Randomized controlled trial of vacuum therapy for intermittent claudication

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ABSTRACT

Objective: The "gold standard" treatment of intermittent claudication (IC) is supervised exercise therapy (SET). Intermittent vacuum therapy (IVT) has recently been promoted as an additional treatment of IC. During IVT, negative pressure and atmospheric pressure are alternatingly applied to the lower extremities, possibly resulting in improved circulation. The aim of this study was to determine a potential additional effect of IVT in IC patients undergoing a standardized SET program.

Methods: IC patients were recruited from three Dutch general hospitals between December 2015 and July 2017. They received a standardized SET program but were also randomly assigned to an intervention group receiving an IVT treatment (−50 mBar negative pressure) or a control group receiving a sham treatment (−5 mBar negative pressure). IVT was provided in a dedicated clinic during 12 sessions of 30 minutes during a 6-week period. The primary outcome measure was a change in maximal treadmill walking distance. Secondary outcome measures were a change in functional treadmill walking distance, 6-minute walk test, ambulatory ability, and quality of life.

Results: A total of 78 patients were randomized, of whom 70 were available for intention-to-treat analysis (control, n = 34; intervention, n = 36). At 6 and 12 weeks, increases in walking distance were of equal magnitude. Median (interquartile range) change in maximal treadmill walking distance during 12 weeks was +335 (205-756) meters in control patients and +250 (77-466) meters in intervention patients (P = .109), whereas functional treadmill walking distance increased +230 (135-480) meters and +188 (83-389) meters (P = .233), respectively. Mean ± standard deviation change in the 6-minute walk test was +36 ± 48 meters and +55 ± 63 meters (P = .823), respectively. Ambulatory ability and quality of life improved equally in both groups.

Conclusions: IVT does not confer any additional beneficial effects in IC patients undergoing a standardized SET program. (J Vasc Surg 2020;71:1692-701.)

Keywords: Peripheral artery disease; Intermittent claudication; Supervised exercise therapy; Vacuum therapy; Negative pressure therapy; Randomized controlled trial

Peripheral artery disease (PAD) is prevalent in 202 million people worldwide and affects 15% to 20% of individuals older than 70 years.[1] Intermittent claudication (IC) is the most frequent symptom of PAD and is associated with ambulatory dysfunction and poor health status. The "gold standard" treatment of IC is supervised exercise therapy (SET) combined with cardiovascular risk management (CVRM).[2-4] Multiple randomized controlled trials (RCTs) and meta-analyses have demonstrated the efficacy of SET regarding an improved walking distance and health-related quality of life.[5-10] Limb revascularization, such as angioplasty or bypass surgery, is currently considered only in patients who fail to favorably respond to SET.

A number of alternative strategies possibly improving the functional impairment associated with lower extremity ischemia by increasing blood flow have hitherto been explored but often to no avail. Vacuum therapy is commonly used to treat wounds by applying negative pressure to the local tissue environment to remove excessive fluid.[11,12] A variant termed intermittent vacuum therapy (IVT) has recently been promoted by commercial parties in a number of European countries as an additional treatment of IC.[13,14] During IVT, negative pressure and atmospheric pressure are alternatingly applied to

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the lower extremities. By doing so, it is speculated that a rhythmic vascular dilation and compression are created that may stimulate circulation and may subsequently improve walking distances and reduce pain. Recently, IVT applied to the lower leg and foot increased foot perfusion in healthy volunteers and patients with PAD.[15,16] However, it is unknown whether IVT exerts any positive clinical effects in patients with IC.

The aim of this study was to determine a potential additional effect of IVT in IC patients undergoing a standardized SET program.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, randomized controlled trial
- **Key Findings:** Intermittent vacuum therapy (IVT) did not lead to any additional beneficial effects on walking distance, self-reported ambulatory ability, or health-related quality of life in 78 patients with intermittent claudication who were treated with a standardized supervised exercise therapy program.
- **Take Home Message:** IVT should not be offered to intermittent claudication patients as adjunctive therapy. Further studies on any potential mechanisms and clinical implications of IVT are needed.

METHODS

Patient recruitment

This RCT was a combined effort of vascular surgery outpatient departments of three Dutch general hospitals (Catharina Hospital, Eindhoven [n = 34]; Máxima Medical Center, Veldhoven [n = 32]; and St. Anna Hospital, Geldrop [n = 12]) between December 2015 and July 2017. The study was evaluated and approved by the Institutional Review Board of the Catharina Hospital, Eindhoven, The Netherlands, and reported according to the Consolidated Standards of Reporting Trials guidelines.[17] Written informed consent was obtained from each patient before enrollment. Demographic information, height, weight, body mass index, cardiovascular risk factors, comorbid conditions, claudication history, and ankle-brachial indices were obtained at the start of the study.

Inclusion and exclusion criteria

Patients with IC (Fontaine stage II/Rutherford class 1-3) were eligible. The diagnosis of lower limb PAD was based on an ankle-brachial index of <0.9 at rest or a drop of >0.15 after exercise.[2-4] Patients were included if they had an indication for treatment with SET, sufficient additional insurance or adequate financial resources for a SET program of 1 year, and motivation to participate in the study (particularly additional travel time investment for treatment with IVT) and provided informed consent. They were excluded if they had a maximal walking distance of >1000 meters at baseline as assessed with a graded treadmill test,[18] inability to complete 12 IVT sessions in the first 12 weeks, prior treatment of PAD in the previous 2 years (conservative or invasive treatment), prior treatment with IVT, cognitive disabilities, inadequate mastering of the Dutch language, contraindications to IVT (pregnancy, infection or inflammation of the lower limbs, abdominal wall hernia), critical limb ischemia, recent (<6 weeks) trauma of the lower limbs, and severe hip or knee osteoarthritis and planned joint replacement therapy. Patient flow is shown in Fig 1.

Randomization and blinding

Participants were randomly assigned to IVT intervention or sham control. Randomization occurred using a computer-generated randomization list and was executed by a researcher who was not involved in the recruitment or data-gathering process. Moreover, all participants received usual care consisting of SET and CVRM. Vascular surgeons, supervising physical therapists who assessed outcome measures, and participants were blinded to group allocation. Staff at the IVT facility was not blinded to group allocation, inherent to the study design.

Interventions

Usual care: SET and CVRM. All participants received usual care including a standardized SET program provided by a certified physical therapist affiliated with ClaudicatioNet, a nationwide community-based network for SET and lifestyle coaching in The Netherlands.[19-21] The SET program was set up to improve walking distance as reported earlier.[5-8] Our program consists of 1 year of supervised, intermittent treadmill walking to near-maximal claudication pain. Patients generally start with two or three sessions of 30 minutes weekly. Volume and intensity are tailored to the individual needs of the patient during the treatment year. All physical therapists provided SET according to the guidelines of the Royal Dutch Society for Physical Therapy.[22] As part of this SET program, all participants were encouraged to also perform additional exercise in their spare time. In line with clinical practice guidelines, they also received best medical therapy including smoking cessation and antiplatelet and lipid-lowering therapy.[2-4] Best medical therapy was customized to individual risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus (DM).

IVT. IVT treatment was performed in a dedicated clinic (Been Kliniek, Eindhoven, The Netherlands) with a Vacumed device (Weyergans High Care AG, Dueren, Germany). The device consists of an airtight vacuum chamber and a pump connected to a pressure control system. During IVT treatments, participants were asked to lay themselves comfortably in a supine position (Fig 2). The lower body was positioned in the vacuum

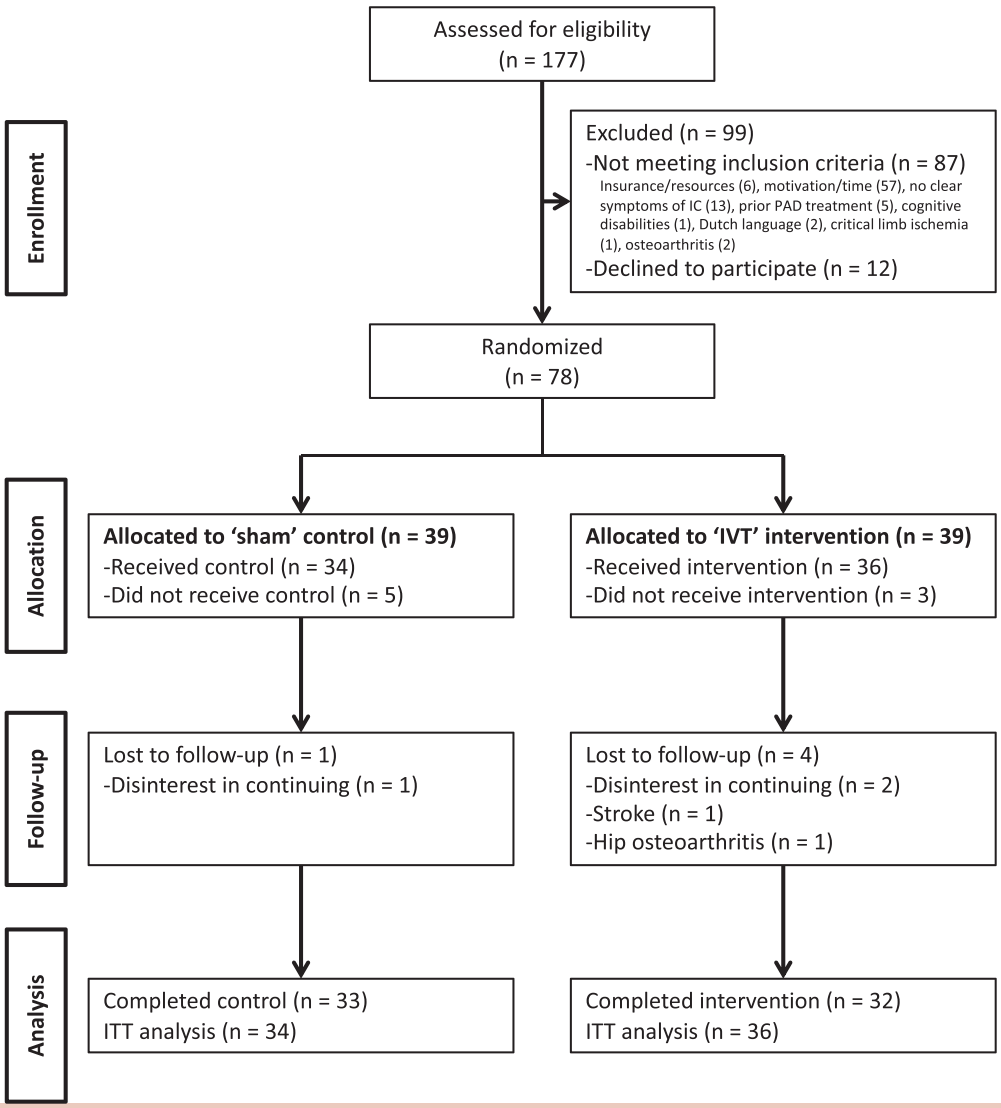

Fig 1. Flow diagram of selection of patients. *IC,* Intermittent claudication; *ITT,* intention-to-treat; *IVT,* intermittent vacuum therapy; *PAD,* peripheral artery disease.

chamber, which was sealed around the participant's trunk with a cuff at the level of the umbilicus to allow application of negative pressure. Negative pressure cycles are created by alternating between removing air and venting the chamber to atmospheric pressure. During IVT treatments, a PAD-specific treatment program was started at the press of a button. IVT was applied using an oscillation protocol with cycles of 9 seconds of negative pressure and 9 seconds of atmospheric pressure. These preprogrammed settings were based on the experience of both the manufacturer and the IVT facility.

Patients randomized to the intervention group received an IVT treatment with a negative pressure of −50 mBar (−37.5 mm Hg). Patients randomized to the control group received a sham treatment with a negative pressure of −5 mBar (−3.75 mm Hg). To put these pressures in context, the intrapleural pressure is −5 mBar under static conditions and −20 mBar during a vigorous inspiration. A typical domestic vacuum cleaner has a suction of about −200 mBar. The control group treatment was designed to be as similar as possible to the intervention group treatment in an attempt to control for the potentially confounding effects of attention and social contact, placebo, and Hawthorne effects of IVT. It was supposed to mimic the experience of undergoing negative pressure without exposing the participant to a possible effective IVT treatment.

Both groups received 12 IVT sessions of 30 minutes during a 6-week period (two per week). IVT treatment started within 1 week after enrollment. No exercise was performed by the participants in the IVT facility during these treatments. However, all participants were encouraged to have an IVT session followed by a SET session on the same day.

To quantify the amount of treatment performed in the intervention and control groups, IVT and SET sessions

Fig 2. Vacumed device (Weyergans High Care AG, Dueren, Germany). The participant's lower body is positioned in an airtight vacuum chamber interfaced with the pressure control system. The chamber is sealed around the participant's trunk at the level of the umbilicus.

were recorded in a logbook by the research staff. The manufacturer (Weyergans High Care AG) and staff at the IVT facility (Been Kliniek) did not have access to outcome data and did not participate in data analysis or preparation of the manuscript.

Outcome measures

The primary outcome measure was a change in maximal treadmill walking distance (MWD). Secondary outcome measures were a change in functional treadmill walking distance (FWD), total distance during the 6-minute walk test (6MWT), self-reported ambulatory ability, and health-related quality of life. Outcome data were obtained by physical therapists at baseline and after 6 weeks and 12 weeks of follow-up.

Graded treadmill test: FWD and MWD. Patients performed a progressive, graded treadmill test (walking speed of 3.2 km/h [2.0 mph] and inclination beginning at 0% grade and increasing by 2% every 2 minutes) to determine study eligibility and to obtain the outcome measures of FWD and MWD.[18] For practical reasons, the maximal inclination was 10%, and the maximal duration was 30 minutes (1600 meters). FWD was defined as the distance at which the patient preferred to stop walking because of claudication pain. MWD was defined as the distance at which the patient had to stop walking because of maximal claudication pain. FWD and MWD are both reliable parameters reflecting walking distance in patients with IC.[23,24]

6MWT. For self-paced exercise performance measurement, patients performed the overground 6MWT in which two cones were placed 10 meters apart in a marked corridor.[25] Patients were instructed to walk as many laps as possible around the cones. The total distance during the 6MWT was recorded. The 6MWT yields highly reliable measurements.[26]

Self-reported ambulatory ability. Self-reported ambulatory ability was obtained using the validated Walking Impairment Questionnaire (WIQ) for PAD patients.[27] It contains three domains to assess walking impairment: walking distance, walking speed, and stair climbing. For each domain, a subscore of the Likert items was calculated. The mean of these domains represents the total WIQ score. The Dutch version of the WIQ using the European metric system is a reliable instrument for assessing walking impairment in patients with IC.[28,29]

Disease-specific quality of life. Disease-specific quality of life was assessed with the Vascular Quality of Life (VascuQol) questionnaire.[30] The VascuQol consists of 25 items, subdivided into five domains: pain, symptoms, activities, social well-being, and emotional well-being. Each item has seven possible options ranging from 1 (worst possible) to 7 (best possible). A summary score, also ranging from 1 to 7 (worst to best), is calculated by adding the score of all items and then dividing the total by 25. The Dutch VascuQol is a reliable questionnaire for assessment of quality of life in patients with IC.[31,32]

Generic quality of life. Generic quality of life was assessed with the EuroQol 5-Dimension 3-Level (EQ-5D) instrument.[33] The EQ-5D consists of a descriptive system and a visual analog scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The VAS records the patient's self-rated health on a vertical VAS. These parameters can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

Statistical analysis

Sample size calculations were performed on the primary outcome measure of MWD. With a sample size of 25 patients per treatment arm, the trial achieved an 80% power to detect a difference in MWD of 200 ± 250 meters using a two-sided independent samples *t*-test and a significance level of $\alpha = .05$. Assuming a 10% withdrawal rate, 30 patients in each group had to be included.

Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means with standard deviations when normally distributed or as medians with interquartile ranges when non-normally distributed. For baseline characteristics, comparisons between groups were performed using χ^2 tests for categorical variables and independent samples *t*-tests for continuous variables. If variables were normally distributed, within-group changes from baseline were analyzed by repeated-

Table I. Baseline characteristics of intermittent claudication (IC) patients randomized to control or intervention

Variables	Control (n = 39)	Intervention (n = 39)	*P* value
Male sex	25 (64)	26 (67)	1.000[a]
Age, years	68 ± 9	67 ± 8	.445[b]
Length, cm	171 ± 9	173 ± 9	.308[b]
Weight, kg	83 ± 17	82 ± 14	.812[b]
BMI, kg/m^2	28 ± 5	28 ± 4	.441[b]
ABI at rest	0.69 ± 0.24	0.69 ± 0.15	.967[b]
ABI after exercise	0.39 ± 0.18	0.40 ± 0.19	.940[b]
Symptoms			.473[a]
Unilateral	23 (59)	18 (46)	
Bilateral	16 (41)	21 (54)	
Smoking			.689[a]
Current	10 (26)	7 (18)	
Former	27 (69)	30 (77)	
Never	2 (5)	2 (5)	
Hypertension	27 (69)	29 (74)	.802[a]
Hypercholesterolemia	26 (67)	17 (44)	.068[a]
Obesity	12 (31)	12 (31)	.800[a]
Coronary artery disease	21 (54)	18 (46)	.651[a]
Congestive heart failure	9 (23)	7 (18)	.780[a]
Atrial fibrillation	4 (10)	2 (5)	.675[a]
COPD	8 (21)	8 (21)	1.000[a]
TIA or CVA	5 (13)	8 (21)	.545[a]
LE neurologic disease	5 (13)	7 (18)	.755[a]
LE orthopedic disease	5 (13)	5 (13)	1.000[a]
Renal insufficiency	6 (15)	4 (10)	.737[a]
DM	5 (13)	13 (33)	.058[a]
History of PAD	11 (28)	14 (36)	.628[a]
Prior SET	2 (5)	3 (8)	1.000[a]
Prior ER	11 (28)	8 (21)	.599[a]
Prior SR	2 (5)	4 (10)	.675[a]

ABI, Ankle-brachial index; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *DM,* diabetes mellitus; *ER,* endovascular revascularization; *LE,* lower extremity; *PAD,* peripheral artery disease; *SET,* supervised exercise therapy; *SR,* surgical revascularization; *TIA,* transient ischemic attack.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.
[a] χ^2 test.
[b] Independent samples *t*-test.

measures analysis of variance, and between-group differences were analyzed by univariate analysis of covariance, controlling for baseline data. If variables were non-normally distributed, within-group changes from baseline were analyzed using the Friedman test, and between-group differences were analyzed using the Mann-Whitney *U* test.

All participants were included in the statistical analysis of baseline, 6-week, and 12-week follow-up data, which was done on an intention-to-treat (ITT) basis. Missing values (3%) were estimated by multiple imputation. To investigate the influence of attrition patterns on study results, all analyses were repeated with the completer data only (excluding imputed data). All analyses were performed with SPSS 24 software (IBM Corp, Armonk, NY). Graphs were created with GraphPad Prism 6 software (GraphPad Software Inc, La Jolla, Calif). Statistical significance was defined as $P < .05$.

RESULTS

Study population. A total of 177 patients were assessed for eligibility, of whom 87 did not meet inclusion criteria (mainly for logistical reasons, lack of time or motivation to travel to and from the IVT facility) and 12 declined to participate, leaving 78 patients (44%) for randomization (Fig 1). Randomization resulted in similar ($P > .05$) baseline characteristics of the groups (Table I). However, there was a trend toward a higher incidence of DM in the intervention group compared with the control group (33% and 13%, respectively; $P = .058$). Eight patients (control, n = 5; intervention, n = 3) had an exercise performance not limited by claudication as determined by treadmill testing. Based on eligibility criteria, these patients did not start with the study, leaving 70 patients for ITT analysis.

Follow-up. In total, 65 patients (93%; control, n = 33; intervention, n = 32) completed the program. Five patients (7%; control, n = 1; intervention, n = 4) discontinued the program before the 12-week end point. The primary reason for discontinuing the program was lack of interest. Two patients in the intervention group discontinued because of an adverse event not related to the study (one stroke and one hip osteoarthritis). Missing data from the five patients who did not complete the study were imputed. Baseline characteristics remained similar between the groups ($P > .05$) after inclusion of only the 65 patients who completed the study (data not shown). Furthermore, no significant group difference was noted for number of dropouts ($P = .185$). At 12 weeks of follow-up, no patient had undergone limb revascularization (eg, angioplasty or bypass surgery).

Adherence to the IVT and SET program. The number of completed treatment sessions in the two groups was similar ($P > .05$). Patients in both groups completed 12 IVT sessions within a median of 5.5 (5.4-5.8) weeks, except for one control patient who stopped the IVT treatment after three sessions for personal reasons. Based on the ITT principle, this patient was included in the analysis. In addition, control patients completed a median of 21 (17-23) SET sessions within 12 weeks, and intervention patients completed a median of 23 (19-25) SET sessions ($P = .064$).

Walking distances. Both groups demonstrated comparable ($P > .05$) walking distances at all time points (Figs 3-5). MWD and FWD increased in both groups (all

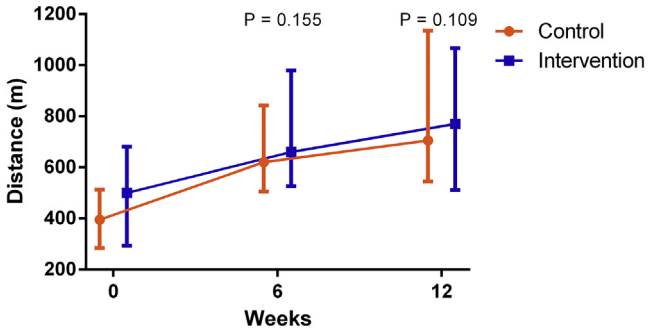

Fig 3. Median maximal treadmill walking distance (MWD) at baseline and after 6 and 12 weeks in the control and intervention groups. The *error bars* represent interquartile range. *P* values represent difference in change from baseline between groups.

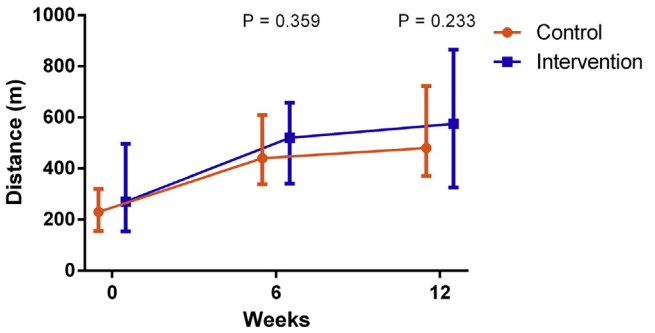

Fig 4. Median functional treadmill walking distance (FWD) at baseline and after 6 and 12 weeks in the control and intervention groups. The *error bars* represent interquartile range. *P* values represent difference in change from baseline between groups.

$P < .001$). At 6 weeks, median (interquartile range) change in MWD was +223 (129-430) meters in the control group and +191 (63-328) meters in the intervention group ($P = .155$), whereas FWD increased +229 (102-345) meters and +180 (75-288) meters ($P = .359$), respectively. At 12 weeks, change in MWD was +335 (205-756) meters in the control group and +250 (77-466) meters in the intervention groups ($P = .109$), whereas FWD increased +230 (135-480) meters and +188 (83-389) meters ($P = .233$), respectively. Analysis of 6MWT data indicated that total distance increased in both groups from baseline to 6 weeks (both $P < .001$) but did not change from 6 to 12 weeks (both $P > .05$). At 6 weeks, mean ± standard deviation change in 6MWT was +34 ± 40 meters in the control group and +44 ± 80 meters in the intervention group ($P = .896$). At 12 weeks, 6MWT increased +36 ± 48 meters and +55 ± 63 meters ($P = .823$), respectively. When analyses were repeated with the completer data only (excluding imputed data), findings were unchanged (data not shown). This indicates that attrition patterns had minimal influence on study results.

To determine whether IVT has differential effects per baseline walking distance, the intervention group was subdivided into a short-distance subgroup (baseline MWD < median) and a long-distance subgroup (baseline MWD ≥ median). However, no differences regarding change from baseline between subgroups were found after 6 weeks (short, +195 [60-290] meters; long, +188 [73-388] meters; $P = .759$) and 12 weeks (short, +196 [62-375] meters; long, +289 [98-648] meters; $P = .271$). Furthermore, after adjustment for DM in a multivariate regression analysis, no significant group effects regarding MWD were found after 6 weeks (β ± standard error = −86 ± 66; $P = .191$) or 12 weeks (β ± standard error = −131 ± 82; $P = .108$).

WIQ. Groups were similar ($P > .05$) at baseline and after 6 and 12 weeks of follow-up on each WIQ measure. Total WIQ score and distance and speed domains improved in both groups, whereas the stair domain improved in the intervention group only (Table II). However, changes in the intervention group were not significantly different ($P > .05$) from those in the control group.

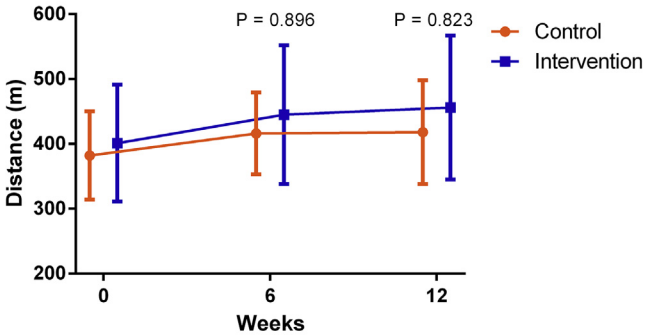

Fig 5. Mean 6-minute walk test (6MWT) at baseline and after 6 and 12 weeks in the control and intervention groups. The *error bars* represent standard deviations. *P* values represent difference in change from baseline between groups.

Health-related quality of life. Groups were similar ($P > .05$) at baseline and after 6 and 12 weeks of follow-up on each health-related quality of life measure. Summary VascuQol score, pain, symptoms, activities, and emotional domains improved in both groups, whereas the social domain improved in the intervention group only (Table III). However, changes in the intervention group were not significantly different ($P > .05$) from those in the control group. The EQ-5D index and VAS score remained unaltered (data not shown).

DISCUSSION

The aim of this study was to determine a potentially beneficial effect of IVT in IC patients undergoing a standardized SET program. The execution of this RCT was prompted by unauthorized claims of commercial parties that IVT is highly effective in the treatment of IC.[13,14] Both groups improved walking distance, self-reported

Table II. Walking impairment questionnaire (WIQ)

Variables	Baseline	6 weeks	12 weeks	*P* value within groups[a]	Change from baseline to 6 weeks	*P* value between groups[b]	Change from baseline to 12 weeks	*P* value between groups[b]
Total score								
Control	0.48 ± 0.18	0.55 ± 0.16	0.58 ± 0.19	**.004**	0.07 ± 0.15	.266	0.10 ± 0.14	.741
Intervention	0.51 ± 0.18	0.61 ± 0.15	0.63 ± 0.18	**<.001**	0.10 ± 0.15		0.13 ± 0.13	
Distance								
Control	0.36 ± 0.23	0.48 ± 0.23	0.48 ± 0.26	**.011**	0.12 ± 0.22	.542	0.12 ± 0.23	.798
Intervention	0.40 ± 0.23	0.54 ± 0.22	0.57 ± 0.27	**<.001**	0.15 ± 0.21		0.18 ± 0.21	
Speed								
Control	0.48 ± 0.21	0.55 ± 0.17	0.60 ± 0.19	**.011**	0.06 ± 0.19	.431	0.12 ± 0.21	.646
Intervention	0.47 ± 0.19	0.54 ± 0.16	0.56 ± 0.17	**.030**	0.07 ± 0.21		0.09 ± 0.18	
Stair								
Control	0.60 ± 0.23	0.62 ± 0.26	0.65 ± 0.24	.495	0.02 ± 0.22	.232	0.05 ± 0.15	.210
Intervention	0.67 ± 0.26	0.74 ± 0.21	0.77 ± 0.22	**.001**	0.07 ± 0.18		0.10 ± 0.14	

Self-reported ambulatory ability measured on a scale of 0 (worst possible) to 1 (best possible). Boldface *P* values are statistically significant ($P < .05$).
[a]Repeated-measures analysis of variance.
[b]Univariate analysis of covariance with baseline measurement as covariant.

ambulatory ability, and health-related quality of life after a regimen of SET. However, the additive effect of IVT was nil.

Reports on the application of "suction devices" to the lower limb for the treatment of PAD date back to the 20th century. Initial studies were limited by the lack of objective outcome variables (ie, use of self-reported walking distance), small sample size, and suboptimal study design. The proposed theoretical foundation for applying an intermittent negative pressure rather than a continuous suction is related to the prevention of a vasoconstrictor mechanism, the venoarterial reflex.[34,35] By applying an intermittent negative pressure, the vasoconstrictor effect of the venoarterial reflex may be circumvented. For instance, arterial blood flow velocity, skin blood flow, and skin temperature decreased after the application of a constant ambient negative pressure of −40 mm Hg to the lower leg and foot in healthy volunteers.[15] Conversely, applying the same negative pressure intermittently (alternating 10 seconds of negative pressure and 7 seconds of atmospheric pressure) increased arterial blood flow velocity in healthy volunteers and PAD patients.[15,16] In addition, a corresponding increase in skin blood flow was observed. These results seemed to suggest that the application of oscillating IVT increases macrocirculation and microcirculation, at least in some healthy volunteers and PAD patients.

There is no high-level evidence suggesting the efficacy of IVT on important outcome parameters in IC patients. Studies assessing the clinical effects of IVT are scarce, and inconclusive published data suggest that IVT offers at most a modest improvement on walking distance. In 1969, the effect of repeated periods of intermittent limb suction was examined in patients with long-standing PAD rejecting surgical treatment.[36] Calf blood flow was said to increase, and 24 of 40 patients (60%) claimed subjective benefit. An early 1990s study randomized 22 IC patients to either IVT or placebo treatment.[37,38] After 25 applications administered during a period of 2 months, pain-free walking distance improved from 53 to 93 meters and maximal walking distance from 99 to 180 meters in the IVT group but not during placebo treatment.[37] A recent case series suggested that IVT may facilitate wound healing.[39] In this study, four patients with PAD and difficult-to-heal ulcers were treated with an 8-week intervention period of −40 mm Hg IVT on the lower limbs for 2 hours per day. Although these observations suggest that peripheral circulation may be enhanced with IVT, care should be taken in interpreting the results of these studies. The reported changes in walking distance with IVT were small and probably clinically insignificant. Furthermore, only a small percentage of PAD patients can feasibly attend IVT several hours per day. In this study, 57 of 177 patients assessed for eligibility (32%) were not included because of lack of time or motivation for IVT. From the patient's viewpoint, IVT may also not be acceptable owing to additional transportation costs. Nevertheless, further studies are needed to elucidate any potential mechanisms and clinical implications of the pulsatile flow observed during IVT.

The results of this RCT are in line with a recently published study.[40] In this study, IVT did not provide relief in 48 IC patients who were randomized to orally given advice of lifestyle changes (tobacco abstinence and physical activities) or IVT treatment thrice weekly for 6 weeks. Walking capacity increased in the control patients but not in the intervention patients, although group differences were not significant. In contrast to our study, blinding was not performed because of the

Table III. Vascular Quality of Life (VascuQoL) questionnaire

Variables	Baseline	6 weeks	12 weeks	*P* value within groups[a]	Change from baseline to 6 weeks	*P* value between groups[b]	Change from baseline to 12 weeks	*P* value between groups[b]
Summary score								
Control	5.12 (4.04-5.53)	5.30 (4.29-5.91)	5.56 (4.58-5.84)	**.001**	0.34 (−0.15 to 0.91)	.156	0.36 (0.14-0.92)	.359
Intervention	5.06 (3.95-5.45)	5.58 (4.53-5.95)	5.72 (4.45-6.23)	**<.001**	0.56 (0.17-1.00)		0.52 (0.33-1.04)	
Pain								
Control	5.00 (4.25-5.75)	5.25 (4.31-5.75)	5.25 (4.38-5.75)	**.022**	0.25 (−0.19 to 0.94)	0.545	0.25 (−0.25 to 0.75)	.214
Intervention	4.88 (4.00-5.50)	5.25 (4.50-5.75)	5.63 (4.56-6.19)	**.008**	0.50 (0.00-1.00)		0.50 (0.00-0.94)	
Symptoms								
Control	4.75 (4.25-5.25)	4.63 (4.06-5.50)	5.00 (4.63-5.50)	**.006**	0.25 (−0.19 to 0.94)	.220	0.50 (0.00-0.75)	.202
Intervention	4.50 (3.50-5.25)	5.00 (4.25-5.50)	5.38 (4.31-5.94)	**<.001**	0.75 (0.00-1.00)		0.50 (0.25-1.25)	
Activities								
Control	4.26 (3.69-5.25)	4.94 (4.03-5.72)	5.25 (4.25-5.63)	**<.001**	0.56 (0.12-1.00)	.256	0.62 (0.19-1.06)	.405
Intervention	4.32 (3.63-5.22)	5.25 (4.38-5.72)	5.25 (4.25-6.13)	**<.001**	0.75 (0.41-1.25)		0.75 (0.28-1.38)	
Social								
Control	5.75 (4.00-7.00)	5.75 (4.13-7.00)	6.00 (4.50-7.00)	.232	0.00 (0.00-0.50)	.583	0.00 (−0.25 to 1.00)	.918
Intervention	5.25 (4.13-6.88)	5.50 (4.00-7.00)	6.25 (4.00-7.00)	**.010**	0.50 (0.00-0.88)		0.00 (0.00-1.00)	
Emotional								
Control	5.57 (4.11-6.71)	5.79 (4.43-6.57)	5.86 (5.00-6.86)	**.001**	0.14 (−0.39 to 0.86)	.170	0.29 (0.00-1.15)	.862
Intervention	5.57 (4.61-6.14)	6.22 (4.86-6.86)	6.43 (4.64-6.97)	**.001**	0.50 (0.00-1.14)		0.36 (0.00-0.97)	

Disease-specific quality of life measured on a scale from 1 (worst possible) to 7 (best possible). Boldface *P* values are statistically significant ($P < .05$).
[a]Friedman test.
[b]Mann-Whitney *U* test.

lack of a placebo treatment. Furthermore, unsupervised lifestyle changes are known to be inferior to SET.

A surprising finding of this RCT is that WIQ stair and VascuQol social domains improved in the intervention group but not in the control group. We have no explanation for the observed improvements rather than chance alone. However, there were no differences between the groups after 6 and 12 weeks, indicating that these changes were not clinically relevant. Also, there tended to be more diabetic patients in the intervention group compared with the control group ($P = .058$). Patients with DM represent a vulnerable subgroup of patients who may respond poorly to a program of exercise rehabilitation.[41] However, after adjustment for DM in a multivariate regression analysis, no significant group effects regarding walking distance, ambulatory ability, or quality of life were found (Appendix, online only).

A unique feature of this RCT was the investigation of the efficacy of IVT against a background of well-founded and evidence-based usual care. It was not our intent to simply compare IVT with SET. Instead, this is the first study to determine the usefulness of IVT as adjunctive therapy. SET programs are widely available and reimbursement is nowadays guaranteed for all patients with IC in The Netherlands. Therefore, it is considered unethical to withhold this effective treatment from patients. Also, from a health perspective, it seems incorrect to deny patients SET as it has positive effects on the complete cardiopulmonary system and vascular risk profile (eg, body mass index and DM).[42] Consequently, participating in IVT only is not a viable alternative for IC patients compared with participating in SET.

The observed effect of SET on walking distance in this RCT is consistent with the results of a recently published Cochrane meta-analysis indicating that SET is an effective treatment of IC and should always be offered as first-line treatment.[10] Exercise-mediated gains in walking distance occur rapidly within the first 3 months of exercise rehabilitation and are maintained with further training. Overall, the primary outcome measure of MWD increased with a median of 285 meters (73%) after 12 weeks, which reflects a clinically relevant improvement. More important, our

results show that SET offers an increase in health-related quality of life that was seen in previous studies as well.[5,10]

Strengths and weaknesses. The strength of this study is the design. All participants received an optimal strategy of usual care consisting of SET and CVRM. In addition, a control group underwent a sham treatment, whereas an intervention group underwent a possible effective IVT treatment. Both groups completed a similar number of treatment sessions, and the overall attrition rate was low (7%). Both participants and physical therapists, who obtained outcome data, were blinded for group allocation. The most important limitation of this study is the relatively low enrollment rate (44%) because of inclusion criteria regarding motivation, time, and additional insurance or financial resources. However, to determine the additive effect of IVT in IC patients after a regimen of SET, we had to ensure that all participants received a sufficient amount of both treatments. Another potential limitation is the absence of objective outcome parameters monitoring blood flow velocity and skin blood flow. Moreover, patients with rest pain and ulcers were excluded. Furthermore, inclusion and exclusion criteria may have created a selection bias toward patients more interested in IVT or exercise and toward those with more financial means or better access to transportation. Conversely, patients with more severe IC may have been denied study participation. Therefore, improvements within groups might be somewhat overestimated. Furthermore, the treatment effect of IVT might differ somewhat between IC patients, depending on how well they comply with SET. However, our results do not suggest such an effect. Moreover, this study did not contain isolated IVT and sham arms because, in our opinion, IVT only is not a viable alternative under current guidelines. In addition, technical aspects of IVT were based on recommendations of both the manufacturer and the IVT facility but may have been suboptimal. The IVT treatment protocol has not been validated with respect to volume or length. However, the IVT pattern (cycles of 9 seconds) and negative pressure (−50 mBar) were similar to those in other studies.[15,16,39,40]

CONCLUSIONS

IVT does not confer any additional beneficial effects on walking distance, self-reported ambulatory ability, or health-related quality of life in IC patients undergoing a standardized SET program. Consequently, IVT should not be offered to IC patients as adjunctive therapy. Further studies on any potential mechanisms and clinical implications of IVT are needed.

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AUTHOR CONTRIBUTIONS

Conception and design: DH, LG, MS, JT
Analysis and interpretation: DH, HF, BD, LG, EC, MS, JT
Data collection: DH, BD
Writing the article: DH
Critical revision of the article: HF, BD, LG, EC, MS, JT
Final approval of the article: DH, HF, BD, LG, EC, MS, JT
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Overall responsibility: JT

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APPENDIX (online only).

Multivariate regression analysis adjusted for diabetes mellitus (DM)

Group effect regarding MWD adjusted for DM
After 6 weeks: $\beta \pm SE = -86 \pm 66$; $P = .191$
After 12 weeks: $\beta \pm SE = -131 \pm 82$; $P = .108$
Group effect regarding FWD adjusted for DM
After 6 weeks: $\beta \pm SE = -42 \pm 46$; $P = .368$
After 12 weeks: $\beta \pm SE = -132 \pm 88$; $P = .133$
Group effect regarding 6MWT adjusted for DM
After 6 weeks: $\beta \pm SE = 11 \pm 17$; $P = .512$
After 12 weeks: $\beta \pm SE = 23 \pm 15$; $P = .125$
Group effect regarding total WIQ score adjusted for DM
After 6 weeks: $\beta \pm SE = 0.028 \pm 0.042$; $P = .503$
After 12 weeks: $\beta \pm SE = 0.024 \pm 0.042$; $P = .564$
Group effect regarding summary VascuQol score adjusted for DM
After 6 weeks: $\beta \pm SE = 0.296 \pm 0.187$; $P = .113$
After 12 weeks: $\beta \pm SE = 0.087 \pm 0.170$; $P = .611$

FWD, Functional treadmill walking distance; *MWD,* maximal treadmill walking distance; *6MWT,* 6-minute walk test; *SE,* standard error; *VascuQol,* Vascular Quality of Life questionnaire; *WIQ,* Walking Impairment Questionnaire.