

This is a postprint version of:

Bø, E., Bergland, A., Stranden, E., Jørgensen, J. J., Sandbæk, G., Grøtta, O. J., & Hisdal, J. (2014). Effects of 12 Weeks of Supervised Exercise After Endovascular Treatment: A Randomized Clinical Trial. *Physiotherapy Research International*.

Title

Effects of 12 weeks of supervised exercise after endovascular treatment: A randomised clinical trial.

Running headline

Exercise therapy after PTA for PAD

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Key words

Endovascular procedures, Exercise, Intermittent claudication

Introduction

Peripheral arterial disease (PAD) affects approximately 20% of people older than 65 years of age, and its prevalence increases with age (Norgren et al. 2007).

Approximately 30% of affected patients have symptomatic PAD with intermittent claudication, including pain or fatigue in the calves, thighs or buttocks when walking that is relieved with rest (Norgren et al. 2007; Olin et al. 2010; Salameh & Ratchford 2009). The treatment goal for PAD is threefold; to reduce the cardiovascular risk factors, to reduce the symptoms in the lower extremities and to improve the patient's health-related quality of life (HRQoL) (Hankey et al. 2006). In the current guidelines, exercise therapy, has a class I, level of evidence A, recommendation for the treatment of claudication in patients with PAD (Olin et al. 2010). Revascularisation, such as surgical or endovascular techniques, can be used as an alternative when symptoms have not improved or have deteriorated with medication and exercise therapy (European Stroke Organisation et al. 2011; Norgren et al. 2007; Olin et al. 2010).

Extensive research on the effects of exercise has shown that regular physical activity has positive effects on quality of life and physical function for patients with intermittent claudication (Ahimastos et al. 2011; Frans et al. 2011(E-pub); Guidon & Mcgee 2010; Lauret et al. 2012). A Cochrane review on the effects of exercise on intermittent claudication by Watson et al. (Watson et al. 2008) in which 22 RCTs were reviewed reported an improvement of 50-200% in walking distance (i.e., an average increase of 82 meters for the pain-free walking distance and an average increase of 113 meters for the maximal walking distance) in a treadmill test. These effects were maintained for up to 2 years. Despite its proven efficacy, supervised exercise training (SET) appears to be an underutilised tool for various reasons, such as availability and the lack of cost reimbursement (Makris et al. 2012). In addition, patient recruitment for the exercise groups and compliance with exercise are other described challenges that may influence the potential of SET (Bartelink et al. 2004; Bendermacher et al. 2006).

Regardless of the general agreement that risk factor modification, medication and exercise should be first-line treatment (Norgren et al. 2007) (European Stroke Organisation et al. 2011), the frequency of using endovascular treatment for treating

intermittent claudication has increased as an alternative to both surgical and exercise treatment (Anderson et al. 2004; Norgren et al. 2007; Pell et al. 1994; Spronk et al. 2009). Since first introduced in the 1960's, percutaneous transluminal angioplasty (PTA), one endovascular treatment technique, has been further developed, and is now a well-established method that aims at dilating the narrowed or occluded area in the arterial vessel (Norgren et al. 2007). Two recently published reviews compared exercise and endovascular therapy for intermittent claudication (Ahimastos et al. 2011; Frans et al. 2011(E-pub)); both concluded that there was no difference between these treatment options based on the currently available evidence. Several authors have suggested the use of SET after endovascular treatment for future research (Bendermacher et al. 2006; Kolh 2010; Spronk et al. 2009) to determine whether both treatment modalities together can increase the effectiveness over one modality alone. The possible advantages of adding SET after PTA are the twofold focus on locally increased blood flow during activity in the treated area after PTA and the general effects of exercise, which also influence the development of general risk factors for further manifestations of cardiovascular disease (American College of Sports Medicine et al. 2011). In particular, we seek to increase the evidence-based knowledge about the effectiveness of interventions that may improve physical function and HRQoL in patients with intermittent claudication. However, little is known about the effects of SET after PTA for PAD. Thus, the aims of this study were to compare the effects of SET after PTA with those of PTA alone on physical function, limb hemodynamics and HRQoL in patients with intermittent claudication. We hypothesised that the group offered SET would walk longer distances and have better HRQoL than the group treated with PTA alone. In addition, we hypothesised that PTA would have higher patency rates when combined with SET.

Methods

Study design

This randomised controlled trial with a parallel group design was conducted at Oslo University Hospital, Aker, Norway, and followed the Consolidated Standards of Reporting Trials statement criteria for reporting clinical trials (CONSORT) (Schulz et al. 2010).

Sample

Patients eligible for participation in this study were those selected to undergo PTA due to intermittent claudication (Fontaine stage II) after being treated with medication and exercise therapy without a satisfactory result. A further requirement was availability to return for hospital-based exercise twice weekly for three months. The exclusion criteria were previous PTA on the same leg during the past two years, a present unsuccessful attempt at PTA, asymptomatic PAD (Fontaine stage I), critical limb ischemia (Fontaine stage III or IV) and reduced walking ability caused by factors other than PAD (i.e., orthopaedic problems, spinal stenosis, angina pectoris or dyspnoea).

Randomisation and blinding

The participants were stratified according to the treatment site (aortoiliac or femoropopliteal) and randomised into the intervention or control group (ratio 3:2) after PTA (Figure 1). A computer-generated block randomised list using consecutively numbered and sealed envelopes was used. The administrative staff prepared the sealed envelopes in advance, and the block size and randomisation list were inaccessible to the project coordinator (E.B.), who enrolled the patients and assigned them to the groups. The assessors were blinded to the group assignment.

(Please insert figure 1 about here)

PTA and post-operative care

PTA is a well-established method that involves dilating the narrowed or occluded area in the chosen vessel. Through an angiosheath, a balloon catheter was inserted over a guidewire to the site of the obstruction. Inflating

the balloon lead to the rupture and flattening of the atherosclerotic plaque (Hatlinghus et al. 1981; Leu 1983). In conjunction with PTA, stenting was used in 21 participants. Both groups received post-operative care in agreement with the ward's usual procedures, and the patients were discharged either the same day or on the first post-operative day. The physician responsible for discharge and the nurse responsible for the patient gave general advice on the importance of exercise, smoking cessation and diet.

Intervention

The intervention group performed hospital-based SET two days per week for 12 weeks. In addition, the participants conducted one home-based exercise session every week, which was logged in a training diary. The group-based SET was based on The Norwegian Ulleval Model (Nilsson et al. 2008), slightly adjusted to be applicable to this patient group. Each SET session lasted for 60 minutes and consisted of warm-up exercises, three high-intensity intervals (each lasting for five to ten minutes), two moderate-intensity intervals (each lasting for five to ten minutes), and cool-down exercises, including stretching. The exercises were simple aerobic dance movements and walking, and involved the use of both upper and lower extremities. During walking the participants walked alternating in a circle in the gym, in the nearby corridor or stair climbing. The exercise intensity was adjusted using the Borg scale of perceived exertion (Borg 1982) and beats per minute of the music pace (Nilsson et al. 2008). During the high-intensity exercises, the participants were motivated to gradually increase their exercise intensity towards 15-17 on the Borg scale. The participants also used this scale to monitor the home-based exercise session each week. No extra equipment was required for this program. Each session had between two and 12 participants. The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise.

Assessments at baseline and three-month follow-up

All measurements were taken at the same visit at baseline (prior to the planned PTA) and three months after the PTA.

The primary outcome was a standardised Six Minute Walk Test (6MWT). The 6MWT was performed in a 30 m pre-marked hospital corridor, and instructions and encouragements were given in accordance with the test's guidelines (Guyatt et al. 1985). This test is well validated for PAD patients and has shown good reliability in this patient group (Mcdermott et al. 2008; Montgomery & Gardner 1998).

Secondary outcomes were grouped by physical function, limb hemodynamics, and HRQoL measurements. The physical function measurements were the maximum walking distance (MWD) and pain-free walking distance (PFW) on a treadmill (graded protocol, 3.2 km/h constant speed, starting with a 0% incline, increasing by 2% every two minutes until reaching 10%) (Gardner et al. 1991). Treadmill testing is a well-accepted means of testing walking distance for this patient group (Hiatt et al. 1995; Olin et al. 2010) and has shown very high reliability (Nicolai et al. 2009). Limb hemodynamics were measured using the ankle-brachial-index (ABI), pulse volume recording (PVR) on the leg, and ultrasound scanning. HRQoL was measured with a generic instrument, the Short Form 36 (SF-36) (Ware & Sherbourne 1992), as well as a disease-specific instrument, the Claudication Scale (CLAU-S) (Spengel et al. 1997). The SF-36 has been used previously in numerous PAD studies and is recommended as one of the most appropriate generic instruments for this patient group with regard to validity, reliability, and responsiveness (Beattie et al. 1997; Chetter et al. 1998). The items on the SF-36 are grouped into a calculated physical and mental component score. CLAU-S is a valid measurement (Mehta et al. 2006). CLAU-S has five subscales: daily life, pain, social life, disease-specific anxiety and psychological well-being.

Statistics

The data are presented as median with minimum and maximum values or exact numbers and percentages (Table 1 and 2). Comparisons between the groups were performed using the Wilcoxon-Mann-Whitney test, as not all variables were normally distributed. Paired t-test was used for comparison between baseline and three months (Table 2). All analyses were conducted

on an intention-to-treat basis. The raw SF-36 scores were coded and recalibrated following standard guidelines (Ware & Sherbourne 1992). P-values ≤ 0.05 were considered statistically significant. The data were analysed using SPSS 20.0 (SPSS Corporation, Chicago, Illinois, USA).

Ethical considerations

All work was conducted in accordance with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (NCT01109732) and was approved by The Regional Ethics Committee for Medical Research of the Eastern Health Region, Norway (2009/2192-1). All participants provided written informed consent.

Results

A total of 50 participants were included in this study. Figure 1 shows the flow of participants through the study. There were no statistically significant differences between the two groups at baseline (Table 1). Concerning gender, there were no statistically significant differences at baseline regarding the variables connected to the main outcome. The general participant characteristics are shown in table 1.

(Please insert table 1 about here)

Patient compliance

In the intervention group, 26 of the 29 patients (90%) completed the intervention, and 21 of these 26 (81%) patients completed more than 80% of the exercise sessions. The reasons for withdrawal were concomitant diseases that were not associated with PAD.

Physical function

Physical function measured by walking distance (6MWT, MWD, and PFWD) showed a statistically significant change from baseline to three months in both the intervention and control groups (all, $p < 0.001$) (Table 2). The intervention group showed a greater median change from baseline to three months in the three different walking distance measurements than the control group did: 15% vs 10% increase, respectively, for the 6MWT; 65% vs 44% increase, respectively, for the MWD; and 293% vs 179%, respectively, for the PFWD.

(Please insert table 2 about here)

Regarding the walking distance results, a greater portion of patients in the intervention group than in the control group showed improvements in the 6MWT, MWD and PFWD (figure 2).

(Please insert figure 2 about here)

Limb hemodynamics

The limb hemodynamics, as measured by the ABI and PVR, also showed statistically significant changes from baseline to three months in both the intervention and control groups ($p < 0.001$). The median difference change from baseline in the ABI was similar for the two groups; however, for PVR, the intervention group had a 50% greater median change than the control group (Table 2).

Ultrasound examination

Ultrasound scanning of the treated area after three months revealed re-stenosis or occlusions in four of the 29 patients (14%) in the intervention group compared to five of the 21 patients (24%) in the control group. Further analysis based on treatment level (aortoiliac or femoropopliteal) showed that all patients with observed re-stenosis or occlusions were treated at the femoropopliteal level. The percentage of re-stenosis or occlusion of the femoropopliteal level was 27% and 45% for the intervention and control groups, respectively (Figure 2).

(Please insert figure 3 about here)

HRQoL

HRQoL, measured using the SF-36, exhibited a statistically significant positive change from baseline to three months for all domains ($p < 0.05$), except mental health ($p = 0.21$). The greatest changes were found in the domains of physical function, physical role, and bodily pain. There was no statistically significant difference between the groups at three months (Table 2). Measured by the disease-specific CLAU-S measurements, all domains had statistically significant positive changes from baseline to three months ($p < 0.05$). The domains of daily life and pain showed greater changes from baseline than the domains of social life, disease-specific anxiety and psychological well-being, which had comparatively smaller changes (Table 2). However, all of the variables except for pain showed a ceiling effect at three months ($> 20\%$ of the highest possible score) (Mchorney & Tarlov 1995), which may indicate that the improvement could have been even greater at three months as the instrument is unable to accurately assess the progress.

Major adverse events

No major adverse events associated with the prescribed exercise and activities were observed.

Discussion

The main finding in the present study was that patients who were offered SET in addition to PTA showed greater improvements in walking distance than participants in the control group. The significant improvements from baseline to three months that were observed in the physical and limb hemodynamic variables were also found for most domains of HRQoL. The two different HRQoL outcome measures, SF-36 and CLAU-S, showed the same tendencies; the greatest changes were found in the more physical domains, with smaller changes in the more psychological and mental domains.

To our knowledge, only two studies on SET following PTA have been previously reported. Mazari et al. (2011) studied patients with femoropopliteal lesions, and Kruidenier et al. (2011) studied patients with primarily aortoiliac lesions. The present results are mostly in agreement with the findings of these studies. Both Mazari et al. (2011) and Kruidenier et al. (2011) found a greater treatment effect for PTA+SET than for PTA alone or SET alone regarding walking distance. Neither study found additional improvements in HRQoL beyond what was observed for any of the treatment strategies alone, as was true for the present study.

The observed improvement of 65.5 meters on the 6MWT in the intervention group is considered clinically important (Gremeaux et al. 2011; Perera et al. 2006). In addition, the improvement in walking distance was even greater when measured using a treadmill than by the 6MWT, and the difference between the groups increased as well. According to a meta-analysis of 18 different exercise studies, even a small positive effect can be considered a great improvement for these patients, who are at risk for further functional decline (De Vries et al. 2005).

Regarding HRQoL, the physical scores changed more than the mental scores in both the SF-36 and the CLAU-S, which may be due to the nature of PAD, as mentioned by previous studies (De Vries et al. 2005; Keeling et al. 2008; Spronk et al. 2007). In agreement with this, the changes in physical score are reflected in the changes observed in the other measures of physical function

in the present study, which are consistent with previous findings (Mazari et al. 2011).

Both groups showed significant improvements in walking distance from baseline to three months. These changes are expected due to the nature of the treatment given. The compliance to exercise in the intervention group was good (10% drop-out) as many exercise intervention studies have high attrition rates (25-50%) (Linke et al. 2011). For the group given additional SET in this study, the walking distances were further improved, although this difference was not confirmed by statistical analysis. This lack of a difference may be due to the small number of participants included in the study. Another reason for this lack of difference between the groups may be that the control group also had the stenosis or occlusion removed, and the control patients were then able to perform physical activity to a greater extent than before and performed this activity outside the hospital-based groups from which they were excluded. The usual regimen after this treatment does include encouragement to engage in exercise, and we did not prevent these participants from exercising.

The tendency of better results for the intervention group than for the control group for the physical measures was not present to the same degree for the HRQoL. The difference between the groups after three months was minimal. One possible reason for this small difference is that the intervention offered was physical exercise, which may not be reflected by an immediate effect in HRQoL instruments. HRQoL is a complex and multifaceted structure and is influenced to a large extent by factors other than purely physical factors (Breek et al. 2002; Gardner et al. 2001; Tsai et al. 2002).

After three months, all observed re-stenosis or occlusions appeared in patients treated at the femoropopliteal level. This result is in line with previous reports of patency rates in which treatment at the femoropopliteal level had lower initial clinical success and patency rates than treatment at the aortoiliac level (Norgren et al. 2007; Thomas & Nassef 2006). For the patients treated at femoropopliteal level in the present study, a higher percentage of re-stenosis or occlusions appeared in the control group than in the intervention group.

The present study's SET was a generic endurance exercise intervention. After PTA, a patient's main obstacle to exercise is no longer the local stenosis or occlusion and is instead more likely deconditioning in general and impaired strength and balance, as described elsewhere (Mcdermott et al. 2012). A general exercise program such as this one may reinforce the availability of supervised exercise and the generalisability of the study for this patient group.

Limitations

Because of slow recruitment, the final sample size of this study was smaller than initially planned. Slow recruitment has been reported for several studies of this patient group and seems to be an extensive problem (Abbott 2012; Greenhalgh et al. 2008; Murphy et al. 2008). We are also aware that subjects enrolled in an intervention trial with an aerobic exercise component are more likely to be fitter and perhaps more engaged than those who refused to take part in the study. Our aim was to see the direct effects of the 12 weeks of intervention, however, a follow-up of three months is limited time with regards to further sustainment or improvement of the results. The participants in the control group were not monitored to assess their participation in independent exercise, and participating in an exercise intervention study, even as part of the control group, may have influenced their level of activity. Last the disease-specific HRQoL instrument CLAU-S showed a ceiling effect at three months, which may have influenced the results.

Conclusion and implication for physiotherapy practice

In this study, we found that SET after PTA for patients with intermittent claudication led to a greater improvement in walking distance after three months in the intervention group than the control treatment, which had PTA alone. These improvements are considered clinically significant for this patient group. The present study's better results of SET after PTA add to the emerging existing evidence of this treatment modality. This should encourage physiotherapy practice to offer SET after PTA for patients who undergo PTA for intermittent claudication.

Acknowledgments

The authors would like to thank Milada Cvancarova Småstuen, Torunn Sætre, Helene Venberget, Irma Arnesen, Steinar Krey Voll, Tone Wagle, Christine S. E. Rolfsrud, and Therese Brovold for their contributions to the study.

Funding

This research received no specific grants from any funding agency in the public, commercial, or non-profit sectors.

Conflicts of interest

The authors report no conflicts of interests.

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Legends

Figure 1. CONSORT diagram of the study. SET = supervised exercise treatment.

Figure 2. Figure 2. Portion of patients that improved from baseline (%) in physical function measured by 6MWT, MWD and PFWD. The dark shaded area in each column is the portion of patients that improved more than 50 meters in the 6MWT and more than 100 % on the MWD and the PFWD, respectively.

6MWT = 6 minutes walking test; MWD = maximum walking distance; PFWD = pain-free walking distance.

Figure 3. Ultrasound scanning – re-stenosis or occlusion at three months.

Table 1. Participant characteristics at baseline.

Table 2. Physical function, limb hemodynamics, and HRQoL. Results from baseline, three months, and three months median change from baseline.

Table 1. Participant characteristics at baseline

	Intervention group n=29	Control group n=21
	Median (min-max) or n (%)	Median (min-max) or n (%)
Demographics		
Age (years)	67 (56 - 83)	67 (49 - 79)
Body mass index (kg/m ²)	26.5 (17.9 - 38.7)	28.7 (20.8 - 36.9)
Gender (men)	14 (48.3)	10 (47.6)
Marital status (married)	18 (62.1)	10 (47.6)
Years of school (>9 years)	22 (75.9)	16 (76.2)
Blood status		
Total cholesterol (mmol/l)	4.6 (3.2 - 7.1)	4.8 (3.0 - 7.0)
HDL (mmol/l)	1.6 (0.9 - 3.3)	1.5 (0.9 - 3.1)
LDL (mmol/l)	2.4 (1.5 - 4.5)	2.5 (1.3 - 4.2)
Triglycerides (mmol/l)	1.2 (0.4 - 3.3)	1.3 (0.6 - 4.8)
HbA1c (%)	6.0 (4.0 - 7.6)	6.0 (5.7 - 8.1)
Smoking status		
Have never smoked	0 (0)	1 (4.8)
Used to smoke	18 (62.1)	11 (52.4)
Currently smoke	11 (37.9)	9 (42.8)
Current medication		
Statins	28 (96.6)	19 (90.5)
Platelet inhibitors	25 (86.2)	20 (95.2)
Anticoagulants	2 (6.9)	0 (0)
Hypertension	15 (51.7)	13 (61.9)
Comorbidity		
Diabetes	3 (10.3)	4 (19.0)
COPD	2 (6.9)	1 (4.8)
Previous cardiovascular events		
Myocardial infarction	8 (27.6)	8 (38.1)
Stroke/TIA	1 (3.4)	0 (0)
Peripheral arterial surgery or endovascular treatment	5 (17.2)	4 (19.0)

HDL = high-density lipoproteins; LDL = low-density lipoproteins; HbA1c = hemoglobin A1c; COPD = chronic obstructive pulmonary disease

Table 2. Physical function, limb hemodynamics, and HRQoL. Results from baseline, three months, and three months median change from baseline

	Baseline Median (min - max)		3 months Median (min - max)		Difference 3 months – baseline Median (min - max)	
	Intervention group n=29	Control group n=21	Intervention group n=29	Control group n=21	Intervention group n=29	Control group n=21
Physical function						
6 MWT (m)	429.5 (224 - 561)	431 (240 - 556)	492 (270 - 595)	487 (240 - 570)	65.5 (-215 - 300)	45 (-14 - 162)
MWD treadmill (m)	385.8 (95.2 - 1174.8)	213.6 (57.9 - 841.1)	584.8 (140 - 1602)	427.2 (37.4 - 854.4)	251.4 (-66.8 - 1121.4)	93 (-53.4 - 679.1)
PFWD treadmill (m)	101.5 (35.6 - 480.6)	94.6 (35.6 - 534)	456.1 (10 - 1602)	267 (2 - 841.1)	297.8 (-91.3 - 1416)	169.1 (-104.8 - 586.8)
Limb hemodynamics						
Ankle Brachial Index (%)	57 (25 - 83)	57 (26 - 81)	100 (39 - 100)	100 (53 - 100)	33 (0 - 71)	32.5 (-4 - 67)
Pulse Volume Recordings (mm)	4 (1 - 9)	4 (2 - 10)	10 (5 - 15)	8 (4 - 15)	6 (0 - 14)	4 (-4 - 8)
HRQoL*						
SF-36						
Physical function (PF)	50 (10 - 77,8)	45 (20 - 70)	80 (30 - 100)	75 (40 - 100)	23.3 (-35 - 80)	26.5 (0 - 55)
Physical role (RP)	62.5 (6,3 - 91,7)	56.3 (12.5 - 100)	81.3 (12.5 - 100)	68.8 (0 - 100)	18.8 (-37.5 - 75)	12.5 (-62.5 - 56.3)
Bodily pain (BP)	42 (0 - 74)	32 (12 - 62)	62 (22 - 100)	51 (0 - 100)	20 (-20 - 100)	15.9 (-51 - 68)
General health (GH)	57 (27 - 92)	57 (10 - 97)	62 (22 - 97)	62 (15 - 97)	10 (-30 - 42)	5 (-25 - 45)
Vitality (VT)	50 (10 - 75)	45 (25 - 75)	60 (10 - 85)	55 (30 - 75)	10 (-15 - 45)	10 (-30 - 35)
Social function (SF)	75 (0 - 100)	75 (25 - 100)	100 (25 - 100)	87.5 (37.5 - 100)	0 (-12.5 - 75)	0 (-37.5 - 50)
Emotional role (RE)	60 (6.7 - 80)	60 (26.7 - 80)	73.3 (0 - 80)	73.3 (26.7 - 80)	6.7 (-40 - 60)	6.7 (-33.3 - 33.3)
Mental health (MH)	64 (4 - 80)	68 (40 - 80)	68 (28 - 80)	68 (40 - 76)	4 (-20 - 40)	0 (-40 - 36)
CLAU-S						
Daily life (DL)	66.7 (16.7 - 97.2)	61.1 (27.8 - 91.7)	91.7 (33.3 - 100)	83.3 (41.7 - 100)	15.3 (-16.7 - 41.7)	22.2 (-33.3 - 58.9)
Pain (P)	53.6 (25 - 95.7)	44.3 (5.6 - 76.2)	76.3 (39 - 100)	76.3 (32.7 - 100)	27 (-11.6 - 53)	31.3 (-8.67 - 53.7)
Social life (SL)	87.5 (18.8 - 100)	93.8 (31.3 - 100)	100 (0 - 100)	100 (68.8 - 100)	0 (-6.25 - 50)	0 (-10.4 - 37.5)
Disease-specific anxiety (DSA)	86.5 (30.8 - 100)	86.5 (18.2 - 98.1)	96.2 (54.3 - 100)	97.9 (33.3 - 100)	5.8 (-18.8 - 57.7)	3.8 (-49.4 - 81.8)
Psychological well-being (PWB)	86.4 (0 - 100)	86.4 (42.5 - 100)	93.2 (9.1 - 100)	88.6 (36.4 - 100)	4.5 (-18.2 - 29.6)	2.3 (-13.7 - 39.8)

6MWT = 6 minutes walking test; MWD = maximum walking distance; PFWD = pain-free walking distance; m = metre; mm = millimetre

* Scale 0-100, higher score reflect better health. SF-36 = Short form 36. CLAU-S = The Claudication. A significant improvement between baseline and three months after PTA was observed for all variables ($p < 0.05$), but SF-36 MH. No significant difference was observed regarding improvement from baseline between the two groups.