Effects of intermittent pneumatic compression treatment on clinical outcomes and biochemical markers in patients at low mobility with lower limb edema

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ABSTRACT

Objective: We aimed to evaluate the effects of intermittent pneumatic compression (IPC) in patients at low mobility with leg edema.

Methods: A pilot, two-arm, randomized controlled clinical trial was performed. Fifty patients (age, 58.4 ± 9 years; male, 14), randomly allocated to a group (IPC) undergoing 1 month (n = 29) of an in-home cycle of IPC and to a control (C) group (n = 21), were studied. Leg edema was evaluated by measuring subcutaneous thickness (high-resolution ultrasound) and circumferences (metric tape), both assessed at different levels of the lower limbs, and volume (water plethysmography). Ankle range of motion (ROM, goniometer), quality of life (QoL) by the 36-Item Short Form Health Survey, and a pool of plasma inflammatory markers were also evaluated.

Results: Edema significantly decreased in the IPC group (for all outcome measures, $P < .0001$), whereas it significantly increased in the C group ($P < .0001$). Ankle ROM was significantly enhanced in the IPC group (dorsiflexion, $P < .0001$; plantar flexion, $P = .002$) and remained stable in the C group. QoL showed an improvement in the IPC group, particularly significant for the general health subscale ($P = .004$), whereas no changes were highlighted in the C group. The two groups exhibited different trends and variations for some plasma inflammatory markers, mainly for granulocyte colony-stimulating factor.

Conclusions: In a sample of patients at reduced mobility with leg edema, IPC treatment was effective in reducing the edema, improving the ankle ROM, and determining a positive impact on QoL together with a slight modulation of some plasma inflammatory markers. (J Vasc Surg: Venous and Lym Dis 2018;6:500-10.)

Keywords: Compression devices; Intermittent pneumatic; Edema; Lymphatic disease; Mobility limitation; Venous insufficiency

Many chronic diseases, particularly neurologic ones, lead to progressive motor dysfunction along with long-term consequences due to the loss of mobility. Hypomobile patients, incapacitated or wheelchair bound for extended periods with their legs hanging down, can develop an impairment of the venous and lymphatic return.[1-5] In addition, in some neurologic disorders, a possible effect induced by the impairment of the autonomic reflexes on vascular functions could also have a role in affecting the venous system's functioning.[6,7] As a result, many patients affected by loss of mobility experience lower limb edema,[1,8] affecting their general condition and raising thrombotic risk.[9-12] Moreover, the persistent venous hypertension generated by the stasis has recently been found to be associated with a pool of circulating inflammatory mediators,[13-17] even potentially implicated in the genesis of deep venous thrombosis (DVT).[18,19] Among the most suitable treatments to counter the peripheral venolymphatic stasis, intermittent pneumatic compression (IPC) seems to be a rational approach in immobile patients.[20] IPC is a noninvasive technique based on the application of inflatable sleeves exercising sequential and intermittent pressures reproducing the same physiologic mechanism of the calf muscle pump during walking. In addition to assisting in the reduction of swelling in the leg, IPC can also enhance the venolymphatic pump, which limits and restores the damaged microcirculation of the skin.[20-25] Its role in phlebology therapy, indicated by national and international guidelines, was stated in the treatment of venous ulcers and for DVT prophylaxis; in lymphology, it plays a key role in the integrated treatment of lymphedema.[26-28]

The aim of this study was to evaluate the effects of IPC therapy on clinical outcomes and quality of life (QoL) and modulation of plasma markers of endothelial

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inflammation in a group of patients at low mobility affected by edema of the lower limbs compared with a control (C) group.

METHODS

Study design and setting

A pilot, single-blinded, two-arm, parallel group, randomized controlled clinical trial was performed. The study was conducted in the Unit of Translational Medicine of the University Hospital of Ferrara, Italy. The study was approved by the ethical committee of Ferrara, Italy (study No. 140486).

Participants

Sixty consecutive patients at low mobility as affected by lower limb edema referred to the vascular diseases outpatient clinic of the Unit of Translational Surgery of the University Hospital of Ferrara, Italy, were enrolled in the study from September 2014 to November 2015. All participants signed a written informed consent form.

Inclusion criteria. Patients aged between 18 and 65 years with reduced mobility as a result of a chronic disease affected by clinically relevant chronic lower limb edema (>6 months) were included in the study.

Exclusion criteria. Patients with DVT in the acute phase (<3 months), malabsorption syndrome, liver cirrhosis, nephrotic syndrome, heart failure (New York Heart Association class III-IV), connective tissue diseases, rheumatic diseases, primary aldosteronism, cancer, corticosteroids, immunomodulator and immunosuppressant therapy, pregnancy, dermatitis, and severe peripheral arterial disease (Leriche-Fontaine stage III-IV) were excluded from the study. Patients with leg ulcers were also excluded in order not to affect the plasma markers of the endothelial inflammation profile.

Randomization

A block randomization with an allocation ratio of 1:1, experimental group and C group, was performed by an investigator with no involvement in the trial using a computer software system. Investigators involved in the enrollment were concealed from the allocation list until the moment of assignment.

Interventions

Patients randomized to the experimental group (IPC group) underwent an in-home cycle of IPC (I-PRESS 4 LEG2; IACER Srl, Venice, Italy) following an established pattern in clinical practice for the prophylaxis of DVT in bedridden patients and for the reduction of lymphatic lakes in patients with lymphedema. This scheme consists of applying the device twice a day, each session lasting 50 minutes, with a setting of 50 mm Hg pressure, for 30 consecutive days. The pressure of 50 mm Hg was chosen according to the international guidelines related to the treatment of leg edema.[29] Such a pressure seemed able to significantly reduce leg edema without creating discomfort[30] and damaging lymphatics.[31] At baseline, each patient of the IPC group was trained to use the device. Patients were also periodically contacted by telephone to ensure the correct execution of the therapy. No intervention was provided for patients allocated to the C group. For both groups, patients were asked to not modify their medical or compression therapy and not to start physical therapy during the study period.

ARTICLE HIGHLIGHTS

- **Type of Research:** Pilot randomized controlled clinical trial
- **Take Home Message:** This pilot controlled study of 50 patients at low mobility with leg edema randomized patients to 1-month in-home intermittent pneumatic compression (IPC) treatment and to a control group. IPC treatment reduced edema, improved quality of life, and slightly modulated some plasma inflammatory markers.
- **Recommendation:** The study suggests that IPC treatment of low-mobility patients induces meaningful improvements in reducing edema, with a positive impact on quality of life and a slight modulation of some plasma inflammatory markers.

Outcome measures

All outcome measures were evaluated at baseline (the day before start of IPC treatment for the experimental group) and after 30 days by the same investigators blinded to the patients' allocation, always in the morning at the same time of the day for each patient.

Clinical outcome measures

Subcutaneous thickness of the lower limbs. The venous-lymphatic edema of the lower limbs was indirectly noninvasively measured by high-resolution ultrasound (MyLab 70 XV; Esaote Genoa, Italy) of the soft tissue with a 12 MHz linear transducer placed longitudinally on the leg. Subcutaneous thickness was measured as the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the muscular fascia. The measurements were taken at eight fixed anatomic points where lymphatic lakes develop with landmarks that allow consistent measurement of the same region of the lower limbs, as follows: saphenofemoral junction; 5 cm below the saphenofemoral junction; middle of the thigh; lower third of the thigh; upper third of the calf; middle of the calf; perimalleolar area; dorsum of the foot.

Circumferences of the lower limbs. Circumferences were measured with a metric tape at standardized points of the lower limb according to international guidelines.[1,3,8] The points were the following: B, minimum circumference of the ankle; B1, circumference at

which the Achilles tendon meets the lower apex of the gastrocnemius muscles (about 10-15 cm proximal to the medial malleolus); C, maximum calf circumference; D, just below the tibial tuberosity; F, at the middle of the thigh, between the median point of the inguinal fold and the tibial tuberosity; G, maximum thigh circumference, about 5 cm below the inguinal fold.

Volume of the distal portion of the lower limbs. The noninvasive evaluation of the volume of the distal portion of the lower limbs was performed using a water plethysmograph. The water plethysmograph is a steel boot-shaped tool able to contain the totality of the foot, ankle, and two-thirds of the calf. The front of the plethysmograph is provided with a draining spout and an adjoining vessel. The instrument is filled up to a level of 13 L. The volume in milliliters of water that leak in the attached vessel after the introduction of the foot and leg in the metal container is considered the indicative parameter of the measurement of limb volume. The procedure was repeated three times for each single limb. The average of the three measurements for each single limb was recorded.

Ankle mobility. The ankle range of motion (ROM) was assessed with a goniometer. Maximal, voluntary (or passive in case of palsy) dorsiflexion and plantar flexion, in the supine, non-weight-bearing position, were measured in both ankles from a neutral 90-degree position.

QoL. The QoL was evaluated by means of the 36-Item Short Form Health Survey (SF-36).[32-34] The SF-36 is a 36-item questionnaire measuring the QoL across eight scaled scores (physical functioning; physical role; bodily pain; general health; vitality; social function; emotional role; mental health) that are both physically and emotionally based. Each scale is directly transformed into a scale of 0 to 100. Higher scores indicate a better-perceived health status.

Plasma inflammatory markers

The measurement of the concentration of a pool of cytokines, chemokines, and growth factors was

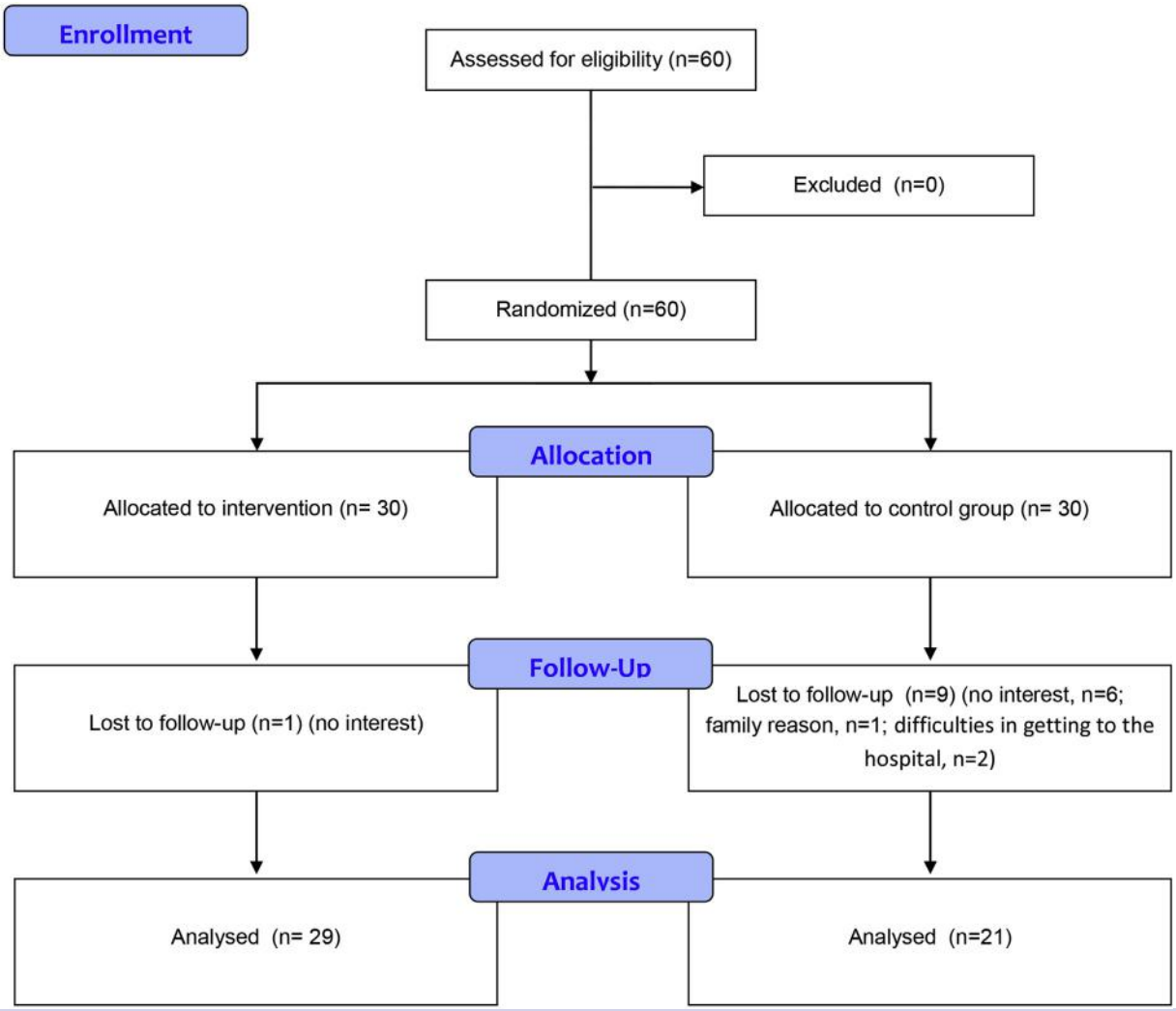

Fig 1. Flow diagram of the study participants.

Table I. Demographics and baseline characteristics of the study participants

	IPC group (n = 29)	C group (n = 21)
Age, years	57.4 ± 9	59.6 ± 8
Sex, male	7 (24)	7 (33)
Body mass index, kg/m^2	27.8 ± 3.4	29.2 ± 3.6
Comorbidities		
Multiple sclerosis	10 (34)	6 (29)
Obesity (BMI >30)	12 (41)	9 (43)
Osteoarthritis	7 (24)	6 (29)
Chronic venous disease	9 (31)	7 (33)
Hypertension	17 (59)	11 (52)
Diabetes	4 (14)	4 (19)

BMI, Body mass index; *C*, control; *IPC*, intermittent pneumatic compression.
Data are expressed as mean ± standard deviation for continuous variables and number (%) for categorical variables.

performed on a plasma sample obtained using a 2.7-mL blood sample taken at the patient's arm. Plasma samples were frozen and thawed only once before performing the MILLIPLEX MAP Human Cytokine/Chemokine Panel (Merck Millipore, Billerica, Mass), a bead-based multiplex immunoassay that allows the simultaneous quantification of the following 29 human cytokines: interleukin (IL) 1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 protein 40, IL-12 protein 70, IL-13, IL-15, IL-17A, epidermal growth factor, eotaxin, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, interferon (IFN) α2, IFN-γ, IFN-γ-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory proteins 1α and 1β, tumor necrosis factor (TNF) α, TNF-β, and vascular endothelial growth factor (VEGF). Samples were processed in duplicate following the manufacturer's recommended protocols and read on a MAGPIX instrument equipped with the MILLIPLEX Analyst Software using a five-parameter nonlinear regression formula to compute sample concentrations from the standard curves.

Statistical analysis

Data are presented as mean ± standard deviation or median (interquartile range). Only data of patients who performed the follow-up evaluation were analyzed. Clinical data relating to the two legs of each patient were averaged to obtain a single numerical value to simplify the analysis and the amount of data to present. The normal distribution of the data was verified by the Kolmogorov-Smirnov test. The baseline characteristics of the two study groups were compared using the Fisher exact test or an unpaired Student *t*-test, as appropriate. To assess the intragroup differences at baseline and at the end of the study, the paired Student *t*-test or Wilcoxon test and paired Student *t*-test with logarithmic transformation were performed as appropriate. One-factor analysis of variance test (post hoc analysis by Scheffé test for all pairwise comparisons) or Kruskal-Wallis test was used to compare the changes in outcome measures between the two study groups (intergroup analysis). To check the consistency of the assessments, a Pearson correlation between circumference values, corresponding subcutaneous thickness, and volume measurements recorded in the two groups both at baseline and at the end of the study was performed. Finally, in the IPC group, a Spearman rank correlation between clinical outcomes and the inflammatory markers that significantly changed was also performed, considering measurements recorded both at baseline and at the end of the study and also their variations from baseline. The significance level was set at $P \leq .05$. Statistical analyses were performed using MedCalc 16.2.0 (MedCalc Software, Ostend, Belgium).

RESULTS

Participants. A total of 60 patients were screened for eligibility. Fig 1 illustrates the recruitment process. Fifty patients (mean age, 58.4 ± 9 years; male, 14) performed

Table II. Correlations between clinical outcome measures

	IPC group (n = 29)				C group (n = 21)			
	Baseline		End		Baseline		End	
	Pearson *r*	*P* value	Pearson *r*	*P* value	Pearson *r*	*P* value	Pearson *r*	*P* value
5 cm below saphenofemoral junction/G	0.78	<.0001	0.50	.006	0.71	.0003	0.67	.001
Middle thigh/F	0.71	<.0001	0.77	.0001	0.65	.002	0.72	.0003
Upper third of calf/D	0.65	.0001	0.76	<.0001	0.64	.002	0.67	.001
Middle calf/C	0.71	<.0001	0.74	<.0001	0.81	<.0001	0.80	<.0001
Perimalleolar area/B	0.80	.0001	0.73	<.0001	0.76	<.0001	0.82	<.0001
Volume/B	0.93	<.0001	0.92	<.0001	0.95	<.0001	0.93	<.0001

C, Control; *IPC*, intermittent pneumatic compression.
Circumference points: *G*, maximum thigh circumference, about 5 cm below the inguinal fold; *F*, at the middle of the thigh, between the median point of the inguinal fold and the tibial tuberosity; *D*, just below the tibial tuberosity; *C*, maximum calf circumference; *B*, minimum circumference of the ankle.
Volumetry data refer to 10 patients for the IPC group and 8 patients for the C group.

Table III. Results of clinical outcomes and comparison between the study groups

	IPC group (n = 29)			C group (n = 21)			
	Baseline	End	*P* value (intragroup)	Baseline	End	*P* value (intragroup)	*P* value (intergroup)
Subcutaneous thickness, mm							
Saphenofemoral junction	21.1 ± 5.7	18.4 ± 4.8[a]	<.0001	21.9 ± 5.5	24.4 ± 5.4[a]	<.0001	.002
5 cm below saphenofemoral junction	15.5 ± 5.7	12.8 ± 5.0[a]	<.0001	17.5 ± 6.7	20.1 ± 6.5[a]	<.0001	<.001
Middle thigh	17.9 ± 7.4	14.8 ± 5.9[a]	<.0001	19.5 ± 8.3	22.9 ± 9.2[a]	<.0001	.004
Lower third of thigh	17.5 ± 8.2	13.8 ± 5.8[a]	<.0001	19.8 ± 8.4	22.6 ± 8.9[a]	<.0001	.001
Upper third of calf	16.9 ± 7.7	13.0 ± 5.5[a]	<.0001	18.6 ± 8	21.9 ± 9[a]	<.0001	.001
Middle calf	16.1 ± 6.2	12.3 ± 4.8[a,c]	<.0001	17.9 ± 6.8[c]	20.7 ± 7.2[a]	<.0001	<.001
Perimalleolar area	17.5 ± 5.4[a,c]	12.8 ± 4.3[a,b,d]	<.0001	19.9 ± 5.5[b]	24.8 ± 6.4[c,d]	<.0001	<.001
Dorsum of the foot	12.7 ± 5.9[a]	8.6 ± 3.5[b,c]	<.0001	14.8 ± 8.3[c]	18.6 ± 9.4[a,b]	<.0001	<.001
Circumferences, cm							
G	62.9 ± 8.9	61.9 ± 8.8	<.0001	65.4 ± 8.1	66.4 ± 8.4	<.0001	.23
F	53.4 ± 7.8	52.2 ± 7.7	<.0001	55.3 ± 9.0	56.4 ± 9.3	<.0001	.30
D	38.8 ± 5.0	37.8 ± 4.9	<.0001	40.5 ± 4.9	41.5 ± 5.3	<.0001	.05
C	40.0 ± 5.6	38.5 ± 5.3	<.0001	41.8 ± 5.4	42.8 ± 5.6	<.0001	.04
B1	30.5 ± 4.7	28.6 ± 4.3[a]	<.0001	31.6 ± 4.5	32.7 ± 4.6[a]	<.0001	.01
B	27.1 ± 3.8	25.2 ± 3.3[a]	<.0001	27.6 ± 3.7	28.8 ± 4.0[a]	<.0001	.008
Volumetry, mL	2660.5 ± 566.4	2478.9 ± 541.2	<.0001	2675 ± 561.8	2792.3 ± 583.2	<.0001	.91
Ankle range of mobility, degrees							
Dorsiflexion	10.3 ± 6.9	12.8 ± 7.5	<.0001	10 ± 6.9	10 ± 6.9	.16	.42
Plantar flexion	12.6 ± 5.7	14.4 ± 6.2	.002	11.8 ± 5.1	11.4 ± 5	.82	.24

C, Control; *IPC*, intermittent pneumatic compression.
Data are expressed as mean ± standard deviation.
Circumference points: *G*, maximum thigh circumference, about 5 cm below the inguinal fold; *F*, at the middle of the thigh, between the median point of the inguinal fold and the tibial tuberosity; *D*, just below the tibial tuberosity; *C*, maximum calf circumference; *B1*, circumference at which the Achilles tendon meets the lower apex of the gastrocnemius muscles (about 10-15 cm proximal to the medial malleolus); *B*, minimum circumference of the ankle.
Symbols [(a,b,c,d)] refer to one-way analysis of variance intergroup post hoc analysis $P < .05$ (Scheffé test for all pairwise comparisons).
Volumetry data refer to 10 patients for the IPC group and eight patients for the C group.

the follow-up evaluation and were analyzed. All patients had bilateral edema and received bilateral IPC treatment. All patients were assessed for chronic venous insufficiency at the screening visit by means of color Doppler ultrasound investigation (MyLab 70) in the standing position with complete scanning of the great saphenous vein and small saphenous vein systems, including junctions and tributaries. In addition, the iliac-femoral and femoral-popliteal venous segments were bilaterally assessed. Reflux was elicited by a squeezing maneuver. Nine patients in the IPC group and seven in the C group were affected by edema with chronic venous disease. Twenty patients in the IPC group and 14 in the C group were affected only by lymphedema. All patients were at low mobility because of neurologic diseases (multiple sclerosis), severe obesity, and severe osteoarthritis. No significant differences in demographics were found between the groups. No adverse events were reported. Baseline characteristics of study participants are shown in Table I.

Clinical outcomes. Ten patients of 29 in the IPC group and 8 of 21 in the C group were not submitted to water plethysmography measurement because of a loss of mobility of the ankle joint or the volume of the limb prevented placement of the feet into the metal container. Circumference values, corresponding subcutaneous thickness, and volume measurements highly correlated in the two groups both at baseline and at the end of the study (Table II). Subcutaneous thickness, circumferences of the lower limbs, volumes of the distal portion, and ankle mobility were comparable at baseline for both groups, whereas a significant difference at the end of the study was detected with respect to the baseline in the IPC group compared with the C group. All the clinical outcomes showed the same trend at the end of the study, namely, a significant improvement for the IPC group (subcutaneous thickness, circumferences, and volume, $P < .0001$; ROM dorsiflexion, $P < .0001$; plantar flexion, $P = .002$) and a significant worsening in the C group (subcutaneous thickness, circumferences, and

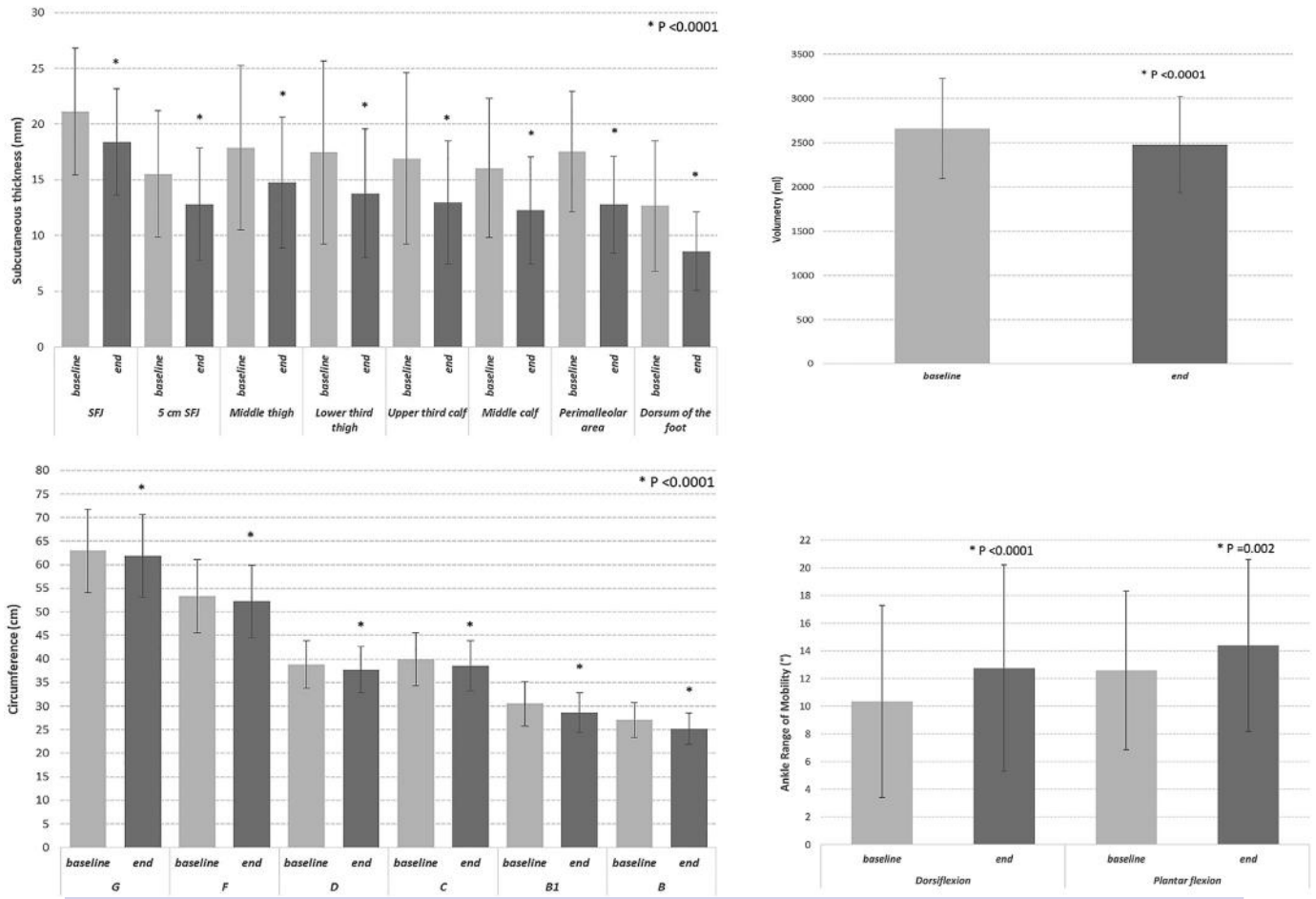

Fig 2. Clinical outcome measures at baseline and end of study in the intermittent pneumatic compression (IPC) group. *SFJ,* Saphenofemoral junction. Circumference points: *C*, maximum thigh circumference, about 5 cm below the inguinal fold; *F*, at the middle of the thigh, between the median point of the inguinal fold and the tibial tuberosity; *D*, just below the tibial tuberosity; *C*, maximum calf circumference; *B1*, circumference at which the Achilles tendon meets the lower apex of the gastrocnemius muscles (about 10-15 cm proximal to the medial malleolus); *B*, minimum circumference of the ankle. *Statistically significant values from baseline.

volume, $P < .0001$) or stability (ROM, $P =$ NS). The two responses were evenly distributed in the two groups. Differences in the intergroup analyses were also highlighted. Data are shown in Tables III and in Figs 2 and 3.

QoL. The two groups were not different at baseline. Most of the SF-36 scale scores increased in the IPC group, significantly for physical functioning ($P = .05$), general health ($P = .004$), vitality ($P = .02$), and mental health ($P = .01$); in the C group, no significant differences were highlighted. Any differences in variations with respect to the baseline data were shown in the between-groups analysis. Data are shown in Table IV.

Plasma inflammatory markers. The two groups, comparable at baseline, showed different trends and variations for some markers at the end of the study, although the difference between groups was not statistically significant. In particular, a significant decrease was highlighted in the IPC group for G-CSF, IFN-γ, IFN-α2, VEGF, and IL-1α, which, on the contrary, all increased in the C group, although not significantly. The C group highlighted a significant decrease for eotaxin, IL-8, monocyte chemoattractant protein 1, and TNF-α; these showed instead an increasing trend in the IPC group (Table V). In the IPC group, a significant direct correlation between G-CSF and middle thigh and lower-third thigh subcutaneous thickness values recorded at the end of the study ($\rho = 0.40$ [$P = .04$] and $\rho = 0.37$ [$P = .05$], respectively) was found, in addition to a significant inverse correlation between IFN-γ and B, B1, and perimalleolar area subcutaneous thickness values recorded at baseline ($\rho = -0.41$ [$P = .03$], $\rho = -0.43$[$P = .02$], and $\rho = -0.41$ [$P = .03$], respectively).

DISCUSSION

This pilot study explored the effects of an IPC device on clinical outcomes and biochemical markers in patients at low mobility with lower limb edema. The main findings were that 1-month application of the IPC device was well tolerated and able to significantly reduce the

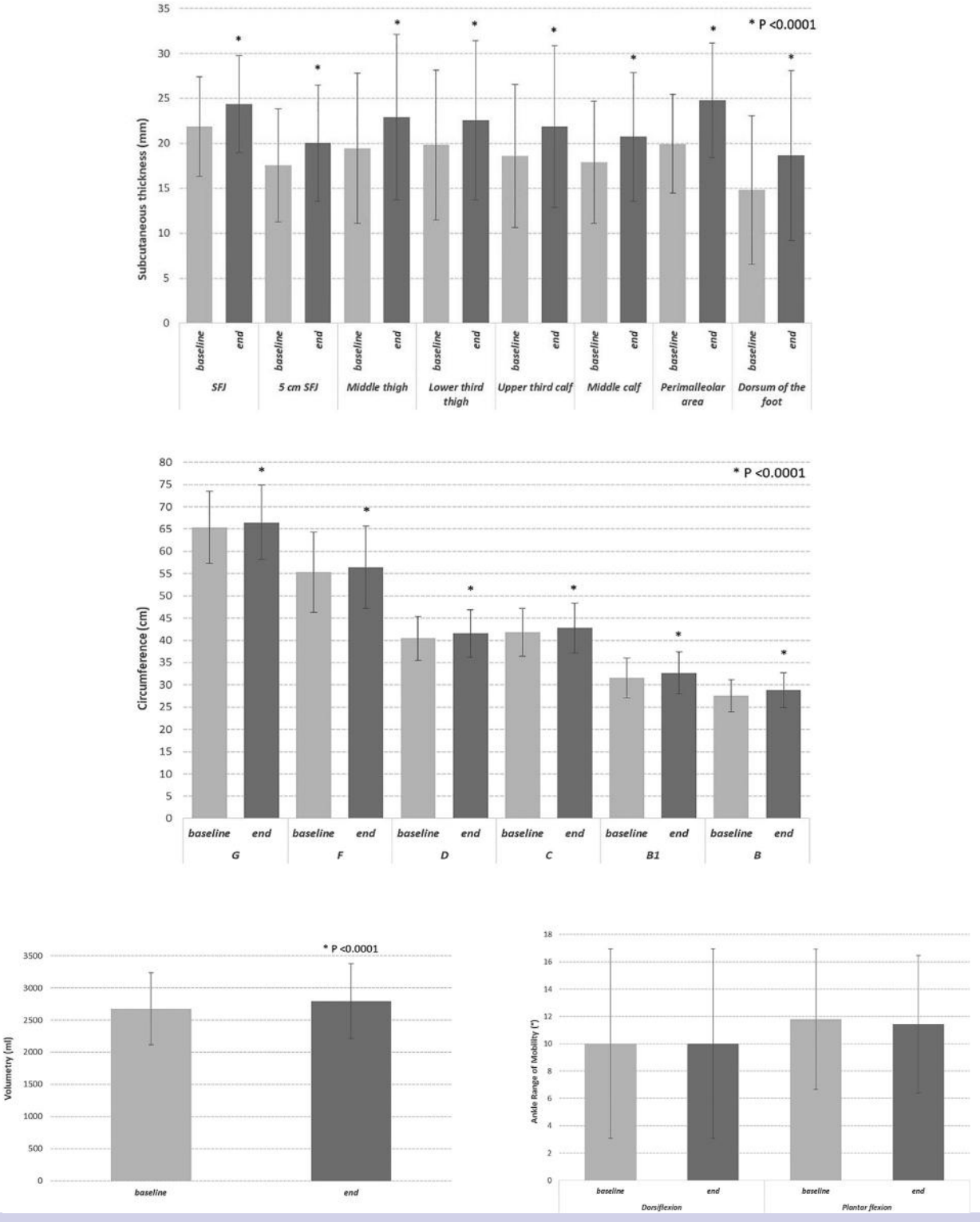

Fig 3. Clinical outcome measures at baseline and end of study in the control (C) group. *SFJ,* Saphenofemoral junction. Circumference points: *G*, maximum thigh circumference, about 5 cm below the inguinal fold; *F*, at the middle of the thigh, between the median point of the inguinal fold and the tibial tuberosity; *D*, just below the tibial tuberosity; *C*, maximum calf circumference; *B1*, circumference at which the Achilles tendon meets the lower apex of the gastrocnemius muscles (about 10-15 cm proximal to the medial malleolus); *B*, minimum circumference of the ankle. *Statistically significant values from baseline.

Table IV. Results of 36-Item Short Form Health Survey (*SF-36*) questionnaire

	IPC group (n = 29)			C group (n = 21)			
SF-36	Baseline	End	*P* value (intragroup)	Baseline	End	*P* value (intragroup)	*P* value (intergroup)
PF	39.7 ± 32.5	45.7 ± 34	.05	38.6 ± 27.7	42.1 ± 30.4	.17	.85
RP	37.9 ± 41	46.6 ± 35.8	.26	31 ± 43.2	40.5 ± 43.6	.13	.61
BP	49.2 ± 26.9	57.3 ± 27.8	.06	52.3 ± 26.5	59 ± 25.6	.09	.54
GH	41.9 ± 21.1	50.2 ± 20.8	.004	40.7 ± 21.3	41.1 ± 21.9	.88	.30
VT	45.3 ± 16.8	51.4 ± 18	.02	42.1 ± 19.9	46.9 ± 13.7	.23	.30
SF	62.7 ± 24.9	62.2 ± 21.9	.89	56.3 ± 21.1	60.6 ± 19.1	.23	.75
RE	57.3 ± 41.7	64.2 ± 39.8	.40	44.3 ± 43.9	58.5 ± 36.4	.15	.55
MH	59 ± 18.8	66.9 ± 15.6	.01	56.4 ± 16.1	60.6 ± 12.2	.14	.12

BP, Bodily pain; *C,* control; *GH,* general health; *IPC,* intermittent pneumatic compression; *MH,* mental health; *PF,* physical functioning; *RE,* role emotional; *RP,* role physical; *SF,* social function; *VT,* vitality.
Data are expressed as mean ± standard deviation.

edema and the associated symptoms with a positive impact on the patients' QoL. In addition, a modulation of some plasma inflammatory markers was also highlighted. To our knowledge, the effects of IPC on plasma inflammatory markers in patients with lower limb edema have never been studied before. Such an investigation might be of interest because chronic lymphatic and venous disorders do not currently have biomarkers useful for practitioners and specialists to assess the effect of the treatment. Another original feature of our study is the selected population that was composed of patients at reduced mobility for different causes, in whom the efficacy of IPC has been poorly tested so far.[20] It is known that the lack of movement can lead to a progressive impairment of the venous and lymphatic return, creating stasis and resulting in edema of the legs, with possible skin changes, ulcerations, and increased risk of DVT. Previous studies of patients affected by neurologic disorders, particularly multiple sclerosis at an advanced stage causing loss of mobility, discovered a high prevalence of edema of the lower limbs attributable to lymphatic stasis[6] and a high frequency of DVT.[9] The edema of lower limbs in immobile patients seems to be a neglected condition in which the conventional therapies also appear not to have a rationale or a proven effectiveness. No drugs seem to be able to oppose the increase of the transmural pressure at the microcirculation level due to the gravitational hydrostatic load. Diuretics are often prescribed, but long-term use is not recommended for possible side effects (diuretic-induced edema, increased risk of cardiac death). The elective and evidence-based treatment of chronic edema is compression therapy (bandaging or hosiery)[1] to reduce swelling by applying a static force around the lower limbs. However, conventional compression therapy can work properly only when the calf muscle pump is activated in standing or during ambulation, both actions difficult for immobile patients. Therapeutic stockings are difficult to be positioned by disabled individuals because they imply the ability to bend and leverage a suitable manual force to widen the compressive device to wear it; the maneuver is difficult even if the immobile patients are assisted, considering also the possible coexistence of reduced ankle range of mobility. Similarly, bandages have to be applied, at the right sub-bandage pressure, by qualified personnel and frequently changed; thus, they are not really feasible for long-term therapy and may be more appropriate in case of concomitant skin ulcerations. In a previous retrospective study, immobile patients with leg edema and trophic skin changes were successfully treated with elastic bandages and stockings but also with associated physical therapy aimed at strengthening the calf muscle and improving the ankle ROM.[5] For all of these reasons, IPC would seem to be a logical approach, for immobile patients or patients with impaired mobility, to prompt the hemodynamic action of normal ambulation.[20] Several studies demonstrated the positive effect of IPC on many hemodynamic parameters[21,23,25] and its efficacy in reducing leg edema and also in healing ulcers. Moreover, the use of IPC resulted in an effective and inexpensive method of reducing the risk of DVT and improving survival in immobile stroke patients in comparison to the use of thigh-length graduated compression stockings.[26] The results of our study can confirm the efficacy of IPC even in our selected population composed of patients at impaired mobility due to neurologic or osteoarticular diseases. All the clinical outcomes we measured mutually support each other as being consistent with demonstrating a decrease in volume of the lower limb; high-resolution ultrasound of the soft tissues clarified it to be related to the reduction of interstitial fluid and not to other contributory factors. In addition, a significant improvement of the ankle ROM before and after IPC treatment was assessed to confirm the role of the edema in the area between the foot and the malleolus as an important contributor to the reduction of ankle joint mobility, in turn limiting the action of the calf muscle pump. We might argue that worsening of

Table V. Results of plasma inflammatory markers

Cytokines, pg/mL	IPC group (n = 29)			C group (n = 21)			
	Baseline	End	*P* value (intragroup)	Baseline	End	*P* value (intragroup)	*P* value (intergroup)
EGF	18.6 (5.1-50.5)	20.2 (4.0-46.8)	.20	30.6 (10.4-54.5)	16.6 (9.4-42.0)	.26	.84
Eotaxin	104.4 (80.2-155.5)	115.5 (78.1-161.8)	.85	125.6 (89.3-178.7)	102 (74.7-148.5)	.002	.64
G-CSF	2.8 (2.8-9.2)	2.8 (2.8-3.4)	.001	2.8 (2.8-8.0)	2.8 (2.8-7.0)	.52	.43
GM-CSF	2.9 (2.9-3.7)	2.9 (2.9-2.9)	.20	2.9 (2.9-3.1)	2.9 (2.9-2.9)	.69	.90
IFN-α2	3.8 (3.8-6.9)	3.8 (3.8-4.7)	.001	3.8 (3.8-4.1)	3.8 (3.8-8.3)	1	.88
IFN-γ	2.0 (2.0-3.7)	2.0 (2.0-2.0)	.003	2.0 (2.0-2.4)	2.0 (2.0-2.0)	.94	.57
IL-10	2.7 (2.7-2.7)	2.7 (2.7-2.7)	.15	2.7 (2.7-2.7)	2.7 (2.7-2.7)	.68	1
IL-12p40	2.8 (2.8-2.8)	2.8 (2.8-2.8)	.62	2.8 (2.8-2.8)	2.8 (2.8-2.8)	.13	.86
IL-12p70	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.31	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.63	.96
IL-13	2.9 (2.9-2.9)	2.9 (2.9-2.9)	.62	2.9 (2.9-2.9)	2.9 (2.9-2.9)	.41	.92
IL-15	1.2 (1.2-1.2)	1.2 (1.2-1.2)	.34	1.2 (1.2-1.2)	1.2 (1.2-1.2)	.36	.97
IL-17	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.06	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.35	.83
IL-1RA	3.8 (2.9-9.1)	2.9 (2.9-6.3)	.35	3.2 (2.9-11.2)	2.9 (2.9-8.8)	.52	.86
IL-1α	4.3 (4.3-12.6)	4.3 (4.3-4.3)	.001	4.3 (4.3-4.9)	4.3 (4.3-4.3)	.63	.66
IL-1β	3.0 (3.0-3.0)	3.0 (3.0-3.0)	.25	3 (3.0-3.0)	3 (3.0-3.0)	.63	.79
IL-2	2.7 (2.7-2.7)	2.7 (2.7-2.7)	.17	2.7 (2.7-2.7)	2.7 (2.7-2.7)	.43	.95
IL-3	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.33	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.33	.99
IL-4	3.9 (3.9-3.9)	3.9 (3.9-3.9)	.30	3.9 (3.9-3.9)	3.9 (3.9-3.9)	.63	.97
IL-5	2.4 (2.4-2.4)	2.4 (2.4-2.4)	.33	2.4 (2.4-2.4)	2.4 (2.4-2.4)	1	.48
IL-6	2.8 (2.8-2.8)	2.8 (2.8-2.8)	.16	2.8 (2.8-3.0)	2.8 (2.8-3.0)	1	1
IL-7	2.5 (2.5-2.5)	2.5 (2.5-2.5)	1	2.5 (2.5-2.5)	2.5 (2.5-2.5)	1	1
IL-8	4.6 (2.8-8.2)	3.2 (2.8-7.5)	.62	4.1 (2.8-6.0)	2.8 (2.8-6.0)	.05	.53
IP-10	394.9 (311.4-617.3)	352.5 (278.3-605.4)	.37	387.6 (244.2-599.4)	394.9 (282.4-710.1)	.45	.91
MCP-1	403.3 (310.3-549.9)	400.4 (309.0-506.2)	.38	419 (349.4-584.0)	403.3 (293.2-517.5)	.02	.73
MIP-1α	3.1 (3.1-3.1)	3.1 (3.1-3.1)	.34	3.1 (3.1-3.1)	3.1 (3.1-3.1)	.33	.85
MIP-1β	7.1 (2.5-12.9)	5.5 (2.5-11.4)	.16	7.9 (2.7-11.8)	3.1 (2.5-10.0)	.18	.78
TNF-α	6.4 (4.6-8.4)	7 (4.2-8.6)	.52	8.7 (5.6-9.7)	6.7 (4.5-8.3)	.002	.42
TNF-β	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.13	2.6 (2.6-2.6)	2.6 (2.6-2.6)	.36	.94
VEGF	5.4 (5.4-16.2)	5.4 (5.4-16.6)	.02	5.4 (5.4-41.7)	5.4 (5.4-7.0)	.47	.89

C, Control group; *EGF*, epidermal growth factor; *G-CSF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IPC*, intermittent pneumatic compression; *IFN*, interferon; *IL*, interleukin; *IL-12p40*, IL-12 protein 40; *IL-12p70*, IL-12 protein 70; *IL-1RA*, IL-1 receptor antagonist; *IP-10*, IFN-γ-induced protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MIP*, macrophage inflammatory protein; *TNF*, tumor necrosis factor; *VEGF*, vascular endothelial growth factor.
Data are expressed as median (interquartile range).

the edema, not related to a change in management and affecting a large number of patients of the C group, was due to pathophysiologic reasons mainly related to the progression of the edema when it was not properly treated and to seasonal variations. The study started around the end of the winter and in spring, and the follow-up evaluations were performed around late spring and summer; thus, the change in temperature could have contributed to worsening of the leg edema. Interestingly, the IPC treatment prevented this worsening. Finally, of note, is the positive impact on QoL highlighted in the patients of the IPC group and the patients' good compliance with and tolerance of the treatment.

It is known that venous hypertension derived from dysfunction or failure of the muscle pump is transmitted into the dermal microcirculation and results in the development of venous microangiopathy leading to chronic inflammation,[1,35] potentially involving cascades of cytokines and chemokines, as also highlighted in patients affected by chronic venous disease.[13,14,36] As a novel feature, we wanted to analyze the circulating levels of a pool of cytokines and chemokines involved in inflammatory and angiogenic processes after 1 month of IPC treatment. Interestingly, we identified a different trend of modulation for some of the plasma inflammatory markers in the treated group with respect to the C group, in particular, by reference to G-CSF, IFN-γ, IFN-α2, IL-17, VEGF, and IL-1α, all of which decreased in the IPC group and increased in the C group. Among those, G-CSF, although slightly, seemed to be the one that showed

the higher variation and the smaller variability within the IPC group at the end of the study with respect to the baseline. G-CSF is a hematopoietic growth factor required for the proliferation and differentiation of hematopoietic precursors of neutrophil granulocytes.[37] G-CSF has been demonstrated to promote the angiogenic process, being capable of inducing migration and proliferation of endothelial cells, in both in vitro and in vivo experiments. Of note, low G-CSF dosages seemed to have the most favorable effects on angiogenesis, whereas higher concentrations showed an inhibitory effect.[38] Again, interestingly, a circulating G-CSF level decrease was also highlighted in a recent study on a population of patients affected by chronic venous disease of the lower legs, aiming to verify the modulation of circulating endothelial cytokines after the surgical suppression of the oscillatory component of venous reflux and resulting in a clinical reduction of postoperative edema.[39] However, on the basis of our data, we cannot state a clear and defined relationship between IPC treatment and the modulation of plasma inflammatory markers. Further studies are needed to confirm our observations and to validate our findings. Finally, with regard to the change of cytokine levels, the basic inflammatory status of the patients included in this study should also be taken into account, especially considering those who were suffering from multiple sclerosis and osteoarticular diseases.

The study has some limitations. First, the small sample size requires us to be cautious in formulating a hypothesis, most of all related to the modulation of the plasma inflammatory markers after an IPC treatment. Furthermore, the size of the two groups was different, with a smaller number of patients analyzed in the C group, and the volume of the distal portion of the lower limbs by water plethysmography was measured only on a small number of patients. Finally, no other inflammatory markers that may have been useful to confirm a hematologic response from IPC (such as plasminogen activator inhibitor 1 or C-reactive protein) were measured, except the described pool of cytokines, chemokines, and growth factors.

CONCLUSIONS

IPC treatment for 1 month in patients at low mobility with lower limb edema was able to induce meaningful improvements in reducing the edema with a positive impact on QoL and a slight modulation of some plasma inflammatory markers. Further investigations involving a wider sample size are needed to confirm our results.

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AUTHOR CONTRIBUTIONS

Conception and design: MT, PZ, AM
Analysis and interpretation: MT, VT, AM
Data collection: MT, VT, ER
Writing the article: MT, AM
Critical revision of the article: MT, VT, ER, PZ, AM
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