Randomized clinical trial

Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease

F. A. K. Mazari, J. A. Khan, D. Carradice, N. Samuel, M. N. A. Abdul Rahman, S. Gulati, H. L. D. Lee, T. A. Mehta, P. T. McCollum and I. C. Chetter

Academic Vascular Surgical Unit, University of Hull, Hull, UK

Correspondence to: Mr F. A. K. Mazari, Academic Vascular Surgical Unit, University of Hull, Vascular Department, 1st Floor, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK (e-mail: fayyaz.mazari@hey.nhs.uk)

Background: **The aim was to compare percutaneous transluminal angioplasty (PTA), a supervised exercise programme (SEP) and combined treatment (PTA plus SEP) for intermittent claudication due to femoropopliteal arterial disease.**

Methods: **Consenting patients with femoropopliteal arterial lesions were randomized to one of three treatment arms: PTA, SEP, or PTA plus SEP. All patients received optimal medical treatment. Patients were assessed at baseline and 1, 3, 6 and 12 months after intervention. Clinical (ankle pressures, walking distances, symptoms) and quality-of-life (QoL) outcomes (Short Form 36, VascuQol) were analysed.**

Results: **A total of 178 patients (108 men, median age 70 years) were included. All three treatment groups demonstrated significant clinical and QoL improvements. One year after PTA (60 patients, 8 withdrew), 37 patients (71 per cent) had improved (16 mild, 16 moderate, 5 marked), nine (17 per cent) showed no improvement and six (12 per cent) had deteriorated. After SEP (60 patients, 14 withdrew), 32 patients (70 per cent) had improved (19 mild, 10 moderate, 3 marked), six (13 per cent) showed no improvement and eight (17 per cent) had deteriorated. After PTA plus SEP (58 patients, 11 withdrew), 40 patients (85 per cent) had improved (18 mild, 20 moderate, 2 marked), seven (15 per cent) showed no improvement and none had deteriorated. On intergroup analysis, PTA and SEP alone were equally effective in improving clinical outcomes, although the effect was short-lived. PTA plus SEP produced a more sustained clinical improvement, but there was no significant QoL advantage.**

Conclusion: **For patients with intermittent claudication due to femoropopliteal disease, PTA, SEP, and PTA plus SEP were all equally effective in improving walking distance and QoL after 12 months. Registration number: NCT00798850 (http://www.clinicaltrials.gov).**

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Introduction

Intermittent claudication (IC) is the most common presentation of peripheral arterial occlusive disease (PAD), with a prevalence of 5–10 per cent in the UK population over 50 years old[1]. Despite its benign course, with more than 80 per cent of patients remaining stable[2], IC confers significant quality-of-life (QoL) limitations[3], and is a known risk factor for coronary and cerebrovascular events[4,5]. The annual mortality rate approaches 5 per cent, three times that of an age- and gender-matched population[6]. Treatment of patients with claudication has two aims: to improve QoL[7] and to reduce deaths from myocardial infarction and stroke[4]. Management options for IC include best medical treatment with risk factor modification (BMT), a supervised exercise programme (SEP), percutaneous transluminal angioplasty (PTA), vasodilator drugs[8] and, occasionally, surgery[9].

PTA is considered the first-line treatment for aortoiliac artery PAD, with good 5-year patency rates[10]. However, in patients with femoropopliteal PAD, the results are less impressive. Consequently, there is lack of consensus for treatment of IC in this group[11]. Supervised exercise is a well established treatment for IC, with clinical and QoL benefits. Previous randomized trials comparing SEP and PTA have failed to identify a clear clinical benefit for either, mainly due to the limited number of trial participants[12–14]. A Cochrane review identified the possibility of bias in the previous trials and the need for a larger one to provide further evidence[15]. Additionally, previous studies did not investigate whether combining the two treatments would be better than either treatment alone. Previous studies have suggested that improvement in clinical parameters after treatment for IC may not mirror the change in QoL[16] as assessed using generic and disease-specific instruments[7,17].

This prospective, single-centre, randomized clinical trial was designed to compare PTA, SEP, and combined treatment (PTA plus SEP) in patients with IC due to femoropopliteal arterial disease.

Methods

The study was approved by the local research ethics committee and conducted in the academic vascular surgical unit of a university hospital. All patients with symptomatic unilateral claudication attending vascular outpatients between September 2002 and April 2007 were screened to assess their suitability for inclusion in the trial.

Duplex ultrasonography was performed in all suitable patients to assess the site, nature and extent of any arterial lesions. The scans were discussed in a weekly vascular multidisciplinary team meeting. Patients with unilateral infrainguinal lesions suitable for angioplasty were identified as potential participants and commenced BMT, comprising antiplatelet therapy (aspirin and/or clopidogrel), smoking cessation advice and support (National Health Service smoking cessation programme, nicotine replacement therapy), and risk factor modification according to evidence-based care pathways (goal-oriented management of diabetes, control of hypertension and treatment of hypercholesterolaemia) within a dedicated nurse-led clinic. Patients were also provided with advice leaflets on physical activity and exercise.

Suitable patients were reassessed after 3 months and included in the trial if their symptoms remained stable. Informed consent was obtained from all participants. Randomization into one of the three treatment arms (PTA, SEP, or PTA plus SEP) was undertaken at this stage using sealed envelopes if all inclusion and exclusion criteria (*Table 1*) were fulfilled. As recruitment for the study started before publication of the current Inter-Society Consensus for the Management of PAD (TASC II) guidelines[11], TASC grading of lesions was undertaken only in retrospect after completion of recruitment.

Interventions

Percutaneous transluminal angioplasty

PTA was performed by a consultant vascular radiologist according to a predefined protocol in accordance with the normal practice of the unit, in a dedicated vascular radiology suite. Access was gained from the contralateral side and diagnostic angiography was performed followed by balloon angioplasty (repeated if required) and completion angiography. Adjunctive procedures or stents were not used in any patient.

Supervised exercise programme

SEP was carried out three times a week for 12 weeks under the supervision of trained physiotherapists or doctors. The SEP was designed specifically for claudicants based on the recommendations of a previous meta-analysis[18], and was tested and validated for clinical and cost effectiveness[19]. Patients were required to attend at least 85 per cent of sessions for successful completion of the SEP. The programme included closed-circuit training on six stations, each lasting for 2 min, with 2 min of brisk walking between each station. Each training session was preceded by gentle warm-up exercises, and followed by gentle stretching and cooling down exercises. Patients completed one full circuit for the first 6 weeks, followed by an additional increment of one station per week for the next 6 weeks, ultimately

Table 1 Inclusion and exclusion criteria for the trial

Inclusion criteria	Exclusion criteria
Symptomatic unilateral intermittent claudication	Critical ischaemia
Femoropopliteal lesion amenable to angioplasty (as discussed in the MDT meeting)	Incapacitating systemic disease
Symptoms stable after 3 months on best medical therapy	Inability to tolerate treadmill testing (unrelated to limb ischaemia)
	Significant ischaemic changes on ECG during treadmill testing
	Ipsilateral vascular surgery within previous 6 months
	Ipsilateral peripheral angioplasty within previous 6 months

MDT, multidisciplinary team; ECG, electrocardiogram.

completing two full circuits at 12 weeks. Details of the six exercise stations are shown in *Table S1* (supporting information).

Combined therapy

Patients in the combined treatment group underwent PTA according to the protocol described above, with commencement of SEP a week after the procedure.

Assessments

Patients were assessed at baseline (before intervention) and at 1, 3, 6 and 12 months after intervention randomization. At each assessment, the patients underwent fixed-load treadmill testing at 2·5 km/h and 10° inclination, to a maximum of 5 min. Clinical indicators of lower limb ischaemia, including resting and postexercise ankle : brachial pressure indices (ABPIs) measured using an anaeroid sphygmomanometer and a 8-MHz hand-held Doppler probe (Huntleigh Technology, Cardiff, UK), IC distance (ICD) and maximum walking distance (MWD) up to a maximum of 215 m (5 min on treadmill), and patient-reported walking distance (PRWD, up to a maximum of 1000 m), were recorded.

In addition, duplex ultrasound imaging was performed at 3 and 12 months in the PTA and PTA plus SEP groups to assess target vessel patency. Patients also completed the Short Form 36 (SF-36®; QualityMetric, Lincoln, Rhode Island, USA) and King's College Vascular Quality of Life (VascuQol) questionnaires for assessment of generic and disease-specific QoL respectively. These instruments have been tested and validated for use in patients with claudication in numerous previous studies[3,17,20].

Outcome measures

Primary outcome measures included MWD, and the physical function (PF) domain of SF-36® at 12 months. Secondary outcome measures included clinical indicators (ABPI, ICD, MWD and PRWD) at all time points, clinical outcomes at 12 months reported according to the International Society for Cardiovascular Surgery (ISCVS) outcome criteria (marked improvement, 3; moderate improvement, 2; mild improvement, 1; no change, 0; mild deterioration, −1; moderate deterioration, −2)[21], restenosis and reintervention rates, generic QoL outcomes reported as SF-36® domain scores and disease-specific QoL outcomes reported as the VascuQol score at all time points.

Sample size calculations

Sample size calculations used 80 per cent power and $\alpha = 0{\cdot}05$, giving a K (constant) value of 7·9. Calculations were performed for all primary and secondary outcome measures using previously published studies. For example, for MWD as a primary outcome measure, data from the Oxford trial paper were used that reported mean(s.d.) MWD as 120(28) m[12]. Using these values, 19 patients were required in each treatment arm to detect a 20 per cent difference in MWD (25 m). Similar calculations were done using ABPI, ICD, domain scores of SF-36® and VascuQol. The largest sample size was calculated using the PF domain of SF-36®. Using a mean(s.d.) PF score of 43(18) from previously published data[22], 50 patients were needed in each treatment arm to detect a 20 per cent difference. Anticipating a 20 per cent dropout rate, the aim was to recruit 60 patients in each treatment arm.

Statistical analysis

Data were recorded in Microsoft® Excel 2007 for Windows® (Microsoft, Redmond, Washington, USA) and analysed using SPSS® version 16.0 (SPSS, Chicago, Illinois, USA) and Stata® release 11·0 SE (StataCorp, College Station, Texas, USA).

Non-parametric statistical tests were used throughout the study after appropriate testing for normality using histograms and statistical tests (Kolmogorov–Smirnov test). Intragroup analysis was performed using the Friedman test to compare differences over the course of the study, and the Wilcoxon signed rank test to compare differences between each pair of time points. Intergroup analysis was done using Kruskal–Wallis ANOVA for continuous variables. Categorical variables were analysed using the χ^2 test for trend, Mann–Whitney *U* test and Fisher's exact test as appropriate. Adjustment was made to *P* values for multiple testing using the Bonferroni method.

Results

Over a 6-year interval between September 2001 and December 2007, 1157 patients were assessed for inclusion in the study; 178 (15·4 per cent) were recruited and randomized into one of the three treatment arms (PTA, 60; SEP, 60; PTA plus SEP, 58). Thirty-three patients (18·5 per cent) later withdrew from the study and 145 (PTA, 52; SEP, 46; PTA plus SEP, 47) completed the 1-year follow-up (*Fig. 1*). There were no significant differences in demographics, risk factors (*Table 2*) or clinical and QoL indicators at baseline among the three treatment groups. Retrospective TASC grading scored 80

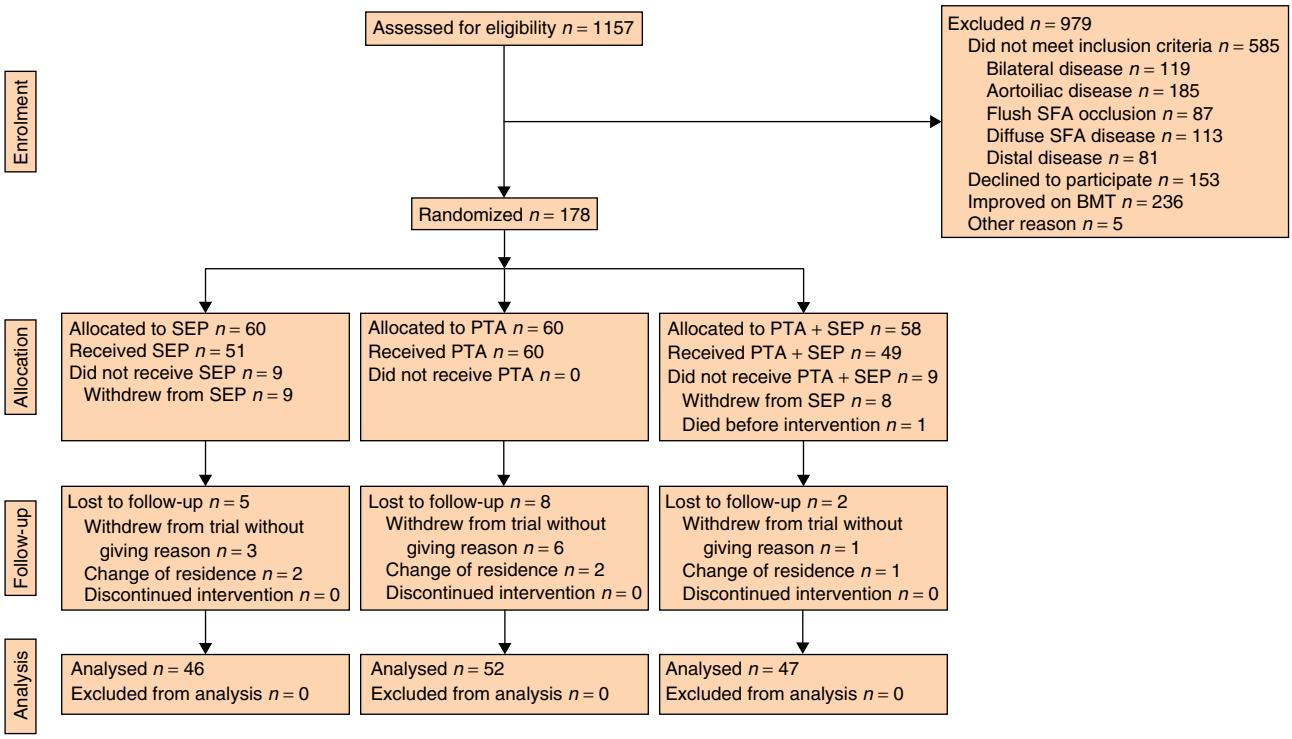

Fig. 1 CONSORT diagram for the trial. SFA, superficial femoral artery; BMT, best medical therapy; SEP, supervised exercise programme; PTA, percutaneous transluminal angioplasty

Table 2 Clinical details of patients in the trial

	PTA ($n = 60$)	SEP ($n = 60$)	PTA + SEP ($n = 58$)	P‡
Age (years)*	70 (63, 75)	69 (63, 76)	69·5 (64, 79)	1·000§
Sex ratio (M : F)	37 : 23	37 : 23	33 : 25	0·659
Side†				0·103
Right	29 (48)	24 (40)	34 (59)	
Left	31 (52)	36 (60)	24 (41)	
Risk factors†				
Diabetes	8 (13)	9 (15)	8 (14)	0·921
Hypertension	40 (67)	40 (67)	34 (59)	0·561
Hypercholesterolaemia	45 (75)	47 (78)	43 (74)	0·705
Current smoker	18 (30)	18 (30)	19 (33)	0·972

*Values are median (95 per cent confidence interval); †values in parentheses are percentages. PTA, percutaneous transluminal angioplasty; SEP, supervised exercise programme. ‡χ^2 test for trend, except §Kruskal–Wallis ANOVA.

lesions as grade A, 66 as grade B, 23 as grade C and five as grade D; four results were missing. Proportions were similar in each treatment group ($P = 0{\cdot}632$).

Intragroup analyses

Clinical indicators of lower limb ischaemia

A statistically significant improvement was seen in all clinical indicators (resting and postexercise ABPI, MWD and PRWD) at all time points, including the final endpoint at 1 year in all three treatment arms except postexercise ABPI in the SEP group (*Fig. 2*; *Table S2*, supporting information).

Clinical outcomes (International Society for Cardiovascular Surgery scores)

At 12 months after treatment in the PTA group, 37 (71 per cent) of 52 patients had improved (mild

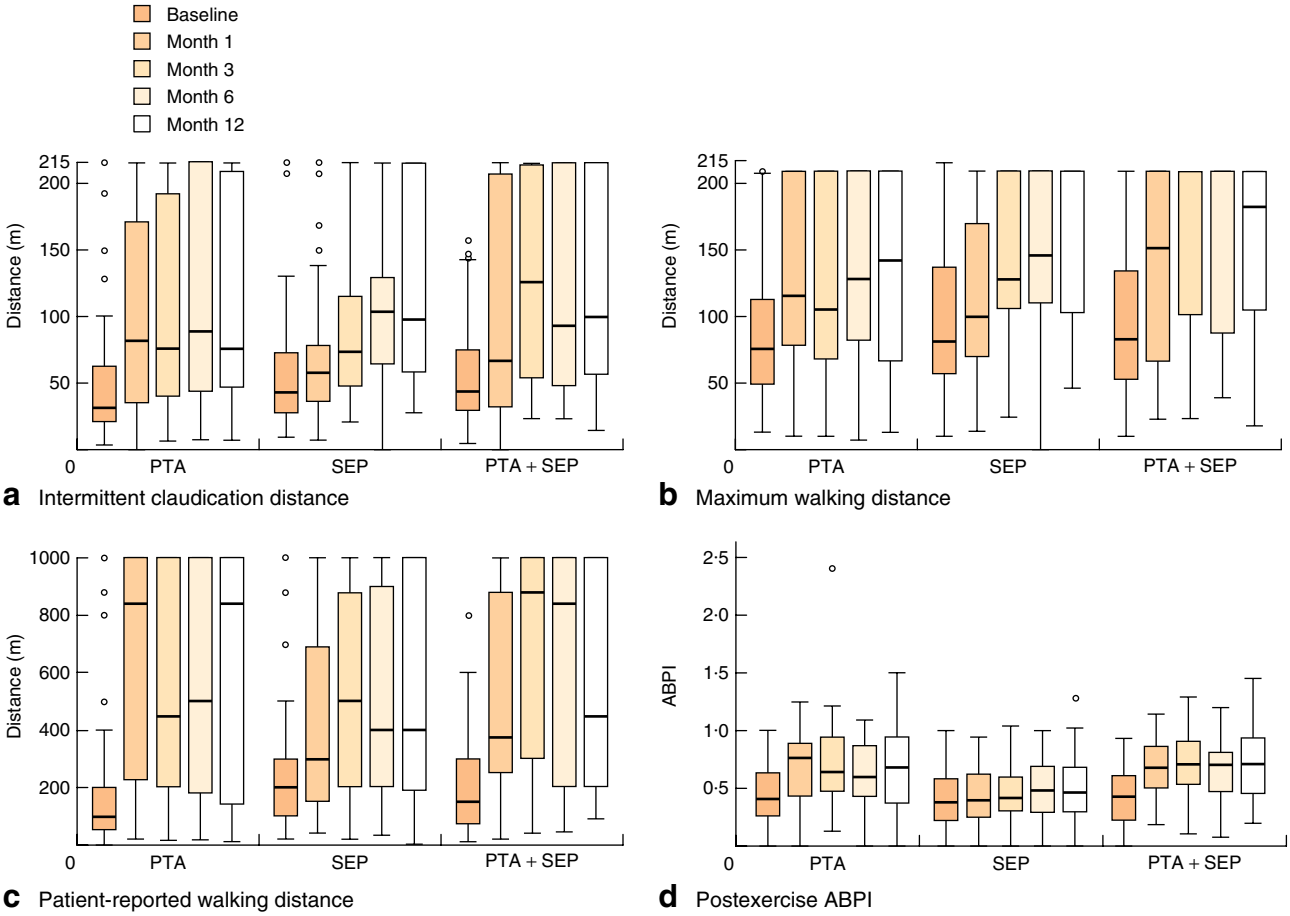

Fig. 2 Box-and-whisker plots representing selected outcomes for the clinical indicators of lower limb ischaemia in trial participants: **a** intermittent claudication distance; **b** maximum walking distance; **c** patient-reported walking distance; **d** postexercise ankle : brachial pressure index (ABPI). Full details of all clinical outcomes can be found in *Table S2* (supporting information). Median values, interquartile ranges (i.q.r.) and up to 1·5 times the i.q.r. (excluding outliers, ○) are denoted by horizontal bars, boxes and whiskers respectively. PTA, percutaneous transluminal angioplasty; SEP supervised exercise programme. There were statistically significant improvements in all groups, but no significant differences between the groups except for postexercise ABPI ($P = 0{\cdot}002$, Kruskal–Wallis ANOVA) (*Table 3*)

improvement, 16 (31 per cent); moderate improvement, 16 (31 per cent); marked improvement, 5 (10 per cent)), nine (17 per cent) demonstrated no change, and six (12 per cent) had deteriorated (mild deterioration, 3 (6 per cent); moderate deterioration, 3 (6 per cent)).

At 12 months after treatment in the SEP group, 32 (70 per cent) of 46 patients had improved (mild improvement, 19 (41 per cent); moderate improvement, 10 (22 per cent), marked improvement, 3 (7 per cent)), six (13 per cent) demonstrated no change, and eight (17 per cent) had deteriorated (mild deterioration, 5 (11 per cent); moderate deterioration, 3 (7 per cent)).

At 12 months in the PTA plus SEP group, 40 patients (85 per cent) had improved (mild improvement, 18 (38 per cent); moderate improvement, 20 (43 per cent); marked improvement, 2 (4 per cent)) after treatment, and seven (15 per cent) demonstrated no change. No patient in this treatment arm reported any deterioration at 1 year.

There were no significant differences in outcomes between the groups ($P = 0{\cdot}211$, χ^2 for trend).

*Quality-of-life indicators (*Fig. 3*;* Table S3, *supporting information)*

Patients in the PTA group had statistically significant improvements in all SF-36® domains and the VascuQol score, except in the vitality (V) domain of SF-36®.

Patients in the SEP group had statistically significant improvements in VascuQol score and in the PF,

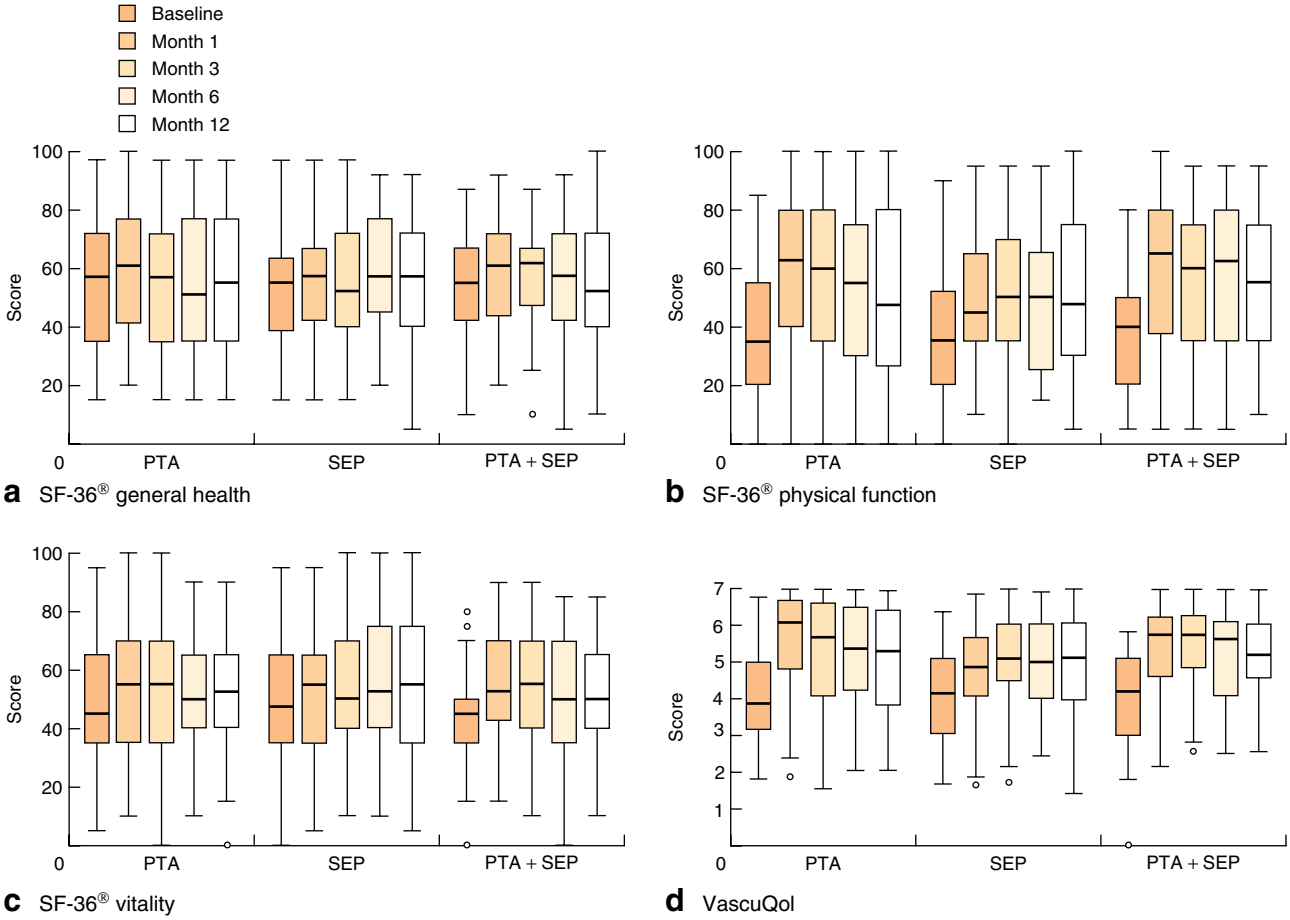

Fig. 3 Box-and-whisker plots representing selected quality-of-life (QoL) outcome indicators for trial participants: **a** general health, **b** physical function and **c** vitality Short Form 36 (SF-36®) domain scores, and **d** King's College Vascular Quality of Life (VascuQol) scores. Full details of all QoL outcomes can be found in *Table S3* (supporting information). Median values, interquartile ranges (i.q.r.) and up to 1·5 times the i.q.r. (excluding outliers, ○) are denoted by horizontal bars, boxes and whiskers respectively. PTA, percutaneous transluminal angioplasty; SEP supervised exercise programme. There were statistically significant improvements in all groups, but no significant differences between the groups (*Table 3*)

role limitation emotional (RE) and mental health (MH) domains. However, no statistically significant improvements were seen in the domains for role limitation physical (RP), bodily pain (BP), general health (GH), V and social functioning (SF).

Patients in the PTA plus SEP group had statistically significant improvements in the VascuQol scores and SF-36® domains for PF, BP and SF. No statistically significant improvements were observed in the domain scores for RP, GH, V, RE and MH.

Intergroup analyses

PTA and PTA plus SEP resulted in a significantly higher median postexercise ABPI compared with SEP alone at 12 months ($P = 0{\cdot}002$). However, there were no statistically significant differences between the three treatment arms in any other clinical indicator, ISCVS outcomes or QoL indicators at 12 months (*Table 3*).

Restenosis and reintervention rates

Duplex ultrasonography was performed at 3 months after intervention in 57 (95 per cent) of the 60 patients in the PTA group and in 48 (83 per cent) of the 58 in the PTA plus SEP group. Significant restenosis (defined by a doubling of peak systolic velocity as standard) was seen in seven (12 per cent) and four (8 per cent) respectively of the scanned patients ($P = 0{\cdot}751$). At the final 12-month follow-up, duplex imaging was done in 35 (67 per cent) of

Table 3 Summary statistics for intergroup comparison of clinical and quality-of-life indicators at 12 months

	*P**
Clinical indicators	
ABPI	
Resting	0·093
After exercise	0·002
Intermittent claudication distance	0·484
Maximum walking distance	0·259
Patient-reported walking distance	0·801
Quality-of-life indicators	
Short Form 36	
Physical function	0·758
Role limitation physical	0·865
Bodily pain	0·284
General health	0·839
Vitality	0·800
Social function	0·701
Role limitation emotional	0·988
Mental health	0·144
VascuQol	0·906

ABPI, ankle : brachial pressure index; VascuQol, King's College Vascular Quality of Life questionnaire. *Kruskal–Wallis ANOVA.

52 patients in the PTA group and in 34 (72 per cent) of 47 in the PTA plus SEP group. Restenosis was identified in 24 (69 per cent) and 23 (68 per cent) respectively of these patients ($P = 0·799$).

Nine (15 per cent) of the 60 patients in the PTA group required reintervention and six (10 per cent) of 60 in the SEP group needed an intervention within 12 months; however, none of the patients in PTA plus SEP group required any reintervention. This difference was not statistically significant ($P = 0·065$).

Discussion

Treatment of IC due to femoropopliteal atherosclerosis has always posed a challenge. Although TASC II provides some guidelines[11], there is no established standard treatment. BMT is initiated in all patients, followed by either SEP or PTA depending on the nature of the lesion, severity of symptoms and suitability for treatment[2,4,8,11]. Both SEP and PTA have been shown to improve clinical and QoL outcomes when compared to conservative medical treatment and unsupervised exercise[14,19,22–28]. Previous trials comparing PTA and SEP were underpowered and hence inconclusive[12,13,15,27]. Furthermore, to date, only one randomized trial has described the combined effect of PTA, SEP and BMT on clinical and generic QoL indicators compared with SEP and BMT[29].

Previously, a statistically significant improvement in clinical indicators was reported at 3 months, with patients in the PTA plus SEP group performing better than those having either PTA or SEP alone[30]. This initial advantage was not sustained at 12 months. Generally, patients who had PTA demonstrated an immediate improvement in all indicators at 1 month after intervention, but with some deterioration at 3 and 6 months, followed by improvement again at 12 months, probably due to reintervention. Patients having SEP lacked this immediate response and showed a more gradual trend of improvement that peaked at 6–12 months, with some deterioration at 12 months in some parameters. Patients who had PTA plus SEP had a combination of the two phenomena: an initial improvement after PTA followed by a sustained improvement lasting throughout the year.

Improvement in ABPI as a result of angioplasty in the PTA and PTA plus SEP groups followed the general trend described previously. However, improvement in resting ABPI after SEP was a novel finding and contradicts previous evidence[13,14,29]. This change was seen as early as 3 months and was sustained at 1 year. Remodelling of the collateral circulation in response to ongoing ischaemia and opening up of preformed collaterals with SEP are likely explanations[30]. ICD and MWD are more reliable clinical indicators of the severity of leg ischaemia than ABPI[11]. Improvements in ICD and MWD had a slightly different trend from ABPI: the results were very variable after PTA, whereas patients who had SEP demonstrated a gradual improvement in ICD up to 6 months with continuing improvement in MWD at 12 months.

The lack of a statistically significant difference between the treatments at 12 months in ICD and MWD can be explained by the ceiling effect as a consequence of capping the treadmill test at 5 min (215 m). Future studies could increase the time cap to 10 or 15 min.

The subjective nature of PRWD limits its value, with a relatively poor correlation with other clinical and QoL domains[17]. Recent studies have demonstrated a better correlation between PRWD and generic QoL indices[31], providing some evidence for its value in clinical trials. In the present study, intragroup and intergroup trends for PRWD were similar to other clinical indicators, demonstrating its sensitivity to change and value as a subjective indicator of leg ischaemia.

Although no statistically significant difference was observed between the three treatments after 12 months, the fact that no patient in the PTA plus SEP group deteriorated or required reintervention by 12 months is clinically significant. The restenosis rates in PTA and PTA plus SEP groups were comparable and similar to previously published values[10,28]. Thus, combining SEP with PTA did not reduce the risk of restenosis, but prevented it

from becoming symptomatic, leading to sustained clinical improvement.

The primary aim of treatment for IC is improvement in QoL[3,7]. Correlation between improvement in clinical and QoL indicators for patients with IC is moderate at best[16,17,31], with relatively better results for disease-specific measures[20]. Previous studies have reported QoL as secondary outcome with sample size calculation performed primarily for clinical outcomes[13,29]. The present study was powered for QoL parameters as the primary outcome measures.

Improvement observed in the disease-specific VascuQol and PF domain scores of generic SF-36® across all treatment groups is in accordance with previous evidence[12,29,32]. In addition, improvement in the BP domain of the SF-36® after treatments involving angioplasty is understandable. However, improvements seen in GH, SF, RE and MH domains in the PTA only group are not consistent with previous studies[13,29,32,33]. Possible explanations include the effect of reinterventions on QoL scores, low baseline in certain domains, the semiordinal nature of SF-36® scoring, or chance. Similarly, improvement in SF-36® RE and MH domains after SEP contradicts previous evidence[19]. The PTA plus SEP group was the only one with results consistent with available evidence[12,13,19].

There are a few limitations of the present study. Only patients with symptomatic, unilateral femoropopliteal arterial disease were included; this represents only 15–20 per cent of patients with IC[1,6], resulting in exclusion of a large number of patients with bilateral or mixed arterial disease. However, this was necessary from a scientific point of view to reduce the influence of confounders, and to provide a robust answer to the treatment controversy in this group. In addition, the time cap of 5 min for the fixed-load treadmill test had a limiting effect on the interpretation of results for ICD and MWD. Finally, the loss to follow-up was more than anticipated in the SEP and PTA plus SEP groups. This was mainly due to the withdrawal of patients from the hospital-based SEP, owing to lack of hospital transport and long distances between patients' homes and hospital. Provision of a community-based SEP could address this issue in future.

This trial demonstrated no statistically significant difference between the three treatments after 1 year. PTA was associated with a high incidence of restenosis, adding both the costs of reintervention and the potential for complications[10]. SEP provided an equally effective alternative, with relatively lower costs[19]; however, patients needed commitment to the programme (3 times a week for 3 months) for an optimal outcome[11,23]. Currently, these services are not provided in the community. Combining the two treatments had a sustained effect, while reducing the rate (and cost) of reinterventions, but still with the difficulties associated with a hospital-based SEP. The provision of this service in the community to reduce patients' time and travelling costs, while delivering a clinically effective treatment, would be optimal. A full economic analysis of the cost-effectiveness of these treatments will help to make rational recommendations.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Stations in supervised exercise programme (Word document)

Table S2 Clinical outcome data (Word document)

Table S3 Quality-of-life indicators at all time points for all treatment arms (Word document)

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