Limaprost alfadex and nonsteroidal anti-inflammatory drugs for sciatica due to lumbar spinal stenosis

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Received: 19 February 2012 / Revised: 2 August 2012 / Accepted: 10 October 2012 / Published online: 23 October 2012
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Abstract

Purpose Limaprost, a prostaglandin E₁ analog, has vasodilatory properties and increases blood flow of the nerve root. However, it has not been clarified whether limaprost affects pain sensation associated with radiculopathy due to lumbar spinal stenosis (LSS). The aim of this study was to compare the efficacy of oral limaprost with nonsteroidal anti-inflammatory drugs (NSAIDs) for radiculopathy.

Methods We performed a multicenter prospective randomized trial. Patients with LSS who had radicular-type neurologic intermittent claudication assessed based on a self-reported diagnostic support tool were randomized into three treatment groups. Limaprost, NSAIDs, or limaprost plus NSAIDs were administered orally for 6 weeks. Leg pain, low back pain (LBP) and the associated symptoms were assessed by a numerical rating scale (NRS) both at rest and on movement as well as the Roland–Morris Disability Questionnaire (RDQ) and Short Form (SF)-36.

Results Sixty-one patients were enrolled in the study. Each treatment finally reduced radicular pain, and the improvement was prominent in a combination treatment. There were no significant differences in radicular pain among three groups at final follow-up. LBP was not influenced by limaprost, and a significant reduction of LBP and RDQ was confirmed in a combination treatment compared with limaprost. Physical function of the SF-36

subscales after a combination treatment showed a marked alleviation compared with NSAIDs.

Conclusions These obtained findings suggest that the effects of limaprost seem to be limited to radicular pain, not for LBP. Overall, a combination treatment might be more effective in the management of radiculopathy induced by LSS than monotherapy with either agent.

Keywords Limaprost · Prostaglandin E₁ · NSAIDs · Sciatica · Lumbar spinal stenosis

Introduction

Lumbar spinal stenosis (LSS) is a well-known spinal disorder among the elderly. LSS is a general term for a complex of symptoms, physical findings, and diagnostic imaging findings resulting from narrowing of the spinal canal, the nerve root canal, or the intervertebral foramina. From a functional standpoint, LSS is categorized into three types: radicular-type, cauda equina-type, and mixed-type [5]. Cauda equina-type is characterized by numbness and burning sensation in the bilateral legs and/or perineal symptoms including urinary disturbances. In contrast, the most significant manifestation of radicular type LSS is unilateral leg pain and/or numbness with or without low back pain (LBP) that may lead to neurologic intermittent claudication (NIC) when patients are standing or walking.

Although the exact mechanisms of NIC have not been clarified, blood flow in the nerve tissue appears to play a pivotal role in the pathogenesis of NIC. A recent study showed the contribution of not only arterial ischemia but also venous congestion to the pathophysiology of nerve function [6]. Furthermore, ischemia in the nerve tissue induces activation of extracellular signal-regulated protein

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kinase, which is involved in pain sensation in superficial dorsal horn neurons as shown in a study using a rat LSS model [11]. Based on this finding, an increase of blood flow in the affected nerve tissue may reduce LSS-induced painful radiculopathy.

Animal models of ischemia for nerve tissue have revealed that prostaglandin E_1 derivative (PGE_1) improves blood flow of cauda equina [17] and sciatic nerve [16], hyperesthesia [20], nerve dysfunction [7], and walking ability [10]. In addition, in a clinical situation, intravenous administration of PGE_1 alleviated Japanese Orthopaedic Association (JOA) scores including LSS-induced subjective symptoms and objective findings, and NIC distance [14]. On the other hand, it is reported that recovery in ambulation and JOA scores is less marked in radicular-type in comparison with other two-types of LSS [13]. Randomized trials have showed that oral administration of PGE_1 improved leg pain, leg numbness, walking ability or quality of life (QOL) [9, 12, 19]. However, it should be noted that the subjects in those randomized studies were non-categorized or cauda equina-type of LSS patients. To our knowledge regarding PGE_1 , the study focused on radicular-type LSS has not been reported previously, indicating the lack of evidence on the effects of PGE_1 to the radiculopathy due to LSS. Accordingly, we attempted to assess whether PGE_1 , which exerts its effects by increasing nerve blood flow, affects painful radiculopathy and health-related QOL in comparison with nonsteroidal anti-inflammatory drugs that are generally used against sciatica.

Methods

Study subjects were recruited from patients who were seen at our 13 affiliated study sites (12 public hospitals and 1 private clinic) from October 2009 to December 2010 with an average five patients each over a period of 15 months. All patients were required to be able to read and understand written instructions and be able to complete the pain assessment forms. Patients, who presented with symptoms suggestive of LSS-induced radiculopathy: pain, numbness, and/or cramps in one or both legs when standing or walking and/or neurological findings corresponding to the affected nerve root, completed a self-administered, self-reported history questionnaire. Consequently, those diagnosed with radicular-type LSS by this tool were qualified to be included in this study.

It is reported that computed tomography or magnetic resonance imaging is often nonspecific, and there are discrepancies between clinical symptoms and imaging findings in LSS [2]. To minimize misdiagnosis and use consistent diagnostic criteria for LSS, the self-administered, self-reported history questionnaire was therefore

used in the current study [8]. It is verified that this tool has a sensitivity and specificity of 84 and 78 %, respectively, and allows us to determine the specific type of LSS. Radiographs and MRI were taken in all patients and used to rule out diseases such as deformities including scoliosis and lumbar kyphosis of more than 10°, disc herniation, infection, tumor and spinal fracture. Exclusion criteria included previous surgery, surgery needed due to progressive and severe neurological deficits, peripheral arterial disease (un-palpation of dorsalis pedis or ankle brachial pressure index <0.9), use of antiplatelet or anticoagulant agents, severe cardiovascular, hepatic or renal disorders, pregnant women, cerebral infarction, parkinsonism, collagen diseases including rheumatoid arthritis, history of gastric ulcers or intestinal bleeding, and psychogenic disorders. To screen for psychogenic disorders, we used the Brief Scale for Psychiatric problems in Orthopaedic Patients (BS-POP), which allows for a quick and easy assessment of psychiatric problems [21]. Once a subject was found eligible to participate in this study, informed consent was obtained. Ethical approval for the study was obtained from a local institutional review board of Fukushima Medical University.

Eligible participants were randomly assigned into limaprost (group A), NSAIDs (group B), and limaprost plus NSAIDs (group C) treatment groups to compare the efficacy and tolerability of treatments for LSS-induced radicular pain and associated symptoms. Block randomization was performed by an independent member of our university hospital, using random number charts and the results were distributed to each study site by sealed envelopes. Group A patients received 5 µg limaprost three times daily. Group B patients received a physician-determined NSAID and gastroprotective agents (independently decided by each doctor) with the recommended standard pharmacological dose. Group C patients received the physician-determined NSAID plus 5 µg limaprost three times daily as well as gastroprotective agents.

If participants had previously received analgesics, muscle relaxants, anticonvulsants, or methycobalamin, a discontinuation period of at least 2 weeks was required before starting study treatment. Each treatment lasted 6 weeks. Additional therapies including physical therapy and any type of injections for pain relief were prohibited throughout the study.

Assessments

Primary outcomes were changes in LBP, radicular pain, leg numbness, and cold sensation of foot assessed by numerical rating scale (NRS). Secondary outcomes were changes in disability, health-related QOL, and subjective satisfaction for each treatment.

NRS

All items of NRS were required for scores in the worst condition that patients had experienced during a few consecutive days and periodically valued on an 11-point intensity by marking on a line from 0 (no symptom) to 10 (worst possible symptom) in a 2-week interval. These symptoms underlying LSS were assessed both at rest and on movement.

RDQ

Disability was assessed using the RDQ Japanese version, an LBP-specific functional disability score; this questionnaire was administered in a 2-week interval. The RDQ includes 24 items that ask about the degree of disability experienced during daily activities such as standing, walking, sitting, getting dressed, and working. Each item in the RDQ can be answered either “Yes” or “No”, and the number of “Yes” results represents the RDQ score; a higher score means greater disability.

SF-36

Changes in health-related QOL were assessed using the SF-36, Japanese version. This questionnaire was administered at the first and final visit to assess physical, social, and mental well-being. Scores were transformed to a scale of 0–100, with a higher score indicating better QOL.

Subjective satisfaction

At final follow-up, overall subjective satisfaction for treatment was determined and compared among treatments groups. The subjective satisfaction was measured on NRS (0–10 points) as well; a higher score means greater satisfaction.

Statistical analysis

Differences in scores of NRS (mean $\pm$ standard error), RDQ (mean $\pm$ standard error), and subjective satisfaction (mean $\pm$ standard error) were assessed using a Wilcoxon signed-ranks test, and the comparison among different treatments at each time point was also assessed using a Kruskal–Wallis rank test followed by Steel–Dwass test. Statistical differences in SF-36 subscales (mean $\pm$ standard deviation) between baseline and final follow-up, and among different treatments were assessed using a paired *t* test, and a one-way analysis of variance (ANOVA) followed by Tukey–Kramer test, respectively. Values of <0.05 were considered to be statistically significant. Data were analyzed with JMP[®] 9.0.2 software (Cary, NC, USA).

It was calculated that a sample size in each group would have 80 % power to detect a mean difference of two points on the NRS, assuming a common standard deviation of 3.0. As the result of calculation, the number above 18 each group was warranted in the current study.

Results

Initially, 65 participants entered the study; however, 4 of the 65 patients discontinued (2 lost to follow-up, 1 for epigastralgia during NSAID treatment, 1 for dry mouth during NSAID plus limaprost treatment). The remaining 61 patients completed the study (Fig. 1). No serious adverse effects occurred in any group. Demographic characteristics at baseline showed no apparent differences in age, sex, and duration from onset of any symptoms among groups (Table 1). Furthermore, there were no significant differences in every parameter at the baseline among three groups.

In the NSAID and combination groups, NSAID use was as follows: 60 mg loxoprofen 3 times daily ($n = 25$), 8 mg

Fig. 1 Participant disposition of 65 eligible participants, two were lost to follow-up and two discontinued because of adverse effects. The remaining 61 participants completed the study

Table 1 Demographic and symptoms characteristics

Group	A	B	C
Age			
Mean	70.6 $\pm$ 7.5	70.2 $\pm$ 8.0	68.0 $\pm$ 6.6
Sex, no (%)			
Female	11 (55)	13 (65)	13 (62)
Male	9 (45)	7 (35)	8 (38)
Duration of symptoms, months (range)	7.3 $\pm$ 10.0 (0.5–36)	8.7 $\pm$ 9.9 (0.5–36)	7.1 $\pm$ 7.5 (0.1–30)

Values present mean $\pm$ SD

Fig. 2 Effects of each treatment on LSS-induced symptoms at rest. The extent of numbness and LBP at rest did not change for any treatment with time course. A sensation of foot coldness was significantly reduced by limaprost and limaprost plus NSAIDs, but not NSAIDs alone. Leg pain at rest was reduced only in the combination treatment group. Comparing limaprost with a combination treatment, an improvement of symptoms was in favor of a combination, though there were no significant differences in score at final follow-up. Each value represents mean $\pm$ SE. * $p < 0.05$; significant difference from baseline. # $p < 0.05$; significant difference between groups

lornoxicam 3 times daily ($n = 5$), 200 mg etodolac 2 times daily ($n = 3$), 100 mg celecoxib 2 times daily ($n = 7$), and 25 mg diclofenac 3 times daily ($n = 1$).

Changes in LBP

As shown in Fig. 2, NRS of LBP at rest was 2.8 ± 0.6 in group A, 2.5 ± 0.6 in group B, and 2.7 ± 0.6 in group C, respectively at baseline. There was no apparent change in each group with time course. Compared group C with group A, a marked reduction in score was detected in group C at 2 weeks after treatment ($p < 0.05$). However, the tendency did not last thereafter.

NRS of LBP on movement was 5.5 ± 0.7 in group A, 5.5 ± 0.7 in group B, and 4.9 ± 0.7 in group C, respectively at baseline (Fig. 3). In group B, the values at 4 and 6 weeks were 4.4 ± 0.6 and 3.9 ± 0.6 , respectively, and there were significant differences compared with baseline value ($p < 0.05$). Likewise, in group C, the values at 2, 4,

and 6 weeks were 3.0 ± 0.6 , 2.4 ± 0.5 , and 2.4 ± 0.6 , respectively, and significant changes in score were confirmed compared with baseline ($p < 0.05$). Throughout the time course, no apparent reduction in LBP on movement was confirmed in group A. Only at 4 weeks after treatment, there was a significant change between group B (4.4 ± 0.6) and group C (2.4 ± 0.5) ($p < 0.05$). Furthermore, a remarkable reduction on movement was detected in group C at 4 and 6 weeks in comparison with group A ($p < 0.05$), and the values at 6 weeks were 4.6 ± 0.6 in group A and 2.4 ± 0.6 in group C, respectively.

Changes in radicular pain

As shown in Fig. 2, NRS of radicular pain at rest was 3.1 ± 0.6 in group A, 2.8 ± 0.6 in group B, and 3.2 ± 0.6 in group C, respectively, at baseline. In group C, the values at 4 and 6 weeks were 1.5 ± 0.5 and 1.5 ± 0.4 , respectively, and there were significant changes compared with baseline value ($p < 0.05$). A marked reduction in score was

detected in group C compared with group A at only 4 weeks after treatment ($p < 0.05$).

NRS of radicular pain on movement was 6.2 ± 0.5 in group A, 5.8 ± 0.5 in group B, and 6.1 ± 0.5 in group C, respectively, at baseline (Fig. 3). Compared with baseline, significant changes were detected at 6 weeks in group A, and from 2 weeks in both group B and C, respectively ($p < 0.05$). The values at 6 weeks were 4.4 ± 0.5 in group A, 3.4 ± 0.5 in group B, and 2.9 ± 0.5 in group C, respectively. There was a significant difference between group A (5.2 ± 0.6) and group C (3.2 ± 0.5) at 4 weeks after treatment ($p < 0.05$), but not at 6 weeks.

Changes in other symptoms associated with radicular-type LSS

NRS of foot cold sensation at rest were 3.6 ± 0.6 in group A, 2.4 ± 0.6 in group B, and 2.7 ± 0.6 in group C, respectively, at baseline. In group A, the value of 2.2 ± 0.4

at 6 weeks was significantly lower than the baseline ($p < 0.05$). The significant reduction in coldness at rest was also detected at 4 and 6 weeks after treatment in group C ($p < 0.05$). Only at 4 weeks, there was a significant change between group A (3.4 ± 0.5) and group C (1.2 ± 0.5) ($p < 0.05$). No apparent change was detected as to score on movement in each comparison.

In terms of foot numbness, NRS on movement was 3.6 ± 0.7 in group A, 4.4 ± 0.7 in group B, and 4.4 ± 0.7 in group C, respectively. In group C, a significant reduction was confirmed only at 4 weeks on movement compared with baseline.

RDQ

RDQ score of 6.0 ± 1.0 in group B at 6 weeks was significantly lower than the score of 8.5 ± 1.1 at baseline ($p < 0.05$). In group C, the scores of 4.0 ± 1.0 at 4 weeks and 3.5 ± 1.0 at 6 weeks remarkably reduced in

Fig. 3 Effects of each treatment on LSS-induced symptoms on movement. The extent of foot coldness did not change for any treatment with time course. There was a significant alleviation of LBP in the NSAID and combination therapy groups. Though the scores for radicular pain at final follow-up were remarkably reduced in each group, the extent was most prominent in the combination group. A combination therapy showed an apparent reduction in LBP throughout the observations compared with limaprost. A transient improvement of numbness was confirmed at 4 weeks after combination therapy. Each value represents mean $\pm$ SE. * $p < 0.05$, significant difference from baseline. # $p < 0.05$, significant difference between groups

comparison with 7.7 ± 1.0 at baseline ($p < 0.05$) (Fig. 4). The scores in group A did not significantly change throughout treatment. At 6 weeks after treatment, the score of 3.5 ± 1.0 in group C was significantly lower than the score of 7.2 ± 1.0 in group A ($p < 0.05$).

SF-36

SF-36 scores at baseline and after 6 weeks of treatment are summarized in Table 2. Neither the scores in group A nor B significantly changed in any subcategory of the SF-36, although the subcategory of body pain in group B tended to show the insignificant improvements ($p = 0.06$). On the other hand, in group C, there were significant improvements for physical function and body pain with time ($p < 0.05$). Furthermore, group C showed significantly better scores for physical function compared with group B at 6 weeks ($p < 0.05$).

Subjective satisfaction

In terms of satisfaction with treatment, scores in group C were significantly higher than those of group A and B until 4 weeks with a peak of 7.5 points at 4 weeks ($p < 0.05$). However, no significant differences were seen after 4 weeks.

Discussion

Our trial showed that not only NSAIDs or a combination therapy but also limaprost therapy finally reduced LSS-induced radicular pain. On the other hand, limaprost did not affect LBP or RDQ, differently from NSAIDs and a combination. A combination therapy tended to result in

better QOL and earlier reduction in both LBP and radicular pain than monotherapy.

Limaprost, a prostaglandin E₁ analog, is a vasodilator that increases blood flow and inhibits platelet aggregation. Oral administration of limaprost is approved for LSS and thromboangiitis obliterans in Japan. Two randomized, double-blind, multicenter, 6-week trials showed a significant reduction of leg pain and numbness for the LSS patients with bilateral intermittent claudication compared with low dose of the agent [9, 19]. Furthermore, a recent randomized study showed that limaprost significantly reduced leg numbness characterized by cauda equina-type LSS compared with NSAIDs, but not LBP or leg pain [12]. However, these clinical studies were not conducted on patients categorized into radicular-type LSS, indicating the existence of uncertain pain state. Assessment of limaprost for painful radiculopathy is thought to be essential to understand the exact therapeutic efficacy, and, in the current study, a common diagnostic tool was used to avoid possible misdiagnosis for radicular-type LSS. There is some evidence that supports the effects of limaprost to neuropathic pain caused by human herpes zoster and animal models [3, 4, 11, 20]. It is therefore assumed that an increment of blood flow in nerve tissue alleviates pain sensation, and thereby limaprost is a good candidate for treatment of LSS-induced sciatica.

Current first line analgesic regimens for sciatica rely on NSAIDs, which are considered to relieve nociceptive pain. According to a recent review of acute and chronic LBP, NSAIDs were shown to provide significantly better pain relief compared with placebo [15]. It is also demonstrated that there were no differences in pain relief between the selective cyclooxygenase-2 (cox-2) inhibiting NSAIDs and traditional NSAIDs for acute and chronic LBP. Based on these findings, the decision regarding the type of NSAID to use in this study was left to the discretion of the physician

Fig. 4 RDQ scores and subjective satisfaction. There was a significant reduction in RDQ scores in the NSAIDs and combination therapy groups. There were no significant differences among any groups in satisfaction with treatment at final follow-up, despite transient favorable outcomes in the combination group compared with other groups. Each value represents mean $\pm$ SE. * $p < 0.05$, significant difference from baseline. # $p < 0.05$, significant difference between groups

Table 2 36-Item Short-Form Health Survey scores

Category/group	Baseline	6 weeks	<i>p</i>
Physical function			
A	62.2 ± 17.8	68.8 ± 16	0.32
B	60.0 ± 22.8	62.1 ± 18.9*	0.51
C	64.5 ± 23.1	75.5 ± 16.8*	<u>0.03</u>
Physical role			
A	60.6 ± 26.2	61.2 ± 25.0	0.95
B	64.7 ± 27.5	65.6 ± 16.9	0.88
C	61.0 ± 25.4	67.3 ± 23.6	0.25
Body pain			
A	37.9 ± 14.5	42.4 ± 21.2	0.48
B	42.5 ± 21.9	51.0 ± 16.4	0.06
C	40.0 ± 19.4	51.7 ± 16.6	<u>0.045</u>
General health			
A	48.4 ± 13.7	54.5 ± 14.9	0.22
B	54.8 ± 14.2	55.1 ± 10.3	0.91
C	51.3 ± 10.6	54.2 ± 11.5	0.43
Vitality			
A	59.1 ± 16.1	52.7 ± 23.3	0.21
B	58.8 ± 20.9	60.8 ± 17.7	0.62
C	52.1 ± 18.9	58.0 ± 21.8	0.36
Social function			
A	66.3 ± 15.8	73.3 ± 24.0	0.18
B	73.8 ± 17.6	80.0 ± 15.4	0.23
C	71.4 ± 22.8	76.2 ± 19.7	0.34
Emotion role			
A	66.7 ± 29.9	67.5 ± 28.7	0.94
B	66.7 ± 30.4	70.0 ± 22.7	0.59
C	66.3 ± 21.2	72.2 ± 20.8	0.35
Mental health			
A	63.5 ± 20.7	62.8 ± 20.1	0.92
B	68.0 ± 20.1	70.8 ± 17.1	0.51
C	63.3 ± 17.8	62.9 ± 16.9	0.91

Values present mean ± SD

p showing comparison of the mean scores of each group

* *p* < 0.05; significant difference between groups

in charge of patients. It is reported that chronic sciatica leads to a mixture of nociceptive and neuropathic pain states [1]. The findings led us to propose that a therapy of NSAIDs plus limaprost treatment would be more effective than either one. Accordingly, a combination therapy of limaprost and NSAIDs was also set in the current study in addition to monotherapy. A period of oral administration was determined for 6 weeks, since aforementioned randomized trials were conducted to follow-up for 6–8 weeks and significant clinical effects are confirmed within the observation periods.

The dynamics of symptoms due to LSS have been attributed to relative hypoxia in the cauda equina and nerve

root secondary to circulatory disturbances, and to increased mechanical pressure [13, 18]. In the present study, LSS-associated symptoms were investigated both at rest and on movement. Pain scores on movement were approximately a twice increase over those at rest as shown in Figs. 2 and 3. Indeed, NRS scores of patients with radicular-type LSS were approximately 5 points in LBP and 6 points in radicular pain on movement with relative high scores, respectively. LBP on movement was reduced among patients receiving NSAIDs with time course. However, limaprost did not affect LBP, reflecting RDQ score. Leg pain was reduced early among patients receiving NSAIDs, and limaprost could affect at 6 weeks after treatment. In comparison with NSAIDs, no significant differences were detected after limaprost treatment in NRS of all symptoms as well as QOL. In this respect, benefits of limaprost for radicular pain caused by LSS are likely to be equivalent to NSAIDs. The efficacy against radicular pain observed at 6 weeks might be due to increased blood flow in nerve tissue. Reduced cold sensation after 6-week limaprost treatment may partially explain such findings. In the current study, the response to limaprost was limited for radicular pain, not LBP. Considering that various factors except for blood flow are involved in induction of LBP, leg pain might be more susceptible to limaprost treatment than LBP. On the other hand, an alleviation following a combination treatment was more prominent and rapid than either monotherapy regarding LBP and radicular pain. It is likely that the interaction between limaprost and NSAIDs resulted in marked changes and consequential pain relief. Thus, a combination therapy might be more favorable in the management of LBP and sciatica caused by LSS.

Physical function of SF-36 subcategories after a combination therapy was superior to NSAIDs in addition to an improvement of physical function and body pain with time course. On the other hand, neither limaprost nor NSAIDs altered QOL, differently from the previous study in which limaprost led to greater benefits for patients with cauda equina symptoms in both physical and mental components compared with NSAIDs [12]. The difference in response of limaprost between radicular and cauda equina types is thought to be of importance to plan a strategy for the LSS-induced symptoms.

Our design flaws include the absence of placebo control, and we cannot rule out that our observations are just mirroring natural course or a general therapeutic placebo effect. Furthermore, there is a possibility that patients receiving a combination therapy feel better because they would have a more serious treatment. However, to our knowledge, less clinical research regarding sciatica is available on the placebo control. The fact seems to be partly because of the difficulty for the placebo use against relatively severe sciatica, though a significant effect to LBP

has been demonstrated in favor of NSAIDs compared with placebo control [15]. Even such a condition, in the present study, limaprost, a vasodilator agent, reduced radicular pain and compared favorably with NSAIDs. However, limaprost was not suitable for the management of LBP. Comprehensively, it was clarified that an administration of both limaprost and NSAIDs at same time is superior to monotherapy with either agent, and thereby recommended as one of primary care for radicular-type LSS. Thus, the present study might be useful in terms of the first trial comparing limaprost with NSAIDs for painful radiculopathy due to LSS. As next steps, further randomized studies with less bias were needed to validate the benefit of limaprost in the treatment of radicular pain on a long-term basis.

Conclusion

Patients with radicular neurogenic intermittent claudication caused by lumbar spinal stenosis received either limaprost, NSAIDs, or a combination of limaprost plus NSAIDs. Limaprost attenuated radicular pain on movement as well as NSAIDs. On the other hand, limaprost did not affect LBP or QOL. A combination of limaprost and NSAIDs resulted in more favorable outcomes compared with monotherapy with either agent.

Acknowledgments The authors gratefully acknowledge medical staffs in 12 affiliated hospitals (Sukagawa hospital, Fukushima prefectural Aizu general hospital, Minamisoma municipal general hospital, Iwaki municipal kyouritsu hospital, Futaba kosei hospital, Fukushima prefectural Minamiaizu hospital, Fukushima prefectural Ono hospital, Shirakawa kosei general hospital, Fukushima red cross hospital, Ohara general hospital, Iwase general hospital, and Fukushima medical university hospital) and 1 private clinic (Ichiro orthopaedic clinic) that participated in the study.

Conflict of interest None.

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