The effect of prostaglandin E_1 derivative for the symptoms and quality of life in patients with lumbar spinal stenosis

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Running title：The QOL in patients with LSS

Abstract

Background. Quality of life (QOL) is a concern in patients with lumbar spinal stenosis (LSS). In this study, QOL was examined using the 5-item EuroQol (EQ-5D).

Methods. QOL and activities of daily living (ADL) were surveyed in 91 patients who visited 18 medical institutions in our prefecture and were diagnosed with LSS-associated intermittent claudication. A second survey was performed after ≥6 weeks in 79 of the subjects to evaluate therapy with limaprost (an oral prostaglandin E1 derivative) or etodolac (NSAIDs). Symptoms, maximum walking time, QOL, ADL items, and relationships among these variables were investigated in all 91 patients. Leg pain, leg numbness, and low back pain while walking were surveyed using VAS scores (0-100).

Results. Leg pain, leg numbness, and low back pain while walking (VAS ≥25) were present in 83.5%, 62.6%, and 54.9% of the patients in the first survey, and about half of the patients had a maximum walking time <15 minutes. The mean EQ-5D utility value for QOL was 0.59±0.12. This value was significantly associated with maximum walking time (p=0.030) based on classification of patients into groups with walking times <7.5, 7.5-15, 15-30 and >30 minutes, showing that maximum walking time influenced health-related QOL. Of the 79 patients who completed the second survey, 56 had taken limaprost and 23 (control group) had received etodolac. Limaprost improved the possible walking time, reduced ADL interference, and significantly increased the EQ-5D utility score, whereas no significant changes occurred in the control group. Maximum walking time prolonged by ≥10 minutes and the EQ-5D utility value improved by ≥0.1 points in significantly more patients in the limaprost group than in the control group.

Conclusion. According to this survey findings at average 8 weeks after administration,

Limaprost improved symptoms, QOL and ADL in LSS patients whereas NSAIDs treatment reduced pain, but did not exert other effects.

Introduction

The number of patients with lumbar spinal stenosis (LSS) has increased with aging of the population. In this disease, the spinal canal is narrowed due to age-related changes in bone and facet joints and thickening of the yellow ligament, causing compression of the cauda equine, nerve roots, and blood vessels distributed in the spinal canal. This induces circulatory disorder and manifests as symptoms such as leg pain, leg numbness, and accompanying gait disturbance with intermittent claudication [1, 2]. These symptoms do not immediately influence survival in most cases, but may reduce quality of life (QOL). NSAIDs and physical therapy are used for conservative treatment, but only a few studies have examined the efficacy of treatment on health-related QOL.

Limaprost is an oral prostaglandin E1 derivative that exhibits diverse effects, including inhibition of platelet aggregation, improvement of erythrocyte deformability, and inhibition of reactive oxygen production, in addition to having a potent vasodilatory action [3, 4]. Limaprost is indicated for thromboangiitis obliterans and acquired LSS because of its effect on improving peripheral circulatory disorder, and is the sole drug for LSS covered by national health insurance in Japan. Increased blood flow in nerve tissue compressed by the narrowed spinal canal is the main mechanism of action of limaprost [5, 6], and this improves leg pain, leg numbness, and intermittent claudication in patients with LSS [4].

The influence of limaprost on QOL has been investigated using the SF-36 health-related QOL scale [7, 8] and it has been shown that limaprost significantly improves the SF-36 subscales of physical functioning, role physical, bodily pain, vitality, and mental health, compared to etodolac [9]. However, few studies have examined the effects of limaprost using other health-related QOL scales, and none have used the 5-item EuroQol (EQ-5D), a simple health-related QOL questionnaire [10,1 1]. Here, we surveyed QOL in

LSS patients based on subjective evaluations made by the patients and investigated the efficacy of limaprost using the EQ-5D. We also investigated the efficacy of limaprost on low back pain and interference with activities of daily living (ADL).

Materials and Methods

Subjects

The subjects were patients who visited 18 medical institutions in our prefecture between July 2006 and November 2009 and were diagnosed as having LSS-associated intermittent claudication. None of the patients were under treatment with a prostaglandin, including limaprost, at the time of hospital visits. The exclusion criteria were (1) congenital spinal canal stenosis, (2) surgical treatment of LSS within 3 months before the study, (3) possible need for block treatment, (4) possible need for surgical treatment for LSS within 3 months, (5) symptoms apparently caused by chronic arterial obstruction, (6) paralysis of the four limbs associated with cerebrovascular disorder and trauma, (7) uncontrollable diabetes (HbA1c>10.4%) or severe neuropathy, (8) serious heart, liver, or renal disease, and (10) unsuitability for the study, as judged by physicians in charge.

In patients who gave informed consent, details of symptoms and ADL were obtained using a survey form, and QOL was surveyed using the EQ-5D questionnaire. The surveys were repeated after an interval of ≥6 weeks medications in as many patients as possible. Changes in drug therapy were avoided during this period, and nerve block injection, physical therapy, and orthotic treatment were prohibited as a rule. Limaprost was administered orally at 15 μg per day, t.i.d. For NSAIDs treatment, etodolac was administered orally at 400 mg per day, b.i.d.

Patients were assigned to limaprost and etodolac (NSAID) in each facility in this order. The study was approved by the Ethics Committee of our University School of Medicine (receipt number: 755).

Evaluation items

The evaluation was performed by the patients through self-completed questionnaires. The maximum walking time (minutes) was surveyed as an index of intermittent claudication. This time was defined as the possible walking time without resting and was classified into 4 categories: <7.5, 7.5-15, 15-30, and >30 minutes, to permit depiction of the data as a histogram. In these 4 categories, the mode and median values both were 5, 10, 20, and 30 minutes, respectively. The following 6 items were evaluated using a VAS: leg pain while walking, leg numbness while walking, low back pain while walking, low back pain while standing up, low back pain while squatting, and low back pain while lying down and sitting up. ADL were evaluated using 5 items: enjoyment of taking a walk; enjoyment of hobby and sports; enjoyment of a group tour; interaction with family and friends, such as going out and visiting; and ability to go shopping. The patients rated these items as 'yes, I can enjoy', 'yes, but I feel pain', 'no, I cannot enjoy' or 'I want to do it, but I cannot'. Each item was scored from 0-3, with a higher score indicating greater severity of interference with ADL. Health-related QOL was evaluated based on scores for each item and the utility value on the EQ-5D [10].

Statistical analysis

The results are presented as means ± standard deviation. A Jonckheere-Terpstra test was

used for evaluation of associations among EQ-5D utility values based on the maximum walking time. Intra-group comparison of the limaprost and control groups was performed by Wilcoxon signed-rank test or paired *t*-test and inter-group comparison was performed by χ^2 test, unpaired *t*-test, and Mann-Whitney U-test, with $p<0.05$ regarded as significant. SAS software (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient background (all patients)

Ninety-one patients were registered in the study. Some data were unavailable in a few cases, and data for these items were analyzed without inclusion of these cases. The mean age was 71.6±7.6 years old and the male:female ratio was 40:51. The impairment patterns were classified into cauda equine type, radicular type, and mixed type in 41, 21, and 23 cases, respectively. The mean maximum walking time was 17.2±12.0 minutes, with 20, 24, 25, and 21 patients classified into 4 categories of <7.5, 7.5-15, 15-30, and >30 minutes, respectively. VAS scores for leg pain and leg numbness were 54.4±29.0 and 44.5±32.8, respectively, and those for low back pain while walking, standing up, squatting, and lying down/sitting up were 32.9±30.8, 31.8±28.8, 30.1±29.2, and 37.9±30.5, respectively (Table 1). A mean EQ-5D utility value of 0.59±0.12 was obtained in 83 patients with full responses for 5 items (Table 1).

Associations of maximum walking time with EQ-5D utility value

The EQ-5D utility value obtained in 83 patients increased as the maximum walking time prolonged in the 4-step classification (<7.5, 7.5-15, 15-30, and >30 minutes), showing a significant association between maximum walking time and QOL (p=0.030, Jonckheere-Terpstra test) (Table 2).

Patient background (79 patients in the evaluation of limaprost therapy)

A second survey was performed ≥6 weeks (6.0-15.7 weeks, mean 8.2±1.3 weeks) after the first survey in 79 of the 91 registered patients to evaluate the effects of drug therapy. Of the 79 patients, 56 were treated with limaprost and 23 (control group) received an NSAID (etodolac) alone. The mean ages of the two groups were 71.3±7.4 and 71.6±8.2 years old, respectively (NS), and the male: female ratios were 20:36 and 14:9, respectively ($p<0.05$; χ^2 test). The impairment pattern was the cauda equine type for nearly half of patients in both groups. The mean maximum walking times before treatment were 17.4±13.6 and 16.2±10.4 min in the limaprost and control groups, respectively (NS). Mean VAS scores for leg pain and leg numbness were 52.9±29.9 and 43.8±32.2, respectively, in the limaprost group, and 57.8±28.6 and 43.4±34.7, respectively, in the control group (all NS). The mean scores for low back pain while walking, standing up, squatting, and lying down/sitting up were 34.8±32.1, 32.3±28.6, 35.0±31.7, and 36.3±29.4, respectively, in the limaprost group, and 32.3±30.3, 27.9±31.2, 22.0±24.8, and 35.3±32.9, respectively, in the control group (all NS). The mean EQ-5D utility values before treatment were 0.59±0.14 and 0.61±0.13 in the limaprost and control groups, respectively (NS) (Table 3).

Changes in maximum walking times and VAS scores in the limaprost and control groups

Maximum walking times in the limaprost and control groups were obtained in 53 and 21 patients, respectively, and symptom VAS scores in the two groups were obtained in 54-56 and 22-23 patients, respectively. Significant improvements in VAS scores for leg pain and leg numbness while walking were noted in both groups. Low back pain while squatting, lying down/sitting up was significantly improved only in the limaprost group (Table 4). The maximum walking time distributions in the 4 categories were improved in both groups, but the numerical time was significantly prolonged only in the limaprost group (Table 5).

Changes in ADL in the limaprost and control groups

ADL scores in the limaprost and control groups were obtained in 37-55 and 16-22 patients, respectively. Based on the scores for ADL interference, significant improvements in 'taking a walk', 'group tour', and 'interaction with family and friends', were found after drug therapy for ≥6 weeks in the limaprost group (Wilcoxon signed-rank test), whereas no significant changes were found for any item in the control group (Table 6).

Changes in EQ-5D domain / utility values in the limaprost and control groups

EQ-5D utility values in the limaprost and control groups were obtained in 51 and 22 patients with full responses for 5 items, respectively. The EQ-5D utility value significantly improved from 0.59±0.14 to 0.70±0.12 in the limaprost group, but showed no significant change (0.61±0.13 to 0.65±0.16) in the control group (Table 7). All domains of the EQ-5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) significantly improved in the limaprost group, but only pain/discomfort showed a significant improvement in the control group (Table 7).

Frequencies of prolongation in the maximum walking time of ≥10 minutes and/or improvement in the EQ-5D utility value of ≥0.1 points

The percentage of patients in whom the maximum walking time was prolonged by ≥10 minutes was significantly (p=0.036) higher in the limaprost group (39.6%) compared to the control group (14.3%). Then, the percentage of patients with improvement of the EQ-5D utility value of ≥0.1 points was significantly (p=0.020) higher in the limaprost group (54.9%) compared to the control group (18.2%) (Table 8).

Discussion

In LSS, symptoms such as leg pain, leg numbness, and accompanying gait disturbance [1,2] may reduce QOL. LSS also causes locomotive syndrome [12] and musculoskeletal ambulation disability symptom complex (MADS) [13], to which greater importance has recently been attached. Prompt action to cope with gait disturbance in LSS is needed to avoid future requirements for support and care and to maintain active walking in elderly people. Gait disturbance associated with LSS is also likely to influence ADL, but there have been few studies of health-related QOL and ADL in patients with LSS.

Limaprost is an oral prostaglandin E1 derivative that increases blood flow in nerve tissue compressed by the narrowed spinal canal in LSS, with a potent effect on improving the peripheral circulation. Thus, in Japan, limaprost treatment for LSS is covered by national health insurance based on clinical verification [6]. Prostaglandin E1 injection was previously

used to treat LSS [14] and limaprost is now included in the treatment guidelines for LSS in Japan [15]. In addition to resolving gait disturbance and preventing locomotive syndrome and MADS, treatment of LSS should also improve health-related QOL and ADL. Thus, we investigated the influence of gait disturbance on items of health-related QOL and ADL in patients with LSS and the effects of limaprost therapy on these items.

About half of the LSS patients in the study stated that their maximum walking time was <15 minutes, and gait disturbance was noted in many patients. The EQ-5D utility value in the LSS patients was 0.59±0.12, which is lower than the reported values of 0.86 and 0.84, respectively, in Japanese patients with type 2 diabetes [16] and stroke [17], suggesting that LSS patients feel that their QOL is impaired. The maximum walking time was strongly associated with the EQ-5D utility value, suggesting that gait disturbance influenced QOL. Therefore, improvement of gait disturbance in LSS treatment is likely to improve QOL.

To evaluate the efficacy of drug treatment of LSS, we performed a retrospective analysis in 79 patients who completed a second survey after ≥6 weeks of treatment with limaprost or a NSAID (etodolac). Symptoms while walking (pain and numbness) and low back pain while moving (squatting, lying down, and sitting up) were significantly improved by limaprost, whereas only symptoms while walking (pain and numbness) were significantly improved in the control (NSAID) group. Inflammatory mediators other than circulatory disorder are important in low back pain and the mechanism of improvement of low back pain by limaprost was unclear. However, the results suggest that neurogenic low back pain due to circulatory disorder was present in the LSS patients. The maximum walking time was significantly prolonged and ADL items of ‘taking a walk’, ‘group tour’, and ‘interaction with family and friends’ were significantly improved by limaprost, in contrast to the absence of effects in the control group. These changes led to significant improvement of the EQ-5D utility value in the limaprost group, but not in the control group. All domains of the EQ-5D (mobility, self-care,

usual activities, pain/discomfort, anxiety/depression) significantly improved in the limaprost group, but only pain/discomfort showed a significant improvement in the control group. Collectively, these results indicate the efficacy of limaprost for comprehensive treatment of health-related QOL, gait disturbance, symptoms while walking, and low back pain upon moving in patients with LSS.

There are some limitations in this study, including the group allocation. Because patients were assigned to limaprost and etodolac (NSAID) in each group in this order, the patients allocated to the limaprost group were twice more than that in the NSAID group. The difference in sample size in the two groups has the potential to impair the power of the analysis. The absence of data for some cases is a further limitation. However, frequencies of prolongation in the maximum walking time of ≥10 minutes and that of improvement in the EQ-5D utility value of ≥0.1 points were significantly higher in the limaprost group compared to the control group. There was also other clear differences between the two treatment groups. The improvement in the EQ-5D utility value was significantly greater in patients in whom the maximum walking time was prolonged by ≥10 minutes than in those in whom the prolongation was <10 minutes (p=0.0321, Mann-Whitney U-test). As the results, the EQ-5D utility value after treatment in the limaprost group was relatively high (0.70). This value is comparable to that reported in LSS patients with improvement after surgical treatment (0.64) [18]. These findings are consistent with the concept that treatment that improves gait disturbance is also likely to improve QOL in patients with LSS, and limaprost may have improved QOL by improving gait disturbance. The pain domain of EQ-5D also improved in the control group, showing the efficacy of NSAIDs for pain, but there was no significant improvement in the anxiety/depression domain. Matsudaira et al. [19] found that 32% of 253 LSS patients were depressive and had a decreased subscale score on the SF-36 mental health scale. Thus, our results are of interest since they suggest that drug therapy may lead to

improvement of mental health in patients with LSS.

In a more recent randomized controlled study of limaprost and NSAIDs (etodolac) using the SF-36, Matsudaira et al. [9] found that limaprost significantly improved the physical function, role physical, bodily pain, vitality, and mental health categories on the SF-36. Our study indicated similar findings. Thus, LSS treatment using drugs such as limaprost, which is aimed at improving gait disturbance, controlling locomotive syndrome and preventing MADS, may also be helpful for improvement of subjective symptoms, impaired ADL, and health-related QOL. However, we note that another limitation of this study was the gender difference between the two treatment groups. In LSS, the spinal canal is narrowed due to age-related changes, causing compression of the cauda equine, nerve roots, and blood vessels distributed in the spinal canal in both men and women. Circulatory disorder and symptoms such as leg pain, leg numbness, and accompanying gait disturbance then occur, probably regardless of gender. Thus, it is unlikely that this limitation will have a major effect on the results in this study. However, it cannot be ruled out that the significant difference between the two groups was due to this and the other limitations described above. A randomized controlled study with an increased number of control cases would be desirable to address these issues.

Conclusion

The mean EQ-5D utility value for quality of life was 0.59±0.12 in lumbar spinal stenosis patients. According to this survey findings at average 8 weeks after administration, Limaprost improved symptomms, quality of life and activities of daily living in lumbar spinal stenosis patients, whereas NSAIDs treatment reduced pain, but did not exert other effects.

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Table 1. Patient background

Item	Value
Age (years)	71.6±7.6 (n=84)
Gender (male/female)	40/51
Duration of illness (years)	5.0±8.0 (n=47)
Disease type (number of patients)	
Cauda equine type	41 (45.1%)
Nerve root type	21 (23.1%)
Mixed type	23 (25.3%)
No description	6 (6.6%)
Maximum walking time (minutes)	17.2±12.0 (n=90)
Maximum walking time distribution	
<7.5 minutes	20 (22.0%)
7.5-15 minutes	24 (26.4%)
15-30 minutes	25 (27.5%)
>30 minutes	21 (23.1%)
No description	1 (1.1%)
VAS (mm)	
Leg pain while walking	54.4±29.0 (n=91)
Leg numbness while walking	44.5±32.8 (n=89)
Low back pain while walking	32.9±30.6 (n=91)
Low back pain while standing up	31.8±28.8 (n=91)
Low back pain while squatting	30.1±29.2 (n=88)
Low back pain while lying down/sitting up	37.9±30.5 (n=89)
EQ-5D utility value	0.59±0.12 (n=83)

Data are presented as the number of cases (N), mean, and standard deviation (SD).

Table 2. EQ-5D utility values in patients with different maximum walking times

Item	Walking time				P
	< 7.5 min	7.5-15 min	15-30 min	≥ 30 min	value
EQ-5D utility values	0.51±0.17 (n=16)	0.59±0.10 (n=23)	0.60±0.10 (n=23)	0.63±0.12 (n=21)	0.030

Data are presented as the number of cases (N), mean, and SD.

P values were obtained using a Jonckheere-Terpstra test.

Table 3. Background of 79 patients in the limaprost and control groups

Item	Control group	Limaprost group	P value [a]
Number of cases	23	56	-
Age (years)	71.6±8.2 (n=21)	71.3±7.4 (n=52)	NS
Gender (male/female)	14/9	20/36	<0.05 [b]
Duration of illness (years)	5.8±10.3 (n=14)	4.5±7.4 (n=28)	NS
Disease type (number of patients)			
Cauda equine type	12 (52.2%)	23 (41.1%)	NS [b]
Nerve root type	7 (30.4%)	13 (23.2%)	
Mixed type	3 (13.0%)	17 (30.4%)	
No description	1 (4.3%)	3 (5.4%)	
Walking time (minutes)	16.2±10.4 (n=21)	17.4±13.6 (n=53)	NS
VAS (mm)			
Leg pain while walking	57.8±28.6 (n=23)	52.9±29.9 (n=56)	NS
Leg numbness while walking	43.4±34.7 (n=22)	43.8±32.2 (n=55)	NS
Low back pain while walking	32.3±30.3 (n=23)	34.8±32.1 (n=56)	NS
Low back pain while standing up	27.9±31.2 (n=23)	32.3±28.6 (n=56)	NS
Low back pain while squatting	22.0±24.8 (n=23)	35.0±31.7 (n=54)	NS
Low back pain while lying down/sitting up	35.3±32.9 (n=22)	36.3±29.4 (n=56)	NS
EQ-5D utility value	0.61±0.13 (n=22)	0.59±0.14 (n=51)	NS [c]

Data are shown as the number of patients or numerical values presented as mean ± SD, with the number of cases in parentheses.

[a] Unpaired t-test unless indicated as [b] χ^2 test or [c] Mann-Whitney U-test.

Table 4. Changes in VAS values for symptoms while walking and for low back pain in the limaprost and control groups

Item	Control group		p value	Limaprost group		P value
	At initiation	At completion		At initiation	At completion	
Leg pain while walking	57.8±28.6 (n=23)	32.6±32.8 (n=23)	0.003	52.9±29.9 (n=56)	35.3±27.4 (n=56)	<0.001
Leg numbness while walking	43.4±34.7 (n=22)	31.7±30.7 (n=22)	0.030	43.8±32.2 (n=55)	34.4±28.7 (n=55)	0.034
Low back pain while walking	32.3±30.3 (n=23)	30.4±29.6 (n=23)	NS	34.8±32.1 (n=56)	30.0±26.7 (n=56)	NS
Low back pain while standing up	27.9±31.2 (n=23)	17.6±26.4 (n=23)	NS	32.3±28.6 (n=56)	28.3±27.6 (n=56)	NS
Low back pain while squatting	22.0±24.8 (n=23)	17.2±21.2 (n=23)	NS	35.0±31.7 (n=54)	20.2±25.6 (n=54)	0.001
Low back pain while lying down/sitting up	35.3±32.9 (n=22)	24.4±27.8 (n=22)	NS	36.3±29.4 (n=56)	22.6±25.8 (n=56)	<0.001

Data are shown as the numbers of cases (N) and the mean and SD of the VAS values for symptoms while walking, standing up, squatting and lying down/sitting up.

P values for comparison of data at initiation and completion were obtained by paired t-test.

Table 5. Changes in maximum walking time and categorized walking time distribution in the limaprost and control groups

Item	Control group		p value	Limaprost group		p value
	At initiation	At completion		At initiation	At completion	
Walking time (minutes)	16.2±10.4 (n=21)	20.2±15.2 (n=21)	0.146	17.4±13.6 (n=53)	25.7±17.1 (n=53)	0.005
Walking time distribution			0.031			<0.001
<7.5 minutes	5 (21.7%)	3 (13.0%)		14 (25.0%)	7 (12.5%)	
7.5-15 minutes	5 (21.7%)	6 (26.1%)		13 (23.2%)	8 (14.3%)	
15-30 minutes	7 (30.4%)	5 (21.7%)		13 (23.2%)	15 (26.8%)	
>30 minutes	4 (17.4%)	7 (30.4%)		13 (23.2%)	23 (41.1%)	
No description	2 (8.7%)	2 (8.7%)		3 (5.4%)	3 (5.4%)	

Data are shown as the number of patients (N) and the mean and SD of the maximum walking time or distribution in 4 categories.

P values for comparison of data at initiation and completion were obtained by Wilcoxon signed-rank test.

Table 6. Changes in activities of daily living (ADL) scores in the limaprost and control groups

Item	Control group		p value	Limaprost group		p value
	At initiation	At completion		At initiation	At completion	
Taking a walk	1.30±0.98 (n=20)	1.15±0.81 (n=20)	NS	1.79±1.12 (n=42)	1.07±1.05 (n=42)	<0.001
Hobbies and sports	1.50±1.21 (n=16)	1.19±0.98 (n=16)	NS	1.49±1.19 (n=37)	1.35±1.25 (n=37)	NS
Group tour	1.06±1.12 (n=16)	1.13±0.89 (n=16)	NS	1.67±1.12 (n=42)	1.10±1.10 (n=42)	0.027
Interactions with family and friends	1.05±0.90 (n=22)	0.82±0.80 (n=22)	NS	0.76±0.84 (n=55)	0.51±0.69 (n=55)	0.027
Going shopping	1.00±0.69 (n=22)	0.95±0.84 (n=22)	NS	0.75±0.81 (n=53)	0.66±0.81 (n=53)	NS

Data are shown as the numbers of cases (N) and the mean and SD of the activities of daily living (ADL) scores.

P values for comparison of data at initiation and completion were obtained by Wilcoxon signed-rank test.

Table 7. Changes in the EQ-5D domain scores and utility value in the limaprost and control groups

EQ-5D domain /utility value	Control group		p value	Limaprost group		p value
	At initiation	At completion		At initiation	At completion	
Mobility	1.77±0.43 (n=22)	1.73±0.46 (n=22)	NS	1.88±0.38 (n=51)	1.67±0.48 (n=51)	0.013
Self-care	1.36±0.58 (n=22)	1.27±0.46 (n=22)	NS	1.24±0.43 (n=51)	1.14±0.35 (n=51)	0.029
Usual activity	1.73±0.55 (n=22)	1.82±0.59 (n=22)	NS	1.73±0.53 (n=51)	1.49±0.50 (n=51)	0.021
Pain/ discomfort	2.18±0.39 (n=22)	1.95±0.58 (n=22)	0.046	2.29±0.46 (n=51)	1.92±0.34 (n=51)	<0.001
Anxiety/ depression	1.50±0.60 (n=22)	1.36±0.58 (n=22)	NS	1.53±0.61 (n=51)	1.16±0.37 (n=51)	<0.001
EQ-5D utility value	0.61±0.13 (n=22)	0.65±0.16 (n=22)	NS	0.59±0.14 (n=51)	0.70±0.12 (n=51)	<0.001

Data are shown as the numbers of cases (N) and the mean and SD of the EQ-5D domain scores and utility values.

P values for comparison of data at initiation and completion were obtained by Wilcoxon signed-rank test.

Table 8. Frequencies of prolongation in the maximum walking time of ≥10 minutes and/or improvement in the EQ-5D utility value of ≥0.1 points in the limaprost and control groups

Item	Control group	Limaprost group	p value
≥10 minutes prolongation of maximum walking time	3 / 21 (14.3%)	21 / 53 (39.6%)	0.036
≥0.1 points improvement of the EQ-5D utility value	4 / 22 (18.2%)	28 / 51 (54.9%)	0.020

Data are shown as the number of patients (N) and the percentage of patients with prolongation in the maximum walking time of ≥10 minutes and/or improvement in the EQ-5D utility value of ≥0.1 points.

P values for comparison of data at initiation and completion were obtained by χ^2 test.