Long term outcomes of a randomised controlled trial of supervised exercise programme, percutaneous transluminal angioplasty and combined treatment for patients with intermittent claudication due to femoropopliteal disease.

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Abstract

Background: To compare the long-term outcomes of angioplasty (PTA), supervised exercise (SEP) and combined treatment (PTA+SEP) in patients with intermittent claudication (IC) due to femoropopliteal disease.

Methods: Patients recruited to PTA, SEP and PTA+SEP arms of RCT were invited for long-term follow-up from 2010 to 2011.Indicators of limb ischaemia were recorded (ankle-brachial pressure indices, treadmill walking distances (ICD, MWD, PRWD). Duplex ultrasound was also performed. Patients completed SF36 and Vascuqol quality of life(QOL) questionnaires.

Results: Of the 178 patients recruited in the trial, 139 were alive at the time of follow-up (PTA=46, SEP=47, PTA+SEP=46). Assessments were completed for 111 patients. Median time to follow-up was 5.2years (IQR 3.8-7.4years). Median age of patients at follow up was 75years. 62.2%(N=69) of patients were symptomatic.16.2%(N= 18) had experienced major cardiovascular event since their last follow-up visit.
Intra-group analysis: Improvement was observed in ankle brachial pressure index (ABPI) in all groups. QOL outcomes were inconsistent across individual groups.
Inter-group analysis: PTA and PTA+SEP groups demonstrated a significantly higher ABPI as compared to SEP group. No significant difference was observed in walking distances, QOL outcomes, restenosis rates, and new ipsilateral and contralateral lesions on duplex scan. Patients required re-interventions in all group (PTA=14, SEP=10, PTA+SEP=6). Number of re-interventions was higher in PTA group(N=29) as compared to SEP(N=17) and PTA+SEP(N=9) but failed to reach statistical significance.

Conclusion: PTA, SEP and combined treatment are equally effective long-term treatment options for patients with femoropopliteal claudication. Addition of SEP to PTA can reduce the symptomatic restenosis and re-intervention rates.

Introduction

Intermittent claudication (IC) is the commonest presentation of peripheral vascular disease that affects 5% of the population over 45 [1, 2]. Treatment of claudication is aimed at improving the quality of life [3]. Risk factor modification and supervised exercise programmes (SEP) are the first line treatments recommended in the most recent treatment guidelines. Percutaneous transluminal angioplasty (PTA) and surgery are used in cases where SEP is not possible or successful [4, 5]. A series of clinical trials have demonstrated no difference between the PTA and SEP for clinical outcomes and quality of life (QOL) in short term follow up [6, 7]. There are only a few studies that report on the long term outcomes in these patients [8, 9]. This study reports on the long term outcomes of one of the largest randomised controlled trials (RCT) comparing PTA, SEP and combined treatment (PTA+SEP) in patients with intermittent claudication due to femoropopliteal atherosclerotic disease [10-12].

Methods

The key features of the original trial including design, eligibility, interventions, outcome measures and sample size calculation are summarised in Table 1. Medical records of all participants who were included in the initial RCT in 2010 & 2011 were checked to assess their current status of health. All alive patients who participated in the initial RCT were contacted via telephone to invite them to take part in the long-term follow up visit. All patients who agreed to come for follow-up were assessed in the vascular laboratory. Demographic details were recorded and a detailed history was obtained including symptoms, risk factors, medical comorbidities, smoking status, any cardiovascular problem since completion of trial follow-ups, surgery, endovascular intervention and amputation. This was cross checked using the clinical and electronic patient records to capture all possible adverse events. Patients then underwent a fixed load treadmill testing (10-degree inclination and 2.5 km/hour) for a maximum of five minutes in accordance with the original trial protocol. Clinical indicators of limb ischaemia were recorded including pre and post-exercise ankle brachial pressure index, intermittent claudication distance (ICD), maximum walking distance (MWD) and the subjective patient reported

walking distance (PRWD). Walking distances were measured and recorded in metres. The ceiling for MWD for patients who completed the treadmill testing without having absolute claudication (AC) was 215 metres. Similarly, the ceiling for PRWD was set at 1600 metres (as per the original trial). The patients also completed the Version 2.0 of the Short Form 36 (SF36®) questionnaire for United Kingdom population for generic quality of life (QOL) and Kings College Vascuqol for disease specific QOL in accordance with the original trial protocol [13, 14]. All patients had an arterial Duplex scan performed on both lower limbs and a detailed assessment was undertaken of the whole arterial tree to identify new and old lesions.

The primary outcome measures were MWD and the physical function (PF) domain of SF36®. Secondary outcome measures included pre and post exercise ABPI, ICD, PRWD, remaining domains of SF36, Vascuqol, re-stenosis, re-intervention and major cardiovascular event rates.

Data Collection was performed on source documents and transcribed onto Microsoft® Excel worksheet (Microsoft Corporation, Redmond, Washington, USA). Statistical analysis was performed using Stata® 12.0 (StataCorp, College Station, Texas, USA) and SPSS® 21.0 (SPSS, Chicago, Illinois, USA). Distribution testing for continuous variables was performed using histograms. Variables with normal distribution were presented as mean with 95% confidence interval (CI), whilst skewed variables were represented as median with 95%CI and interquartile range (IQR). Hypothesis testing was performed for inter-group comparison using Kruskal Wallis ANOVA. Categorical variables were compared using Chi square test. Significance level was set at 5%. Bonferroni correction was applied for multiple testing in post-hoc analyses, where applicable. No correction was applied when a single test was used for hypothesis testing across the groups. The analysis in the primary trial was performed on intention-to-treat basis. This principle was followed in the current study and all patients were analysed in the groups they were randomised to. However, final analysis was performed on per-protocol basis as patients who died prior to follow-up or those who were lost to follow-up were excluded, as accurate data imputation was not possible due to staggered follow-up.

Additional approvals were obtained from the trust and local research and ethics committee for the long-term follow-up visit as this was not included in the original trial protocol (Reference HEY-REF-2424). The follow-up expenses were internally funded by the Academic Vascular Surgery Unit of the University of Hull. The trial was registered with www.clinicaltrials.gov (Trial ID NCT00798850).

Results

178 patients were recruited in the initial trial. 25% (N=39) had died prior to the long term follow-up visit. The follow-up assessments were completed for 62.3% (N = 111) of the trial patients (**CONSORT diagram, Figure 1**). Median time to long-term follow up was 5.2 years (95%CI 4.6 to 5.7 years, IQR 3.8 to 7.4 years). Median age of the patients at follow-up was 75 years (95% CI 72 to 77 years, IQR 68 to 79 years). 62.2% (N = 69) of the patients were symptomatic at the time of follow-up. 18.0% (N = 20) of these patients were actively smoking at the time of follow up. 16.2% (N = 18) of these patients had experienced major cardiovascular event like myocardial infarction, stroke or major amputation since their last follow-up visit. Basic demographics, clinical status and treadmill testing outcomes at long-term follow up are summarised in **Table 2**.

1) Intra-group analyses

(a) Clinical indicators of lower limb ischaemia

No group demonstrated a sustained improvement in MWD. All groups demonstrated an improvement in ABPI. However, the improvements in ICD and PRWD were not consistently sustained at long term (**Table 3**).

(b) Quality of life outcomes

QOL outcomes demonstrated mixed outcomes across the treatment arms. No single domain score of the SF36® or Vascuqol score demonstrated improvement across all three treatment arms. (**Table 4**).

2) Inter-group analyses

(a) Clinical indicators of lower limb ischaemia

Patients in the PTA and the PTA+SEP group demonstrated a significantly higher median resting and post-exercise ABPI (RABPI, PABPI) as compared to the SEP only patients at long-term follow-up. However, there was no statistically significant difference between the three treatment arms in any other clinical indicator (**Table 5**, **Figure 2**).

(b) Quality of life outcomes

No statistically significant difference was observed between the three treatment arms in any domain of the SF36 or the Vascuqol score at the long-term follow-up visit (**Table 5, Figure 3 & 4**).

3) Re-stenosis and Re-intervention rates

Arterial duplex ultrasonography was performed in 94.60 % (N=105) of the patients who completed the long-term follow up. A significant stenosis at the site of the index lesion (defined as doubling of peak systolic velocity across the lesion on duplex scanning) was observed in most of the patients in all three treatment arms. New lesions on the same side were detected in two-thirds of the patients with a similar distribution across the three treatment arms. Stenotic lesions on the contralateral side were also detected in all treatment arms with relatively higher distribution in the PTA+SEP and the SEP only groups as compared to the PTA only group. The number of patients

requiring re-intervention was the lowest in the PTA+SEP arm (N=6); followed by the SEP arm (N=10) and the PTA arm (N=14) respectively. Similarly, the highest numbers of repeat angioplasty procedures were performed in the PTA arm followed by the SEP and the PTA+SEP arms. PTA group also had the highest number of surgical revascularisation procedures performed. Conversely, PTA+SEP group did not have any surgical revascularisation procedures. However, these differences failed to reach the threshold for statistical significance (**Table 6**).

Discussion

A lack of long-term patient follow-up has always been a problem in the previous PAD trials. The long-term outcomes have been reported in one previous trial with a small number of patients who completed the follow-up [8]. Several systematic reviews and meta-analyses have confirmed a dearth of evidence as long-term outcomes are seldom reported in RCTs comparing angioplasty and the exercise-based treatments for IC [15-17]. The long-term follow-up was completed in 80% of patients in this trial who were alive at the time of follow-up. This makes it one of the largest series to date reporting on these outcomes. Only recently, the long-term outcomes from another trial comparing the PTA and the SEP have been published with very similar findings to this study [9].

Twenty-two percent of the trial participants died before the long-term follow-up giving an annual mortality rate of four to five percent. This is similar to the previously reported rate ranging from five to thirteen percent [18-20]. Considering

the median age of the deceased, the results of this study support the reported reduction in life expectancy of up to ten years in patients with IC [19-21].

The difference amongst the three treatment arms in the ABPI is similar to what was observed at the primary endpoint. Interestingly, it did not have any bearing on the walking distances. This observation is contradictory to the previous evidence that supports a trend of initial improvement followed by some long-term deterioration in due to disease progression and attrition of the treatment effect [21-24]. Moreover, the PABPI demonstrated a trend of continuing improvement in all three treatment arms. The sustained long-term improvement in the ABPI at rest and post-exercise in the SEP only treatment arm is also a novel finding of this study. Re-interventions may have a strong role in producing these trends. However, collateral remodelling may also have a part to play. This certainly requires further investigation.

Although the re-stenosis and re-intervention rates did not show any statistically significant difference in the long-term, these findings require careful interpretation. Re-stenosis of the primary lesion and new ipsilateral lesions on duplex scanning were observed in all treatment arms in a similar proportion. Contra-lateral lesions were more prevalent in the SEP and the PTA+SEP arms. As ipsilateral and contralateral re-vascularisation procedures were more frequent in the PTA arm, it is evident that bilateral symptomatic lesions were picked up and treated more frequently in this group. Patients in the combined treatment arm (PTA+SEP) had the lowest number of re-interventions performed with no surgical revascularisation on either side. When compared to the PTA+SEP arm, patients required twice as many procedures in the SEP arm and three times as many procedures in the PTA

arm. The relatively small numbers may account for the lack of statistical significance but these findings are highly relevant in the clinical context. Addition of SEP to PTA seems to have a lasting effect in preventing an early treatment failure with a considerable reduction in the requirement for further interventions in the long-term. Further studies are required to investigate the long-term difference in re-intervention rates with an appropriate power and sample size calculation.

There are a number of limitations to this study. Firstly, addition of the long-term follow-up as a protocol exception coupled with staggered recruitment into the primary trial, precluded a time fixed long-term follow-up visit. Consequently, some patients had a much shorter interval to the follow-up. It may be appropriate to consider these results as intermediate to long-term to account for this variability. Secondly, the trial was powered to look at a 20% difference in primary outcomes at twelve months. As only 62% of the trial patients were included in this study, it did not have sufficient power to show a statistical difference between groups. Thirdly, the results are applicable to femoropopliteal claudicants due to strict inclusion criteria. Fourthly, the time cap of five-minutes for fixed-load treadmill testing made it difficult to reach absolute claudication, thus limiting the interpretation of results for the ICD and the MWD. Recent trials that compared these parameters without time cap have demonstrated a significant difference in these outcomes [7, 25]. Finally, the lack of information regarding actual cause of death for the deceased makes it difficult to interpret the true number of cardiovascular events in this cohort.

This RCT has profound clinical and economic implications for patients with the infra-inguinal PAD. It has demonstrated that there is no statistical difference in

the short or the long-term outcomes amongst the three treatments. However, the differences in re-intervention are clinically relevant and cannot be ignored. The new guidelines from the National Institute of Health and Care Excellence (NICE) and the American Heart Association (AHA) recommend the SEP as a first-line treatment [4, 26]. PTA remains a clinically effective first-line treatment modality in patients with IC who fail to improve symptomatically with SEP [4, 26-28]. PTA does not confer the additional benefits of lifestyle change, balance improvement and motivational therapy [29-31]. Addition of SEP to PTA provides these benefits and also helps to reduce the number of symptomatic re-stenoses and re-interventions as shown in this trial. Studies have reported a higher incidence of re-interventions following the primary PTA as compared to the primary SEP as demonstrated in this trial [9, 32]. These findings support the provision of the SEP preferentially, prior to offering the PTA as per the recent guidelines [4, 26]. However, an individual exception has to be made for the patients who are unable to take part in an exercise programme due to the co-morbidities, physical limitation, or a lack of resources for the convenient provision of the SEP [33].

References

1. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;**20**(2): 384-392.

2. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral

artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**(9901): 1329-1340.

3. Chetter IC, Scott DJ, Kester RC. An introduction to quality of life analysis: the new outcome measure in vascular surgery. *Eur J Vasc Endovasc Surg* 1998;**15**(1): 4-6.

4. NICE. Lower limb peripheral arterial disease: diagnosis and management. In: CG147. London: National Institute for Health and Care Excellence; 2012.

5. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**127**(13): 1425-1443.

6. Creasy TS, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg* 1990;**4**(2): 135-140.

7. Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA, Thompson SG, Mimic Trial P. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *Eur J Vasc Endovasc Surg* 2008;**36**(6): 680-688.

8. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg* 1996;**11**(4): 409-413.

9. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial. *Br J Surg* 2013;**100**(9): 1164-1171.

10. Mazari FA, Gulati S, Rahman MN, Lee HL, Mehta TA, McCollum PT, Chetter IC. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. *Ann Vasc Surg* 2010;**24**(1): 69-79.
11. Mazari FA, Khan JA, Carradice D, Samuel N, Abdul Rahman MN, Gulati S, Lee HL, Mehta TA, McCollum PT, Chetter IC. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg* 2012;**99**(1): 39-48.
12. Mazari FA, Khan JA, Carradice D, Samuel N, Gohil R, McCollum PT, Chetter IC. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg* 2013;**100**(9): 1172-1179.
13. Ware JE, Jr. SF-36 health survey update. *Spine* 2000;**25**(24): 3130-3139.
14. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg* 2001;**33**(4): 679-687.
15. Frans FA, Bipat S, Reekers JA, Legemate DA, Koelemay MJ. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. *Br J Surg* 2012;**99**(1): 16-28.
16. Ahimastos AA, Pappas EP, Buttner PG, Walker PJ, Kingwell BA, Golledge J. A meta-analysis of the outcome of endovascular and noninvasive therapies in the treatment of intermittent claudication. *J Vasc Surg* 2011;**54**(5): 1511-1521.
17. Spronk S, Bosch JL, Veen HF, den Hoed PT, Hunink MG. Intermittent claudication: functional capacity and quality of life after exercise training or percutaneous transluminal angioplasty--systematic review. *Radiology* 2005;**235**(3): 833-842.
18. Muluk SC, Muluk VS, Kelley ME, Whittle JC, Tierney JA, Webster MW, Makaroun MS. Outcome events in patients with claudication: a 15-year study in 2777 patients. *J Vasc Surg* 2001;**33**(2): 251-257; discussion 257-258.

19. Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Cardiol* 2001;**87**(12A): 3D-13D.
20. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, Ruckley CV. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996;**25**(6): 1172-1181.
21. Aquino R, Johnnides C, Makaroun M, Whittle JC, Muluk VS, Kelley ME, Muluk SC. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. *J Vasc Surg* 2001;**34**(6): 962-970.
22. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, Group TIW. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;**45 Suppl S**: S5-67.
23. McDermott MM, Guralnik JM, Ferrucci L, Criqui MH, Greenland P, Tian L, Liu K, Tan J. Functional decline in lower-extremity peripheral arterial disease: associations with comorbidity, gender, and race. *J Vasc Surg* 2005;**42**(6): 1131-1137.
24. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, Taylor LM, Vonesh E, Martin GJ, Clark E. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA* 2004;**292**(4): 453-461.
25. Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, Smits TM, van Brussel JP, Stultiens GN, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, van Petersen A, Woltman K, Hulst I, van Sambeek MR, Rizopoulos D, Rouwet EV, Hunink MG. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial. *JAMA* 2015;**314**(18): 1936-1944.
26. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA, World Heart F, the Preventive Cardiovascular Nurses A. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a

guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;**124**(22): 2458-2473.
27. Nylaende M, Abdelnoor M, Stranden E, Morken B, Sandbaek G, Risum O, Jorgensen JJ, Lindahl AK, Arnesen H, Seljeflot I, Kroese AJ. The Oslo balloon angioplasty versus conservative treatment study (OBACT)--the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2007;**33**(1): 3-12.
28. Fowkes FG, Gillespie IN. Angioplasty (versus non surgical management) for intermittent claudication. *Cochrane Database Syst Rev* 2000(2): CD000017.
29. Gohil RA, Mockford KA, Mazari FA, Khan JA, Van Vanicek N, Chetter IC, Coughlin PA. Percutaneous transluminal angioplasty results in improved physical function but not balance in patients with intermittent claudication. *J Vasc Surg* 2013;**58**(6): 1533-1539.
30. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, Coughlin PA. Balance impairment, physical ability, and its link with disease severity in patients with intermittent claudication. *Ann Vasc Surg* 2013;**27**(1): 68-74.
31. Giugliano G, Di Serafino L, Perrino C, Schiano V, Laurenzano E, Cassese S, De Laurentis M, Schiattarella GG, Brevetti L, Sannino A, Gargiulo G, Franzone A, Indolfi C, Piscione F, Trimarco B, Esposito G. Effects of successful percutaneous lower extremity revascularization on cardiovascular outcome in patients with peripheral arterial disease. *International journal of cardiology* 2013;**167**(6): 2566-2571.
32. Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. *Clinical physiology and functional imaging* 2008;**28**(1): 32-37.
33. Spronk S, White JV, Ryjewski C, Rosenblum J, Bosch JL, Hunink MG. Invasive treatment of claudication is indicated for patients unable to adequately ambulate during cardiac rehabilitation. *J Vasc Surg* 2009;**49**(5): 1217-1225; discussion 1225.