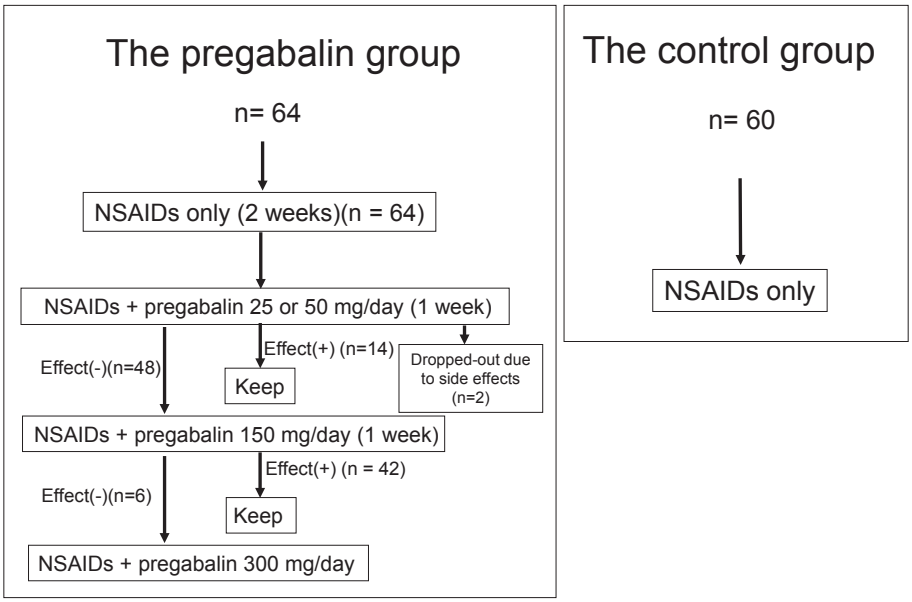

Fig. 1. The dosage flowchart in the pregabalin and control groups.

Table 2. Demographics and clinical characteristics of the study subjects

Patient demographics	Pregabalin group (n = 62)	Control group (n = 60)	Statistical significance
Age (years)	68 (range 36–85)	68 (range 46–84)	N.S.
Sex (male/female)	29/33	30/30	N.S.
ASA physical status (I/II)	32/30	32/25	N.S.
Current smoker	5	4	N.S.
Manual laborer (%)	30	25	N.S.
Professional qualification	12	8	N.S.
Clinical features	**Pregabalin group (n = 62)**	**Control group (n = 60)**	**Statistical significance**
Mean duration of pain (months)	26.4	20.1	N.S.
Less/greater than 3 months after the onset of pain	21/41	36/24	$p<0.05$
Affected spinal level (L3–4/L4–5/L5–S1)	9/45/8	8/50/2	N.S.
Proportion of the types of NIC (radicular/caudal/mixed)	38/10/14	32/14/14	N.S.
Distance causing NIC (< 100 m/100–500 m/ >500 m)	15/41/6	13/38/9	N.S.
Cause of LSS (lumbar SP/DO)	49/13	36/24	N.S.
NRS before pharmacotherapy	8.2 ± 0.133	7.9 ± 0.128	N.S.
RDQ before pharmacotherapy	19.1 ± 0.68	15.4 ± 1.57	N.S.

mean±standard error
N.S. : Not significant
ASA : American Society of Anesthesiologists
NIC : Neurogenic intermittent claudication
LSS : Lumbar spinal stenosis
SP : Spondylosis
DO : Degenerative spondylolisthesis
NRS : Numerical rating scale
RDQ : Roland-Morris Disability Questionnaire

Table 3. Changes in the NRS and RDQ scores with pharmacotherapy for each type of NIC

Scores	NRS		RDQ	
Duration of pain / Type of NIC	Less than 3 months before pharmaco-therapy	Greater than 3 months before pharmaco-therapy	Less than 3 months before pharmaco-therapy	Greater than 3 months before pharmaco-therapy
Radicular	N.S.	$p<0.001$	N.S.	$p<0.05$
Caudal	N.S.	N.S.	N.S.	N.S.
Mixed	N.S.	$p<0.05$	$p<0.05$	$p<0.001$

NRS : Numerical rating scale
RDQ : Roland-Morris Disability Questionnaire
NIC : Neurogenic intermittent claudication
N.S. : Not significant

leg symptoms for less than 3 months to cases with leg symptoms for greater than 3 months, with a larger proportion of cases having leg symptoms for less than 3 months in the control group.

NRS scores before pharmacotherapy were not significantly different between the two groups (Table 2). NRS scores after 3 months of pharmacotherapy in patients with all types of NIC with leg symptoms for less than 3 months were not significantly different between the two groups (Table 3). There were, however, significant differences in the NRS scores after 3 months of pharmacotherapy in patients with radicular ($p<0.001$) and mixed ($p<0.05$) types of NIC, but not for caudal type NIC, with leg symptoms for greater than 3 months between the two groups (Table 3).

RDQ scores before pharmacotherapy were also not significantly different between the two groups (Table 2). RDQ scores after 3 months of pharmacotherapy in patients with radicular and caudal types

of NIC with leg symptoms for less than 3 months were not significantly different between the two groups (Table 3). However, RDQ scores after 3 months of pharmacotherapy in patients with mixed type NIC with leg symptoms for less than 3 months were significantly lower in the pregabalin group than in the corresponding control group ($p<0.05$) (Table 3). There was no significant difference in RDQ scores after 3 months of pharmacotherapy in patients with caudal type NIC with leg symptoms for greater than 3 months between the two groups (Table 3). However, RDQ scores after 3 months of pharmacotherapy in patients with radicular ($p<0.05$) and mixed ($p<0.001$) types of NIC with leg symptoms for greater than 3 months were significantly lower in the pregabalin group than in the corresponding control group (Tables 3).

Finally, six LSS patients with leg symptoms for greater than 3 months in the pregabalin group and 22 those in the control group underwent spinal surgery after 3 months of pharmacotherapy ($P<0.05$).

DISCUSSION

The present study demonstrated that, in LSS patients treated for less than 3 months after the onset of leg symptoms, there was no significant difference between the two groups in all types of NIC, while in LSS patients in whom the interval between onset of leg symptoms and therapy was greater than 3 months, NSAID and pregabalin combination therapy appeared to be more effective than NSAID monotherapy for the relief of leg symptoms due to LSS in radicular and mixed types of NIC, but not for caudal type NIC. Moreover, LSS patients with leg symptoms for greater than 3 months who received NSAID and pregabalin combination therapy had a lower incidence of spinal surgical therapy than those who received NSAID monotherapy.

If conservative therapies for LSS patients, which include pharmacotherapy, block therapy, and/or exercise therapy, fail for 3 to 6 months, surgical therapy is usually considered[13]. In our hospital, LSS patients with leg symptoms due to LSS are started on conservative therapies, and subsequent next therapies include surgical therapy if conservative therapies fail for 3 to 6 months. In primary care for patients with leg symptoms due to LSS it may be especially important how the therapies are conducted during the initial several months. Therefore, therapeutic policies involving pharmacotherapy, block therapy, exercise therapy, and/or surgical therapy in order to improve the leg symptoms due to LSS should be made on a case by case basis. Hence, the focus was on examining the therapeutic efficacy of pregabalin for patients with leg symptoms due to LSS during the initial 3 months, because pharmacotherapy is comparatively easy to introduce in primary care, especially in patients who are at high risk for surgical therapy.

Pregabalin is a well-accepted option for neuropathic pain due to its analgesic, anxiolytic, and antiepileptic properties[17-20]. It is a structural analog of GABA that potently and selectively binds to the alpha$_2$-delta subunit of voltage-dependent calcium channels. Potent binding at this site reduces calcium influx at nerve terminals, thereby reducing the release of several excitatory neurotransmitters, including glutamate, noradrenaline, and substance P, accounting for its therapeutic effects.

LSS may occur at different levels in the spinal canal, sometimes occurring at more than one level at the same time. Nerve roots in the cauda equina may be compressed in central canal stenosis. Lateral recess stenosis and foraminal stenosis, on the other hand, may cause compression of the nerve roots while sparing the spine[21,22]. It is believed that, although the leg symptoms of LSS are mainly caused by mechanoreceptive compression of nerve rootlets and the cauda equina, they are also associated with inflammation, ischemia, malnutrition, nerve degeneration, and nerve injury. Hence, the leg symptoms due to LSS have a complicated pathophysiology. This can result from postural changes or persistent compression of the nerve root and/or cauda equina while walking. Therefore, leg symptoms due to LSS are necessarily associated with NIC. NIC is thought to be provoked by alteration of the microcirculation supplying the nerve and the subsequent lack of nutrient supply.

It has been demonstrated that pregabalin is very effective for neuropathic pain, but it has little therapeutic effect on inflammatory and nociceptive pain. Recent studies using pain DETECT have demonstrated that the neuropathic pain component was greater than the other components in chronic LBP patients[23], and that patients with neuropathic back and leg pain reported significantly higher pain, disability, anxiety, depression and reduced quality of life and passive straight leg raising than patients with nociceptive pain[23,24].

The present study demonstrated that there were no significant differences in the therapeutic efficacy of NSAID monotherapy and its combination with pregabalin for radiculopathy, including mixed type NIC, in patients with leg symptoms for less

than 3 months. While the inflammatory pain component may play a very important role in the pathomechanism of radiculopathy in patients with leg symptoms for less than 3 months, the neuropathic pain component may play a more important role than the inflammatory and nociceptive pain components in the pathomechanism of radiculopathy in patients with leg symptoms for greater than 3 months, as was demonstrated by the significant difference in the therapeutic efficacy of the two pharmacotherapies for mixed type NIC in patients with greater than 3 months of leg symptoms.

Leg numbness is a characteristic symptom of caudal type NIC that differs with the pathomechanism of radiculopathy. The symptoms of caudal type NIC include hypalgesia more often than hyperalgesia. It may be considered that while mechanoreceptive compression plays an important role in the pathomechanism of caudal type NIC, nerve degeneration also contributes, because although the symptoms of caudal type NIC are improved by laminotomy, the leg numbness at rest generally persists. Thus, the pathomechanism of caudal type NIC may be different from the typical neuropathic pain component. The present study demonstrated that both therapies had few effects on caudal type NIC at any time, suggesting that inflammatory, nociceptive, and neuropathic pain components probably play negligible roles in the pathomechanism of caudal type NIC, making it necessary to consider alternative therapy in patients with caudal type NIC. Hence, it is very important to evaluate the pathomechanism of leg symptoms due to LSS to determine the type of NIC, which in turn will aid in determination of the appropriate therapeutic plan.

The present study has some limitations that require attention. First, the follow-up period in this study was short. The efficacy of pregabalin combination therapy needs to be evaluated by long-term follow-up in the future to evaluate, for example, whether NSAID and pregabalin combination therapy can avoid leg symptoms due to LSS. Second, this study, being a retrospective cohort study, was open to selection bias. For example, the ratio of cases with leg symptoms for less than 3 months to cases with leg symptoms for greater than 3 months was found to be a limitation in this study. The number of patients with spondylolisthesis in the control group was double that in the pregabalin group. However, there were no significant differences between the two groups in patients with spondylolisthesis, as shown in Table 2 ($p<0.05$). Third, three different NSAIDs were used in this study. A future study needs to be performed with standardization of the NSAIDs used.

In conclusion, within 3 months after the start of pharmacotherapy, combination therapy with NSAID and pregabalin was more effective for relief of leg symptoms due to LSS than monotherapy with NSAID in patients with leg symptoms for greater than 3 months, but not in patients with leg symptoms for less than 3 months, preventing the aggravation of subjective symptoms in LSS patients with the pathomechanism of radiculopathy for greater than 3 months.

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ETHICS

This study was approved by the ethics committees of the participating research institutions.

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