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Clinical Study

Comparative study of the efficacy of limaprost and pregabalin as single agents and in combination for the treatment of lumbar spinal stenosis: a prospective, double-blind, randomized controlled non-inferiority trial

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Abstract

BACKGROUND CONTEXT: Although the simultaneous management of neuronal ischemia-related pain and compression-demyelination–related neuropathic pain is considered optimal in treating lumbar spinal stenosis (LSS), the effect of combination therapy with pregabalin and limaprost has not been elucidated.

PURPOSE: This study aimed to compare the effects of limaprost and pregabalin individually and in combination for the treatment of LSS.

STUDY DESIGN: This is a prospective, double-blind, double-dummy, randomized controlled trial.

PATIENT SAMPLE: The sample consists of patients with LSS.

OUTCOME MEASURES: The baseline-adjusted Oswestry Disability Index (ODI) score, visual analog scale (VAS) scores for leg pain, the European Quality of Life-5 dimensions (EQ-5D), and initial claudication distance (ICD).

METHODS: The present study (ClinicalTrials.gov, number NCT01888536) was a prospective, double-blind, double-dummy, randomized controlled trial designed to determine the efficacy of limaprost in alleviating leg pain, improving disability, and increasing walking distance in persons with degenerative LSS in three different treatment groups: limaprost alone, pregabalin alone, and combined limaprost and pregabalin through 1:1:1 allocation. The primary outcome was the baseline-adjusted ODI score at 8 weeks after treatment. The non-inferior margin of the ODI was set at δ=10 points.

RESULTS: The baseline-adjusted ODI score (primary outcome) at 8 weeks after treatment in the limaprost group was not inferior to those in the pregabalin and limaprost+pregabalin groups. The overall changes of the baseline-adjusted ODI scores, VAS scores for leg pain, the EQ-5D, and ICD during the follow-up assessments over an 8-week period (secondary end point) were not different among the three groups. The baseline-adjusted ODI scores and VAS scores for leg pain decreased

FDA device/drug status: Approved (limaprost); Approved (pregabalin).

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significantly over time after treatment in all three groups. The baseline-adjusted EQ-5D score and ICD also increased significantly over time after treatment in all three groups.
CONCLUSIONS: The efficacy of limaprost for lumbar spinal stenosis was not inferior compared with that of pregabalin or the combination of limaprost and pregabalin in terms of disability. Therefore, combined treatment with limaprost and pregabalin does not provide additional relief in symptoms in patients with LSS compared with monotherapy with limaprost or pregabalin.

Keywords: Lumbar spinal stenosis; Limaprost; Pregabalin; Combined treatment; Non-inferiority trial, randomized controlled trial; Oswestry disability index; Visual analog scale; European Quality of Life 5 dimension (EQ-5D); Initial claudication distance

Introduction

Lumbar spinal stenosis (LSS) can preclude physical activity and daily exercises in elderly patients because of the presence of back and leg pain associated with neurogenic claudication (pain in the buttocks or legs on walking or standing that disappears when sitting or during lumbar flexion). Although the exact mechanisms of neurogenic claudication remain unknown, ischemia in the nerve tissue is considered to have a pivotal role in its pathogenesis [1–3]. Recently, a neuropathic pain mechanism was also implicated in the genesis of leg pain in patients with LSS because compressed nerve roots exhibit edema, fibrosis, demyelination, and axonal degeneration of the involved neural elements [4–6].

Based on these findings, pharmacologic research for the development of materials to increase blood flow in the affected nerve tissue has been conducted. Limaprost is an oral prostaglandin E_1 derivative with diverse effects, including inhibition of platelet aggregation, improvement of erythrocyte deformability, and inhibition of reactive oxygen production, in addition to potent vasodilation [7,8]. Limaprost improves peripheral arterial circulation and increases blood flow in the compressed nerve tissue [8], thereby improving leg pain, leg numbness, and intermittent claudication in patients with LSS [9–13]. Gabapentin or pregabalin is also used in relieving neuropathic pain associated with various clinical conditions [14]. Recent studies demonstrated that these drugs are effective in relieving leg pain in patients with LSS [4,5,15–17].

The simultaneous management of neuronal ischemia-related pain and compression-demyelination–related neuropathic pain is considered the optimal treatment plan for LSS. Moreover, it is unknown whether limaprost or pregabalin is more effective in relieving leg pain, improving quality of life, and increasing walking ability. Furthermore, the effect of combination therapy with pregabalin and limaprost has not been elucidated. Therefore, in the present study, we aimed to compare the effects of limaprost and pregabalin as single agents and in combination on disability, leg pain, and walking distance in a single trial walk.

Materials and methods

Study design and participants

This study was approved by the hospital institutional review board, and all participants provided written informed consent before study enrollment. The present study was a prospective, double-blind, double-dummy, randomized controlled trial that was designed to determine the efficacy of limaprost (Young-Jin Pharm. Co., Seoul, Korea) in alleviating leg pain, improving disability, and increasing walking distance in individuals with degenerative LSS. The enrolled patients were divided into three treatment groups: limaprost alone, pregabalin alone, and combined treatment with limaprost and pregabalin (Fig. 1). The inclusion criteria were as follows: (1) age of 20–75 years and (2) a diagnosis of LSS. Lumbar spinal stenosis was diagnosed if one or more of the following symptoms were present: walking intolerance because of neurogenic claudication in a 20-minute walking trial, a visual analog scale (VAS) score of more than 3 for pain, numbness, or tingling sensation in the buttocks and lower extremities, and motor weakness along with bladder and bowel dysfunction. On the baseline treadmill walking test, we considered neurogenic claudication, represented by pain, numbness, or tingling sensation of the legs that occurred within 15 minutes of treadmill walking at a velocity of 3 km/h, at an incline of 0 degrees, and with a back extension posture. The exclusion criteria included pregnancy or expected pregnancy in women who did not agree to use proper contraception; galactose intolerance; any concurrent serious medical condition such as sepsis or cancer that would cause disability or decrease patients' general health status; cauda equina syndrome; acute osteoporotic compression fracture; walking intolerance caused by ankle, knee, and hip joint pain associated with osteoarthritis; a history of epidural steroid injection within the last month; a diagnosis of coronary or peripheral arterial occlusive disease within the last 6 months; a diagnosis of avascular necrosis at the hip joints; necrotic ulcerative lesion in the legs; a history of lumbar spine surgery; and chronic kidney disease (blood creatinine>twice the upper limit of normal), as well as the enrollment in other clinical trials within the prior 3 months. The present trials from enrollment to final follow-up were performed at seven tertiary care teaching institutions between February and October 2013. Patients were randomly assigned through 1:1:1 allocation to the limaprost, pregabalin, or combination treatment groups. This randomization was performed using a computer-generated randomization list, which was concealed from the investigators.

Interventions

All participants received treatments (limaprost, 5 μg 3 times per day; pregabalin, 75 mg 3 times per day; combination