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Title:

Extracorporeal shockwave therapy for intermittent claudication: medium-term outcomes from a double-blind randomised placebo-controlled pilot trial.

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Abstract

Objectives: Peripheral arterial disease most commonly presents as intermittent claudication (IC). Early evidence has suggested that extracorporeal shockwave therapy (ESWT) is efficacious in the short-term for the management of IC. The objective of this pilot trial was to evaluate the medium-term efficacy of this treatment.

Methods: This double-blind randomised placebo-controlled pilot trial randomised patients with unilateral IC in a 1:1 fashion to receive ESWT or a sham treatment for three sessions per week over three weeks. Primary outcomes were maximum walking distance (MWD) and intermittent claudication distance (ICD) using a fixed-load treadmill test. Secondary outcomes included pre- and post-exertional ankle-brachial pressure indices (ABPIs), safety, and quality of life (QoL) assessed using generic (SF36, EQ-5D-3L) and disease-specific (VascuQol) measures. All outcome measures were assessed at 12-months post-treatment.

Results: 30 participants were included in the study (ESWT n=15; Sham n=15), with 26 followed-up and analysed at 12 months (ESWT n=13; Sham n=13). Intragroup analysis demonstrated significant improvements in MWD, ICD and post-exertional ABPIs ($p<0.05$) in the active treatment group, with no improvements in pre-exertional ABPIs. Significant improvements in QoL were observed in 3 out of 19 domains assessed in the active group. A re-intervention rate of 26.7% was seen in both groups.

Conclusions: These findings suggest that ESWT is effective in improving walking distances at 12 months. Although this study provides important pilot data, a larger study is needed to corroborate these findings and to investigate the actions of this treatment.

ISRCTN: NCT02652078.

Keywords: peripheral arterial disease; intermittent claudication; extracorporeal shockwave therapy; randomised controlled trial

Introduction

Peripheral arterial disease (PAD) is an age-related atherosclerotic condition with an estimated worldwide prevalence of 3-10%, increasing to 20% in those aged over 70 years[1]. PAD most commonly presents as intermittent claudication (IC). The physical, psychological and social limitations associated with IC often dramatically impair quality of life[2].

Initial management of IC includes risk factor modification, such as smoking cessation[3]. Individuals with PAD are advised to continue walking, and given best medical therapy including anti-platelet agents and statins[4]. NICE guidelines recommend supervised exercise programmes (SEP) as the first-line intervention for the management of IC[5], due to the compelling evidence of the clinical and symptomatic benefits[6,7]. Despite this, patient uptake and adherence is poor, and the provision of SEP is far from universal[8,9]. This suggests that an alternative effective treatment option for IC which is safe, well tolerated and acceptable to patients may be of great benefit for this patient group.

Extracorporeal shockwave therapy (ESWT) is an established therapy that has been used in urological and musculoskeletal medicine since the early 1980s, in particular for the treatment of urolithiasis and delayed fracture healing[10–13]. Early studies using ESWT in IC suggested positive effects but lacked scientific rigour[14]. We have recently demonstrated that ESWT is safe, tolerable and clinically efficacious at 4, 8 and 12 weeks post-treatment in a randomised double blind placebo-controlled trial for IC[15]. This study aimed to determine the medium term efficacy in patients from the Shockwave 1 trial[15].

Methods

Ethics

Ethical approval was granted from NRES Committee East of England (IRAS ID 166137) and the trial was conducted in accordance with the ethical standards of the Committee on Human Experimentation from the Declaration of Helsinki 1975. Written informed consent was provided by all participants.

Participants

Participants were recruited over a 6 month period from a single, tertiary, vascular surgical unit in a university teaching hospital following the trial protocol[16]. Prior to enrolment all patients had been offered a SEP but had declined participation. Participants were given walking advice in line with routine care.

The criteria for inclusion in the study included a diagnosis of PAD with symptomatic unilateral calf claudication and post-exertional ankle brachial pressure index (ABPI) <0.9 and best medical therapy. Participants were excluded from the trial if they were on warfarin therapy, had a diagnosis of malignancy, or had unilateral thigh IC or bilateral IC in any location.

Randomisation

Patients were randomised in a 1:1 fashion using an online randomisation tool (Sealedenvelope.com, London, UK) to either the intervention (ESWT) group or sham control group (SG) by a single investigator [TC].

Treatments

All treatments were performed by a single investigator [TC] three times each week for three weeks. Participants in the ESWT received 6000 shockwave impulses using the Piezowave 2 shockwave device at each treatment session. Impulses were delivered to the calf muscle, split evenly between the medial and lateral heads of the gastrocnemius. Delivery of shockwaves was set at 5Hz with an energy flux density of 0.16mJ/mm^2 thus each treatment session lasted approximately 20 minutes.

SG patients received an identical procedure to the active treatment group at each session except that the ESWT device was not activated; instead a recording of the noise of the active device was played from an audio player mounted on the equipment to replicate the 5Hz impulse delivery of an active shockwave treatment.

Outcomes

Primary outcomes; were maximum walking distance (MWD) and intermittent claudication distance (ICD) measured on a treadmill set to 2.5km/hr at a 10 degree incline up to a maximum of 10 minutes, supervised by a blinded trial investigator [AH]. Participants were asked to report the time at which claudication pain began (ICD) and then asked to continue walking to maximum tolerable distance (MWD).

Secondary outcomes; included ABPI measured using a sphygmomanometer and an 8-MHz hand-held Doppler probe (Huntleigh Technology, Cardiff, UK) before and immediately after each treadmill test. Generic Quality of life (QoL) was assessed using the generic Short-Form 36 (SF36®; QualityMetric, Lincoln, Rhode Island, USA) and EuroQoL 5 dimensions 3L (EQ-5D-3L^{TM}; EuroQol Research Dimension) questionnaires. Disease-specific QoL was assessed using the the King's College Vascular Quality of Life (VascuQol) questionnaire.

Sample Size

Data was used from a similar non-randomised trial[17] where n=12, maximum walking distance was significantly increased at 4 weeks (151±37% from baseline, P<0.01). To replicate this and detect a change of 51 metres in the ESWT group assuming that the standard deviation is 37.00 metres, and no change in the SG, 13 patients per group (26 in total) were required to achieve 90% power with 5% significance. To account for a 10% loss to follow up, a sample size of 30 was deemed appropriate.

Blinding

All participants were blinded to the treatment they received throughout the whole study, with a single unblinded investigator [TC] performing all treatments. A second investigator who was blinded to the group allocations carried out the consultations and assisted with any QoL questions [JG]. All walking assessments and ABPI measurements were performed by a third blinded investigator [AH].

Statistical Analysis

Baseline descriptive statistics were calculated for each group (mean (SD) and n (%)). A p-value of <0.05 was considered to indicate statistical significance. All analyses were undertaken using the SPSS® computer package, version 23.0 (SPSS, Chicago, USA).

Comparison of demographical data was performed using an X^2 test for categorical variables, with continuous variables analysed using a 2-sample independent t-test. Primary and secondary outcomes were analysed using parametric methods based upon results of normality statistical tests (Kolmogorov-Smirnov) and histograms.

Primary analysis of all outcome measures was intergroup analysis on an intention-to-treat (ITT) basis, with walking distances also analysed on a per-protocol (PP) basis to examine the outcomes for any participant who did not undergo re-vascularisation. Intergroup analysis was conducted using a one-way analysis of co-variance (ANCOVA) to compare results between the groups at 12 months controlling for baseline variances. 95% confidence intervals for mean difference between groups were recorded for intergroup analyses.

Secondary analysis of all outcome measures was intragroup analysis on an ITT basis, with walking distances also anlaysed on a PP basis to exclude those undergoing re-vascularisation. Intragroup analysis was performed using a one-way analysis of variance (ANOVA) with repeated measures, with Greenhouse-Geisser correction applied when Mauchly's test of Sphericity was significant. *Post-hoc* analysis was conducted using Bonferroni to compare differences within groups over time. 95% confidence intervals for mean difference between baseline and 12 months were recorded for intragroup analyses.

Results

81 patients were screened for eligibility, of the 81 screened, 30 were eligible and consented to participate. Patients were excluded either because they chose not to participate (n=31), or because they did not meet the inclusion criteria (n=20). Reasons for not fulfilling inclusion criteria were: bilateral claudication (n=7); warfarin therapy or other anticoagulants (n=5); no indication of pain during the treadmill walk test at 1.5mph and 10 % incline (capped at 10 minutes) (n=5); and a post-exercise ABPI >0.9 (n=3).

Fifteen participants were randomised to ESWT and fifteen to SG. All 30 participants received their allocated 9 treatment sessions over 3 weeks. Four participants were lost to follow-up during the initial study phase. A total of n=26 patients (n=13 per group) remained in follow up and were analysed at 12-months post-treatment. A summary of participant flow through the trial can be seen in Figure 1.

Demographics (Table 1)

Demographic information was recorded at the baseline visit, as well as at the 12 month visit to assess for any changes. At 12-months characteristics remained similar between groups with the exception of clopidogrel therapy (p=0.039) which was significantly higher in the SG.

Primary Outcomes

Intergroup analysis: there was a non-significant difference in MWD between the ESWT (191.9m ± SD 156.7) and SG (116.8m ± SD 76.3) using ITT analysis at 12 months post-treatment, $F(1,23)=3.093$, p=0.092 [-13.52,166.92]. Using PP, the mean MWD at 12 months was 208.0m (± SD 184.3) in the ESWT compared to 94.8m ± (SD 45.7) in the SG. The mean MWD was also non-significant using this analysis $F(1,15)=2.496$, p=0.135 [-30.65,206.28].

Despite no significant differences between groups, a distinct trend for improvement was seen in the ESWT that was not present in the SG.

ICD at 12 months was not significantly different between the ESWT (151.5m ± SD 155.6) and SG (83.6m ± SD 56.7) using an ITT analysis, $F(1,23)=2.447$, p=0.131 [-22.07,159.00]. A PP analysis also showed a non-significant difference between ESWT (163.5m ± SD 182.9) and SG (57.2m ± SD 32.7), $F(1,23)=1.491$, p=0.241 [-53.58,197.29].

Intragroup analysis: at 12 months a significant improvement in the ESWT MWD from baseline was observed using an ITT analysis, $F(2.2,26.2)=6.173$, p=0.005 [-37.48,220.96], which was not seen in the SG. *Post-hoc* analysis of the ESWT highlighted a significant change in MWD at 12 months when directly compared to baseline (p=0.031). Comparison of MWD at 12 months to other post treatment time point MWD was non-significant (p=0.653, p=0.444 and p=0.117 [4, 8 and 12 weeks respectively]). This significant improvement in the ESWT was also seen using a PP analysis, $F(2.2,17.9)=5.617$, p=0.011 [-97.72,308.50], which was not observed in the SG.

At 12 months there was also a significant improvement in ICD from baseline in the ESWT group using an ITT analysis $F(2.3,27.3)=5.384$, p=0.008 [-41.82,225.92], which was not seen in the SG. *Post-hoc* analysis of the ESWT showed that the change in ICD when directly compared to other post treatment time points was non-significant (p=0.362 for baseline and p=1.000 for 4, 8 and 12 weeks). This significant improvement in the ESWT was also observed using a PP analysis, $F(2.2,17.9)=4.915$, p=0.017 [-106.27,311.44], which was not seen in the SG.

Results of both ITT and PP intragroup analyses for MWD and ICD can be found in Table 2.

Ankle-Brachial Pressure Indices

Both pre- and post-exertional ABPIs were non-significant between groups at 12 months. The mean pre-exertional ABPI for the ESWT was 0.79 (± SD 0.35) compared to 0.76 (± SD 0.39) in the sham group, $F(1,23)=0.002$, p=0.967 [-0.24,0.25], whereas the post-exertional ABPI was 0.53 (± SD 0.34) compared to 0.47 (± SD 0.41) in the ESWT and SG respectively, $F(1,23)=0.101$, p=0.754 [-0.25,0.34].

Intragroup analysis showed a non-significant improvement in pre-exertional ABPIs, $F(4,48)=1.173$, p=0.335 [-0.14,0.36]; however post-exertional ABPIs in the ESWT were significantly improved over the 12 month period, $F(4,48)=2.809$, p=0.036 [-0.05,0.41], which was not observed in the SG. *Post-hoc* analysis of the ESWT showed that the change in post-exertional ABPIs when directly compared to other time points was non-significant (p>0.05). A summary of these findings can be found in Table 3.

Quality of Life (Table 4)

EQ-5D-3L: there were no significant differences in EQ-5D-3L index or VAS between the two groups at any time point. Intragroup analysis showed no significant improvement in either domain.

SF36: There was no significant difference between the two groups in any of the domains at 12 months. Intragroup analysis of the SF36 domains highlighted a significant improvement in the role-physical domain, $F(4,40)=2.614$, p=0.049 [-3.63,53.63], and vitality domain, $F(4,40)=4.608$, p=0.004 [-9.47,31.06], but not in the other domains or summary scores. *Post-hoc* analysis of these domains showed a significant difference between baseline and 4 weeks (p=0.034), and between baseline and 8 weeks (p=0.021), for the SF36 vitality

domain, but no other significant pairwise comparisons (p>0.05). No significant pairwise comparisons were found in the SF36 role-physical domain (p>0.05).

VascuQol: At 12 months, there was a significant difference in the VascuQol activities domain score for the ESWT compared to the SG, $F(1,23)=5.147$, p=0.033 [0.11,2.27], but not in any of the other domains. Intragroup analysis showed no significant improvements in all VascuQol domains or VascuQol index score, apart from the VascuQol pain domain which was significantly improved, $F(4,40)=2.684$, p=0.045 [-0.83,3.35], suggesting less pain and better QoL; *post-hoc* analysis highlighted no significant differences when directly comparing time-points.

Re-interventions

Between the 12 week and 12-month follow-up, a total of 8 participants (4 from each treatment arm) underwent a re-vascularisation procedure following the primary study intervention. All 4 participants from the SG received percutaneous transluminal angioplasty (PTA) as their re-intervention, whereas 3 participants from the AG received PTA with the fourth participant undergoing a femoropopliteal bypass. A re-intervention rate of 26.7% was therefore observed in both ESWT and SG. These interventions had been arranged by clinicians after the patient had declined SEP but before enrolment in trial. Re-interventions were therefore not related to a symptomatic deterioration during the trial.

Discussion

The purpose of this research was to investigate the medium term effects of ESWT on clinical and quality of life outcomes. This research was the first study known to investigate this therapy for a follow-up period of 12 months.

At 12 months in the ESWT group there was a statistically significant improvement in both MWD and ICD, both of which more than doubled. Much smaller improvements were observed in the SG. This suggests that an intensive three week course of shockwave therapy is effective in producing durable, medium-term beneficial effects on walking. Comparing these improvements to those reported in a number of reviews, ESWT appears to be non-inferior to supervised exercise therapy for improving walking distances[18–20]. However, supervised exercise programmes (SEP) for claudication are generally recommended to last at least 3 months to maximise benefit. The prolonged duration of SEPs has been cited as a common reason for patients with IC declining participation. The relatively short 3 week duration of ESWT may appeal to patients, perhaps making it a more acceptable option than SEP. This is evident as 31 out of 60 declined to participate (48% uptake rate) compared to the 33% uptake rate reported in SEP[8].

There were no changes in pre-exertional ABPIs observed at 12 months, however a statistically significant overall improvement in post-exertional ABPIs was observed which did not concur with earlier findings[15]. Improvements in vascular supply to the legs, measured using the ABPI, is an important indicator of diagnosis of peripheral arterial disease, yet is limited as a prognostic marker[21]. Similarly, although SEP is clinically efficacious for the treatment of IC, studies have shown that it does not result in an improvement in ABPI[22]. The value of ABPI to assess intervention effectiveness is thus probably limited to those involving

direct revascularisation (e.g. angioplasty or bypass). Further examination of the cause of this significant improvement in post-exertional ABPI is needed to exclude operator variability.

Whilst this research demonstrates that ESWT is effective in improving walking distances, there are little in the findings that support a positive impact on quality of life. When comparing domains at all time-points in this trial, there are a variety of significant domains that are inconsistent across the follow-up points[15]; this lack of consistency suggests a possible Type 2 statistical error. Data in this RCT failed to show that ESWT provides a measurable improvement in QoL as previously reported for trials in SEP or PTA[7,23,24]. A larger randomised controlled trial powered for QoL domains is needed.

With no complications or safety concerns reported, shockwave therapy can be viewed as a non-invasive, safe alternative to the current treatment options and would appear to be as safe as SEP[25], and potentially safer than PTA[26].

The underlying mechanism of action of shockwave therapy in claudication is not well understood, but has been hypothesised to involve angiogenesis and vasculogenesis[27]. Studies investigating angiogenic factors suggests a complex interplay between vascular endothelial growth factor (VEGF), placental growth factor (PlGF), hypoxia-inducible factor 1 (HIF-1) and stromal cell-derived factor 1 (SDF-1) is responsible for induction of angiogenesis and arteriogenesis[28–31]. Human endothelial progenitor cells (EPCs) are also believed to play a role in vasculogenesis through VEGF and SDF-1 receptors that enable them to target sites of ischaemia[32]. From these studies it appears that the angiogenic changes are multifactorial in nature, suggesting that an interplay of multiple angiogenic and vasculogenic factors occurs post-treatment. These studies are limited in that they primarily focus on animal studies, therefore future research into understanding the mechanism of action of ESWT in

humans should be a priority. Future trials should therefore conduct muscle biopsies to establish the local effects on tissues, and inflammatory markers should be assessed due the induced inflammatory response of the gastrocnemii muscles.

There are a few limitations of the present study. ESWT may be seen as a ‘quick fix’ for IC by patients, which in comparison to SEP, does not encourage such patients to make healthy lifestyle changes[33]. In combination with the lack of promotion of exercise further, it may provide reasoning behind the number of participants undergoing re-vascularisation in the ESWT group. Therefore, perhaps ESWT followed by SEP may be more suitable to combine the durability and longevity of this treatment with the management of overall cardiovascular fitness.

One possible explanation for the lack of intergroup significance in walking distances at 12 months is the ceiling effect, a consequence of capping the treadmill test at 10 minutes (500m). Participants who could walk further than this distance did not reach their true maximum walking distance; similarly, some participants may not have suffered claudication pain at this distance, and did not reach their true ICD. Ultimately this has likely to have resulted in skewed mean walking distances that may not be truly representative. Future studies that don’t cap the treadmill test would be more accurate at measuring the true MWD and ICD in these patients.

A further limitation of this study is that patients with bilateral or proximal intermittent claudication were excluded. As a result, only a small proportion (of approximately 15-20%) of the disease population were eligible for inclusion in this trial[34]. Exclusion of these patients reduced the effect of confounding factors; however future research should investigate

whether ESWT is effective in patients with more proximal arterial disease and perhaps patients with severe limb ischaemia.

Conclusion

This single centre pilot randomised controlled trial has demonstrated that ESWT is efficacious in significantly improving walking capacities in patients with unilateral calf claudication. With no significance between the active and sham groups, it is difficult to determine the true benefits of shockwave therapy when compared to a sham control. However, these findings suggest this novel therapy to be safe and durable at 12 months, a good indicator of a potential alternative for the treatment of IC. Due to the reduced commitment and workload compared to SEP, ESWT may be more acceptable to many patients, thus increasing uptake rates, a key drawback to SEP. The non-invasiveness, safety, and costs may also support ESWT over PTA. Whilst this study provides important initial pilot data, a larger study with a longer follow-up is warranted to corroborate the findings of this trial. Further work is needed to investigate the mechanism of action of shockwave therapy and subsequent effects on the body, and to evaluate the economic aspect of this treatment.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Table 1. Comparison of demographic data at 12 months (n=30) to baseline (n=26).

	Baseline			12 Months		
	Sham Group	Active Group	P-Value †	Sham Group	Active Group	P-Value †
Male : Female	9:6	9:6	1.000	8:5	9:4	.443
Mean Age ± SD (Years)	67.5±9.26	64.3±9.37	.829‡	71.2±7.64	66.7±9.43	.197‡
Smoking Status						
Never Smoked	2	1	.543	2	0	.141
Stopped Smoking	9	8	.713	7	8	.691
Currently Smokes	4	6	.439	4	5	.680
Diabetes						
IDDM	1	0	.309	1	0	.308
Non-IDDM	3	5	.409	3	4	.658
Hypertension	10	9	.705	9	8	.680
Ischaemic Heart Disease	6	4	.439	5	3	.395
History of CVA	1	1	1.000	1	1	1.000
Aspirin Therapy	10	10	1.000	10	8	.395
Clopidogrel Therapy	5	3	.409	7	2	.039*
Cilostazol Therapy	1	0	.309	1	0	.308
Naftidrofuryl Therapy	1	3	.283	2	3	.619
Statin Therapy	11	13	.361	11	10	.619

*Indicates significant values, where $p<0.05$; †X^2 test for trend, except ‡2-sample t-test. CVA, Cerebrovascular Accident; IDDM, Insulin Dependent Diabetes Mellitus; Non-IDDM, Non-Insulin Dependent Diabetes Mellitus.

Table 2. Comparison of mean walking distances at 12 months to baseline using an intention-to-treat and per-protocol intragroup analysis.

	Sham Group (MWD)	Active Group (MWD)	Sham Group (ICD)	Active Group (ICD)
Baseline (m)	96.4 ± 70.4 *(n = 15)*	94.8 ± 45.7 *(n = 15)*	57.0 ± 53.2 *(n = 15)*	58.1 ± 32.6 *(n = 15)*
12 Month (ITT) (m)	116.8 ± 76.3 *(n = 13)*	191.9 ± 156.7 *(n = 13)*	83.6 ± 56.7 *(n = 13)*	151.5 ± 155.6 *(n = 13)*
P-Value (ITT)	.287	.005*	.485	.008*
12 Month (PP) (m)	85.2 ± 54.6 *(n = 9)*	208.0 ± 184.3 *(n = 9)*	57.2 ± 32.7 *(n = 9)*	163.5 ± 182.9 *(n =9)*
P-Value (PP)	.883	.011*	.078	.017*

*indicates significant values, where $p<0.05$. Group data presented as mean ± SD. ICD, Intermittent Claudication Distance; ITT, Intention-to-Treat Analysis; MWD, Maximum Walking Distance; PP, Per-Protocol Analysis.

Table 3. Comparison of mean pre- and post-exertional ankle-brachial pressure indices at 12 months to baseline using an intention-to-treat intragroup analysis.

	Sham Group (Pre-Exertional ABPI)	Active Group (Pre-Exertional ABPI)	Sham Group (Post-Exertional ABPI)	Active Group (Post-Exertional ABPI)
Baseline	0.67 ± 0.27 *(n = 15)*	0.67 ± 0.24 *(n = 15)*	0.32 ± 0.24 *(n = 15)*	0.37 ± 0.23 *(n = 15)*
12 Month	0.76 ± 0.39 *(n = 13)*	0.79 ± 0.35 *(n = 13)*	0.47 ± 0.41 *(n = 13)*	0.53 ± 0.34 *(n = 13)*
P-Value	.279	.335	.354	.036*

*indicates significant values, where p<0.05. Group data presented as mean ± SD. ABPI, Ankle-Brachial Pressure Index.

Table 4. Table of all Quality of Life (QoL) domains at baseline and 12 months with intergroup comparison.

	Baseline			12 Months		
	Sham Control Group	**Active Treatment Group**	**P-Value †**	**Sham Control Group**	**Active Treatment Group**	**P-Value ‡**
EQ-5D-3L Index	0.651 ± 0.20 *(n=15)*	0.720 ± 0.15 *(n=15)*	.297	0.640 ± 0.17 *(n=13)*	0.743 ± 0.23 *(n=13)*	.271
EQ5D-3L VAS	5.3 ± 2.18 *(n=15)*	6.6 ± 2.13 *(n=15)*	.095	5.7 ± 1.33 *(n=13)*	6.7 ± 2.01 *(n=13)*	.340
SF36 Physical Functioning	28.00 ± 16.35 *(n=15)*	46.78 ± 20.17 *(n=15)*	**.009***	33.46 ± 15.20 *(n=13)*	60.00 ± 26.69 *(n=13)*	.079
SF36 Role-Physical	32.92 ± 27.29 *(n=15)*	47.92 ± 28.71 *(n=15)*	.154	43.75 ± 31.15 *(n=13)*	67.79 ± 29.96 *(n=13)*	.097
SF36 Bodily Pain	36.17 ± 18.47 *(n=15)*	40.17 ± 24.30 *(n=15)*	.616	43.75 ± 31.17 *(n=13)*	69.79 ± 29.96 *(n=13)*	.109
SF36 General Health	36.33 ± 22.48 *(n=15)*	56.00 ± 17.65 *(n=15)*	**.013***	39.62 ± 18.08 *(n=13)*	55.38 ± 28.25 *(n=13)*	.909
SF36 Vitality	41.67 ± 22.24 *(n=15)*	46.67 ± 16.34 *(n=15)*	.489	39.42 ± 27.53 *(n=13)*	53.85 ± 18.84 *(n=13)*	.109
SF36 Social Functioning	50.00 ± 27.14 *(n=15)*	67.50 ± 28.27 *(n=15)*	.095	51.92 ± 24.92 *(n=13)*	78.85 ± 29.04 *(n=13)*	.105
SF36 Role-Emotional	53.89 ± 34.34 *(n=15)*	70.56 ± 30.84 *(n=15)*	.173	56.41 ± 36.98 *(n=13)*	75.64 ± 30.33 *(n=13)*	.375
SF36 Mental Health	62.67 ± 21.62 *(n=15)*	76.67 ± 17.31 *(n=15)*	.080	65.38 ± 26.65 *(n=13)*	75.00 ± 20.21 *(n=13)*	.850
SF36 Health Transition	28.33 ± 20.85 *(n=15)*	43.33 ± 22.09 *(n=15)*	.066	46.15 ± 13.87 *(n=13)*	59.62 ± 28.02 *(n=13)*	.409
SF36 Physical Component Summary	33.36 ± 18.14 *(n=15)*	47.72 ± 18.66 *(n=15)*	**.041***	41.28 ± 25.91 *(n=13)*	62.54 ± 22.70 *(n=13)*	.080
SF36 Mental Component Summary	52.06 ± 21.96 *(n=15)*	65.70 ± 16.50 *(n=15)*	.065	53.29 ± 25.91 *(n=13)*	70.83 ± 21.52 *(n=13)*	.440
VascuQol Pain	3.48 ± 1.19	3.63 ± 1.18	.731	3.90 ± 1.18	4.78 ± 1.82	.178

	(n=15)	*(n=15)*		*(n=13)*	*(n=13)*	
VascuQol Symptoms	4.58 ± 1.43 *(n=15)*	4.63 ± 1.38 *(n=15)*	.923	4.85 ± 0.92 *(n=13)*	5.52 ± 1.07 *(n=13)*	.082
VascuQol Activities	3.00 ± 0.87 *(n=15)*	3.68 ± 1.23 *(n=15)*	.093	3.24 ± 1.10 *(n=13)*	4.67 ± 1.50 *(n=13)*	**.033***
VascuQol Social	3.90 ± 1.87 *(n=15)*	4.53 ± 1.74 *(n=15)*	.345	3.73 ± 1.63 *(n=13)*	5.08 ± 2.18 *(n=13)*	.187
VascuQol Emotional	3.95 ± 1.41 *(n=15)*	4.70 ± 1.39 *(n=15)*	.152	4.26 ± 1.52 *(n=13)*	5.43 ± 1.67 *(n=13)*	.250
VascuQol Index	3.78 ± 1.22 *(n=15)*	4.24 ± 1.23 *(n=15)*	.319	4.00 ± 1.12 *(n=13)*	5.09 ± 1.53 *(n=13)*	.096

*Indicates significant values, where $p<0.05$. ‡P-values calculated through univariate analysis using a one-way ANCOVA, except †2 sample independent t-test. Data presented as mean ± SD. SF36, Short-Form 36 ®; EQ-5D-3L, EuroQol 5 Dimensions-3L™; VascuQol, King's College Vascular Quality of Life.

Figure Legends

Figure 1. CONSORT diagram of patient flow in trial. ABPI, Ankle-Brachial Pressure Index; IC; Intermittent Claudication.

Supplementary Data

Supplementary Data 1. Completed CONSORT checklist.