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Title:

A double-blind, placebo-control, randomized trial of extracorporeal shockwave for claudication

Subtitle:

A novel therapy for symptomatic peripheral arterial disease

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Key points

Question: Can extracorporeal shockwave therapy improve quality of life and walking distances in patients with lower limb intermittent claudication?

Findings: In this double-blind, placebo-controlled, randomized trial that included 138 patients, patients receiving extracorporeal shockwave therapy had statistically higher measures of quality of life and walking distances when compared to patients receiving placebo.

Meaning: Given the increasing prevalence of peripheral arterial disease, and the low uptake and adherence to supervised exercise programs among patients with intermittent claudication, extracorporeal shockwave therapy is a safe, non-invasive and efficacious alternative with comparable improvements in quality of life and walking distances to supervised exercise.

Abstract

Importance: Lower limb intermittent claudication limits function and quality of life. Supervised exercise programs are not readily available, and a non-invasive alternative is required.

Objective: Pilot data in extracorporeal shockwave therapy for claudication showed a likely benefit in walking distances. The aim of this study was to assess extracorporeal corporeal shockwave therapy in improving quality of life in patients with claudication.

Design: Double-blind, placebo-controlled, randomized trial. Patients were randomised at 1:1 ratio to extracorporeal shockwave therapy or placebo. Recruitment was between June 2015 and January 2020, with 12 week follow up ending March 2020. Statistical analysis was completed by May 2021.

Setting: Single tertiary centre for vascular surgery. Participants recruited from the outpatient setting.

Participants: A convenience sample of patients with claudication, to be managed conservatively, who refused or were unable to participate in supervised exercise, were eligible. Patients on anticoagulation therapy or with an active cancer were excluded. 522 patients were screened, 389 were eligible and 138 consented to participate and were randomized.

Intervention: 3 times weekly for 3 weeks, the intervention group received 100 impulses of 0.1mJ/mm per cm^2 in an area of the gastrocnemius muscle. The steps for treatment were replicated for the control group, without delivering the treatment.

Outcomes:

Primary outcome was the physical functioning domain of SF-36 quality of life questionnaire at 12-week follow-up. Secondary outcomes included walking distances, ankle brachial pressure index, and other quality of life measures.

Results:

138 patients recruited and randomized. 67% were male with a mean age of 67 years.

The intervention group had a significantly higher physical function score at 12 weeks (Estimate median difference 3.83, 95% CI [0, 7.66], p=0.033). However, this significance did not remain when adjusting for covariates (p=0.07). At 12-weeks the intervention group had significantly longer pain-free and maximum walking distances (pain-free estimate median difference 34.08, 95% CI [11.36, 56.80], p=0.004) (maximum estimate median difference 51.37, 95% CI [10.65, 86.50], p=0.013).

Conclusions and Relevance:

This is the first double-blind, placebo-controlled, randomized trial to consider extracorporeal shockwave therapy for the management of intermittent claudication. It has demonstrated efficacy for walking distances, may have a positive effect on quality of life, and can provide a safe, non-invasive alternative.

Trial registration

clinicaltrials.gov: NCT02652078

Introduction

An estimated 237 million people worldwide suffer with lower limb peripheral arterial disease (1) with this number expected to rise due to population ageing (2). Intermittent claudication (IC) is the most common symptomatic manifestation of peripheral arterial disease (3) and limits physical function, walking distances and quality of life (4,5)

The current first-line recommendations for the management of IC consist of smoking cessation, best medical therapy, cardiovascular risk reduction and supervised exercise (6,7). Despite overwhelming evidence for the clinical and cost effectiveness of supervised exercise (8) its utility is limited by suboptimal provision, uptake and adherence rates (9–13). A non-invasive, efficacious, and cost-effective intervention, that is more appealing to patients and easy to implement may be an attractive alternative.

Extracorporeal shockwave therapy (ESWT) was originally used in urological lithotripsy and has since been utilized in the treatment of musculoskeletal disorders (14), wound healing (15–17) and myocardial ischaemia (18,19). Its use in peripheral arterial disease is less established with small studies reporting heterogenous outcomes (20). Our group has conducted a pilot study on the use of ESWT in patients with IC (21,22), showing it to be safe and well tolerated with a likely benefit on pain free walking distance. However, to date there is no evidence of the effect of ESWT on quality of life in patients with IC. The aim of this study was to address this evidence gap and assess the effects of ESWT on quality of life in patients with IC.

Methods

A double-blind, placebo-controlled, randomized trial was conducted at a university teaching hospital that is a tertiary referral center for vascular surgery. The trial was reviewed by a

regional research ethics committee and full ethical approval was granted by the UK Health Research Authority (REC reference: 14/EE/1257). It was also compliant with the Declaration of Helsinki (1975)(23) and all participants provided written, informed consent prior to any trial procedures. The trial was prospectively registered on a recognized trial registry (*clinicaltrials.gov:* NCT02652078).

Participants

A convenience sample of participants were identified and screened at the outpatient vascular surgery service, where a diagnosis of stable calf IC (Fontaine II with no change in symptoms in a 3-month period prior to recruitment) was made by a vascular surgeon and treated conservatively with best medical therapy, smoking cessation advice and exercise advice. All participants were offered supervised exercise and had either declined participation or had already completed the local 12-week program and remained significantly symptomatic. Participants were deemed eligible if they were over the age of 18 years, were able to provide written, informed consent and adhere to the trial protocol, and had either unilateral lower limb IC or if bilateral, had an index leg that was symptomatically worse. Participants were not eligible if they had contraindications to the use of ESWT including active malignancy, anti-coagulation therapy, known coagulopathies or were pregnant at the time of screening.

Randomization

Participants were randomized at a 1:1 ratio using computer-generated numbers in random permuted blocks, with allocation sequence concealment to all investigators, via an online randomization tool (Sealed Envelope Ltd, London, UK, www.sealedenvelope.com) to either ESWT (intervention group) or a placebo treatment (control group). Randomization allocation was concealed from both the participants and the outcome assessors.

Intervention

Participants in both groups received a total of 9 treatment sessions over a 3-week period. At each session, participants were positioned prone to expose their calf muscles for treatment and were facing away from the equipment.

The treatment and placebo protocol have been previously published (24). The intervention group received 100 impulses of 0.1mJ/mm per cm^2 in an area of 6cm by 5cm per head of gastrocnemius muscle of the index leg, using the PiezoWave 2 shockwave system (Elvation Medical Inc. Duluth, GA, USA). The identical steps for treatment were replicated for the control group, including having the system display on with the correct settings, the application of ultrasound gel and the passage of the transducer over the same area, without delivering the shockwave treatment. Instead, a recording of the sound of the active shockwave treatment was used to simulate the delivery of ESWT, via an MP3 speaker mounted on the device. All participants were followed up at 4 weeks, 8 weeks, and 12 weeks after the first treatment session.

Outcomes

All outcome measurements were assessed at all time-points by assessors blinded to group allocation. The primary outcome was Physical Functioning as measured by the Medical Outcomes Survey – Short Form 36 (SF-36) quality of life questionnaire at 12-week follow-up.

Secondary outcome measures were pre-planned and included pain-free and maximum walking distance assessed via a standardized treadmill test. The treadmill protocol was constant-load and was performed at 1.6 miles per hour and 10% incline for a maximum of 10 minutes.

Patients began walking on the treadmill and indicated when their IC pain occurred, which was recorded as the pain-free walking distance. Maximum walking distance was recorded when the patient could no longer continue due to maximal claudication pain or when 10 minutes had elapsed. For patients unable to walk at 1.6 miles per hour, the speed was reduced by the outcome assessor, but remained constant at all follow-up visits to ensure standardization. Ankle brachial pressure index was measured at rest and immediately following the treadmill protocol. Laser doppler flowmetry, used to assess microcirculatory blood flow of the skin on the medial aspect of the calf and the dorsum of the foot, was also undertaken for a period of 5 minutes at rest and immediately following the treadmill protocol using the moorVMS-LDF2 laser doppler monitor (Moor Instruments Ltd, Axminster, UK). Additional quality of life measures were assessed using the EuroQol-5 Dimension 3-Level (EQ-5D-3L), the remainder of SF-36 domains, and the disease specific Vascular Quality of Life questionnaire (VascuQoL).

Power calculation and sample size

In order to demonstrate at least a 10-point difference in SF-36 physical functioning domain with 80% power and 5% significance, 55 participants were required for each treatment group (25). Based on the completion rates of the local supervised exercise program and the results of the internal pilot study (21), we allowed for a 20% attrition rate resulting in a total sample size of 138 participants required to achieve power.

Statistical Analysis

Data was analyzed using SPSS (IBM, Version 28, New York, USA). A *p*-value of <0.05 was considered statistically significant. Outcome measures were analyzed on an intention-to-treat basis, according to the randomization group.

Baseline characteristics and outcome measures are presented as means and standard deviations for parametric data, medians, and interquartile range (IQR) for non-parametric data. The Shapiro-Wilk test was used to determine the normality of distribution. Mann-Whitney U and Kruskal-Wallis tests were used to estimate the difference in outcomes between groups. Hodges-Lehmann estimator used to provide an estimate of the median differences between groups with 95% Confidence Intervals. Secondary analysis by one-way analysis of co-variance (ANCOVA) using rank transformation of non-parametric data was carried out to compare outcomes at follow up, controlling for baseline characteristics.

This trial is reported in line with the CONSORT guidelines (26).

Results

Between June 2015 and January 2020, 522 patients were assessed for eligibility, and 389 (75%) patients were eligible. Of these, 138 (35.5%) consented to participate and were randomized (Figure 1). Table 1 summarizes the participants' baseline characteristics. All patients were White/Caucasian, reflecting the demographics of the local population (27).

Throughout the study period there were no side effects or serious adverse events recorded that were related to the ESWT. One patient in the intervention group withdrew during the treatment period because they were unable to tolerate lying flat and prone due to dyspnoea.

Primary outcome

Normalized medians of the physical functioning domain of the SF-36 questionnaire at 12-week follow up were significantly higher in the intervention group (41.3 [IQR 31.2 – 46.1] when compared to the control group (34.6 [IQR 28.8 – 42.7]; (p=0.03); estimate median difference

3.83; 95% CI [0.00, 7.66]. There were no statistically significant intragroup differences at any follow up timepoint.

Secondary outcomes

Other Quality of Life Outcomes (Table 2)

Short Form 36 domains

No statistically significant intergroup differences in the other SF-36 domain scores were observed at baseline, or at 8 or 12 weeks. At 4-weeks follow up, the intervention group demonstrated significantly better scores in the SF-36 General Health (p=0.004) and, Vitality (p=0.03) domains, and the Physical Component Summary (p=0.02) than the control group (Table 2).

The intervention group showed statistically significant improvement in multiple domains of SF-36 between baseline and follow up. The Physical Component Summary score had a statistically significant increase between baseline and all follow up time points (4-week p=0.02; 8-week p=0.01; 12-week p=0.05). The score for Bodily Pain was significantly increased between baseline and 4-week (p=0.007) and baseline and 8-week (p=0.02). The score for Vitality was significantly increased between baseline and 4-week (p=0.009).

The control group had a statistically significant improvement in only one component of SF-36, Bodily Pain, between baseline and 4-week (p=0.02).

EuroQol-5 Dimension 3-Level

No statistically significant intergroup differences in the EQ-5D-3L VAS scores were observed at baseline, or at 8 or 12 weeks. At 4-weeks the intervention group demonstrated significantly

better scores than the control group (p=0.03). There were no statistically significant intragroup differences.

Vascular Quality of Life

No statistically significant intergroup or intragroup differences in VascuQoL questionnaire scores were observed at baseline or at any time during follow up.

Pain-free walking distance

No statistically significant intergroup differences in pain-free walking distance were observed at baseline. Thereafter, pain free walking distances were significantly greater in the intervention group at 4, 8 and 12-weeks (Table 3). Statistically significant intragroup improvements in pain free walking distances were observed in both the intervention ($p<0.001$) and the control group ($p<0.001$).

Maximum walking distance

No statistically significant intergroup differences in maximum walking distance were observed at baseline or at 4 weeks. Thereafter, maximum walking distances were significantly greater in the intervention group at 8 and 12-weeks (Table 3). Statistically significant intragroup improvements in maximum walking distances were observed in both the intervention ($p<0.001$) and the control group ($p<0.001$).

Ankle Brachial Pressure Index

No statistically significant intergroup or intragroup differences in ankle brachial pressure index pre or post exercise were observed at baseline or at any time during follow up. (Supplementary Table 1).

Laser Doppler Flowmetry

No statistically significant intergroup or intragroup differences in Laser Doppler Flowmetry pre or post exercise were observed at baseline or at any time during follow up. (Supplementary Table 2).

Secondary analysis

Secondary ANCOVA analysis, adjusting for baseline values, showed that a history of coronary artery disease appears to have a significant effect on physical functioning domain of the SF-36 questionnaire and there was no statistically significant difference in the physical functioning domain at 12-week follow up $F(1,94)=3.394$, $p=0.07$.

As above, after adjustment for baseline values, SF-36 General Health and Vitality domains continue to be significantly higher in the intervention group when compared to the control group at 4-week follow up (General Health $F(1,97)=6.321$, $p=0.014$; Vitality $F(1,97)=6.213$, $p=0.014$).

After adjustment for baseline values, pain-free walking distances continue to be significantly higher in the intervention group when compared to the control group at all follow up points (4-week $F(1,99)=5.562$, $p=0.02$; 8-week $F(1,81)=9.774$, $p=0.002$; 12-week $F(1,78)=10.779$, $p=0.002$).

After adjustment for baseline values, maximum walking distances continue to be significantly higher in the intervention group when compared to the control group at 12-week follow up ($F(1,92)=9.456$, $p=0.005$).

Discussion

In patients with IC who have declined or completed a supervised exercise program, ESWT is safe, well tolerated, and efficacious delivering benefits in walking distances and quality of life. Supervised exercise is the recommended first-line treatment for IC, but suffers from uptake and completion rates as low as 25% and 75% respectively (9–12). Of the 389 patients eligible for this study, 138 (35.5%) agreed to participate, and of these, 110 (80%) completed the intervention and follow up. Additionally, many of these participants had previously declined participation in an exercise program. Therefore, ESWT appears to be a potential alternative to supervised exercise for patients with IC that can improve patient choice and increase access and engagement with non-invasive treatment.

With regards to the primary outcome, the median improvement in the SF- 36 domain of physical functioning at 12-week follow up was of a magnitude similar to that associated with a 12-week supervised exercise program (8). Post-hoc secondary analysis however, revealed that this difference in physical functioning was no longer significant when accounting for baseline characteristics that can affect outcomes in lower limb peripheral arterial disease in general, though a trend did remain ($p=0.07$). In this cohort, a history of coronary artery disease/ischaemic heart disease, significantly affected the physical functioning score as well as a difference between groups at baseline, likely representing a chance imbalance at randomization.

Nevertheless, there were statistically significant differences between groups in the General Health and Vitality domains of the SF-36, which were not influenced by baseline differences. This therefore suggests ESWT does have a positive effect on quality of life.

The remaining SF-36 domains and other measures of quality of life did not show statistically significant improvements. However, the median scores in the intervention group were consistently higher than in the control group. The lack of statistical significance may be due to the trial being powered to detect a significant change in the SF-36 physical functioning domain, therefore lacking the power to detect changes in other quality of life domains. It is also important to note that the aim of the intervention was not to eradicate claudication symptoms, but rather to reduce them to enable patients to mobilize further. This means that there will be a continuing impact of IC on quality of life, which can skew the results obtained from a disease specific quality of life questionnaire such as the VascuQol influencing the lack of a significant change. This will especially apply to patients with bilateral claudication, as the intervention only treated the index leg.

With regards to other secondary outcomes, walking distances improved at each time point, peaking at 12-week follow-up. The improvements in the intervention group were comparable to those provided by exercise therapy and represented a small to moderate minimal clinically important difference (31,32). Importantly, the control group also had a significant increase in their objective walking distances suggesting adequate blinding, and validating our placebo treatment protocol (20). Another possible explanation for these increases is continuing to check that participants did not discontinue and were appropriately taking their statin and antiplatelet therapy at every follow up point, ensuring strict adherence to best medical therapy. This, coupled with constant smoking cessation and exercise advice and encouragement throughout the trial period is something that patients are unlikely to receive as part of routine clinical practice but has a positive impact on their IC.

Nevertheless, given that the conservative management approach used within both groups conformed to latest guidance (6,7), the significant increase in walking distances and quality of life measures in the intervention group can be attributed to the effects of ESWT. Future research should perhaps investigate various doses and durations of ESWT, compare ESWT with supervised exercise, investigate the potential additive effects of the two interventions, and consider the potential mechanism of action for ESWT. A previously postulated mechanism of action i.e. upregulation of angiogenic factors (33), does not appear to be evident at a macrovascular level nor is it superficial enough to be adequately detected by laser doppler flowmetry. Other proposed mechanisms of action such as neural stunning, resulting in reduction in ischaemic pain in patients with critical limb threatening ischaemia (34), might have a role in the effects of ESWT seen in this study. However from the current evidence it is unclear whether this reduction in pain is due solely to neural stunning or due to angiogenesis and vasodilation (33).

A final, but important consideration, is that our findings further the suggestion that quality of life in patients with IC cannot be solely assessed via the functional outcome of walking distance, but requires generic and disease specific quality of life tools. However, our findings also demonstrate the impact that concurrent comorbidities have on such tools. As such, future research in patients with lower limb peripheral arterial disease should adopt patient reported health related quality of life measures as primary endpoint, whilst stratifying for the impact of concurrent comorbidities (4,35,36).

Limitations

This study is not without limitations. Firstly, post-hoc secondary analysis revealed that the difference in physical functioning as measured by the SF-36 questionnaire was no longer

significant when adjusting for baseline characteristics, in particular a history of coronary artery disease.

The study is also limited by the use of a constant load treadmill test, for assessing walking distances. Though a reliable test, especially when assessing maximum walking distance in patients with IC (38), it has disadvantages in terms of test, re-test reliability compared to a graded treadmill test and may not be as closely related to every day walking as the 6-minute walking test (39).

Lastly, this is a single center trial of a modest convenience sample. Future research should aim for a multi-center trial to allow for generalizability of results and will be of great interest for comparison with the current recommendation of supervised exercise therapy.

Conclusions

To our knowledge this is the first adequately powered, double-blind, placebo-controlled, randomized trial to consider ESWT for the management of lower limb IC. It has successfully demonstrated efficacy for improving walking distances within a comparable cohort of patients with IC, whilst suggesting a potential positive effect on quality of life. Further trials are required to compare this treatment to the current available treatment, including a supervised exercise program, and identify the potential mechanism of action.

Acknowledgements

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Mr Paris Cai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no conflicts of interest to declare.

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List of Figures and Tables

426 Table 1: Baseline characteristics.

Baseline Demographics	**Intervention Group n = 68**	**Control Group n = 70**
Male sex (%)	44 (64.7)	48 (68.6)
Female sex (%)	24 (35.3)	22 (31.4)
Age Mean ± SD (years)	66 ± 10.7	67 ± 8.5
BMI Median (IQR) (kg/m^2)	27.9 (24.3-30.9)	27.8 (24.1-29.9)
Smoking status (%) • Current smoker • Ex-smoker • Never smoker	 31 (45.6) 33 (48.5) 4 (5.9)	 25 (35.7) 38 (54.3) 7 (5.6)
Diabetes (%)	16 (23.5)	25 (35.7)
HTN (%)	40 (58.8)	43 (61.4)
Hx CAD/IHD (%)	22 (32.3)	31 (44.3)
Hx CVA (%)	7 (10.3)	6 (8.6)
Hx Resp (%)	16 (23.5)	17 (24.3)
Fontaine Classification • Fontaine IIa • Fontaine IIb	 5 (7.3) 63 (92.6)	 9 (12.9) 61 (87.1)
Site of claudication • Calf (%) • Calf and thigh (%)	 62 (91.2) 6 (8.8)	 66 (94.3) 4 (5.7)
Bilateral claudication (%)	7 (10.3)	8 (11.4)

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428 KEY

429 BMI – Body Mass Index

430 HTN – Hypertension

431 CAD – Coronary Artery Disease

432 IHD – Ischaemic Heart Disease

433 CVA – Cerebrovascular Accident

434 Resp – Respiratory Disease

435 Table 2: Median quality of life measures at all time points.

	Intervention Group (n=55)	Control Group (n=55)	p value	Estimate median difference [95% CI]
Baseline				
SF-36 PF	36.5 (30.8 – 44.2)	33.0 (26.9 – 38.9)	0.05	3.82 [0, 5.74]
SF-36 RP	39.1 (31.3 – 48.2)	37.0 (30.2 – 43.1)	0.18	2.25 [0, 6.73]
SF-36 BP	38.2 (30.6 – 43.5)	38.2 (30.6 – 42.2)	0.32	0 [0, 4.03]
SF-36 GH	43.2 (35.2 – 50.8)	38.4 (30.8 – 47.5)	0.07	3.33 [0, 7.13]
SF-36 VT	46.7 (40.7 – 49.6)	43.7 (32.5 – 49.6)	0.16	2.97 [0, 5.94]
SF-36 SF	42.3 (32.3 – 53.6)	42.3 (32.3 – 47.3)	0.06	5.01 [0, 10.02]
SF-36 RE	45.7 (31.8 – 56.2)	42.2 (28.3 – 56.2)	0.33	0 [0, 6.97]
SF-36 MH	50.9 (42.4 – 58.7)	45.6 (37.8 – 56.1)	0.11	2.62 [0, 7.84]
SF-36 PCS	36.1 (31.3 – 41.7)	34.0 (27.6 – 39.8)	0.09	2.46 [-0.46, 5.32]
SF-36 MCS	49.5 (43.1 – 58.3)	45.6 (35.4 – 56.4)	0.16	3.16 [-1.02, 7.49]
EQ-5D VAS	0.66 (0.53 – 0.68)	0.65 (0.38 – 0.66)	0.15	0 [0, 0]
VascuQol	4.4 (3.33 – 5.5)	4.2 (3.2 – 4.8)	0.13	0.36 [-0.12, 0.84]
4-week follow up				
SF-36 PF	39.4 (32.6 – 44.6)	36.5 (28.8 – 44.2)	0.11	2.37 [0, 5.75]
SF-36 RP	40.3 (34.7 – 52.7)	39.2 (32.5 – 48.2)	0.11	2.25 [0, 6.74]
SF-36 BP	42.2 (37.3 – 51.5)	38.2 (34.2 – 46.3)	0.19	3.23 [0, 4.44]
SF-36 GH	43.7 (38.7 – 53.2)	38.0 (33.2 – 46.1)	**0.004**	5.71 [2.38, 9.51]
SF-36 VT	49.6 (45.9 – 55.6)	46.7 (34.8 -55.6)	**0.03**	2.98 [0, 8.91]
SF-36 SF	47.3 (37.3 – 57.3)	42.3 (37.3 – 52.3)	0.37	0 [0, 5.01]
SF-36 RE	49.2 (35.3 – 56.2)	42.2 (31.8 – 56.2)	0.26	0 [0, 6.96]
SF-36 MH	56.1 (42.4 – 58.7)	50.9 (40.4 – 58.7)	0.19	2.62 [0, 5.24]
SF-36 PCS	39.7 (33.9 – 44.5)	35.9 (31.0 – 40.2)	**0.02**	3.86 [0.78, 6.53]
SF-36 MCS	53.5 (43.5 – 60.0)	49.3 (40.6 – 59.3)	0.27	2.32 [-1.73, 6.61]
EQ-5D VAS	0.66 (0.60 – 0.69)	0.66 (0.36 – 0.69)	**0.03**	0.03 [0, 0.07]
VascuQol	5.3 (4.2 – 5.9)	4.8 (3.9 – 5.6)	0.14	0.32 [-0.12, 0.80]
8-week follow up				
SF-36 PF	42.2 (31.2 – 46.1)	36.5 (30.3 – 42.7)	0.08	3.83 [0, 7.66]
SF-36 RP	39.2 (32.5 – 52.1)	39.2 (30.2 – 43.7)	0.14	4.49 [0, 8.98]
SF-36 BP	42.2 (34.2 – 49.9)	38.2 (34.2 – 46.3)	0.17	3.63 [0, 4.83]
SF-36 GH	43.7 (36.2 – 50.8)	40.4 (33.2 – 48.4)	0.14	3.32 [-0.95, 7.14]
SF-36 VT	49.6 (38.5 – 55.6)	43.7 (37.7 – 49.6)	0.09	2.98 [0, 8.91]
SF-36 SF	47.3 (37.3 – 57.3)	42.3 (37.3 – 52.3)	0.17	5.01 [0, 10.02]
SF-36 RE	45.7 (31.8 – 56.2)	42.2 (35.3 – 56.2)	0.66	0 [-3.48, 6.96]
SF-36 MH	53.5 (43.0 – 58.7)	48.3 (37.8 – 58.7)	0.37	2.61 [-2.62, 5.24]
SF-36 PCS	41.2 (35.9 – 46.0)	35.9 (30.7 – 40.9)	**0.02**	4.18 [0.74, 7.38]
SF-36 MCS	52.6 (39.9 – 59.0)	47.2 (39.7 – 57.5)	0.53	1.52 [-2.97, 6.53]
EQ-5D VAS	0.66 (0.60 – 0.69)	0.66 (0.50 – 0.66)	0.10	0.03 [0, 0.09]
VascuQol	5.2 (3.8 – 5.8)	4.6 (3.8 – 5.3)	0.08	0.44 [-0.08, 0.92]
12-week follow up				
SF-36 PF	41.3 (31.2 – 46.1)	34.6 (28.8 – 42.7)	**0.03**	3.83 [0, 7.66]
SF-36 RP	41.4 (32.5 – 48.2)	39.2 (32.5 – 48.2)	0.39	2.24 [-2.24, 6.73]
SF-36 BP	40.2 (34.2 – 46.7)	38.2 (30.6 – 46.7)	0.48	0 [-0.80, 4.43]
SF-36 GH	44.4 (35.6 – 50.8)	38.0 (33.2 – 46.1)	0.06	4.75 [0, 8.55]

SF-36 VT	49.6 (40.0 – 55.6)	43.7 (37.7 – 52.6)	0.20	2.97 [-2.97, 5.95]
SF-36 SF	47.3 (32.3 – 57.3)	42.3 (37.3 – 47.3)	0.31	0 [0, 10.20]
SF-36 RE	45.7 (35.3 – 56.2)	42.2 (28.3 – 56.2)	0.42	0 [0, 6.96]
SF-36 MH	52.2 (40.4 – 58.7)	48.3 (40.4 – 56.1)	0.28	2.61 [-2.62, 5.24]
SF-36 PCS	40.8 (33.5 – 45.4)	36.6 (31.4 – 43.7)	0.12	2.75 [-0.71, 6.02]
SF-36 MCS	48.7 (39.4 – 58.6)	46.4 (37.7 – 57.4)	0.47	1.71 [-2.88, 6.90]
EQ-5D VAS	0.66 (0.59 – 0.69)	0.66 (0.50 – 0.67)	0.67	0 [-0.03, 0.03]
VascuQol	4.9 (3.9 – 5.9)	4.9 (3.6 – 5.5)	0.48	0.16 [-0.36, 0.64]

436

437 KEY

438 PF – Physical Function

439 RP – Role Physical

440 BP – Bodily Pain

441 GH – General Health

442 VT – Vitality

443 SF – Social Functioning

444 RE – Role Emotional

445 MH – Mental Health

446 PCS – Physical Component Summary

447 MCS – Mental Component Summary

448

449 Table 3: Median pain free and maximum walking distances at all trial time points.

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Walking distance Meters (IQR)	Intervention Group (n=55)	Control Group (n=55)	p value	Estimate median difference [95% CI]
Baseline Pain Free	49 (32.7 – 82.4)	40 (22.7 – 72.1)	0.10	8.77 [-2.13, 18.99]
Baseline Maximum	85 (55.4 – 132.5)	93 (47.5 – 141.1)	0.93	-1.03 [-22.01, 17.75]
4-weeks Pain Free	87 (58.2 – 127.8)	58 (30.5 – 110.9)	**0.03**	20.03 [2.14, 38.34]
4-weeks Maximum	142 (90.3 – 176.1)	103 (54.1 – 195.1)	0.12	22.94 [-6.90, 52.54]
8-weeks Pain Free	98 (56.1 – 147.1)	60 (37.1 – 91.2)	**0.006**	31.95 [10.61, 57.10]
8-weeks Maximum	158 (107.5 – 256.8)	110 (62.4 – 200.6)	**0.04**	38.34 [1.30, 73.76]
12-weeks Pain Free	106 (67.5 – 157.6)	70 (43.5 – 106)	**0.004**	34.08 [11.36, 56.80]
12-weeks Maximum	172 (118.6 – 239.3)	114 (68.7 – 200.9)	**0.01**	51.37 [10.65, 86.50]

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