Patient-Based Outcomes Using the Walking Impairment Questionnaire for Patients With Peripheral Arterial Occlusive Disease Treated With Lipo-PGE₁

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Background: Patients with peripheral arterial occlusive disease (PAD) experience deteriorating ambulatory function and consequently impaired quality of life (QOL). QOL in patients receiving prostaglandin E₁ in lipid microspheres (lipo-PGE₁; Liple®) for the treatment of PAD has not been evaluated using the Japanese version of the Walking Impairment Questionnaire (WIQ).

Methods and Results: Data from 169 patients (98 men, 71 women; mean [median] age, 74±10 [74] years) with an ankle-brachial pressure index <0.9 were analyzed. WIQ scores and symptom scores significantly improved after lipo-PGE₁ treatment ($P<0.01$). Physicians' assessments of global improvement significantly correlated with all 4 WIQ subscales ($R\leq 0.31$).

Conclusions: WIQ is a valid tool for evaluating therapeutic response in patients with PAD. Lipo-PGE₁ improves QOL as evaluated by patients themselves. (*Circ J* 2010; **74**: 365–370)

Key Words: Intermittent claudication; Lipo-PGE₁; Peripheral arterial occlusive disease (PAD); Quality of life (QOL); Walking Impairment Questionnaire (WIQ)

In Japan, the number of patients with peripheral arterial occlusive disease (PAD; known as arteriosclerosis obliterans) is increasing as the population ages and eating habits become more westernized; hence, more cases of PAD are being seen in routine clinical practice. The intermittent claudication associated with PAD causes ambulatory function to deteriorate, with consequent decreases in the quality of life (QOL) for many patients.¹ Moreover, it has been shown that the reduced maximal walking distance because of PAD is an independent long-term predictor of cardiovascular death.² Against this background, and with the considerable diversification of treatment for PAD including drug therapy,³ exercise therapy,⁴ endovascular intervention,⁵ and surgical procedures,^{6,7} greater importance is being placed on evaluating the effects of treatment. To evaluate the effects of drug therapy, painless walking distance, maximal walking distance, the Walking Impairment Questionnaire (WIQ),³ and the SF-36 questionnaire are used. In surgery, indicators of therapeutic effect include the relationship between limb amputation level and inpatient period or activities of daily living,⁶ and change in the ankle-brachial pressure index (ABI) after autologous progenitor cell transplantation.⁷

The main method of evaluating ambulatory function in patients with PAD is measurement of maximal walking distance and time in the treadmill exercise test. However,

this method is not considered to accurately reflect patients' walking ability in daily life. Therefore, the disease-specific WIQ, which evaluates the effect of PAD on walking ability in daily life, was devised to assess therapeutic response.^{8–10}

In the present study, PAD patients were treated with prostaglandin E₁ in lipid microspheres (lipo-PGE₁; Liple®) while undergoing evaluation of QOL by WIQ. The results were then compared with those obtained by physicians who recorded symptom scores and global improvement.

Methods

Patients

Invited to participate were patients with symptomatic, physician-diagnosed PAD and ABI <0.9 who were receiving treatment at 74 participating institutions in Japan between May 2005 and October 2006. The ABI objectively evaluates limitations on ambulatory function in PAD patients with claudication. ABI values correlate closely with severity of PAD and with mortality.¹¹ As the severity of PAD (graded according to the Fontaine classification of clinical symptoms) increases, the ABI decreases.¹² A 2-year study has confirmed that the lower the baseline ABI, the higher the risk of being unable to walk for 6 consecutive minutes.¹³ The TransAtlantic Inter-Society Consensus (TASC)¹⁰ and TASC

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Table 1. Change in the Mean WIQ Scores After Lipo-PGE₁ Treatment

Baseline ABI	WIQ subscale	Baseline (%)	End of study (%)	Change (%)	P value
<0.9 (n=169)	Pain	39.6±25.7	60.1±24.0	20.4±22.9	<0.001
	Walking distance	22.6±25.7	34.0±31.8	11.4±22.1	<0.001
	Walking speed	23.9±23.3	36.3±29.7	12.4±20.2	<0.001
	Stair climbing	23.8±26.6	35.7±33.3	11.9±19.0	<0.001
0.8–<0.9 (n=55)	Pain	36.4±20.9	61.4±23.0	25.0±18.6	<0.001
	Walking distance	22.8±25.2	32.1±28.8	9.3±22.6	0.004
	Walking speed	23.4±20.9	35.8±26.6	12.4±25.2	<0.001
	Stair climbing	23.0±23.8	34.0±29.0	11.0±19.3	<0.001
0.5–<0.8 (n=98)	Pain	42.9±28.0	60.0±24.8	17.1±25.0	<0.001
	Walking distance	23.4±26.5	35.2±34.5	11.8±22.0	<0.001
	Walking speed	25.4±25.2	37.0±32.3	11.2±17.4	<0.001
	Stair climbing	23.7±28.1	35.7±36.2	12.0±19.3	<0.001
<0.5 (n=16)	Pain	31.3±23.3	56.3±23.3	25.0±20.4	<0.001
	Walking distance	16.9±23.2	33.3±24.8	16.4±21.0	0.007
	Walking speed	16.4±17.6	36.6±23.6	20.2±15.6	<0.001
	Stair climbing	26.6±28.2	41.2±28.9	14.6±16.9	0.004

Walking impairment was assessed by the WIQ on a scale of 0% (unable to perform because of severe impairment) to 100% (no impairment).

WIQ, Walking Impairment Questionnaire; Lipo-PGE₁, prostaglandin E₁ in lipid microspheres; ABI, ankle-brachial pressure index.

II¹¹ recommend measurement of the ABI in all new patients with intermittent claudication. Because the ABI can be decreased even in asymptomatic PAD patients, it is the most commonly used screening test in Japan for PAD.¹⁴ Scores for WIQ, the primary endpoint, were stratified by ranges of baseline ABI values. To calculate ABI, systolic blood pressure was measured in both arms and legs by cuff sphygmomanometry. According to a baseline ABI 0.8–<0.9, 0.5–<0.8, or <0.5, the patients were classified as having mild, moderate or severe PAD, respectively.

All patients gave informed consent to enter this study and for their individual data to be anonymously submitted to the sponsor.

Intervention

Patients received lipo-PGE₁ 5–10 µg once daily (usual recommended dose in Japan) by intravenous injection or infusion. Drug administration was performed according to the dosing instructions (package insert). Treatment of each individual patient was done at the discretion of attending physicians. Although no restriction was placed on the dose or dosing interval, the standard treatment period was set at 8 weeks.

Endpoints

Main outcome measures were the Japanese version of WIQ as proposed by the Japanese College of Angiology,¹⁵ which was completed by the patients themselves, and physicians' assessments of subjective symptom scores before and after treatment. WIQ is a valid tool for detecting improvement or deterioration in daily walking ability of patients with intermittent claudication.¹⁶ By asking questions designed to assist patients in describing their degree of difficulty in walking during the past week, the WIQ assesses walking ability on a score of 0 (unable to perform because of severe impairment) to 100 (no impairment). Symptoms such as "sense of coldness", "numbness", and "pain at rest" were graded as: 1, none; 2, mild; 3, moderate; and 4, severe; "pain at rest" was graded as: 1, no pain experienced; 2, pain experienced rarely (analgesics not needed); 3, sometimes need analgesic for

pain; 4, regularly need analgesic for pain; and 5, could not sleep at night because of pain despite the use of analgesic. At the end of the study, physicians assessed global improvement in each of their patients on the basis of ABI score, symptoms, personal interviews etc.

Statistical Analysis

WIQ scores were regarded as discrete data, and a non-parametric statistical analysis was mainly used. No missing values were complemented. For data that included missing values, no score was calculated for any of the WIQ subscales. To examine the correlation between WIQ score and physician assessment, the Spearman rank correlation coefficient (R) was calculated. For comparison of scores before and after lipo-PGE₁ treatment according to the severity of PAD, the Wilcoxon signed rank test was used. Subgroups were compared by Steel–Dwass test or Tukey test as the multiplicity adjustment. Exploratory analysis of the risk factors for a change in the WIQ score was done by multiple regression analysis. For all statistical tests, a 2-sided significance level of 5% was used. Statistical calculations were performed using SAS version 9.1.3 (SAS, Cary, NC, USA).

Results

Patients

Case report forms were collected from 524 patients at 74 institutions in Japan. Of these, 355 patients did not meet the inclusion criteria, so data for the remaining 169 patients were analyzed for efficacy. Of the 524 enrolled patients 521 were included in the analysis of safety after exclusion of 3 patients who did not receive lipo-PGE₁.

Among the 169 patients included in the evaluation of efficacy the proportion of male patients was slightly higher (58.0%). Mean age (±SD) was 73.5±10.3 years; 78.7% were aged ≥65 years. Mean ABI at baseline was 0.69±0.14. The most frequent comorbid condition was hypertension (49.7%), followed by diabetes mellitus (30.2%) and dyslipidemia (23.7%). The major concomitant drugs were antiplatelet

Table 2. Change in Symptom Score After Lipo-PGE₁ Treatment in Patients Stratified by Baseline ABI

Baseline ABI	Symptom	Score	No. of patients (%)		P value
			Baseline	Study end	
0.8–<0.9 (n=54)	Sense of coldness	1	3 (5.6)	12 (22.2)	<0.001
		2	13 (24.1)	37 (68.5)	
		3	35 (64.8)	4 (7.4)	
		4	3 (5.6)	1 (1.9)	
	Numbness	1	3 (5.6)	7 (13.0)	<0.001
		2	18 (33.3)	41 (75.9)	
		3	30 (55.6)	5 (9.3)	
		4	3 (5.6)	1 (1.9)	
	Pain at rest	1	4 (7.4)	13 (24.1)	<0.001
		2	26 (48.2)	37 (68.5)	
		3	16 (29.6)	4 (7.4)	
		4	7 (13.0)	0 (0.0)	
		5	1 (1.9)	0 (0.0)	
0.5–<0.8 (n=97)	Sense of coldness	1	7 (7.1)	27 (27.6)	<0.001
		2	34 (34.7)	52 (53.1)	
		3	51 (52.0)	17 (17.4)	
		4	5 (5.1)	1 (1.0)	
	Numbness	1	14 (14.3)	29 (29.6)	<0.001
		2	35 (35.7)	54 (55.1)	
		3	45 (45.9)	14 (14.3)	
		4	3 (3.1)	0 (0.0)	
	Pain at rest	1	16 (16.3)	32 (32.7)	<0.001
		2	37 (37.8)	46 (46.9)	
		3	17 (17.4)	12 (12.2)	
		4	24 (24.5)	6 (6.1)	
		5	3 (3.1)	1 (1.0)	
<0.5 (n=16)	Sense of coldness	1	1 (6.3)	5 (31.3)	<0.001
		2	3 (18.8)	8 (50.0)	
		3	7 (43.8)	3 (18.8)	
		4	5 (31.3)	0 (0.0)	
	Numbness	1	2 (12.5)	4 (25.0)	<0.001
		2	3 (18.8)	11 (68.8)	
		3	8 (50.0)	1 (6.3)	
		4	3 (18.8)	0 (0.0)	
	Pain at rest	1	4 (25.0)	10 (62.5)	0.002
		2	4 (25.0)	4 (25.0)	
		3	5 (31.3)	1 (6.3)	
		4	1 (6.3)	1 (6.3)	
		5	2 (12.5)	0 (0.0)	

"Sense of coldness" and "numbness" were graded as: 1, none; 2, mild; 3, moderate; 4, severe. "Pain at rest" was graded as: 1, no pain experienced; 2, pain experienced rarely (analgesics not needed); 3, sometimes need analgesic for pain; 4, regularly need analgesic for pain; and 5, can not sleep at night because of pain despite the use of analgesic. Lipo-PGE₁, prostaglandin E₁ in lipid microspheres; ABI, ankle-brachial pressure index.

agents (30.2%), nonsteroidal antiinflammatory drugs (20.7%), prostaglandin derivatives (17.8%), and other drugs indicated for the treatment of PAD (23.7%).

Effect of Lipo-PGE₁ Treatment

In patients stratified across all baseline ABI values, statistically significant ($P<0.01$) improvements were found for all WIQ subscales following lipo-PGE₁ treatment for the standard treatment period (ie, 8 weeks) (Table 1). Among the 169 patients analyzed for efficacy, ABI values were measured at both baseline and at the end of treatment period in 158 and of these, in all patients with ABI <0.9 , the mean ABI increased from 0.69 ± 0.14 at baseline to 0.77 ± 0.17 at the end of treat-

ment period, showing a statistically significant difference ($P<0.001$). Furthermore, improvement of ABI after lipo-PGE₁ treatment tended to increase with the severity of PAD.

Table 2 shows the scores for 3 symptoms ("sense of coldness", "numbness", and "pain at rest") at baseline and after lipo-PGE₁ treatment. Statistically significant ($P<0.01$) improvements were noted for all, regardless of baseline ABI. No interpretation was possible, however, for scores of "ulcers" because of limited data.

Table 3 shows the global improvement according to the baseline ABI. Global improvement tended to be greater in patients with more severe PAD at baseline. The proportion of patients with "slightly improved" or better global improve-

Table 3. Global Improvement According to Baseline ABI

Baseline ABI	Global improvement	No. of patients (%)
<0.9 (all patients)	Markedly improved	18 (10.7)
	Improved	61 (36.1)
	Slightly improved	72 (42.6)
	Unchanged	18 (10.7)
	Worsened	0 (0.0)
0.8–<0.9	Markedly improved	5 (9.1)
	Improved	21 (38.2)
	Slightly improved	25 (45.5)
	Unchanged	4 (7.3)
	Worsened	0 (0.0)
0.5–<0.8	Markedly improved	12 (12.2)
	Improved	32 (32.7)
	Slightly improved	40 (40.8)
	Unchanged	14 (14.3)
	Worsened	0 (0.0)
<0.5	Markedly improved	1 (6.3)
	Improved	8 (50.0)
	Slightly improved	7 (43.8)
	Unchanged	0 (0.0)
	Worsened	0 (0.0)

ABI, ankle-brachial pressure index.

ment was 92.7% among the patients with ABI 0.8–<0.9, 85.7% for those with 0.5–<0.8, and 100.0% for those with <0.5.

Correlation Between WIQ Score and the Global Improvement and Symptom Scores

Table 4 shows the Spearman rank correlation coefficients for correlation between the pre- and post-treatment change in the WIQ score and the physicians' assessments of global improvement.

In the overall patient group with ABI <0.9, R was statistically significant in all 4 WIQ subscales: "walking distance", "walking speed", and "stair climbing", $R \leq 0.45$; "pain", $R = 0.31$. Thus the scores for each subscale correlated slightly or substantially with global improvement. In patients with mild PAD (ABI 0.8–<0.9), R was statistically significant for

all 4 WIQ subscales. Significant correlations were also found in 3 subscales for patients with moderate PAD (ABI 0.5–<0.8; $R \leq 0.44$), whereas in those with severe PAD (ABI <0.5), a slight correlation was found between global improvement and "walking distance" ($R \leq 0.26$).

Global improvement and symptom scores correlated well (**Table 4**). In particular, significant correlations were noted between global improvement and symptoms such as "sense of coldness" and "pain at rest", irrespective of the baseline ABI.

No interpretation was possible for the correlation coefficient in patients with ulcers because of the limited sample size (among patients with ABI 0.8–<0.9, $n = 2$; 0.5–<0.8, $n = 7$; <0.5, $n = 1$).

In all patients (ABI <0.9), a "sense of coldness" correlated significantly with "pain" ($R \leq 0.4$), whereas slight correlations ($R \leq 0.3$) were found for other WIQ subscales. In patients with ABI 0.8–<0.9 significant correlations were noted between "sense of coldness" and "pain", "pain at rest" and "pain", and "pain at rest" and "stair climbing" (all $R \leq 0.5$) as well as between "numbness" and "pain" ($R \leq 0.4$). In patients with ABI 0.5–<0.8, a "sense of coldness" correlated significantly with "pain" and "walking speed" (both $R \leq 0.4$). In patients with ABI <0.5, "pain at rest" correlated significantly with "pain" ($R \leq 0.4$).

Safety

Nine adverse reactions were experienced by 9 (1.7%) of the 524 patients: rash ($n = 2$), phlebitis ($n = 1$), and vascular disorder ($n = 1$), as well as the following 5 serious adverse reactions, each occurring in 1 patient: cerebral hemorrhage, asthma, cardiac failure, infection, and localized infection. These serious adverse reactions were assessed to have no definite causal relationship with lipo-PGE₁.

Discussion

WIQ is a disease-specific patient questionnaire that has been validated as a useful instrument for measuring community walking ability (walking endurance and walking velocity) in individuals with PAD and intermittent claudication.¹⁷ In the present study, lipo-PGE₁ treatment resulted in significant improvements in walking ability as revealed by WIQ scores as well as by physicians' assessments of symptom scores and global improvement.

Table 4. Correlation Between Global Improvement and Change in the WIQ and Symptom Scores According to Baseline ABI

	Overall (ABI <0.9)		ABI 0.8–<0.9		ABI 0.5–<0.8		ABI <0.5	
	R	P-value	R	P-value	R	P-value	R	P-value
WIQ subscale	n=169		n=55		n=98		n=16	
"Pain"	0.312	<0.001	0.450	<0.001	0.274	0.006	0.011	0.968
"Walking distance"	0.471	<0.001	0.494	<0.001	0.470	<0.001	0.262	0.326
"Walking speed"	0.452	<0.001	0.403	0.002	0.507	<0.001	0.007	0.978
"Stair climbing"	0.463	<0.001	0.553	<0.001	0.445	<0.001	0.166	0.540
Symptom	n=167		n=54		n=97		n=16	
"Sense of coldness"	0.554	<0.001	0.408	0.002	0.632	<0.001	0.643	0.007
"Numbness"	0.391	<0.001	0.253	0.065	0.426	<0.001	0.638	0.008
"Pain at rest"	0.499	<0.001	0.449	<0.001	0.513	<0.001	0.513	0.042
"Ulcers"	0.061	0.433	–	–	0.079	0.442	–	–

Significance of absolute R-values: $0 \leq R \leq 0.2$, almost no correlation; $0.2 \leq R \leq 0.4$, slight correlation; $0.4 \leq R \leq 0.7$, substantial correlation; $R \geq 0.7$, strong correlation.

WIQ, Walking Impairment Questionnaire; ABI, ankle-brachial pressure index.

Overall, global improvement correlated highly significantly with the change in the WIQ scores of our PAD patients with ABI <0.9. Notably, in patients with relatively mild disease (ABI 0.8–<0.9) global improvement significantly correlated with all 4 WIQ subscales. Moreover, in patients with ABI 0.5–<0.8 significant correlations were noted in 3 WIQ subscales, whereas a slight correlation was found only for “walking distance” in severely affected patients with ABI <0.5. Significant correlations were also noted between various WIQ subscales and symptom scores as evaluated by physicians. Our results imply that improvements in a “sense of coldness” and “pain at rest” were largely responsible for enhancing the WIQ scores.

Physicians’ assessments of global improvement and symptom scores correlated significantly ($R \geq 0.5$) in patients with ABI <0.5. Substantial correlation was found between assessments of global improvement and symptom scores regardless of ABI value. The present study confirms that physicians’ assessments of their patients’ symptoms were accurate.

Although the beneficial effects of prostaglandin E₁ against PAD are well documented, its precise mechanism of action seems complex and multifactorial. Lipo-PGE₁ exerts its peripheral vasodilation effect by increasing cAMP, decreasing cellular calcium ions, and relaxing vascular smooth muscle. Improved walking capacity might further promote vasodilation and enhance leg circulation. The peripheral vessels are collateral vessels and microvessels rather than occluded vessels, and their dilation may also induce local (ie, leg) antiinflammatory effects and thereby improve vascular endothelial function. There is evidence that prostaglandin E₁ down-modulates soluble adhesion molecules involved in vascular inflammation, such as VCAM-1,¹⁸ as well as levels of monocyte chemoattractant protein-1, an important chemokine implicated in proatherogenic foam cell recruitment and formation.¹⁹ Hence, lipo-PGE₁ may improve vascular endothelial function in addition to its vasodilating effect.

Building on earlier pioneering work on cell therapy for patients with critical limb ischemia (CLI),²⁰ Kajiguchi et al⁷ recently reported encouraging results of a trial of autologous progenitor cell transplantation for therapeutic angiogenesis in a cohort of no-option patients with CLI. Although lipo-PGE₁ has not been reported to contribute to PAD treatment by favorably influencing endothelial precursor cells, this agent is shown to induce neovascularization by increasing production of vascular endothelial growth factor²¹ and has stimulated angiogenesis in a rat sponge model.²² Thus lipo-PGE₁ may elicit several anti-ischemic effects in the legs in concert.

In the present study, various antiplatelet agents, antipyretic analgesics, and prostaglandin derivatives were used concomitantly with lipo-PGE₁. Therefore, to verify the contributory effect of lipo-PGE₁, separate analyses were done before and after lipo-PGE₁ treatment for groups using and not using each concomitant drug. In all subgroups, significant improvements of all WIQ subscale scores were found after lipo-PGE₁ treatment (data not shown); there were no significant differences between patients using or not using concomitant drugs. Therefore, the clinical effect was probably related to lipo-PGE₁ alone. Lipo-PGE₁ can be expected to produce significant improvements regardless of the use of concomitant drugs for the treatment of PAD.

Our results agree with those of a randomized double-blind comparative study that showed clinical benefits of treatment with prostaglandin E₁ in patients whose response was assessed by WIQ, as well as by a simplified version of SF-36, a general

health-related QOL questionnaire.²³ Moreover, Fukuhara and Esato treated PAD patients with Liple[®] for 2 months and observed improvements of both emotional and physical QOL based on the results of SF-36 and physicians’ assessments of symptoms.²⁴ Therefore, our results from a disease-specific questionnaire, the WIQ, which also showed significant improvements related to lipo-PGE₁ treatment, are in close accordance with those obtained from the widely used SF-36 tool.

Conclusions

Lipo-PGE₁ (Liple[®]) significantly ($P < 0.01$) improved WIQ scores and symptom scores in patients with PAD and an ABI <0.9. Physicians’ assessments of global improvement significantly correlated with the WIQ scores. Our results suggest that WIQ is a valid tool for evaluating therapeutic response, and that lipo-PGE₁ improves walking ability and QOL as self-evaluated by patients with PAD.

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Disclosure

The authors have no conflict of interest to declare.

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