A prospective randomized controlled study with intermittent mechanical compression of the calf in patients with claudication

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Objectives: The study tested the feasibility of using a new portable mechanical compression device for the treatment of claudication. The device applies intermittent non-pneumatic mechanical compression (IMC) to the calf. It was hypothesized that it can offer a low-cost convinient option for patients and achieve good compliance and improved clinical outcomes.

Methods: Thirty patients were enrolled in a randomized controlled single blind study. Fourteen patients were assigned to active IMC. Sixteen control patients continued with medical treatment alone. Outcomes were recorded at baseline, after one month, three months, and six months. The study examined changes in exercise tolerance using Initial Claudiacation Distance (ICD) and Absolute Claudiaction Distance (ACD) as well as ankle-brachial index at rest (ABI-r) and post-exercise (ABI-pe). All patients had stable claudication due to peripheral arterial disease (PAD) and were already under best medical treatment (BMT). To be eligible for inclusion, patients had to be between the ages of 50 and 75 years, had to have stable claudication with an absolute claudication distance >40 meters but <300 meters on a standardized treadmill stress test (3.8 km/h at a 10% grade), have a resting ABI in the affected limb <0.8 with a drop of at least 0.15 following exercise, in whom surgical intervention was not expected for at least three months. Fourteen patients were assigned to active IMC consisting of compressions 65 mm Hg in amplitude, applied for three 3-second compressions/minute, two hours/day for three months. Sixteen control patients continued with BMT alone.

Results: One month after treatment, ICD increased by 66% ($P = .001$), ACD increased by 51.75% ($P = .005$), and ABI-pe increased by 42% ($P = .01$). Treatment effects were maintained or further improved after three months. ABI-r did not increase at any time. Compliance exceeded 80%. Three months following cessation of therapy, claudication distances and ABI-pe did not decrease significantly.

Conclusions: We concluded that the use of IMC of the calf for three months increased claudication distances and led to objective improvements in ABI-pe. Intermittent mechanical compression may be a useful approach to patients with continued claudication despite standard medical treatment. (J Vasc Surg 2010;51:857-62.)

Intermittent claudication due to peripheral artery disease (PAD) affects 10% of the population above 70 years of age,[1,2] with an estimated 12 million sufferers in the USA and 15 million in Europe.[3] The progressive aging of the population will lead to a significant increase in the worldwide prevalence of claudication in coming decades, with a corresponding economic impact.

The main goals of treatment for claudication are to improve exercise tolerance (eg, as indexed by distance walked until the onset of leg pain and the total distance a patient is capable of walking) and to minimize potential progression to critical limb ischemia (which can lead to ulcers and necrosis, sometimes requiring amputation). The standard therapeutic options for achieving these goals include participation in structured programs of regular exercise, pharmacological treatments, control of associated medical diseases or risk factors, percutaneous transluminal angioplasty, and revascularization surgery. These options, however, are not applicable to all patients with claudication and are not always effective, especially in the long term. For example, the use of pharmacologic agents believed to be potent enhancers of blood flow, demonstrated only modest improvements in exercise tolerance.[4] Regarding more invasive approaches, the risks of perioperative morbidity and mortality, the long term risks of graft failure and restenosis following transluminal angioplasty suggest prudence when it comes to mechanical intervention, be it surgical or endovascular.[5]

Intermittent pneumatic compression (IPC) is a treatment modality that has been used extensively for patients with lymphoedema and in the prophylaxis of deep vein thrombosis (DVT).[6] Prior studies have also demonstrated that IPC increases lower limb arterial flow and could therefore be useful in patients with PAD.[7] Indeed, therapeutic effects have been identified in studies showing a 3.2 ± 1.6-fold increase in resting popliteal artery blood flow in patients with claudication in response to IPC applied to the calf[8] and isotope studies showing an increase in calf muslce perfusion with IPC applied to the foot.[9] Although promis-
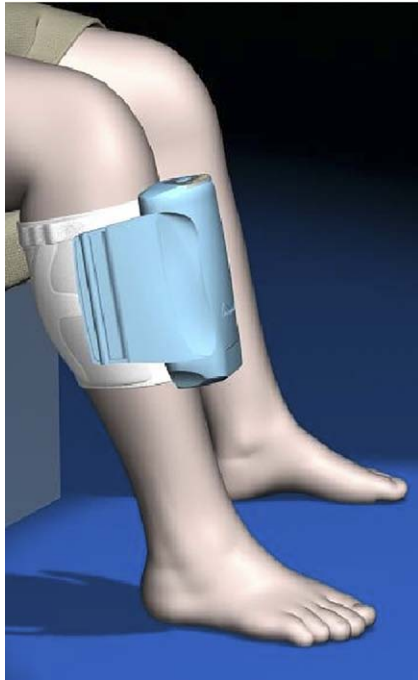
Fig 1. FM220 positioned on the calf. The cloth sleeves around the calf generate intermittent electrical mechanical compression.

ing, the use of IPC devices for claudication has not been pursued extensively because of certain limitations. These include the relatively high cost of IPC devices, patient discomfort that may be experienced with the relatively high compression pressures needed to increase arterial flow, and the need for total patient immobility during treatment sessions. As a result, even when prescribed, patient compliance can be low, sub-optimal levels of compression are frequently used to avoid pain, and patients frequently discontinue treatment. The cumbersome design and also the cost of the device are therefore prohibitive factors in making IPC a chronic home care option.

Recently a new, non-pneumatic electrical portable device for intermittent mechanical compression (IMC) has been developed (the FM220, FlowMedic, Caesarea, Israel), that is placed around the calf and generates intermittent electrical mechanical pressure on the calf muscle (Fig 1). We hypothesized that use of IMC with the FM220 could be a new treatment option for intermitent claudication. Therefore, the objective of the present prospective study was to evaluate the safety and effectiveness of IMC used daily for three months to enhance exercise tolerance and haemodynamic parameters in the lower limb in patients with intermittent claudication due to PAD. Patients were randomized to IMC in addition to best medical therapy (BMT) versus continued BMT alone. The possibility of comparing IPC treatment in a separate study group was considered but rejected due to the aforementioned limitations of IPC that would have significantly complicated the study and due to the fact that IPC is not considered a standard treatment.

METHODS

This was a prospective, randomized, controlled single blind study that enrolled 30 patients with stable claudication due to PAD. This sample size was selected justified by previous studies of IPC that enrolled patients with similar characteristics and were able to demonstrate improvements in total walk distance (ie, the absolute claudication distance [ACD]), distance to the onset of claudication (ie, the initial claudication distance [ICD]), and in the ankle-to-brachial index (ABI).[10-13] To be eligible for inclusion, patients had to be between the ages of 50 and 75 years, had to have stable claudication in only one leg as a result of a femoropopliteal affection with an absolute claudication distance >40 meters but <300 meters on a standardized treadmill stress test (3.8 km/h, 10% grade), have a resting ABI in the affected limb <0.8 with a drop of at least 0.15 following exercise, in whom surgical intervention was not expected for at least three months. Patients were excluded if they had diabetes, were smokers, or had undergone prior surgical or endovascular procedures. The presence of diabetes complicates the evaluation of claudication distances because peripheral neuropathy can mask claudication pain and can also lead to neuropathic pains. Changes in smoking habits can also significantly impact on walk distance even in the short term.[14] However, changes in smoking habits are notoriously difficult to control in clinical trials.[15] Thus, our aim was to control, as much as possible, factors which could potentially confound our ability to assess the direct impact of IMC on symptoms and arterial pressure in the leg. In addition, it was required that patients had stable claudication, evidenced by demonstrated stability of absolute claudication distance on two stress tests performed one week apart; patients with over 20 meters difference in ACD between the two tests were excluded. This study was approved by the local ethics committee and all patients provided informed consent prior to initiation of study related tests and treatments.

Randomization and treatments. Patients who satisfied the inclusion and exclusion criteria were randomized in a 1:1 ratio between a control group (n = 16) who continued to receive best medical treatment only or to an IMC treatment group (n = 14), which received medical treatment plus active treatment with the FM220 device. Patients were stratified between the groups to ensure comparability with respect to age and gender.

Patients in both study groups received best medical treatment for at least one month prior to study enrollment which, based on TASC II Guidelines[16] and as is routine in our clinic, included instructions to exercise for one hour per day and antiplatelent therapy (aspirin or clopidogrel), treatment with statins, antihypertension treatment (with an ACE-inhibitor), and a hemorreological agent (pentoxifylline). In addition, medications were kept constant during the entire six-month study period in all the patients.

Patients randomized to the treatment group were trained in the use of the FM220 IMC device and were

instructed to use the device for at least two hours per day on the calf of the affected limb for three months.

In order to operate the device, the patient applies a cloth sleeve that holds the FM220 device in place around the calf. The device includes an electric motor that pulls on the straps of the sleeve and exerts a fixed compression pressure of approximately 65 mm Hg for three seconds, three times per minute during the treatment. These treatment parameters were selected according to prior studies in which the impact of IMC on popliteal arteral flow was optimized.[7]

The device also includes integrated software that records the duration of use for each day and allows monitoring of the degree of compliance with the prescribed two hour/day, seven days/week, three-month treatment prescription. In order to assess compliance in an unbiased way, the patients were not informed of the existence of this software during the study.

Clinical evaluations and measurements. Following enrollment, a detailed medical history was obtained and a physical examination was performed. Also, the ankle-brachial index was determined at rest (ABI-r) and post-exercise (ABI-pe) following the standardized treadmill exercise test (performed at 3.8 km/h with a gradient of 10%). The ABI was calculated by dividing the larger of systolic pressures measured in the dorsalis pedia artery and the posterior tibial artery of the affected limb by the larger of the systolic pressures measures in the brachial arteries of the two arms.[17] ABI-pe was determined, as described in earlier literature, as the ABI measured one minute following completion of exercise.[18]

As indicated above, all patients were subjected to two baseline stress tests on which ICD and ACD were measured. The ICD was defined as the distance walked before the onset of pain in the calf of the affected limb. The ACD was defined as the distance at which ischemic pain forced the patient to stop exercising. The results of the second test were used as baseline values to which treatment period tests were compared.

Repeat measurements of ABI-r, ABI-pe, ICD and ACD were obtained at study months one and three (ie, during the period of treatment) and six months (ie, 3 months after ending treatment) to evaluate both the long term effects of IMC treatment and the durability of the effect following cessation of treatment. In all cases, measurements of ABI-r, ABI-pe, ICD, and ACD were carried out by an investigator who was blinded to study group assignment. Both control and treatment group followed a same protocol of visits and were informed at the same terms about the study in order to minimize the potential differences in patient motivation.

Statistical analysis. Absolute and percent changes in ABI-r, ABI-pe, ICD, and ACD were calculated for each followup examination relative to their respective baseline values. Results obtained in each group were expressed as average (± standard deviation) or median (95% confidence intervals [CI]) values. Within group comparisons were made using a Wilcoxon test for matched variables. Between

Table I. Baseline demographic and data

	Treatment group (n = 14)	Control group (n = 16)	P
Age (years)	58.9	59.1	N.S.
Male/Female (n)	12/2	14/2	N.S.
Symptom furation (months)	35 ± 18	31 ± 15	>.10
Hypertension (%)	50	50	N.S.
Hyperlipidemia (%)	64	62.5	N.S.
Baseline ABI-r (m)	0.63 ± 0.09	0.59 ± 0.02	N.S.
Baseline ABI-pe (m)	0.22 ± 0.10	0.24 ± 0.06	N.S.
Baseline ICD (m)	150 [100;300]	145 [90, 210]	N.S.
Baseline ACD (m)	171 [102;300]	166 [150, 200]	N.S.

ABI, Ankle-brachial index; *ABI-r,* Ankle-brachial index at rest; *ABI-pe,* Ankle-brachial index post-exercise; *ACD,* absolute claudication distance; *ICD,* Initial claudication distance.
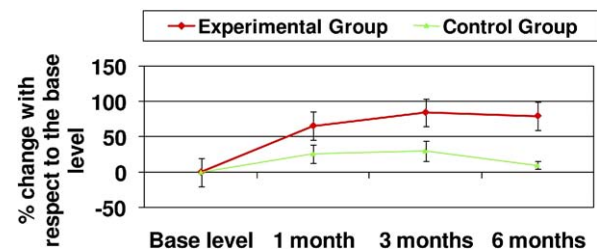Values are means ± SD or median [1st quartile, 3rd quartile].

Fig 2. Initial claudication distance. *P* values for between group comparisons: one month (*P* = .001); three months (*P* = .002); six months (*P* = .002).

group comparisons were made using an OR-Mann Whitney test for independent variables. Bonferroni corrections were used in cases of multiple comparisons. All tests were two-sided and a probability value (*P*-value) of 0.05 or less was considered as statistically significant.

RESULTS

Baseline characteristics of the study participants, summarized in Table I, show that the groups were well matched for age, gender, and severity and duration of symptoms. Furthermore, patients reported that they had not experienced significant changes in their symptoms of claudication over the last 12 months prior to the study.

At the end of the first month of follow-up, ICD increased by 66% (*P* = .001, from a median of 150 [100; 300] meters to 250 [237.5; 310] meters; 95% CI [11; 139]) and ACD increased by 52% (*P* = .005, from a median of 171 [102-300] meters to 260 [235-320] meters; 95% CI [20; 131]) in the ICM treatment group (Figs 2 and 3). Concomitantly, ABI-pe increased by 42% (*P* = .01, from the baseline value of 0.22 to 0.31; 95% CI [0.09; 0.12]). However, there was no significant change in ABI-r (3.17% change, *P* = .18; Figs 4 and 5). In sharp contrast, there were not significant changes in ICD, ACD, ABI-pe or ABI-r in the control group (*P* > .1 for all parameters) during this same period.
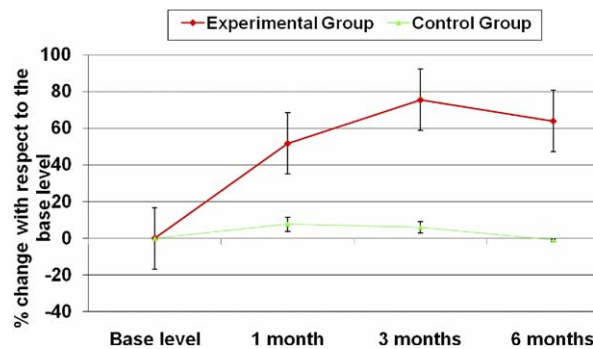
Fig 3. Absolute claudication distance. *P* values for between group comparisons: one month (*P* = .005); three months (*P* = .002); six months (*P* = .002).
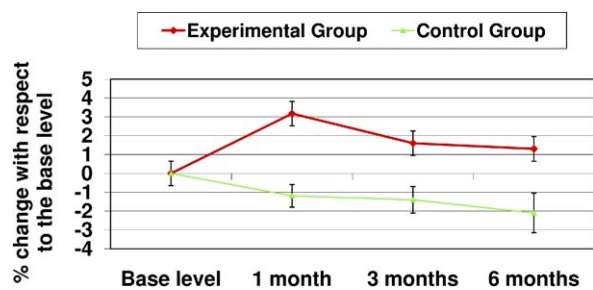

Fig 4. Ankle-to-brachial index at rest. No significant differences.
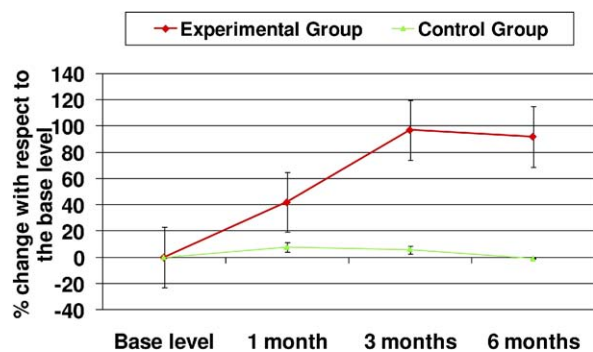

Fig 5. Post-exercise ankle-to-brachial index. *P* values for between group comparisons: one month (*P* = .01); three months (*P* = .002); six months (*P* = .003).

By the end of the three-month treatment period, the initially observed improvements in the ICD and ACD trended further higher in the ICM treatment group, attaining values of 85% (*P* = .002; 95% CI [81; 237]) and 75.5% (*P* = .002; 95% CI [91.7; 218]) compared with their respective values (Figs 2 and 3). ABI-pe continued to increase substantially, attaining a value that was 97% (*P* = .003; 95% CI [0.09; 0.33]) above its baseline value (Figs 2-5). There were no changes in ABI-r throughout the study period. Similarly, there were no significant changes in any of the study parameters in the control group through the end of the first three-month study period.

In the post-treatment evaluation at six months (three months after cessation of IMC treatment), the claudication distances and the ABI-pe in the IMC treatment group remained significantly better than in the control group and did not differ significantly from their respective values measured at three months. In the control group, these values again did not show significant changes from baseline.

Patient compliance with IMC treatment was indexed by the number of hours the device was used (as recorded by the device's internal software) expressed as a percent of the expected number of hours had the patients used the device two hours each day as originally instructed. Compliance was 82% at the end of the first study month, and 78% at the end of the third month of treatment. All patients in both groups completed the study and all follow ups were performed as scheduled.

DISCUSSION

Devices that apply positive pressure to the lower extremeties have been investigated for nearly a century as prophylaxis for deep vein thrombosis,[19] for treatment for lymphedema,[20] and for the treatment of peripheral arterial disease.[21] Gaskell and Parrot,[9] as early as 1977, demonstrated that mechanical compression improves blood flow to the lower limbs of seated arteriopathic patients using radioactive Xe^{133} to measure tissue perfusion. More recently, Morgan et al[22] used non-invasive duplex color flow imaging and demonstrated increases in popliteal artery volume flow induced by short-cycle mechanical compressions applied to the leg. Several subsequent studies have corroborated these early findings.[8,11,23-26] These prior results have been obtained with pneumatic compression devices that apply compressive forces over much of the lower extremity and, in some cases, the foot.

In view of the clinical promise but practical limitations inherent to pneumatic compression devices (the relatively high cost of IPC devices, patient discomfort, and the need for total patient immobility during treatment sessions), we have investigated a new compact and portable device that applies compressive forces generated by a miniature electric motor to the calf muscle. This device is just designed for ambulatory use, in a sitting position.

The major findings of the present study are that when used in patients with claudication for two hours per day for up to three months, intermitent mechanical compression (IMC) provided by this device results in statistically and clinically significant improvements in initial and absolute claudication distances with increased post-exercise ABI. The latter finding provides important objective evidence indicating that IMC treatment improves ability to perfuse the leg during exercise. The finding that post-exercise ABI increases progressively over time and persistence of the effect at least three months following cessation of treatment further supports a fundamental beneficial effect on vascular vasodilatory capacity. The fact that resting ABI did not change in response to IMC also implies that the mechanism of action of this form of therapy is related to improvement in vasodilatory capacity and not to an effect on the under-

lying vascular structure or anatomy. It is also noteworthy that there were no adverse effects observed associated to the use of the IMC device.

The observed insignificant changes in claudication distances and resting and post-exercise claudication distances observed in the control group, which received best medical treatment and unsupervised physical exercise are congruent with prior published data.[27] Specifically, it has been shown that unsupervised exercise and pharmacotherapy in patients with claudication does not provide significant symptomatic benefits in a majority of patients. In any case, this control group represents the patients we find in clinical pratice in the best case scenario.

Another promising aspect of the present results relates to the high rates of tolerability and patient compliance with IMC treatment using the FM220 device. All pateints completed the study and, based on automated device tracking tools, there was ~80% compliance with a two hour/day prescription. In contrast, rates of compliance are significantly less with pneumatic devices. For example, Kakkos et al[26] and Ramaswami[11] each reported a treatment regimen completion rate of only 35% with pneumatic calf and foot mechanical compression devices. This large difference in compliance is expected to complicate potential studies aiming at comparing IPC and IMC and will require a larger study population to account for this aspect. Moreover, we found that the improvement in these patients in our study who were not as compliant was lesser (43% in ACD at one month), although without statistical signification. Regarding the cost, IMC device is ~$900 and patients must spend ~$10 per month in disposable sleeves for one leg affected while IPC systems reach ~$1500 and the investment in disposable sleeves is ~$400.

Also, supervised exercise programs have been shown to be effective in terms of significantly improving exercise capacity.[28] However, these programs are not available in the majority of medical centers and the high cost and low rates of compliance makes them prohibitive for many health systems and difficult to launch.

As discussed above, the improved post-exercise ABIs observed following three months of IMC implies improved vasodilatory mechanisms in the treated leg. Such improvements could result from several different mechanisms. First, there is mounting evidence that IMC improves perfusion and tissue oxygenation during periods of active treatment.[22-24] This is believed to be due to differential pressure drops in the arteries and veins during the rapid release of the compression that increases arterio-venous pressure gradients, thus increasing blood flow. Such periodic increases in blood flow during periods of IMC treatment could help restore endothelial function which, in turn, could improve the ability of the endothelium to release vasodilatory factors (eg, nitric oxide and prostacyclin) in response to increased shear stresses during exercise. Other potential mechanism may relate to a modulation of the local veno-arterial reflex (a local, sympathetic nervous system-mediated reflex that modulates precapillary sphincter tone[15]) and the possibility that increased flow may stimulate the formation of collat-

erals which, in the long term, can improve perfusion of the leg. However, these explanations are speculative, and the present study was not designed to study the mechanisms of action.

By design, the present study excluded patients with diabetes mellitus and who were smokers. It will therefore be interesting to confirm the present results in smokers and in patients with diabetes, provided the relevant factors can be contolled during the study period.[15]

CONCLUSION

The results of the present study show that two hours of daily IMC on the calf provided by the FM220 device used by patients with peripheral artery disease at home for three months significantly increases claudication distance and is associated with objective improvement in limb perfusion. Clinical benefits are observed within a month of treatment and objective evidence (in the form of improved post-exercise ABIs) improve over time and persist for at leat three months following cessation of treatment. IMC with this device was well tolerated and there is a high degree of compliance.

AUTHOR CONTRIBUTIONS

Conception and design: JdH
Analysis and interpretation: JdH
Data collection: JdH, AF, SB, JF
Writing the article: JdH
Critical revision of the article: JdH, FA
Final approval of the article: JdH, FA, AF, SB, JF
Statistical analysis: JdH
Obtained funding: JdH, FA
Overall responsibility: JdH, FA

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