A randomized controlled trial of treatment with intermittent negative pressure for intermittent claudication

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ABSTRACT

Objective: We investigated the effects of lower extremity intermittent negative pressure (INP) treatment for 1 hour two times daily for 12 weeks on the walking distance of patients with intermittent claudication (IC).

Methods: Patients with IC were randomized to treatment with −40 mm Hg INP (treatment group) or −10 mm Hg INP (sham control group). Pain-free walking distance (PWD) and maximal walking distance (MWD) on a treadmill, resting and postexercise ankle-brachial index, resting and postischemic blood flow (plethysmography), and quality of life (EQ-5D-5L and Vascuqol-6) were measured at baseline and after 12 weeks of treatment.

Results: A total of 72 patients were randomized, and 63 had data available for the intention-to-treat analyses. The between-group comparisons showed a significant change in the PWD, favoring the treatment group over the sham control group (estimated treatment effect, 50 m; 95% confidence interval [CI], 11-89; $P = .014$). The PWD had increased by 68 m ($P < .001$) in the treatment group and 18 m ($P = .064$) in the sham control group. No significant difference was found in the change in the MWD between the two groups (estimated treatment effect, 42 m; 95% CI, −14 to 97; $P = .139$). The MWD had increased by 62 m ($P = .006$) in the treatment group and 20 m ($P = .265$) in the sham control group. For patients with a baseline PWD of <200 m (n = 56), significant changes had occurred in both PWD and MWD between the two groups, favoring the treatment group (estimated treatment effect, 42 m; 95% CI, 2-83; $P = .042$; and estimated treatment effect, 62 m; 95% CI, 5-118; $P = .032$; respectively). Both overall and for the group of patients with a PWD <200 m, no significant differences were found in the changes in the resting and postexercise ankle-brachial index, resting and postischemic blood flow, or quality of life parameters between the two groups.

Conclusions: Treatment with −40 mm Hg INP increased the PWD compared with sham treatment in patients with IC. For the patients with a baseline PWD of <200 m, an increase was found in both PWD and MWD compared with sham treatment. (J Vasc Surg 2020;■:1-9.)

Keywords: Intermittent claudication; Intermittent negative pressure treatment; Peripheral artery disease

Peripheral artery disease (PAD) affects >235 million people globally, and the prevalence is increasing.[1] Intermittent claudication (IC) is a common symptom in patients with PAD characterized by muscle discomfort in the lower limb that is provoked by exercise and relieved by rest[2] and is associated with reduced ambulatory activity and quality of life.[3,4] Participation in supervised exercise therapy (SET) programs increase the walking capacity of patients with IC[5,6] and is the first-line treatment, together with smoking cessation and pharmacologic secondary prevention.[7] However, the availability of SET programs is low,[8] and many patients are unwilling or unable to participate.[9] Consequently, home-based exercise programs and different treatment devices have been suggested as alternative treatment options.[10-12]

Methods using intermittent negative pressure (INP) applied to the lower body or extremities to improve

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blood flow in patients with PAD have been described since the early 20th century.[13-15] Several studies have suggested positive effects on walking distance in patients with IC.[16-18] However, two recent studies did not find any additional effects of INP treatment on walking capacity.[19,20] Because the treatment intensity and duration varies among previous studies and the results differ, the clinical effect of INP treatment for patients with IC remains uncertain.

The aim of the present study was to investigate the clinical effects of treatment with −40 mm Hg INP for 1 hour in the morning and 1 hour in the evening for 12 weeks in patients with IC. We hypothesized that this treatment would improve the pain-free walking distance (PWD) and maximal walking distance (MWD) compared with sham treatment.

ARTICLE HIGHLIGHTS

- **Type of Research:** A multicenter, prospective, randomized controlled trial
- **Key Findings:** Treatment of intermittent claudication with lower extremity intermittent negative pressure for 1 hour twice daily for 12 weeks increased the pain-free walking distance in the treatment group (n = 38) receiving −40 mm Hg intermittent negative pressure compared with the sham control group (n = 34) receiving −10 mm Hg intermittent negative pressure.
- **Take Home Message:** Treatment with lower extremity intermittent negative pressure increased the pain-free walking distance compared with sham treatment for patients with intermittent claudication. For the patients with the most symptomatic disease, an increase occurred in both pain-free and maximal walking distance compared with sham treatment.

METHODS

Participants. We performed a multicenter trial, enrolling patients from the outpatient clinics at three vascular surgery departments in Norway (Oslo University Hospital, Oslo; Sørlandet Hospital, Kristiansand; and St Olavs Hospital, Trondheim) from January to September 2019. Data collection was completed in December 2019. Patients with an ankle-brachial index (ABI) of ≤0.9 or incompressible arteries and a radiologic diagnosis of PAD and IC were assessed for eligibility. Patients who had been scheduled for or who had undergone endovascular or open surgical revascularization within the previous 3 months were considered ineligible. The exclusion criteria were: inability to provide an informed consent; inability to perform a treadmill test; inability to independently operate the treatment device; the presence of severe heart disease; the presence of severe chronic obstructive pulmonary disease; and a baseline MWD of >1000 m measured on a treadmill with a ramp protocol.[21] All patients were offered the best medical treatment according to the guidelines from the European Society of Cardiology and the European Society for Vascular Surgery.[7]

INP treatment. INP was applied in a pressure chamber sealed around the lower leg. A pump unit (FlowOx 2.0; Otivio AS, Oslo, Norway) removed air from, and vented, the pressure chamber (Fig 1), producing alternating 10 seconds negative pressure and 7 seconds atmospheric pressure. The patients in the treatment group received −40 mm Hg INP, and the sham control group received −10 mm Hg INP. The devices were otherwise identical. These INP levels were chosen according to the findings from a recent study from our research group demonstrating that −40 mm Hg INP induced an acute increase in blood flow in the treated extremity in patients with PAD, in contrast to −10 mm Hg INP which did not significantly affect blood flow.[22]

All patients were instructed to treat themselves at home for 1 hour in the morning and 1 hour in the evening for 12 weeks. They were trained in the use of the INP device before the start of treatment. The daily treatment time was recorded by the device, allowing for the analysis of compliance data after the intervention period. To avoid the direct effects of treatment on the test results, the patients were instructed not to use the device on the day of the 12-week follow-up examination.

Randomization and blinding. Patients were randomized to the treatment group or sham control group in a 1:1 ratio using a computer-generated randomization list. Labeling of the treatment devices was performed by the producer (Otivio AS) by a person not involved in patient recruitment or data collection. The patients and personnel with patient contact during the study period were unaware of the group allocation. The statistical analyses were also performed without knowledge of the treatment group.

Clinical evaluation and measurements. Clinical evaluation and measurements were performed by the same person at baseline and after 12 weeks of treatment. The primary outcome measures were the changes in PWD and MWD. The pain-free walking time and maximal walking time were measured with the patients walking on a treadmill using a ramp protocol at a constant speed of 3.2 km/h starting at a 0% slope and increasing the slope by 2% every 2 minutes.[21] The patients were asked to specify the most limiting leg after the baseline treadmill test, which was chosen as the treatment leg.

Before the treadmill test, the resting ABI was measured with the patient in a supine position according to the guidelines from the American Heart Association.[23] The

Fig 1. Device for lower extremity intermittent negative pressure (INP) treatment. INP is generated in a pressure chamber sealed around the patient's lower leg by a pump unit that removes air from, and vents, the pressure chamber. Provided by Otivio AS, Oslo, Norway.

postexercise ABI was measured with the patient in supine position within 1 minute after the end of the treadmill test.

Resting blood flow was measured with the patient in the supine position using strain-gauge plethysmography (Domed Filtrass Angio, Krailling, Germany) of the lower leg at the point of maximal circumference. The plethysmograph records the rate of change in volume expansion for the area under the strain-gauge during proximal venous occlusion on the thigh, and the blood flow values are calculated.[24] Postischemic blood flow was measured using the same strain-gauge plethysmograph after 3 minutes of arterial occlusion obtained by inflating the thigh cuff to 250 mm Hg. For safety reasons, patients who had previously undergone bypass surgery in the leg were excluded from the present examination, as were patients who experienced unbearable pain during occlusion.

All the patients were requested to complete the EQ-5D-5L and Vascuqol-6 quality of life questionnaires at baseline and after 12 weeks of treatment. The EQ-5D-5L questionnaire consists of a visual analog scale and a descriptive system.[25] Using each patient's score in the descriptive system, an index value was calculated (EQ-5D-5L index) based on a value set validated for Denmark.[26] The Vascuqol-6 is a health-related quality of life questionnaire for patients with PAD validated for Norway,[27] consisting of six disease-specific items with a total score ranging from 6 to 24, with a higher score indicating better health.

Statistical analysis. The data are presented as the mean ± standard deviation for continuous variables and numbers and percentages for categorical variables, unless otherwise stated. Normality was assessed by histograms, Q-Q plots, and residual plots. The baseline characteristics between the groups were compared using independent samples *t*-tests for continuous variables and χ^2 tests for categorical variables. Differences within the groups were analyzed using paired sampled *t*-tests. Differences between groups were evaluated using univariate analysis of covariance, adjusting for differences in baseline data.[28] All subjects with pre- and post-treatment data were included in the intention-to-treat analyses. *P* values ≤.05 were considered statistically significant. Analyses were performed using Stata, version 16 (StataCorp, College Station, Tex).

In a comparable population of patients with IC, the pain-free walking time on a treadmill was 146 ± 112 seconds.[29] Assuming an increase in pain-free walking time of 87 seconds (76 m) as a clinically important difference,[30] 26 patients per treatment arm were required to detect a treatment effect, given 80% power and a 5% significance level. Assuming a withdrawal rate of 25%, we aimed to include 35 patients in each group.

Ethics. The Regional Committee for Medical and Health Research Ethics in Norway approved the present study (reference no. 2018/748), which was registered at ClinicalTrials.gov (identifier, NCT03640676). All the patients provided written informed consent before inclusion.

RESULTS

A total of 85 patients were assessed for eligibility. Of the 85 patients, 2 did not meet the inclusion criteria (baseline MWD >1000 m), and 11 patients declined to participate, leaving 72 patients (85%) for randomization (Oslo University Hospital, n = 46; St Olavs Hospital, n = 5; Sørlandet Hospital, n = 21; Fig 2). At baseline, a significantly higher prevalence of diabetes was present in the treatment group compared with the sham control group (*P* = .008). No significant differences were found between the two groups for all other demographic variables (Table I).

Walking distance. The between-group comparisons showed a significant difference in the change in the PWD, favoring the treatment group compared with the sham control group (estimated treatment effect, 50 m; 95% confidence interval [CI], 11-89; *P* = .014; Table II). At baseline, the PWD was 109 ± 70 m in the treatment group and 111 ± 77 m in the sham control group (Table I). After 12 weeks of treatment, an increase in the PWD of 68 m had occurred in the treatment group (95% CI, 33-103; *P* < .001) and 18 m in the sham control group (95% CI, −1 to 38; *P* = .064; Fig 3).

The between-group comparisons showed no significant differences in the change in the MWD after 12 weeks of INP treatment (estimated treatment effect, 42 m; 95% CI, −14 to 97; *P* = .14; Table II). The baseline MWD was 267 ± 177 m in the treatment group and 263 ± 170 m in the sham control group (Table I). After 12 weeks of

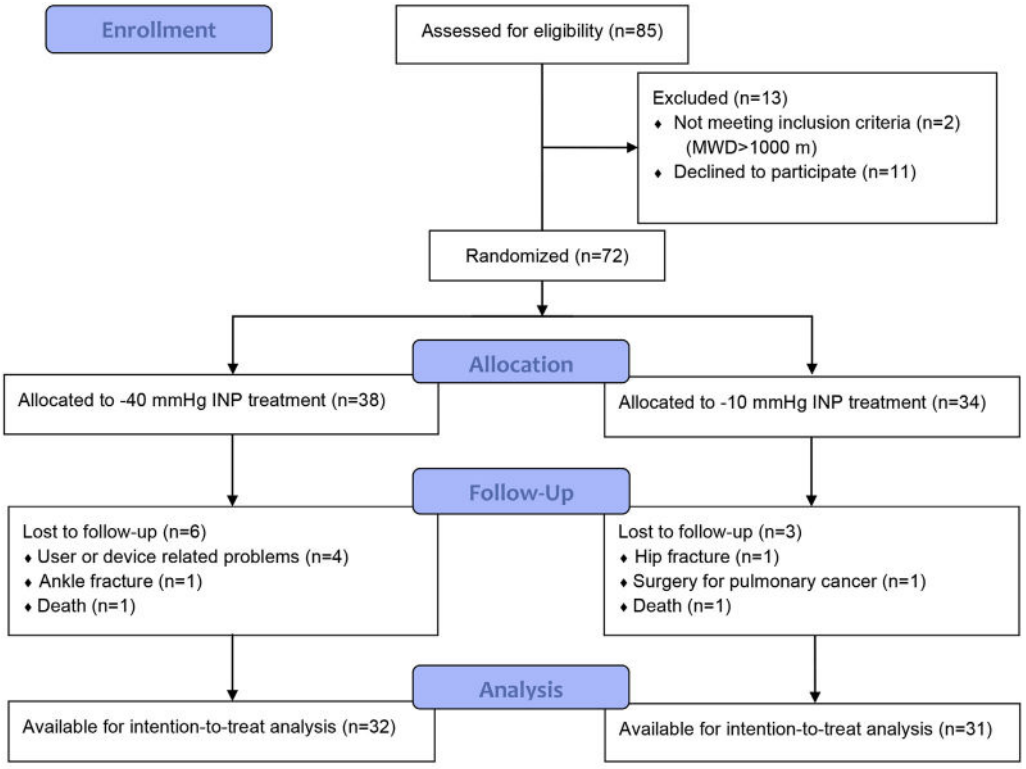

Fig 2. CONSORT (consolidated standards of reporting trials) flow diagram showing inclusion, exclusion, treatment allocation, and outcomes. *INP,* Intermittent negative pressure; *MWD,* maximal walking distance.

treatment, an increase had occurred in the MWD of 62 m in the treatment group (95% CI, 19-105; $P = .006$) and 20 m in the sham control group (95% CI, −16 to 57; $P = .27$; Fig 3).

Of the 63 patients who had completed the 12-week intervention period, 56 (89%) had had a baseline PWD of <200 m. For these patients, the between-group comparisons showed statistically significant differences in the changes in both PWD and MWD, favoring the treatment group (estimated treatment effect, 42 m; 95% CI, 2-83; $P = .042$; and estimated treatment effect, 62 m; 95% CI, 5-118; $P = .032$, respectively; Table III).

ABI, blood flow measurements, and quality of life. At baseline, the resting ABI was 0.53 ± 0.16 in the treatment group and 0.56 ± 0.15 in the sham control group (Table I). No significant changes were found in the resting or postexercise ABIs across the groups ($P = .65$ and $P = .19$, respectively), and the plethysmography measurements did not show significant changes in the resting or post-ischemic blood flow across the groups ($P = .34$ and $P = .58$, respectively) after 12 weeks of treatment. Furthermore, no significant changes were observed in the quality of life questionnaire scores (EQ-5D-5L index, $P = .67$; EQ-5D-5L visual analog scale score, $P = .29$; Vascuqol-6, $P = .89$) across the groups after 12 weeks of treatment (Table II). Relative within-group changes for all outcome variables after 12 weeks of treatment are illustrated in the Supplementary Fig (online only).

Compliance, discontinuation, and adverse events. The mean daily treatment time was 1.8 ± 0.2 hours in the treatment group and 1.8 ± 0.5 hours in the sham control group ($P = .63$). Six patients in the treatment group and three patients in the sham control group were lost to follow-up (Fig 2). Four patients in the treatment group discontinued treatment because of issues related to use of the treatment device. One patient in the treatment group and one patient in the sham control group discontinued because of severe trauma (ankle fracture and hip fracture, respectively), and one patient in the sham control group discontinued because of surgery for pulmonary cancer. One patient in each group died, both of cardiac arrest (unrelated to the INP sessions) during the 12-week intervention period. No further serious adverse events were reported.

DISCUSSION

The main finding from the present study was that treatment with −40 mm Hg INP for 1 hour in the morning and 1 hour in the evening for 12 weeks increased the PWD compared with sham treatment for patients with IC. For the patients with a baseline PWD of <200 m

Table I. Baseline patient characteristics

Variable	Treatment group (n = 38)	Sham control group (n = 34)	*P* value
Age, years	72 ± 8	73 ± 6	.59[a]
Male sex	25 (66)	26 (76)	.32[b]
Body mass index, kg/m^2	27.3 ± 4.2	26.9 ± 4.0	.74[a]
Smoking			.92[b]
Current	14 (37)	11 (32)	
Previous	19 (50)	18 (53)	
Never	15 (39)	5 (15)	
Comorbidity			
Diabetes mellitus	18 (47)	6 (18)	.008[b]
Chronic renal failure	5 (13)	4 (12)	.86[b]
Hypertension	32 (84)	28 (82)	.83[b]
Hypercholesterolemia	22 (58)	27 (79)	.051[b]
Coronary artery disease	17 (45)	18 (53)	.49[b]
Cerebrovascular disease	8 (21)	8 (24)	.80[b]
Antiplatelet agent	32 (84)	27 (79)	.60[b]
Anticoagulant agent	6 (16)	8 (24)	.41[b]
Statin	32 (84)	31 (91)	.37[b]
Antihypertensive agent	34 (89)	31 (91)	.81[b]
Treated leg, right	19 (50)	22 (65)	.21[b]
Disease location			.81[b]
Suprainguinal	6 (16)	4 (12)	
Infrainguinal	23 (61)	23 (68)	
Supra- and infrainguinal	9 (24)	7 (21)	
Previous revascularization in treated leg	16 (42)	12 (35)	.55[b]
PWD, m	109 ± 70	111 ± 77	.90[a]
MWD, m	267 ± 177	263 ± 170	.94[a]
Resting ABI	0.53 ± 0.16	0.56 ± 0.15	.33[a]
Postexercise ABI	0.35 ± 0.17	0.33 ± 0.13	.52[a]
Vascuqol-6	13.4 ± 3.0	13.7 ± 3.3	.68[a]
EQ-5D-5L index	0.65 ± 0.20	0.70 ± 0.12	.20[a]

ABI, Ankle-brachial index; *MWD,* maximal walking distance; *PWD,* pain-free walking distance.
Data presented as mean ± standard deviation for continuous variables and as number (%) for categorical variables.
[a]Independent samples *t*-test.
[b]χ^2 Test.

(clinically classified as Fontaine IIb, corresponding to Rutherford class 2-3), both PWD and MWD increased in the treatment group compared with the sham control group.

To the best of our knowledge, the present study is one of the first double-blind randomized controlled trials to show that INP treatment increases the walking distance for patients with IC. Our findings are in line with the results reported by a placebo controlled study from Denmark, which also described an effect on walking distances.[18] However, only the within-group changes had been reported in that study.[18] Older studies have reported similar findings for patients with PAD,[13,16,17,31] but these were mainly case reports and patient series. However, two recent placebo controlled trials concluded that INP treatment does not provide additional effects to SET or home-based physical activity and lifestyle changes in increasing the walking capacity in patients with IC.[19,20] One explanation might be that the effect of increased physical activity surpasses the potential effects of INP treatment. Another explanation might be that the patients were treated with INP for only 30 and 40 minutes two and three times each week for 6 weeks, respectively, because that INP system required in-hospital treatment instead of at-home treatment. Hence, the frequency and length of the INP treatments were significantly lower than those used in the present study. Because INP applied to the lower leg induces acute

Table II. Analysis of covariance for all patients (N = 63)

Variable	No. available for analysis	Estimated treatment effect (95% CI)	*P* value
PWD, m	63	50 (11-89)	.014
MWD, m	63	42 (−14 to 97)	.14
Resting ABI	60	0.01 (−0.04 to 0.07)	.65
Postexercise ABI	47	0.04 (−0.02 to 0.10)	.19
Blood flow, mL/100 mL tissue			
Resting	59	0.5 (−0.6 to 1.6)	.34
Postischemic	53	0.4 (−1.1 to 2.0)	.58
Vascuqol-6	63	−0.11 (−1.53 to 1.31)	.89
EQ-5D-5L index	57	0.01 (−0.05 to 0.08)	.67
EQ-5D-5L VAS	63	5.3 (−4.7 to 15.4)	.29

ABI, Ankle-brachial index; *CI,* confidence interval; *MWD,* maximal walking distance; *PWD,* pain-free walking distance; *VAS,* visual analog scale.

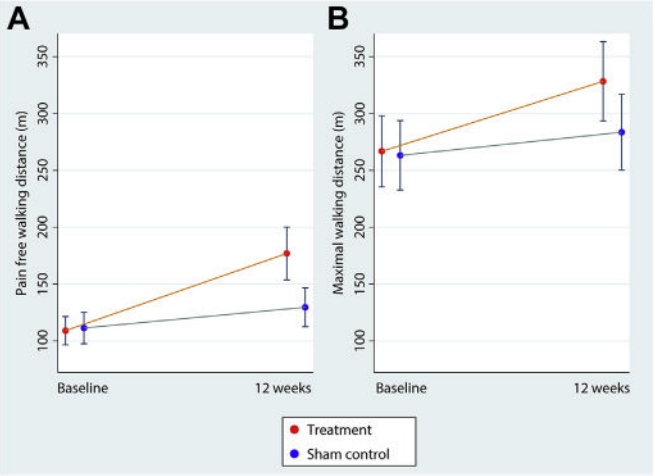

Fig 3. Pain-free walking distance (PWD) **(A)** and maximal walking distance (MWD) **(B)** at baseline and after 12 weeks of treatment. *Dots* indicate mean values; *error bars,* standard errors.

rhythmical fluctuations in blood flow,[22,32,33] which might promote long-term favorable effects leading to an increased walking capacity, it is reasonable to assume that a higher treatment frequency would be favorable and might also be necessary to achieve clinical effects.

In patients with a baseline PWD of <200 m, we observed an increase in both PWD and MWD in the treatment group compared with the sham control group. Although determined from a subgroup analysis, this finding indicates that the patients with the most symptomatic disease might benefit the most from INP treatment. Multiple studies have documented the beneficial effects of SET programs on walking capacity, functional status, and quality of life in patients with IC.[5,34-38] However, a systematic review from 2016 concluded that only one third of patients with IC were suitable for or willing to undertake SET.[9] Hence, the current guidelines recommending SET might not be applicable to most patients with IC. Although SET should be the first choice of treatment for patients with IC, INP treatment might be a useful supplement when SET is unavailable or for patients unable or unwilling to participate in SET.

The between-group changes in PWD in the present study were lower than assumed in the power calculations. However, to the best of our knowledge, no consensus has been reached regarding the minimal clinically important difference in walking performance after interventions in patients with IC. It is probably dependent on the disease severity, comorbidities, and the patient's subjective judgment. Pharmacologic agents such as cilostazol and pentoxifylline have market approval in Europe and the United States, with an indication of improving leg symptoms in patients with IC. A Cochrane review from 2014 estimated that cilostazol could increase the PWD by 31 m (95% CI, 22-40) and MWD by 43 m (95% CI, 18-68) compared with placebo.[39] Another Cochrane review from 2015 reported an improvement in PWD of −33.8% to 73.9% and in MWD of 1.2% to 156% with pentoxifylline. However, statistical tests were not performed because of insufficient data.[40] In the present study, we found an estimated treatment effect on the PWD of 50 m and a treatment effect for patients with a PWD <200 m of 42 m for PWD and 62 m for MWD. Thus, INP treatment is competitive to drug treatment in increasing the walking capacity of patients with IC.

Treatment of the calf or foot using intermittent pneumatic compression (IPC) has also been suggested to improve the walking distance for patients with IC.[11] Both INP and IPC increase arterial blood flow acutely when applied to the lower limb,[22,33,41] which might increase arterial shear stress, thereby inducing flow-mediated vasodilatation.[22,42] However, IPC is applied over a smaller area on the calf or foot and might not have the same microvascular effects on the whole lower leg compared with INP.

Endovascular or open surgery can be considered for patients with IC who have severely disabling symptoms and do not respond to SET.[7,43,44] A Cochrane review from

Table III. Analysis of covariance for baseline pain-free walking distance <200 m subgroup (N = 56)

Variable	No. available for analysis	Estimated treatment effect (95% CI)	*P* value
PWD, m	56	42 (2-83)	.042
MWD, m	56	62 (5-118)	.032
Resting ABI	53	0.00 (−0.06 to 0.06)	.91
Postexercise ABI	44	0.04 (−0.03 to 0.10)	.27
Blood flow, mL/100 mL tissue			
Resting	53	0.7 (−0.4 to 1.8)	.20
Postischemic	47	0.3 (−1.4 to 2.0)	.74
Vascuqol-6	56	−0.25 (−1.80 to 1.29)	.75
EQ-5D-5L index	53	0.02 (−0.05 to 0.08)	.61
EQ-5D-5L VAS	55	4.5 (−6.4 to 15.5)	.41

ABI, Ankle-brachial index; *CI,* confidence interval; *MWD,* maximal walking distance; *PWD,* pain-free walking distance; *VAS,* visual analog scale.

2018, which compared endovascular revascularization and conservative treatment of IC, reported a moderate effect on MWD and a large effect on PWD after 6 to 12 months.[45] However, no clear differences were shown between the groups after long-term follow-up.[45] Different outcome measures and study designs did not allow for direct comparisons to the findings in the present study. However, the effect of INP treatment after 3 months should be subject to further research.

In the present study, we did not observe any differences across the groups in the resting or postexercise ABI after 12 weeks of treatment. This is in line with the findings from a systematic review on the effects of exercise on IC, reporting an increased walking capacity without finding significant changes in the ABI.[5] Although we found an effect of INP treatment on walking distance, we did not find any differences in the quality of life parameters across the groups after 12 weeks of treatment. This does not correspond with the findings from studies investigating the effects of SET in IC.[36,38] One explanation might be that the improvement in the quality of life after participation in SET is also related to other factors than just the improvement in walking distance, such as increased physical activity and social interactions, which might not be obtained using INP treatment alone. Another explanation might be that the present study was underpowered to detect changes in quality of life across the groups.

The treatment group received −40 mm Hg INP, which is the standard INP level provided by the Conformitè Europëenne–marked FlowOx system commercially available in Europe. This INP level seemed to be well tolerated, and it is possible that a higher level could have been used. However, in a previous study from our research group, we did not observe any significant difference in the acute increase in arterial or skin blood flow at −60 mm Hg INP compared with −40 mm Hg INP.[22] Whether subgroups of patients could benefit from a higher INP level requires further investigation.

The prevalence of diabetes was higher in the treatment group than in the sham control group. Patients with diabetes are more prone to microangiopathy. Hence, the clinical effects observed in the present study could have resulted from positive effects on the arterial circulation or microcirculation, or both.

One patient in each group died of cardiac arrest during the intervention period. No clinical evidence was found to support a causal relationship between these events and the use of the treatment device or participation in the present study. The number of deaths in the present study did not allow for further statistical interpretations but underscores the high mortality for patients with symptomatic PAD.[46]

The present study had some limitations. We used −10 mm Hg INP in the sham device to make it appear identical to the active device without affecting the arterial blood flow. The similarity in compliance between the groups and the low withdrawal rate in the sham control group indicates that the patients really were unaware of their treatment allocation. However, a small effect might have resulted from the repetitive exposure to −10 mm Hg INP, leading to an underestimation of the treatment effect. More patients were lost to follow-up in the treatment group than in the sham control group because of user- or device-related problems. The use of the device requires some technical, cognitive, and motor capacity. In addition, some patients with a very small circumference of the lower leg might experience difficulty in achieving airtightness of the pressure chamber. Hence, the difference in those lost to follow-up between the two groups might have been random. Measurements of PWD is based on a subjective report of the onset of pain by the patient during the treadmill test. Thus, the results might have been affected by the fact that individuals might perform differently when they are being observed. However, in a double-blind, randomized controlled trial, the risk of bias from this phenomenon seems low. The patients were recruited from

the vascular surgery departments at three hospitals in Norway. Thus, one should be careful about generalizing the results to other patient populations or settings. However, whether the results from the present study are also applicable to patients with more severe stages of PAD should be the subject of further research.

CONCLUSIONS

The results from the present study have shown that treatment with −40 mm Hg INP for 1 hour in the morning and 1 hour in the evening for 12 weeks increased the PWD compared with sham treatment in patients with IC. For patients with a baseline PWD of <200 m, treatment with −40 mm Hg INP increased both PWD and MWD compared with sham treatment.

AUTHOR CONTRIBUTIONS

Conception and design: HH, IM, JH
Analysis and interpretation: HH, EP, LH, JH
Data collection: HH, EP, JH
Writing the article: HH
Critical revision of the article: HH, EP, LH, IM, AS, JH
Final approval of the article: HH, EP, LH, IM, AS, JH
Statistical analysis: HH, LH
Obtained funding: Not applicable
Overall responsibility: HH

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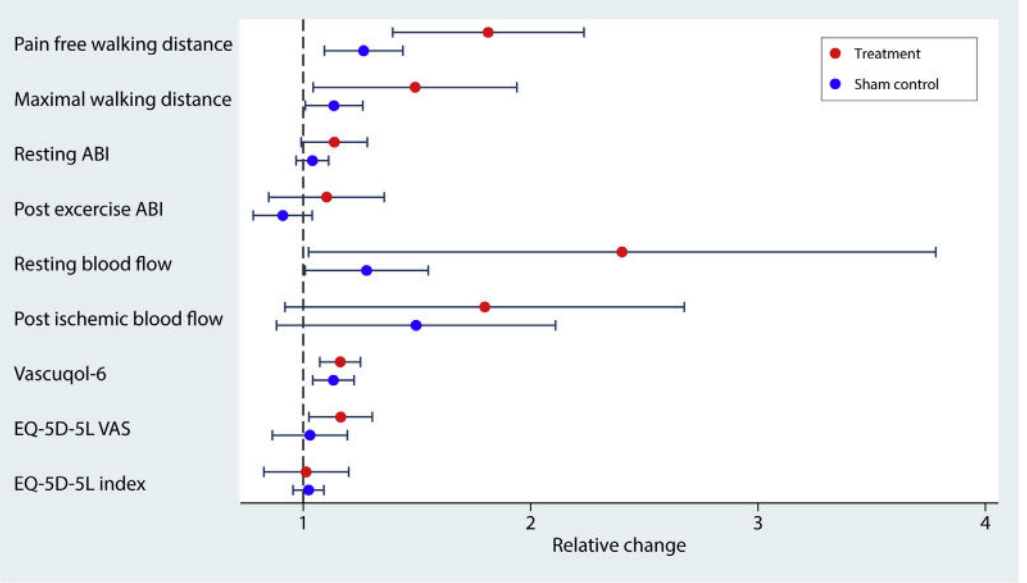

Supplementary Fig (online only). Relative within-group changes for all outcome variables. *Dots* indicate mean values; *error bars,* 95% confidence intervals. *ABI,* Ankle-brachial index.