Title: A systematic review of the uptake and adherence rates to supervised exercise programmes in patients with intermittent claudication.

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Introduction: Intermittent claudication (IC) is a common and debilitating symptom of peripheral arterial disease and is associated with a significant reduction in a sufferer's quality of life. Guidelines recommend a supervised exercise programme (SEP) as the primary treatment option; however, anecdotally there is a low participation rate for exercise in this group of patients. We undertook a systematic review of the uptake and adherence rates to supervised exercise programmes for individuals with IC.

Methods: The Medline, Embase and PubMed databases were searched up to January 2015 for terms related to supervised exercise in peripheral arterial disease. The review had three aims: firstly to establish the rates of uptake to SEPs, secondly the rates of adherence to programmes and finally to determine the reasons reported for poor uptake and adherence. Separate inclusion/exclusion criteria were applied in selecting reports for each aim of the review.

Results: Only 23 of the 53 potentially eligible papers for uptake analysis identified on literature searches reported any details of screened patients (n = 7517) with only 24.2% of patients subsequently recruited to SEPs. Forty-five percent of screen failures had no reason for exclusion reported. 67 papers with 4012 patients were included for analysis of SEP adherence. Overall 75.1% of patients reportedly completed a SEP, however only one paper defined a minimal attendance required for SEP completion. 54.1% of incomplete adherence was due to patient withdrawal and no reason for incomplete adherence was reported for 16% of cases.

Discussion: Reporting of SEP trials was poor with regard the numbers of subjects screened and reasons for exclusions. Only approximately 1 in 3 screened IC patients was suitable for and willing to undertake SEP. Levels of adherence to SEPs and definitions of satisfactory adherence were also lacking in the majority of the current literature. Current clinical guidelines based upon this evidence base may not be applicable to the majority of IC patients and changes to SEPs may be needed to encourage/retain participants.

Introduction

Intermittent claudication (IC) is the most common symptom of peripheral arterial disease (PAD), affecting 5 % of the population over the age of 50 years [1] and 20 % of the population over 70 years [2]. IC is due to muscle ischemia precipitated by exercise and is frequently associated with a reduction in walking capabilities [3]. Supervised exercise programmes (SEPs) for patients with claudication have been demonstrated to improve walking distances and be cost effective [4]. Current clinical guidelines recommend that all patients with IC are enrolled on a group-based SEP [5, 6]. Furthermore, centres should consider a programme comprised of intermittent walking to near maximal or maximal pain, three times a week, for a minimum of 12 weeks [7].

Although it is agreed that supervised exercise should be the first line treatment, there is evidence suggesting that relatively few patients are suitable for and will agree to participation in an SEP[8].Many who commence an SEP fail to complete the programme of classes. Clearly the clinical and cost effectiveness of SEPs for managing the population of IC patients as a whole may be significantly affected by poor recruitment and adherence to programmes.

This review has 3 aims, firstly to establish from the existing literature the levels of uptake of SEPs in published trials, which we defined as the proportion of screened patients who went on to commence an SEP. Secondly to determine patient adherence to SEPs, which was defined as the proportion of patients who commenced an SEP and subsequently completed all sessions. Thirdly to explore what reasons were reported for lack of uptake or adherence in IC patients.

Methods

A systematic review of randomised and non-randomised clinical trials (RCTs) including a SEP arm was performed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for reporting of search results[9].

Search Strategy

Systematic review was performed using Medline, Embase and CENTRAL. The search strategy aimed to include any trials which included SEP either as the control arm or as the primary intervention. Search terms used were:

'peripheral arterial disease' [OR] 'intermittent claudication' [OR 'claudication' [OR] 'ischemia' [AND], 'exercise' [OR] 'running' [OR] 'exercise therapy' [OR] 'exercise movement' [OR] 'training' [AND] 'supervised'.

Searches were limited to run from 1947 to January 2015. The search was limited to full text articles relating to adults (over 18 years of age) and published in English. Abstracts identified by the database search were independently interrogated for relevance by two reviewers (AH & TC). Citations from the full texts of relevant reports were hand searched for other relevant references.

Inclusion criteria

Two cohorts of reports were selected from within the search results, firstly to assess data on rates of uptake, then data on rates of adherence to SEPs. Both cohorts were then examined for reporting of reasons for poor uptake and adherence. For both searches, we included randomised and prospective non-randomised studies that investigated the role of SEPs in patients diagnosed with Intermittent Claudication (Fontaine II/ Rutherford 1-3).These were either diagnosed clinically or by interview/ questionnaire. We included any form of SEP regardless of the structure, duration, frequency or intensity of training utilised. Papers were only included if they specifically reported the numbers of subjects recruited to, commencing and completing the SEP. Any studies including patients who were asymptomatic were excluded.

Rate of SEP Uptake cohort:

In an attempt to avoid bias, studies were excluded from this cohort if they included any active interventions other than an SEP (e.g. medications/supplements, angioplasty, surgery). The rationale for exclusion was so that patients refusing to participate would not have been deterred by the possibility of randomisation to any treatment other than the SEP. Data was collected to include numbers screened and numbers of patients who were subsequently allocated to an SEP and attended at least one session.

Adherence to SEPs cohort:

All Studies involving an SEP arm versus any other comparator arm were included in this cohort. Data extraction was then limited to the subjects assigned to the SEP arm(s) with regard to rates of SEP adherence.

Data extraction

Any disagreement as to inclusion of a report between the two assessing investigators (AH,TC) was settled by consensus with a third (GS). Data extraction was then performed by two investigators (AH, TC) using a standardised data extraction sheet. Data regarding research unit and country, target population, numbers of patients initially screened/referred for SEP, number of participants enrolled to SEP, reasons for non-enrolment, number of dropouts prior to completion of SEP, reasons for dropout and description of the supervised exercise protocol, (frequency, duration, content) were collected.

Results

Search results

The search yielded a total of 333 reports of which 11 were duplicates. Of the remaining 322, 67 were appropriate for inclusion in one or both sections of the planned analysis. The inclusion/exclusion process is summarised in figure 1.

Included trials

Our analysis included 67 trials, all of which utilised some form of SEP in claudicants and recorded details of recruited subjects and numbers of those who commenced and completed an SEP. 52 reports were from randomised trials and the remainder were prospective case control or cohort studies. The total of recruited subjects within the 67 papers was 5817, with 4094 subjects assigned to a study arm which included a SEP. SEPs differed widely between reports both in duration (varying from 4 weeks to 12 months) and in type of exercise undertaken (resistance, aerobic, combination - upper/ lower limb). Included studies are summarised in Table 1.

Author	Year	Total Recruited	Assigned SEP	% Uptake	% Adherence	SEP Duration	X Per week	Type

						(Weeks)		
Allen[10]	2014	27	27	100	100	12	3	Aerobic
Andreozzi[11]	2008	44	44	100	100	6	3	Walking
Beckitt[12]	2012	38	27	100	100	12	3	Mixed
Beckitt[12]	2012	56	42	100	100	12	3	Mixed
Bendermacher[6]	2007	39	39	100	60	52	3	Mixed
Bo[13]	2013	50	29	100	100	12	3	Walking
Bronas[14]	2011	40	20	100	100	12	3	Mixed
Cheetham[15]	2004	59	29	100	100	12	1	Mixed
CLEVER[16]	2012	119	51	96	92	26	3	Walking
Collins[17]	2005	52	27	100	85	24	3	Walking
Collins[18]	2012	146	103	100	94	24	3	Walking
Crowther[19]	2009	21	10	100	100	52	3	Walking
Degischer[20]	2002	69	38	100	100	12	3	Walking
Delaney[21]	2014	35	35	100	77	12	3	Mixed
Duscha[22]	2011	78	78	100	35	12	3	Walking
Fokkenrood[23]	2015	47	47	100	87	12	3	Mixed
Frans	2010	101	101	100	71	12	3	Walking
Gardner[24]	2012	142	106	100	76	104	3	Walking
Gardner[25]	2014	180	60	100	87	12	3	Walking
Gardner[26]	2005	77	77	100	83	24	3	Walking
Gardner[27]	2001	61	31	90	100	24	3	Walking
Gelin[28]	2001	264	73	100	59	24	3	Walking
Greenhalgh[29]	2008	144	60	100	82	24	1	Mixed
Hiatt[30]	1990	25	14	100	71	12	3	Walking
Hiatt[31]	1994	29	19	100	100	12	3	Walking OR Resistance
Hiatt[32]	2011	69	69	100	86	24	3	Walking
Hobbs[33]	2007	38	19	84	100	12	2	Walking
Hodges[34]	2008	28	14	50	100	12	2	Walking
Janusek[35]	2014	85	85	100	79	12	3	Walking
Jones[36]	2012	22	12	100	100	12	3	Walking
Jones[37]	1996	23	23	100	52	12	2	Walking
Kakkos[38]	2005	36	12	100	50	24	3	Walking
King[39]	2012	12	12	100	92	12	3	Mixed
Kruideiner[40]	2011	70	35	100	77	52	3	Mixed
Kruideiner[41]	2009	349	297	92	47	52	3	Mixed
Leicht[42]	2011	25	12	100	67	52	3	Walking
Mazari[43]	2012	178	118	85	93	12	3	Mixed
Meneses[44]	2011	34	34	100	88	52	2	Mixed
Mika[45]	2005	98	49	100	16	12	3	Walking
Mika[46]	2006	60	30	100	90	12	3	Walking
Mika[47]	2011	68	34	100	88	12	3	Walking

Mockford[48]	2014	51	51	100	96	12	3	Mixed
Nicolai[49]	2010	304	202	99	45	12	3	Walking
Parmenter[50]	2013	22	15	100	93	24	3	Resistance
Regensteiner[51]	1996	29	19	100	79	12	3	Mixed
Sakamoto[52]	2009	118	118	100	54	52	3	Walking
Savage[53]	2001	21	21	52	100	12	3	Walking
Schlager[54]	2011	40	20	100	100	24	2	Walking
Slordahl[55]	2005	16	16	100	100	8	3	Aerobic
Spronk[56]	2010	151	75	100	96	24	2	Walking
Stewart[57]	2008	60	30	100	91	24	2	Mixed
Tew[58]	2009	57	29	100	93	12	2	aerobic
Treat-Jacobson[59]	2009	62	37	100	78	12	3	Walking
Tsai[60]	2002	64	32	100	85	12	3	Walking
Van Pul[61]	2012	775	775	100	59	24	3	Walking
Versluis[62]	2013	10	10	100	100	12	2 / 3	Walking
Walker[63]	2000	52	52	100	92	6	2	Mixed
Wang[64]	2007	22	17	77	100	12	3	Walking
Wang[65]	2008	27	14	100	100	12	3	Walking
Wang[66]	2010	10	10	100	100	8	3	Strength
Zweirska[67]	2005	104	71	100	87	24	2	Aerobic

Uptake of supervised exercise

53 studies met the inclusion criteria for the uptake of an exercise protocol section of the review. However, only 23 of the 53 papers gave any details of total numbers of potential participants screened for participation. Within these reports 1820 subjects recruited from 7517 screened (24.2%).

Analysis of recruited patients from all 53 studies, showed 3296 were assigned to study arms which included a SEP as an intervention. There was a 98.1% rate of subjects assigned to SEP arms commencing SEP intervention following randomisation (3235 of 3296 subjects).

Supervised Exercise adherence

An additional 14 papers met the criteria for inclusion in the adherence to exercise programmes section of the review. These reports included comparator interventions of arterial surgery, angioplasty and medical therapies either alone or as adjuvants to SEP. A total of 67 papers were included in this analysis with a total of 5817 recruited subjects.

Any patient assigned to any arm which required SEP was included in the assessment of adherence to programmes. Of the 4012 subjects who commenced an SEP in the included trials, 3015 were reported as having adequately completed the exercise programme for inclusion in the analysis (75.1%). No paper gave a clear definition of the number of sessions attended that was considered the minimum for a subject to have completed the SEP intervention.

Eight reports included specific comments regarding levels of adherence with the programmes. Descriptions of adherence were as overall percentage attendance at sessions in 3 papers[63, 68, 69] percentage of subjects attending at least a certain proportion of total sessions in 3 papers [14, 32, 59] and two papers reported both[60, 69].

Reasons for screen failure and poor uptake or adherence

Screen failures:

The level of detail in reporting reasons for screen failures was highly variable, with two papers accounting for every patient[57, 70], whilst several others reported only "screen failure" in accounting for patients who were not recruited.

Of the 23 reports specifying total numbers of patients screened, with a cumulative total of 7517 screened for 1820 patients recruited, there were 5697 screen failures. Of these screen failures, 2566 (45%) did not have a reason for screen failure specified (reported only as "screen failure" or "other"). A further 614 patients had a list of reasons for exclusions reported but without quantifying the number of patients excluded for each reason. Thus only 2517 screen failures had quantified reasons for non-inclusion and these are shown grouped into categories and ranked by frequency in table 2.

10 papers reported uptake of less than 100% with 89 randomised patients failing to commence SEP. Five reports (33 patients) stated only "did not receive intervention" or gave no reasons for incomplete uptake. Where reasons were reported, patient withdrawal was the most frequent and insurance, exacerbation of co-morbidities or death also reported.

Poor adherence:

Again, reports varied widely in level of detail provided as to reasons for incomplete adherence to SEPS. Forty five of the 67 papers with a total of 3518 SEP patients reported incomplete adherence amongst 1066 study patients (30.3%). Of these 171 patents (16%) did not have a reason for incomplete adherence specified (no reasons given in report or "other specified"). A further 71 patients had a list of reasons for incomplete adherence reported but without quantifying the number of patients associated with each reason. Thus only 824 patients had quantified reasons for incomplete adherence and these are shown grouped into categories and ranked by frequency in table three.

Discussion

SEPs have been shown to be both clinically and cost effective in treatment of IC and there is a wealth of evidence supporting the recommendation of SEP as the first line treatment for IC. However the results of this review suggest that this evidence may not be universally applicable to the IC population as a whole.

The majority of trials included in this review gave no indication of numbers of IC patients screened for inclusion which makes the application of their results difficult. Where screening information was reported many of the reasons for non-inclusion are not recorded. For those with reasons for exclusion, almost 1 in 3 were excluded due to refusal on the part of the patient (30.6 %).Co-morbidities preventing exercise followed (16.2 %) with inability to attend classes due to location or timing (11.7 %) preventing a further 1 in 4 from participating. Clearly the results presented here may include some level of negative bias as participants were being screened / assessed for inclusion in both a clinical trial as well as an SEP, potentially reducing the numbers of eligible or amenable recruits. However, approximately only 1 in every 3 of the screened IC patient population is eligible and willing to be included in an SEP as part of the included trials. This finding is very similar to results reported by Muller-Buhl in a prospective observational study who found that only 36% of their referrals to a SEP for IC were suitable for participation[8]. Thus the patients studied in the majority of the included trials, which represent the bulk of the available evidence upon which current recommendations are based, may therefore represent a better motivated and less co-morbid cohort within the overall population of IC patients.

For subjects who were willing and able to participate the rate of uptake once allocated to a SEP as part of a trial was excellent (98.1%).This may however be an effect of selection bias in that this group has agreed to participate in SEP in a trial and is likely a subsection of claudicants with a high level of motivation or willingness to change. Data from our own SEP (personal communication) and those of Muller-Buhl suggest that as few as 24% of eligible patients will actually attend SEP sessions despite initially agreeing to participate when referred.

Overall adherence was reported as 75% for those subjects allocated to SEP though very few reports gave any specific figures for adherence within their study populations. Furthermore only one defined a target figure for attendance that determined acceptable attendance. It is very possible that the specifics of the SEP might influence the rate of uptake and adherence. There was a very wide range of SEPS included in this review (table 1) including aerobic and resistance training with varied frequencies over markedly different durations. It is also interesting to note that those trials with the lowest levels of uptake and adherence tended to be those with longer duration, frequency and reduced variety in the activity performed.

Patient lack of motivation was a major reason for screen failure and for poor adherence as shown in Table 2 and 3. Improving this willingness to exercise relies on an understanding of why patients refuse to undertake SEP, which is not available in the included reports. However vascular patients are often a group who have made certain unhealthy lifestyle choices and whom are perhaps amongst the least likely patients to embrace an ongoing commitment to taking responsibility for their own health[71]. A further point to note is that current recommendations [7, 72] promote walking to the point of claudication and beyond This pain may discourage some patients from participating. A review by Parmenter et al [73] has provided evidence to suggest that clinically relevant improvements in walking distance can be attained at a lower threshold and without inducing pain. A further review by Al-Jundi et al [74] also highlights this point concluding that avoidance of painful exercise may lead to higher participation rates and make it more likely for patients to maintain behavioural changes in the longer term.

Co-morbidities were the reason a significant proportion of patients were not enrolled in or failed to complete SEPs in this review. To highlight this further, death was the third most frequent reason reported for incomplete adherence to SEP. Some of these patients are simply unable to exercise to any extent due to arthritis, angina or breathlessness rendering them entirely unsuitable for SEP. Others may not be referred due to the perception that systemic cardiovascular disease may make it unsafe for IC patients to undertake exercise. This was challenged in a systematic review of SEP safety which noted an all-cause

complication rate of one event per 10,340 patient-hours of SEP [75]. However this review was based upon published trials of SEP (similar to those included in this review, many of which will have already excluded the more co-morbid patients) and so again may not reflect the risk for the IC population as a whole.

Other reasons given for non-inclusion or poor adherence were mainly logistical (travel, work/family commitment). It may be argued that a way of improving the participation rate for IC patients would be to promote unsupervised exercise; the old "go home and walk" [76] adage but comparisons of supervised versus unsupervised exercise clearly demonstrates that this is not an effective treatment strategy. It also has worse adherence rates in comparison to supervised programmes [6]. To counter this there has been a greater interest in the "home-exercise" programme (HEP) which is potentially more convenient for patients particularly within the working demographic range. A systematic review [74] has provided some evidence that HEP can demonstrate improvements in walking distances and quality of life in patients with IC. Though the authors conclude that this improvement was still not equivalent to that achieved by an SEP and, in common with the findings of this review, the studies included did not clearly present exercise adherence or decline rates [74]. Additionally, the use of personal health-devices such as pedometers or smart phone apps has also had some beneficial effects in the IC population [25]. These can be used in conjunction with a home-exercise programme to help the clinician monitor the patient's compliance to the exercise training. They may also have a motivational effect via visual and quantitative feedback.

It remains to be established exactly what might constitute the "ideal" exercise training programme and indeed there may well be different ideal programmes for clinical effectiveness and for patient satisfaction, uptake and adherence. Evidence of efficacy for the patients who have undertaken SEP is compelling and improving the uptake of SEP for those able to exercise is a significant challenge. Examining the reasons for poor uptake and or adherence may allow SEP providers with insight as to how to increase participation in SEP.

Conclusions

Details of populations screened, reasons for exclusion and definitions of adequate uptake and adherence were lacking in the majority of reports. Where data was reported, only 1 in 3 patients screened were suitable for and willing to undertake SEP. This has potential implications for the recommendation of SEP as first line treatment for *all* IC patients as there may be a significant proportion of patients where SEP treatment is not accepted or possible. Future reports regarding SEP trials need to include full details of screened populations, and rates of uptake and adherence to exercise. This will ensure more consistent reporting of data and allow for findings to be interpreted with greater clarity.

Ultimately the prescription of SEP in the IC population is effective and beneficial but the results from this review suggest that it is not a "one-size fits all" model. Future research into the development of more accessible and or acceptable SEPS may improve current uptake and adherence rates.

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