Intermittent gait disturbance in idiopathic normal pressure hydrocephalus

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博士論文

Intermittent gait disturbance in idiopathic normal pressure hydrocephalus

（特発性正常圧水頭症における間欠性歩行障害）

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Title:

Intermittent gait disturbance in idiopathic normal pressure hydrocephalus

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Abstract

Objectives

We identified intermittent gait disturbance (IGD) observed in the mild stage of idiopathic normal pressure hydrocephalus (iNPH). The first purpose of this study was to clarify the temporal gait profile of IGD during long distance gait. The second purpose was to confirm the difference in treatment effect after cerebrospinal fluid (CSF) shunting in patients with and without IGD.

Materials and Methods

Fourteen consecutive iNPH patients with mild gait disturbance with a timed up-and-go (TUG) of less than 20 seconds were prospectively enrolled in the study. All patients were asked “Do you experience gait difficulty after over five minutes of walking?” Seven "yes" patients formed the IGD group, and seven "no" patients formed the persistent gait disturbance (PGD) group. One day before and seven days after CSF shunting, gait function was evaluated by the 6-minute walk test (6MWT) and TUG.

Results

Preoperatively, all patients in the IGD group demonstrated features of IGD during the 6MWT, characterized by a progressive pattern of decreased gait speed and step length with increased cadence and absence of leg pain. Postoperatively, these features of IGD improved in all patients. In the PGD group, preoperative walking did not significantly worsen during the 6MWT and did not significantly change seven days after treatment. Improvement of gait symptoms one week after CSF shunting could be detected with 6MWT instead of TUG.

Conclusions

IGD is not a rare symptom in mild stage of iNPH and may serve as an important clinical diagnostic marker for identifying mild iNPH patients.

Key words: idiopathic normal pressure hydrocephalus, intermittent gait disturbance, intermittent claudication, CSF shunting, 6-minute walk test, gait disorder

Introduction

Gait disturbances in idiopathic normal pressure hydrocephalus (iNPH) have been historically characterized by a persistent broad-based, short-stepped 'magnetic' gait.[1–4] However, the precise temporal nature of long distance gait has not been accurately described. We have recently identified an intermittent type of gait disturbance (IGD) in iNPH patients using the 6-minute walk test (6MWT).[5] This pattern was particularly seen in mild and early stages of iNPH and seemed to be related to falls. Typically, patients complain about falling, but do not mention deterioration of gait after a walking load. Furthermore, IGD is difficult to identify in the examination room, because it is not apparent in short distance walking. Gait disorders in iNPH are usually considered to be a persistent, not transient deficit. Perhaps for this reason, evaluation of gait function included only used short-distance gait testing, such as the TUG,[2,6] the 10 to 25 meters walk test,[7–9] or other gait scoring systems that employ short distance gait measures.[10,11]

The 6MWT is widely used as gait loading test; reliability and validity of the 6MWT have been established as a tool to evaluate walking endurance for the heart and lung diseases.[5] However, 6MWT has not been applied to evaluate gait performance of iNPH patients. The purposes of this study were to clarify the temporal gait profile of IGD during long distance gait and to confirm the difference in treatment effect after cerebrospinal fluid (CSF) shunting in patients with and without IGD. A discussion of the pathophysiological mechanisms of IGD in iNPH and the implications of IGD as an early diagnostic marker of iNPH are presented.

Materials and methods

Patients

Fourteen iNPH patients (11 men, 3 women, mean age 75.6 ± 4.1) with mild gait disturbance, which was defined as a timed 3-meter up-and-go test (TUG) of 20 seconds or less, were included in this study. Diagnostic criteria leading to CSF shunting are the national iNPH guidelines:[12] (1) individuals with symptomatic onset at the age of 60 or older; (2) the existence of at least two items from the triad of gait disturbance, cognitive impairment, and urinary incontinence; (3) MRI-detected ventricular dilation (Evans Index > 0.3) accompanied by narrowing of the CSF space in the high convexity and interhemispheric fissure; (4) CSF pressure of 200 mmH_2O or less and normal CSF laboratory findings; (5) clinical symptoms not completely explained by other neurological or non-neurological conditions; (6) absence of other conditions associated with ventricular dilation, such as subarachnoid hemorrhage, head injury, meningitis,

congenital hydrocephalus, or aqueductal stenosis; and (7) a positive clinical response to a CSF tap test. Exclusion criteria included any neurological, orthopedic, or internal organ disorders influencing gait. Exclusion criteria also included neurogenic intermittent claudication (IC) and vascular IC, which may present IGD.

A questionnaire was answered by all patients using the interrogative: “Do you experience gait difficulty after over five minutes of walking?” Based on this response, seven patients who answered "yes" formed the IGD group, and seven patients who answered "no" formed the persistent gait disturbance (PGD) group.

Twelve patients underwent lumboperitoneal (LP) shunting, and two patients underwent ventriculoperitoneal (VP) shunting. A Codman-Hakim programmable valve was implanted in all cases, and its initial pressure settings were determined according to the patient’s height and weight with reference to Miyake’s quick reference table (QRT).[13,14]

Gait function was evaluated by registered physical therapists using the TUG[15] and 6MWT[5] one day before (pre-OP) and one week after (post-OP) CSF shunt surgery. Cognitive function was evaluated pre-operatively by speech therapist using the Mini-Mental State Examination (MMSE)[16] and Frontal Assessment Battery (FAB) .[17]

Pre- and post-shunt gait assessment

The TUG was consecutively performed three times over a period of 3 minutes and average times were calculated. The 6MWT was performed according to the standardized protocol of the American thoracic society.[5] Prior to starting the 6MWT, patients were at rest in the sitting position for at least 10 minutes. The total gait distance and gait performances, including parameters of cadence, step length, and gait speed at 60 second intervals, were measured during the 6MWT. Pulse rate was continuously monitored using a pulse oximeter throughout the 6MWT. Walking effort was evaluated based on the degree of increase in pulse rate.

In order to eliminate the potential influence of footwear in the overall time of the TUG and 6MWT,[18] all tests were performed using sneaker type footwear. For patients judged to be at risk of falling, an examiner followed all subjects at one-step behind each patient to prevent falling without interfering with their walking pace.

Evaluation of iNPH symptom improvement 3 months after surgery

Prior to surgery and 3 months after surgery, gait, cognitive, and urinary disturbance were evaluated by iNPH Grading Scale (iNPHGS)[10] The treatment effect of CSF shunting was evaluated by iNPHGS. In the IGD group, the presence of IGD was

evaluated by physician interview at 3 months after surgery.

Statistical analysis

The Wilcoxon signed-rank test was conducted to measure differences between the pre-OP and post-OP results of the TUG and the total distance of the 6MWT. Analysis of step length, cadence, and pulse recordings during the 6MWT were conducted using two-way repeated measures ANOVA with two factors as time periods (1-min serration) between the pre-OP and post-OP periods for each group. The chronological changes of these gait factors in the 6MWT were also analyzed by two-way repeated measures ANOVA compared with the first one minute. The alpha level was set at 0.05. Data were presented as the mean ± standard deviation of the mean.

Ethics statement

The study protocol was approved by the ethics committee at the Osaka Medical College (No. 1555), and written informed consent was obtained from all patients or their caregivers. The study was carried out according to the Declaration of Helsinki.

Results

There were no significant differences in demographic data between the two groups (table 1, 2).

Gait analysis of the IGD group by the 6MWT

In the IGD group, pre-operatively all patients exhibited gradual aggravation of gait with increased walking time, and all gait parameters, including step length, cadence, and velocity, changed proportionally with gait loading (Fig. 1a-c). Step length and walking speed decreased significantly after three minutes, and cadence also increased significantly after three minutes compared with the initial 1-min recording. None of the patients complained of either hip or leg pain during the 6MWT. Propulsive gait was not observed in the beginning of the 6MWT before shunt surgery in all patients, however, propulsive gait was found in the latter half of the 6MWT before shunt surgery in four patients of IGD group. The gait disturbance that appeared in the second half of the 6MWT recovered after a few minutes break.

The pre-operative parameters of shortened step length, increased cadence, and reduced gait velocity after 3 minutes of gait loading observed in the IGD group significantly improved post-operatively (Fig. 1a-c). Consequently, the pre-operative

total walking distance of 236.5 ± 34.2 meters was significantly lengthened to 305.1 ± 29.6 meters after CSF shunting ($P = 0.018$; Fig. 3a).

Gait analysis of the PGD group by the 6MWT

In the PGD group, pre-operatively all patients showed no significant aggravation of gait during gait loading (Fig. 2a-c). Furthermore, no significant improvements were observed in step length, cadence, and velocity after CSF shunting (Fig 2 a-c). However, total distance of the 6MWT in pre-operative test was slightly elongated compared with that in post-operative PGD test (PGD: pre-OP = 319.6 ± 20.6 meters vs post-OP = 327.4 ± 22.0 meters, $P = 0.063$; Fig. 3c).

Gait analysis by the TUG

There were no significant differences between the pre- and post-operative TUG results both in the IGD (pre-OP = 13.8 ± 2.3 seconds vs. post-OP = 13.3 ± 2.1 seconds, $P = 0.151$) and PGD group (pre-OP = 12.8 ± 2.0 seconds vs. post-OP = 12.3 ± 2.2 seconds, $P = 0.176$; Fig.3b-d).

Pulse rate changes during the 6MWT

There were no significant changes in pulse rate observed during the pre- and post-operative 6MWT both in the IGD and PGD group (Fig 1d and Fig 2d). Therefore, pre- and post-operative walking effort was determined to be unchanged.

Symptomatic recovery 3 months after CSF shunting

In all cases, except for the IGD case 2, iNPHGS showed improvement of 1 or more (table 1, 2). After CSF shunting, the symptom of IGD rapidly disappeared in all cases, including case 2.

Discussion

Intermittent gait disturbance: A common but hidden symptom at the mild stage of iNPH

This is the first report to describe a pattern of intermittent gait disturbance (IGD) in the mild stage of iNPH. Extended distance walking tests using the 6MWT showed that gait disturbance worsened proportionally with gait loading. The main characteristic of IGD is a progressive pattern of decreased gait speed and step length with increased cadence and absence of leg pain. Although the step width has not been evaluated in this study, the video movie shows that another characteristic of IGD is that it does not

involve wide base in IGD. The reason why the step width is not wide may be related to the fact that the gait disturbance is in the mild stage. The fact that no difference in pulse rate was observed before and after shunting suggested that fatigue may not be a causative factor in IGD associated with iNPH.

Gait difficulty is a well-known core symptom in iNPH patients and is typically characterized by signs of reduced gait velocity, diminished stride length, and reduced floor-to-floor clearance. Currently, all these signs have been shown to improve after treatment with CSF shunting.[2,4,19,20] However, to date, the temporal nature of gait disturbance during long distance gait in iNPH has not been accurately described.

In contrast, we have shown that the TUG was not able to detect significant improvements in gait following CSF shunting in iNPH patients, especially with regards to the subtle features of IGD, while results using the 6MWT clearly demonstrated improvements after shunting. The reason that TUG is invalid in the detection of IGD is that although TUG is a complicated task including muscular strength and balance such as turning, standing and sitting, there is no aspect of walking load at all. Therefore, we postulate that the reason why IGD has not been previously recognized as a clinical feature of iNPH is that testing has focused on observation and evaluation of short distant gait only. In our study, 50% of the patients diagnosed with mild iNPH presenting with a TUG of less than 20 seconds showed signs of IGD. Therefore, although the sample size was too small, our findings suggest the possibility that IGD may be a common finding in the early stage of iNPH. IGD may be a pre-clinical or hidden feature in iNPH, and this suggests the potential usefulness of IGD as a diagnostic tool for early diagnosis of iNPH. Further studies may more accurately identify the role of IGD in iNPH and may reveal a spectrum of gait disorders in iNPH, presumably with onset of initially intermittent gait dysfunction followed by progression to a complete persistent gait disturbance.

In the PGD group, improvement in walking function could not be detected with TUG and 6MWT before and after surgery. However, the fact that iNPHGS improved in all cases of PGD group at 3 months after shunt surgery means that all patients in the PGD group are definite iNPH in Japan guide lines.[12] This discrepancy is thought to arise from postoperative evaluation being performed only seven days after surgery. Seven days after surgery, it seems that the symptomatic improvement process is still in progress and the influence of surgical invasion and perioperative exercise restriction remains. On the contrary, despite such non-optimal conditions, improvement of IGD at 6MWT indicates that IGD is a highly reversible symptom expected to be improved by shunt surgery.

Intermittent gait disturbance and intermittent claudication

Longer distance gait testing using the 6MWT revealed the subtle features of gait in IGD, which included decreases in gait speed and step length with increases in cadence proportional to gait distance. These features resemble well-known forms of intermittent claudication (IC), such as vascular IC (VIC) and neurogenic IC (NIC). VIC is typically caused by obstructive atherosclerosis and involves both decreases in step length and gait speed due to accompanying lower limb weakness or pain.[21,22] In contrast, NIC is usually caused by spinal stenotic nerve root compression and is also associated with decreases in step length and gait speed with progressive radiating lower limb pain after sustained gait.[23,24]

However, there are potentially three major differences between the features of IGD and the classical types of IC. First, in contrast to VIC and NIC, IGD in iNPH does not seem to be associated with either lower limb pain or weakness induced by ambulatory loading. Second, cadence was shown to gradually increase in IGD, while cadence is reported to decrease in VIC and NIC because of leg pain or weakness.[21,23] We believe the increasing cadence observed in IGD is a compensatory mechanism for decreases in gait speed and shortening of step length. Third, IGD in iNPH is frequently associated with balance disturbances, such as propulsive gait, which increases the inherent risks of falling. These potential differences between IGD and IC are summarized in table 3. However, as there is a fundamental common point that it develops gait disturbance accompanying walking load and is reversible, IGD may be termed hydrocephalic IC as a new category of IC.

Ischemic mechanism in early stage of iNPH

Gait difficulty in VIC and NIC is thought to be related to progressive ischemia of muscles and nerves with walking load.[25,26] Because both IGD and other types of IC have a progressive onset, it is possible that ischemia is also involved in the pathogenic mechanism of IGD. Although the exact ischemic pathophysiological mechanisms underlying gait disturbances in iNPH are still controversial, a model of vascular compression and successive decrease in cerebral blood flow (CBF) has been proposed by Batman et al.[27] Another research has been directed at investigating the nature of decreased CBF in the frontal lobe and periventricular white matter.[8,28,29] Our results tend to support an ischemic mechanism for the onset of symptoms in iNPH patients in the early stage because of the short temporal relationship of symptoms with progressive gait loading.

Intermittent gait disturbance as a mild and early sign of iNPH

Preoperative gait and cognitive function tests indicate that the IGD group is in the mild stage. Regarding gait function, a preoperative TUG of 13.8 seconds (10.9-16.6) in the IGU group can be regarded as a mild stage. The normal range of TUG is still controversial. For individuals without disability between 70 and 89 years of age, the TUG has been reported to range from 7 to 12 seconds.[30] In the geriatric population, TUG scores greater than 13.5 seconds have been associated with an increased risk of falls.[31] As for cognitive function, the pre-operative mean MMSE of 27 was within the normal range as adjusted for age.[32,33] The pre-operative mean MMSE in prior studies on the surgical treatment of iNPH, such as the SINPHONI, SINPHONI-2, and Kuopio NPH study, were 25, 23, and 20, respectively.[2,34,35] Furthermore, since iNPH is a progressive disease, the mild stage can be interpreted as being an early stage.

Keys for recognizing intermittent gait disturbance

An important key for recognizing IGD is appropriate early patient questioning especially in the outpatient setting, when the subtle early signs of gait disturbance induced by gait loading first appear. These early signs may go unnoticed by the patient or primary care physician or may be masked by presentation as falls, and can only be uncovered and clarified by detailed direct questioning such as: “Do you experience gait difficulty after over five minutes of walking?”. In addition, when considering the indications for shunting in iNPH patients with mild symptoms, we have recommended long distance gait testing as an adjunct to standard guideline testing of gait function.

Conclusions

IGD is a novel and previously unnoticed feature of mild iNPH. IGD is characterized by a decrease in step length and gait speed and by an increase in cadence without leg pain after gait load. Long distance walking tests, such as 6MWT and asking questions focusing on IGD in falling elderly patients may lead to identification of IGD. Further studies on IGD may lead to earlier diagnosis of iNPH with possible improved surgical outcomes.

Acknowledgements

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Conflict of interest

The authors declare that they have no conflict of interest.

Table 1

Characteristics of the IGD patients

	Patiens	Age	Sex	Surgery	MMSE (pre-OP)	FAB (pre-OP)	iNPHGS (pre-OP)			iNPHGS (post-OP 3month)		
							G	C	U	G	C	U
	1	79	M	LP	27	14	2	2	1	1	0	1
	2	73	M	LP	30	12	1	1	1	1	1	1
	3	77	F	LP	28	12	2	2	1	1	1	1
	4	76	M	LP	26	12	2	2	2	1	1	1
	5	83	M	VP	26	12	2	1	1	0	1	1
	6	71	M	LP	28	13	2	1	1	1	1	0
	7	69	M	LP	25	7	1	2	2	1	0	0
Mean ± S.D.		76.0 ± 2.9			27.1 ± 1.7	11.7 ± 2.2	1.7 ± 0.5	1.6 ± 0.5	1.3 ± 0.5	0.9 ± 0.4	0.7 ± 0.5	1.1 ± 0.3

LP : lumbo-peritoneal shunt, VP : ventriculo-peritoneal shunt, MMSE : mini-mental state examination, FAB : frontal assessment battely, iNPHGS : iNPH grading scale, G : gait, C : cognitive, U : urinaly

Table 2

Characteristics of the PGD patients

	Patiens	Age	Sex	Surgery	MMSE (pre-OP)	FAB (pre-OP)	iNPHGS (pre-OP)			iNPHGS (post-OP 3month)		
							G	C	U	G	C	U
	8	73	F	LP	26	12	2	2	1	1	1	1
	9	77	M	VP	29	16	2	1	1	1	0	1
	10	83	M	LP	26	12	1	2	2	1	1	1
	11	69	M	LP	29	18	1	1	1	0	0	0
	12	71	F	LP	30	11	1	1	1	0	0	0
	13	81	M	LP	21	9	2	2	2	1	1	1
	14	72	M	LP	25	11	2	2	1	1	1	1
Mean ± S.D.		75.1 ± 5.3			26.5 ± 3.1	12.7± 3.1	1.6 ± 0.5	1.6 ± 0.5	1.3 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.7 ± 0.5

LP : lumbo-peritoneal shunt, VP : ventriculo-peritoneal shunt, MMSE : mini-mental state examination, FAB : frontal assessment battely, iNPHGS : iNPH grading scale, G : gait, C : cognitive, U : urinaly

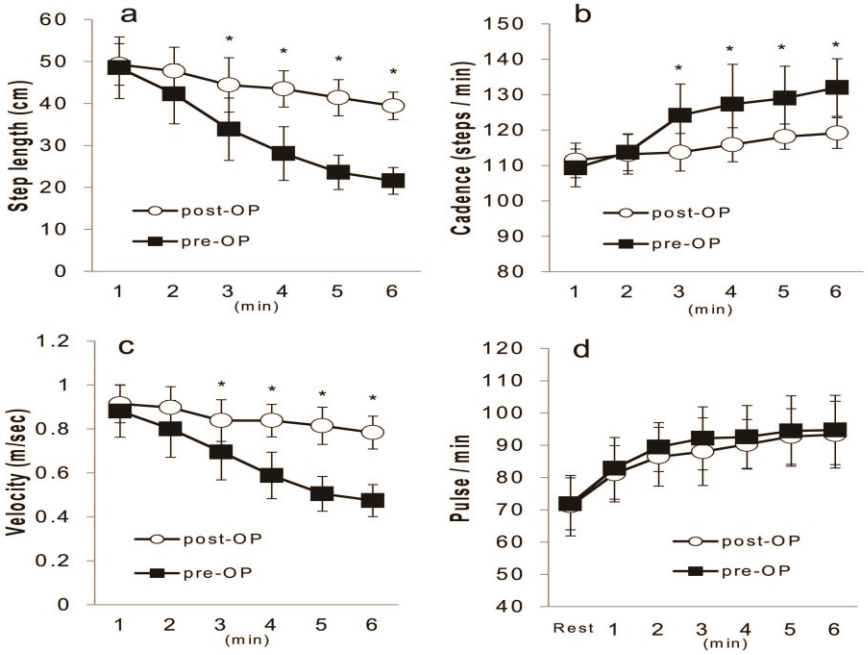
Table 3

Characteristics of intermittent gait disturbance (IGD)

Gait paramaters after gait load	IGD	Neulogenic IC	Vascular IC
Leg paine	none	positive	positive
Balance disturbance	positive	none	none
Gait speed	↓	↓	↓
Step length	↓ ↓	↓	↓
Cadance	↑ ↑	↓ →	↓

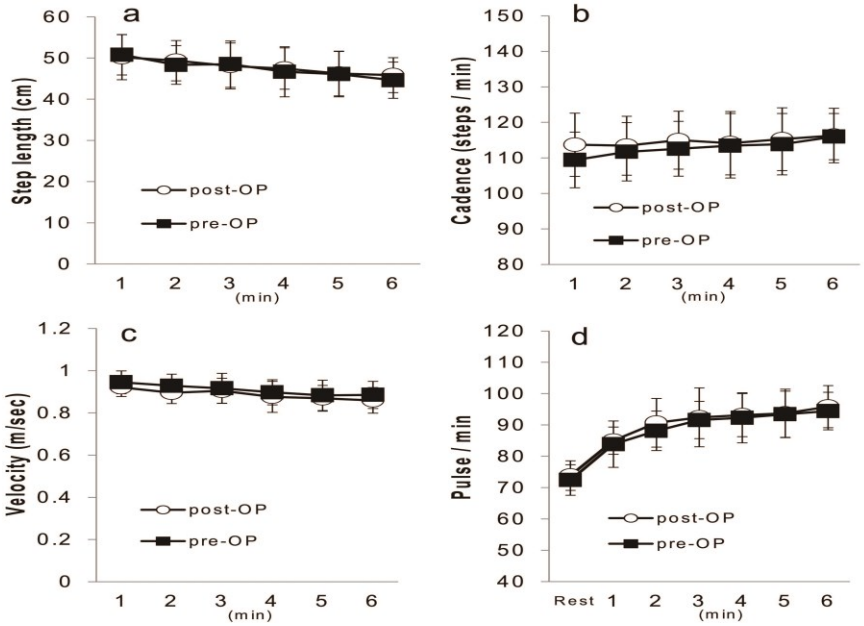
IC, intermittent claudication; IGD, intermittent gait disturbance

Figure 1



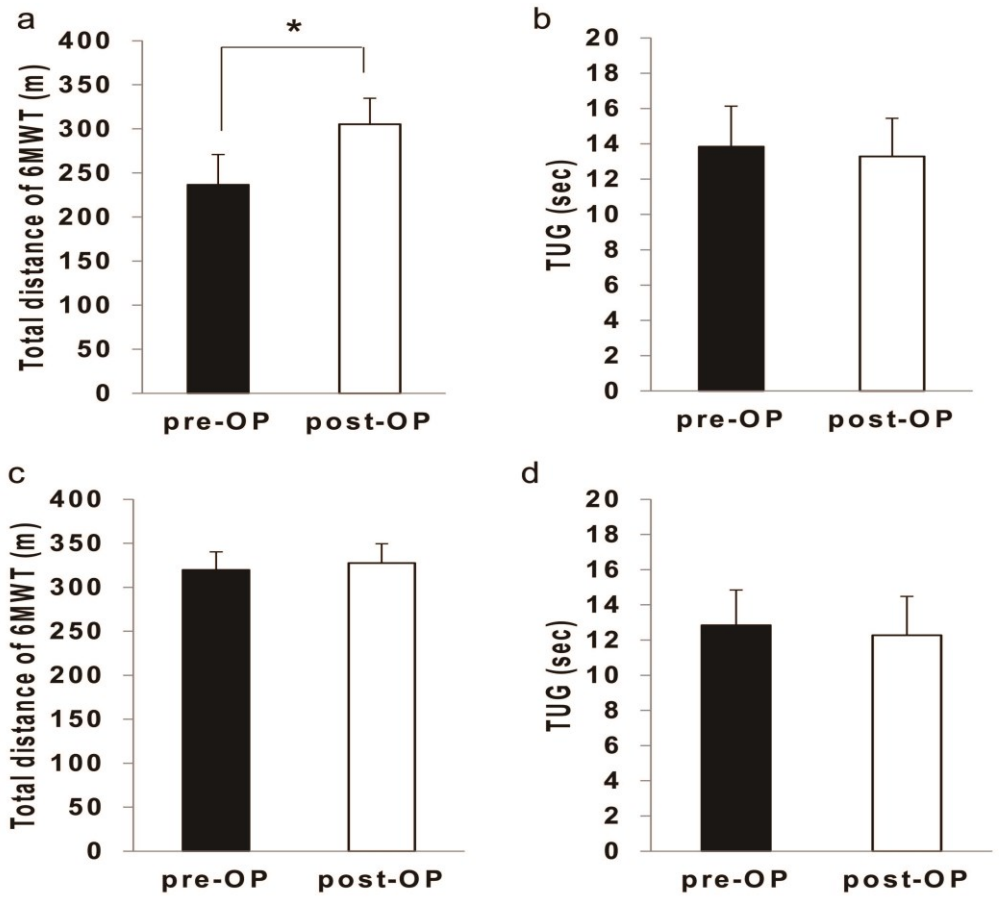
Averaged step length (a), cadence (b), and velocity (c) per minute for the 6MWT in the IGD group. Pre-operative gait parameters with gait loading significantly improved post-operatively. Asterisks indicate significant changes as compared with pre-operative 6MWT ($p < 0.05$). There were no significant differences in pulse rate between the pre-operative and post-operative 6MWT (d).

Figure 2



Averaged step length (a), cadence (b), and velocity (c) per minute for the 6MWT in the PGD group. Pre-operative gait parameters with gait loading did not improve post-operatively. There were no significant differences in pulse rate between the pre-operative and post-operative 6MWT (d).

Figure 3



The total walking distance (a) for the 6MWT in the IGD group was significantly lengthened post-operatively ($p = 0.018$). Asterisks indicate significant changes as compared with pre-operative 6MWT ($p < 0.05$). There was no significant difference between the pre-operative and post-operative TUG in the IGD group (b). In the PGD group, no significand difference between the pre-operation and post-operation was observed not only at TUG (d) but also at 6MWT (c). 6MWT, 6 Minute Walk Test; TUG, timed 3-m up-and-go test; CSF, cerebrospinal fluid

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