ELSEVIER

Clinical Research, Basic Science

Lower Extremity Intermittent Negative Pressure for Intermittent Claudication. Follow-Up after 24 Weeks of Treatment

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Background: Treatment with lower extremity intermittent negative pressure (INP) of -40 mm Hg for one hour twice daily for 12 weeks, increases walking capacity in patients with intermittent claudication (IC). However, the effects of INP treatment beyond 12 weeks have not been elucidated. The aim of the present study was to investigate the clinical effects of INP treatment after 24 weeks in patients with IC.

Methods: This was a follow-up study after a randomized sham-controlled trial, where patients randomized to the active treatment group were offered to continue treatment for 12 additional weeks (24 weeks in total). Treatment with -40 mm Hg INP was applied in a pressure chamber sealed around the lower leg, and the patients were instructed to treat themselves at home one hour in the morning and one hour in the evening. Pain free walking distance (PWD), maximal walking distance (MWD), resting ankle-brachial index (ABI) and post exercise ABI were measured at baseline, after 12 and 24 weeks.

Results: Ten out of 32 patients (31%) from the active treatment group in the initial trial were included in this follow-up study. At baseline, PWD was (mean ±SD) 151 ± 91 m and MWD was 362 ±159 m. There was a significant increase in both PWD and MWD after 24 weeks of treatment, compared to baseline (ANOVA; P= 0.006 and P= 0.012, respectively). Post hoc tests revealed that PWD increased significantly from baseline to 12 weeks (mean 81 m; 95% CI [6, 156]; P = 0.032), and that MWD increased significantly from 12 to 24 weeks (mean 145 m; 95% CI [22, 268]; P = 0.018). There were no significant changes in resting ABI or post exercise ABI during the 24-week treatment period (ANOVA; P= 0.157 and P= 0.450, respectively).

Conclusion: Both PWD and MWD improved after treatment with – 40 mm Hg INP for one hour twice daily for 24 weeks, compared to baseline. The main improvement in PWD occurred during the first 12 weeks of treatment, whereas the main improvement in MWD occurred between 12 and 24 weeks of treatment.

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INTRODUCTION

Peripheral artery disease (PAD) is associated with significant morbidity, increased mortality, and decreased quality of life. About one third of the patients diagnosed with PAD suffers from intermittent claudication (IC).[1] Management of cardiovascular risk factors including pharmacological secondary prevention, and supervised exercise therapy (SET) are the first line treatments for patients with IC.[2] The purpose is to lower the risk of cardiovascular events, and to improve, stabilize or slow down the progression of leg symptoms. However, as the availability and adherence to SET programs are low,[3,4] other treatment modalities have been suggested.[5]

Lower extremity intermittent negative pressure (INP) treatment increases blood flow, reduces leg symptoms and has been suggested as a treatment option for patients with PAD in several studies.[6-12] In a recent double-blind randomized sham-controlled trial from our research group, we found that treatment with lower extremity INP one hour twice daily for 12 weeks increased walking capacity in patients with IC compared to sham treatment.[12] However, the potential clinical effects of continued INP treatment beyond 12 weeks have not been elucidated. The aim of the present study was therefore to investigate the clinical effects of INP treatment after 24 weeks in patients with IC. We hypothesized that patients with IC would continue to improve walking capacity from 12 to 24 weeks of INP treatment.

METHODS

Participants

The present study was a follow-up after a randomized controlled trial investigating the clinical effects of INP treatment for one hour, twice daily for 12 weeks in 63 patients with IC (active treatment n=32, sham treatment n=31).[12] After 12 weeks of treatment, patients in the active treatment group receiving -40 mmHg INP were offered to continue treatment for 12 additional weeks (24 weeks in total). The patients were instructed to treat themselves at home one hour in the morning and one hour in the evening. The patients' most symptomatic leg identified after a treadmill test at baseline was chosen as the leg to be treated.

INP Treatment

INP of -40 mmHg was applied in a pressure chamber sealed around the patient's lower leg in cycles of 10 s negative pressure and 7 s atmospheric pressure generated by a pumping device, as previously described[12] (Fig. 1).

Fig 1. Device for lower extremity intermittent negative pressure treatment. Intermittent negative pressure is generated in a pressure chamber sealed around the patient's lower leg by a pump unit that is removing air from and venting the pressure chamber.

Variables

Background variables were recorded based on a standardized registration form. Pain free walking distance (PWD), maximal walking distance (MWD), resting ankle-brachial index (ABI), and post exercise ABI were measured at baseline, at 12 weeks and at 24 weeks of INP treatment. ABI was measured according to the guidelines from The American Heart Association.[13] PWD and MWD were measured on treadmill with a ramp protocol.[14] Post exercise ABI was measured within one minute after the end of the treadmill test.

Statistics

Continuous variables are presented as mean ±standard deviation and categorical variables as number (%). Normality was assessed with histograms, qq-plots, and residual plots. Repeated measures analysis of variance (ANOVA) was performed to determine if there were changes in PWD, MWD, resting ABI and post exercise ABI over the 24-week treatment period. The assumption of sphericity was assessed with Mauchly's test. Bonferroni correction was performed for post hoc comparisons of baseline vs. 12 weeks and 12 weeks vs. 24 weeks. P-values <0.05 were considered statistically significant. All analyses were performed

Table I. Patient's characteristics at baseline

Age (years)	71 ±7
Male sex	7 (70)
Body Mass Index (kg/m^2)	26.5 ±2.8
Smoking	
Current	3 (30)
Previous	5 (50)
Never	2 (20)
Diabetes mellitus	4 (40)
Chronic renal failure	0 (0)
Hypertension	9 (90)
Hypercholesterolemia	9 (90)
Coronary artery disease	5 (50)
Cerebrovascular disease	2 (20)
Antiplatelet agent	9 (90)
Anticoagulant agent	2 (20)
Statin	9 (90)
Antihypertensive agent	9 (90)
Localization of disease	
Suprainguinal	2 (20)
Infrainguinal	6 (60)
Supra- and infrainguinal	2 (20)
Previous intervention in treated leg	6 (60)
Pain free walking distance (m)	151 ±91
Maximal walking distance (m)	362 ±159

Continuous variables are presented as mean ±standard deviation, categorical variables are presented as number (%).

using Stata version 16 (Stata Inc. North Station, TX, USA).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (ref: 9006) and was a follow-up study after a recent randomized controlled trial (NCT03640676). Written informed consent was obtained from all patients before inclusion.

RESULTS

Of the 32 patients randomized to the active treatment group in the initial trial, 10 patients (31%) volunteered to continue treatment for 12 additional weeks (24 weeks in total) and were included in the present follow-up study. Mean age was 71 ± 7 years, and seven patients were men. Two patients had suprainguinal disease, six patients had infrainguinal disease, and two patients had both supra- and infrainguinal disease (Table I).

At baseline, PWD was 151 ± 91 m. A repeated measures ANOVA showed that 24 weeks of INP treatment had a statistically significant effect on PWD ($F(2,18)=6.95$; $P=0.006$) (Fig. 2). Post hoc tests revealed that PWD increased significantly from baseline to 12 weeks (mean 81 m; 95% CI [6, 156]; $P=0.032$), but there was no significant change in PWD from 12 to 24 weeks (mean 19 m; 95% CI [-56, 94]; $P=1.00$).

At baseline, MWD was 362 ± 159 m. For MWD, Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(2)=8.86$; $P=0.012$), hence a repeated measures ANOVA with Greenhouse-Geisser correction ($\varepsilon=0.5989$) was performed, showing that 24 weeks of INP treatment had a statistically significant effect on MWD ($F(1.198,10.780)=8.55$; $P=0.012$) (Fig. 3). Post hoc tests showed no significant change in MWD from baseline to 12 weeks (mean 38 m; 95% CI [-85, 161]; $P=1.00$), but a significant increase in MWD from 12 to 24 weeks (mean 145 m; 95% CI [22, 268]; $P=0.018$).

At baseline, resting ABI was 0.53 ±0.12, and post exercise ABI was 0.28 ±0.12 . There were no significant effects of INP treatment on resting ABI or post exercise ABI during the 24- week treatment period ($F(2,18)=2.06$; $P=0.157$ and $F(2,11)=0.86$; $P=0.450$, respectively)

DISCUSSION

In the present study we found that patients with IC receiving treatment with -40 mm Hg INP twice daily for 24 weeks increased both pain free- and maximal walking distance, compared to baseline. The main increase in PWD occurred during the first 12 weeks of treatment, whereas the main increase in MWD occurred from 12 to 24 weeks of treatment.

Several studies have suggested clinical effects of INP treatment on walking distance in patients with IC.[9-11] In a recently published randomized controlled trial from our research group,[12] we found a significant effect of INP treatment on PWD compared to sham treatment after 12 weeks. Further, a subgroup analysis showed a significant effect on both the PWD and the MWD compared to sham treatment for the patients with the most symptomatic disease (baseline PWD<200 m).[12] The present follow-up study is to our knowledge the first study that describe clinical effects of INP treatment beyond 12 weeks.

In the present study, we observed an increase in PWD during the first 12 weeks, whereas MWD increased during the last 12 weeks of the 24-week treatment period. This may be explained by the fact that many patients with IC have a low exercise capacity due to concomitant heart and lung diseases, which in addition to the leg pain, may restrict their MWD. An initial improvement in PWD may allow

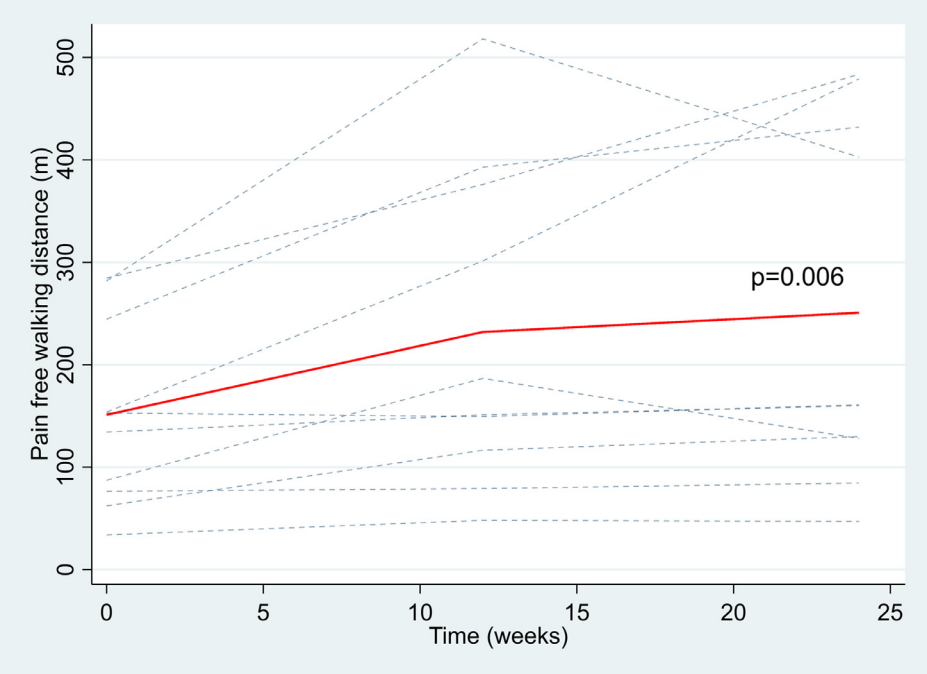

Fig. 2. Pain free walking distance plotted at baseline, 12 weeks, and 24 weeks of treatment with lower extremity intermittent negative pressure. Blue dashed lines represent individual patients ($n = 10$), red line represents the mean values at each time point. Overall P-value for repeated measures ANOVA is presented.

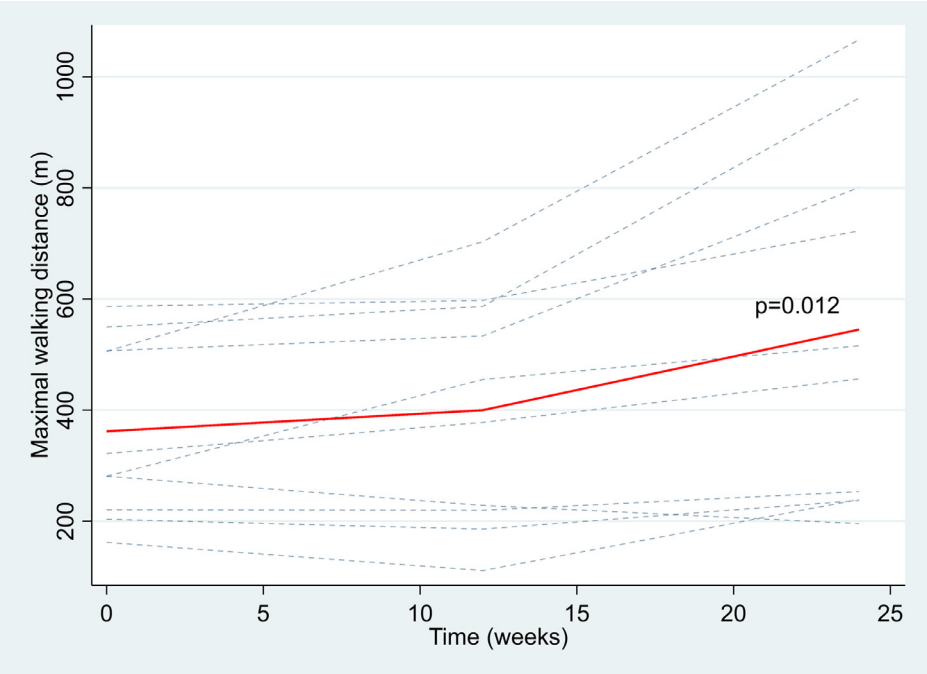

Fig. 3. Maximal walking distance plotted at baseline, 12 weeks, and 24 weeks of treatment with lower extremity intermittent negative pressure. Blue dashed lines represent individual patients ($n = 10$), red line represents the mean values at each time point. Overall *P*-value for repeated measures ANOVA is presented.

for more physical activity, which in turn improves the exercise capacity and the MWD. Participation in SET programs is shown to be effective and recommended for the treatment of IC[2], but is limited by poor adherence and low availability.[3,4] One reason for the poor adherence might be that the patients are exposed to pain during the exercise. The improvement in PWD obtained during 12 weeks of INP treatment may be sufficient to increase the adherence to SET, but the effects on MWD which seems to occur somewhat later also suggests that INP treatment could be a valuable supplement for IC patients when SET is unavailable, for example in rural areas.

The mechanisms of INP treatment resulting in long lasting effects in patients with PAD is not fully understood. However, it is shown that application of INP acutely increases arterial and skin blood flow.[15,16] The fluctuations in arterial flow promoted by INP leads to increased arterial shear stress, which induces flow-mediated vasodilation, and are thought to result in longer-lasting positive effects on the micro- and macro circulation in the treated extremity.[16,17] Hence, the improvement in walking capacity observed in patients with IC after long-term INP treatment can be interpreted as improved micro- and macro circulatory conditions in the treated extremity. This might also be applicable to patients with more advanced stages of PAD, as the underlying pathophysiology is the same. For patients with critical limb ischemia, endovascular or open surgical revascularization is the corner stone treatment, but have limitations related to patency, patient comorbidity and localization and extent of the disease. INP treatment could be an option for patients with critical limb ischemia not amenable for endovascular or open surgery, or as a supplement after endovascular or open surgical interventions with high risk of restenosis or graft occlusion. Whether INP treatment could contribute to limb salvage for patients with critical limb ischemia, or improve patency after endovascular or open surgical procedures should be subjects to further research.

In the present study, we did not observe any statistically significant increase in the PWD from 12 to 24 weeks of treatment. It might be that the main effect on PWD occurs during the first 12 weeks of treatment, however it may most likely be explained by lack of power due to the relatively low number of patients included in this follow-up study. Further, we did not observe changes in resting ABI or post exercise ABI during the study period. This is in line with studies investigating the effects of SET in patients with IC, showing increased walking capacity after SET without improvement in ABI.[18]

There are some limitations in this study. One patient peaked the treadmill test after 24 weeks of treatment, which probably have resulted in an underestimation of the treatment effect. The changes in walking distances observed in the present study are based on within group comparisons, without a control group. However, the effects on walking distances after the first 12 weeks are well documented in a double-blind randomized sham-controlled trial.[12]

CONCLUSION

In this follow-up study of 10 patients with IC, there were improvements in PWD and MWD after treatment with – 40 mmHg INP for one hour twice daily for 24 weeks. The improvement in PWD occurred during the first 12 weeks of treatment, whereas the improvement in MWD occurred between 12 and 24 weeks of treatment.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: HH, EMP, IM, AS, JH
Collected the data: HH, EMP, AS, JH
Performed the analysis: HH, LØH
Wrote the paper: HH
Revised the paper: HH, EMP, LØH, IM, AS, JH

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