

TITLE: Exercise rehabilitation for patients with critical limb ischemia peripheral arterial disease after revascularization: a single center pilot randomized controlled trial assessing quality of life and functional capacity after a 12-week rehabilitation program compared with best medical therapy

BACKGROUND

Definitions

Peripheral arterial disease (PAD) refers to narrowing and occlusion of arteries supplying oxygenated blood to non-coronary and non-intracranial circulatory systems. This term is typically used to describe disease in the legs though it also affects upper extremities, renal and mesenteric vessels (Hiatt et al., 2008). Atherosclerosis is a key cause of PAD and is the main focus of this particular study. Other more rare conditions that can lead to PAD include anatomical/congenital variation, fibromuscular dysplasia (FMD), vasculitides, trauma and localized radiation (Gerhard-Herman et al., 2017; Hirsch et al., 2006).

PAD patients present with a wide range of symptoms. Patients who are non-ambulatory or with subclinical levels of disease may be asymptomatic and unaware of the disease process. Symptomatic patients typically experience leg pain with walking or physical activity, which is referred to as intermittent claudication (IC) (Dormandy & Rutherford, 2000; Hiatt et al., 2008; Norgren et al., 2007). In more advanced chronic disease states with severely compromised blood flow to the tissues, patients may have leg pain at rest or even non healing wounds that can lead to tissue loss which is defined as critical limb ischemia (CLI) (Hiatt et al., 2008; Hirsch et al., 2006; Varu, Hogg, & Kibbe, 2010). These clinical presentations have led to the development of two main classification systems that describe the severity of PAD; the Fontaine classification and Rutherford classification (Table 1.)

Fontaine		Rutherford		
Stage	Clinical presentation	Grade	Category	Clinical presentation
I	Asymptomatic	0	0	Asymptomatic
II	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

Table 1. Fontaine and Rutherford classification of PAD (Dormandy & Rutherford, 2000)

Patients with intermittent claudication typically experience leg pain associated with walking or other physical activity which is relieved with a short period of rest. Pain may be present in calves, thighs and/or buttocks depending on the anatomical level of disease (Criqui & Aboyans, 2015; Gerhard-Herman et al., 2017). Validated questionnaires can be used as a diagnostic tool to rule out other causes of the patient's symptoms (Criqui et al., 1996; Leng & Fowkes, 1992; Rose, 1962). It is important to note that symptoms can be highly variable in severity depending on level of activity.

The ankle brachial index (ABI) should be used as an initial assessment for the confirmation of the presence and severity of PAD (Gerhard-Herman et al., 2017; Norgren et al., 2007; Schroder et al., 2006). ABI is a ratio of systolic blood pressure in the brachial artery to the highest measured blood pressure at the ankle. This test has been shown to be highly specific but not sensitive to the presence of PAD (Khan, Farooqui, & Niazi, 2008; Lijmer, Hunink, van den Dungen, Loonstra, & Smit, 1996). An ABI of <0.9 is indicative of PAD and values <0.4 are used as a threshold for CLI. For ABI values >1.3 , the vessels are deemed non-compressible and further evaluation is required. (Gerhard-Herman et al., 2017; Hirsch et al., 2006; Khan et al., 2008). In these patients with non-compressible vessels or CLI, it is appropriate to obtain a toe-brachial index (Gerhard-Herman et al., 2017).

In patients with severe symptoms and who may require revascularization, diagnostic imaging is required. Imaging techniques for anatomic assessment include duplex ultrasound (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA) or direct conventional angiography (Gerhard-Herman et al., 2017; Norgren et al., 2007). These diagnostic tests can be costly, time intensive, invasive, and may expose patients to risks, particularly when iodinated contrast is used. This is why it is important to have a thorough clinical assessment and management plan for these patients.

Epidemiology

A recent systematic review reports a global estimate of 202 million people living with PAD as of 2010 (Fowkes et al., 2013). Previously thought to be predominant in high income countries, this systematic review suggests that almost 70% of people suffering from PAD reside in lower and middle income countries. This systematic review compared global prevalence of PAD between 2000 and 2010 which showed a global increase in PAD of approximately 23.5%. The data show that PAD generally affects men and women at similar rates, with a slightly higher prevalence in women at older ages. This differs from previous works that suggested higher rates among men than women. The prevalence of PAD increases with increasing patient age, with a sharp rise in numbers ≥ 70 years of age (Criqui & Aboyans, 2015).

An elegant and powerful comment written by Hirsch and Duval (2013) describe PAD as a global pandemic given that it affects more than 200 million people worldwide. PAD greatly affects people's quality of life with a high degree of morbidity and mortality making this an important and relevant area of research. To put in context, as of 2011 approximately 34 million people were living with HIV. By comparison, PAD has a higher prevalence, morbidity and mortality compared with HIV (Hirsch & Duval, 2013).

Patients with CLI are the focus of this study. Although the incidence is clear, it is estimated that in Europe and North America there are 500-1000/1 million new cases of CLI every year. These patients exhibit the most severe form of the disease with guarded prognoses. At one year, there is a 10-40% mortality rate and up to 40% amputation rate in patients with critical limb ischemia. Only 45% of patients are alive with two limbs one year after a diagnosis of CLI (Hirsch et al., 2006; Norgren et al., 2007). These patients tend to be in extremely poor health with multiple comorbidities that are further outlined below.

Risk Factors

Patients with PAD typically have numerous risk factors that contribute directly to their atherosclerotic disease. These risk factors are commonly shared with other cardiovascular diseases. The key risk factors include smoking, diabetes, hypertension and dyslipidemia. Smoking is the number one risk factor linked to PAD, and has been shown to be a higher risk factor for PAD compared with other CV diseases (Cole et al., 1993; Norgren et al., 2007) (Agarwal, 2009). Current smokers have the highest risk for PAD, though any history of smoking does increase chances of getting the disease (Cole et al., 1993; Willigendael et al., 2004). There is also a strong association between diabetes and PAD. Specifically, the longer the duration of the disease, the higher the risk of developing PAD (Hirsch et al., 2006; Norgren et al., 2007). Furthermore, patients with diabetes have worse outcomes than those without, with higher rates of amputation and cardiovascular death (da Silva et al., 1996; Takahara et al., 2010). Systolic hypertension is a significant risk factor for PAD. The relative risk is only moderate with hypertension but given its ubiquitous presence in an aging population, it is highly relevant in assessment of patients with PAD (Bavry et al., 2010). Increased total cholesterol and low high-density lipoprotein (HDL) HDL have been shown to be independent risk factors in patients with PAD. Finally, there are several blood markers that have been linked to PAD including hyperhomocysteinemia, elevated C-reactive protein (CRP) and elevated fibrinogen (Norgren et al., 2007).

Patients with PAD typically have coexisting cardiovascular diseases as expected given the common risk factors outlined above. These patients are at significantly higher risk for angina, myocardial infarct (MI), congestive heart failure, stroke and TIA. Therefore it is crucial to ensure that risk factors are addressed and modified in this PAD population for improved functional status and longevity (Norgren et al., 2007).

Risk factor management

Risk factor management is critical for PAD patients with the goal of improving symptoms and preventing disease progression. Smoking cessation should be a primary focus. Patients who smoke should be repeatedly encouraged to quit by providing tools such as counselling and suitable pharmacotherapy. Hypertension control should be initiated with blood pressure targets of 140/90 or 130/80 for patients with diabetes. First line agents include angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). Calcium channel blockers and beta-blockers are also appropriate for use in this population. Dyslipidemia needs to be controlled with efforts to decrease LDL-C to < 2.0 mmol/L with statins as first line agents. Diabetic patients should optimize blood glucose level with a target HbA1C of <7%. Antiplatelet therapy should be initiated in symptomatic patient or when other risk factors are present. Dual anti-platelet regimes are particularly helpful for patients with PAD. Exercise interventions should be encouraged in all patients with PAD. Given that exercise is the focus of this research, it is described in greater detail below (Gerhard-Herman et al., 2017; Hirsch et al., 2006; Norgren et al., 2007).

Revascularization

In patients who have progressed to critical limb ischemia, treatment goals are to relieve pain, heal wounds and prevent limb loss. In addition to risk factor management and medical therapy, these

patients require revascularization procedures. Depending on the extent and location of disease, the techniques used may be endovascular/interventional, surgical or hybrid-based (Varu et al., 2010).

Limb salvage rates are thought to be similar with both endovascular and open techniques, however the data are limited and there is a large ongoing randomized controlled trial addressing this issue (Adam et al., 2005; Albers, Romiti, Brochado-Neto, De Luccia, & Pereira, 2006; Romiti et al., 2008). Endovascular techniques offer a less invasive option with typically only one or two small ($\leq 5\text{mm}$) groin incisions to access the affected vessels. It also has an advantage of lower morbidity and with open bypass procedures (Adam et al., 2005). Endovascular options typically require iodinated contrast, which may expose the patients to a risk of kidney injury, which is not uncommon in this population given their comorbidities, and in particular a high frequency of diabetes. While open bypass procedures may be associated with higher wound complication rates, they have been shown to have better long-term patency compared with endovascular interventions (Romiti et al., 2008; Varu et al., 2010).

Balloon angioplasty with and without stenting can be used to open narrowed or occluded vessels. In patients with longer lesions and more diffuse disease open surgical bypass techniques are typically used to provide revascularization to ischemic limbs (Gerhard-Herman et al., 2017; Hirsch et al., 2006; Norgren et al., 2007). In some cases, a hybrid approach is used with a combination of balloon angioplasty, stenting and surgical bypass. In cases where there are no revascularization options, patients may require a primary amputation of their limbs to manage pain and/or infection (Gerhard-Herman et al., 2017; Varu et al., 2010).

It is important to note that in Canada, and specifically in Calgary, revascularization is reserved with patients who have critical limb ischemia or severely life-limiting claudication. Many institutions do offer revascularization (typically endovascular) for patients who have IC. This is relevant given that patients with CLI have end-stage disease as noted previously, and typically have a significantly greater number of comorbidities.

Outcomes after revascularization

Patency and limb salvage are the primary measures for revascularization success in CLI patients. Primary and secondary patency rates at one year are significantly lower with endovascular compared with open surgical techniques, while limb salvage rates are similar in both groups (Romiti et al., 2008). Table 2. shows results from a meta-analysis comparing endovascular versus open bypass outcomes in patients with CLI. While limb salvage rates are similar, this analysis does not capture the frequency of re-interventions for either modality. Conte et al. (2009) showed in a meta-analysis of infra-inguinal surgical bypass procedures that only 61% of patients remain free from any amputation or re-intervention at one year. That number is significantly higher in the endovascular group (Conte et al., 2009).

It is important to note that limb salvage rates always surpass patency rates regardless of treatment modality. This is because revascularization allows patients to heal ischemic wounds and hopefully increase ambulation which will assist with collateral vessel development.

Table 2. Meta-analysis of 1-month to 3-year patency, limb salvage, and patient survival (%) in patients with critical limb ischemia comparing percutaneous transluminal angioplasty vs bypass grafting					
Result	1 month	6 months	1 year	2 years	3 years
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
<i>P</i>	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
<i>P</i>	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

Exercise and Peripheral arterial disease

There has been a tremendous amount of research showing the advantages of exercise training for patients with IC (Aggarwal et al., 2016). Supervised exercise programs (SEP) are recommended as a first line of treatment for patients with PAD (Milani & Lavie, 2007; Murphy et al., 2012). In patients with IC, supervised exercise programs have been shown to have superior results compared with endovascular revascularization with respect to functional capacity (Murphy et al., 2012; Perkins, Collin, Creasy, Fletcher, & Morris, 1996; Spronk et al., 2009). Unfortunately, once a patient has reached the most severe stage of PAD in the form of CLI, exercise is no longer an appropriate initial treatment modality and they typically require some surgical or endovascular intervention. For patients with IC who do not have access to SEP, a home exercise program (HEP) may be a viable alternative (Aggarwal et al., 2016; Gardner, Parker, Montgomery, Scott, & Blevins, 2011; McDermott et al., 2009). SEP and HEP both increase maximal walking distance, functional capacity and quality of life in patients with IC, with outcomes slightly favoring SEP.

Exercise Modality

Walking is the most common modality of exercise prescribed and studied in patients with IC which may be a challenge in patients who have difficulty ambulating. There are a limited number of studies that have used alternative training strategies with variable outcomes (Parmenter, Dieberg, & Smart, 2015; Parmenter, Raymond, Dinnen, Lusby, & Fiatarone Singh, 2013). Both arm and leg cycle-ergometry have been shown to be viable exercise modalities for patients with IC, and can improve maximal walking distance (MWD) (Zwierska et al., 2005). A recent study also showed that calf-raises done 3 times per day for eight weeks can cause greater improvements in MWD compared with patients who completed a more traditional walking training program (Van Schaardenburgh, Wohlgend, Rognmo, & Mattsson, 2017). Most of the studies employing exercise modalities other than walking typically include a small number of subjects, with limited positive outcomes. These alternative exercise modalities are arguably

more important and applicable to patients with PAD, particularly those with more severe symptoms as these patients will have the greatest mobility challenges as a limiting factor in exercise participation. Resistance training has shown to be beneficial in PAD patients but is rarely emphasized as a treatment modality. Furthermore, alternative activities such as yoga, pilates or aquatic exercise have not been investigated in this patient population and may have benefits that have not yet been elucidated.

Exercise Training Post-Revascularization

Only a small number of studies have evaluated SEP after revascularization. Four RCTs have compared patients who have undergone revascularization for intermittent claudication via endovascular approach and were subsequently enrolled in exercise programs versus best medical therapy (Bo et al., 2013; Greenhalgh et al., 2008; Kruidenier et al., 2011; Mazari et al., 2010). All of these studies showed significant improvements in walking distance and quality of life for patients enrolled in the exercise programs. There are three RCTs comparing exercise versus BMT in post peripheral bypass surgery which showed similar results of significantly increased walking distance and QoL in the post-op exercise group (Badger, Soong, O'Donnell, Boreham, & McGuigan, 2007; Jakubseviciene et al., 2014; Lundgren, Dahllof, Lundholm, Schersten, & Volkmann, 1989). Out of all of these studies, only Badger et. al (2007) showed an improvement in ABI in patients who had undergone bypass surgery for revascularization and participated in a post-operative exercise program versus bypass surgery and BMT alone. Jakubseviciene et. al (2014) and Lundgren et al (1989) had patients participating in HEP, which also showed significantly better walking distances and QoL compared with the BMT groups. Currently, there are no studies evaluating the efficacy of HEP alone compared to SEP after revascularization.

All of the studies described here were primarily treating patients with IC. Only Jakubsvieciene et al. (2014) and Badger et al (2007) included patients with PAD and rest pain. **To date, there are no studies dedicated to patients with critical limb ischemia comparing outcomes for exercise training versus BMT post revascularization.** All of these studies exclusively evaluate patient-related outcomes such as walking distance, functional capacity and QoL. While these parameters are tremendously important, there are no data regarding how post treatment exercise training may affect amputation rates, readmission to hospital or reintervention rates in the PAD patients with critical limb ischemia. Such parameters are defined as major adverse limb events (MALE).

Health Economics

The 1992 Canadian Heart Health survey showed a significant economic benefit for all participants who participated in an exercise program, both supervised and unsupervised. In patients with known cardiovascular disease, a SEP showed significant cost savings for years of life (Lowensteyn, Coupal, Zowall, & Grover, 2000). In patients with IC, studies have shown that SEP is more cost- effective than endovascular interventions as a primary treatment modality. Furthermore, although the initial cost of SEP may be slightly greater when compared with HEP, it has greater cost-effectiveness up to five years (Fokkenrood et al., 2014; Reynolds et al., 2014; Spronk et al., 2009). There has been no data evaluating the cost benefits associated with CLI patients who have undergone revascularization. Given that re-interventions are frequent (and costly), post revascularization exercise training may be of significant and substantial benefit in patients with CLI.

Summary

Exercise training is a proven effective treatment for patients with PAD with significant functional, psychosocial and economic benefits. In current practice, there are no guidelines for exercise training and rehabilitation for patients who have progressed to CLI and have undergone revascularization. While it may be a challenge given the severity of disease and number of comorbidities in this patient population, it is great a disservice to deny these patients exercise rehabilitation given the possible advantages for their functional capacity, quality of life and even survival. Randomized controlled trials (RCT) are necessary to determine the precise role of exercise rehabilitation in patients with CLI. An RCT will provide guidance for regarding exercise tolerance, appropriate exercise modalities as well as the challenges and benefits of exercise rehabilitation in this critically ill population.

Objectives:

The aim of this pilot study is to develop a better understanding of the role for supervised exercise rehabilitation programs (SEP) in CLI patients after revascularization.

Our key objectives are as follows:

- 1) Our primary objective is to show that a 12-week SEP will improve functional capacity and quality of life in patients with CLI after revascularization. We will assess the feasibility for completion of a 12-week SEP in patients with CLI who have undergone revascularization.
- 2) Our secondary objective is to monitor major adverse limb events (MALE) and survival in patients who complete a 12-week SEP after revascularization.

Hypotheses:

- 1) We hypothesize that PAD-CLI patients who participate in an exercise rehabilitation after they have undergone revascularization will have a greater improvement in functional capacity and quality of life compared with patients treated with best medical therapy alone.
- 2) We hypothesize that PAD-CLI patients who participate in an exercise rehabilitation after they have undergone revascularization will have fewer MALE and improved survival compared with patients treated with best medical therapy alone.

OUTCOME MEASURES:

Primary outcome measures:

Our primary outcome measure for this project will be change in functional capacity as measured by a 6-minute walking test (6MWT) or maximal pain-free walking distance on a treadmill.

Secondary outcome measures:

- 1) Quality of life based on questionnaires validated for patients with PAD, the SF-36 and VQ6
- 2) Completion of a 12 week supervised exercise program
- 2) Freedom from MALE
- 3) Target vessel and/or bypass patency
- 4) Survival at 1, 3 and 5 years

STUDY DESIGN

This study is a two phase, single-center, non-blinded randomized controlled trial. The first phase of the trial will include 20 patients; 10 assigned to post-operative exercise rehabilitation and 10 to best medical therapy. The primary objective of Phase I is to assess for feasibility and safety of this randomized controlled trial in CLI patients after revascularization. We will assess rate of enrollment, adherence to the exercise regimen and any unforeseen barriers or challenges that patients may encounter with the rehabilitation program.

If Phase I of the trial confirms that the exercise program is feasible and safe for CLI patients post-revascularization, we will proceed with Phase II of the trial. The primary objective for Phase II is to determine if a supervised exercise rehabilitation program will improve walking distance after revascularization compared with patients treated with best medical therapy. Phase II will also compare quality of life outcomes between the two groups.

STUDY POPULATION

The population to be studied in this group is patients with PAD and CLI Fontaine classification III and IV. This means that these patients will have ischemic rest pain in their legs and/or non-healing ischemic ulcers on their feet.

ENROLLMENT

Patients will be identified on a referral basis through our outpatient vascular surgery clinic. The seven practicing vascular surgeons in Calgary will be informed of the current study. Patients who have undergone revascularization for CLI will be identified for consideration of participation in this study within six months of their procedure. All surgical and ischemic wounds to be deemed sufficiently healed prior to assessment for fitness in the study. Once the attending vascular surgeon considers the patient fit to participate, the research coordinator will assess the patient for possible inclusion in the study.

Inclusion Criteria

- 1) Ambulating prior to procedure
- 2) Living independently prior to procedure
- 3) Available to attend all SEP and follow-up appointments
- 4) PAD Fontaine class III and IV (rest pain and tissue loss)
- 5) Entry with consent of vascular surgeon
- 6) Ischemia secondary to TASC A-D lesions identified on imaging (CTA or angiogram)
- 7) Able to understand and sign informed consent
- 8) >18 years of age

Exclusion Criteria

- 1) Confined to wheelchair
- 2) Patients with exercise tolerance limitations due to other co-morbidities such as cardiorespiratory, musculoskeletal, or peripheral neuropathy. (NYHA class III and IV)
- 3) PAD Fontaine class I and II (asymptomatic, claudication)
- 4) Patients with ongoing tissue loss that limits ambulation
- 5) Patient with previous revascularization procedures
- 6) Patients undergoing revascularization for acute limb ischemia events

SAMPLE SIZE

There are currently no data evaluating outcomes of post-revascularization supervised exercise programs in patients with critical limb ischemia, however these studies have been completed in claudication

patients. Studies on PAD claudication (Fontaine class II) patients who have undergone revascularization followed by SEP have all shown significant improvement in functional capacity compared with best medical therapy alone. These previous studies that showed consistently a 20% greater increase in walking distance in the post-revascularization SEP group compared with Best Medical Therapy (BMT) post-revascularization. Given this previous data, 64 patients are required to have a 80% chance of detecting, with a two-sided significance of 0.05, an increase in the primary outcome measure of a 20% greater increase in distance for the 6MWT in the experimental group compared with the control group. Final sample size will be adjusted for expected attrition.

METHODS

INTERVENTION

Patients included in the study will be identified in the vascular surgery outpatient clinic or through Emergency department as requiring revascularization secondary to critical limb ischemia. Patients will be approached regarding study participation prior to the revascularization procedure. After eligibility is confirmed and patients have signed informed consent, patients will be randomized to one of two groups:

- 1) Best Medical Therapy (BMT)
- 2) BMT + Supervised Exercise Program (SEP)

The patient will undergo the revascularization procedure and any adjunctive treatment such as wound care/debridement or minor amputation (toes, trans-metatarsal amputation). All surgical wounds and ischemic ulcers will require assessment by attending surgeon for adequate healing prior to initial assessment at the exercise facility. This may require as little as one week or as long as 6 weeks to achieve sufficient healing. The exercise assessment and program delivery will take place at a cardiac rehabilitation facility that has extensive experience in managing patients with cardiovascular disease and PAD in the post op setting.

Best medical therapy

All patients in the study will be assessed and monitored by internal medicine specialists as well as the vascular surgery team for management of PAD risk factors including, but not limited to: hypertension, smoking cessation, dyslipidemia and diabetes. The patients will be prescribed appropriate pharmacotherapy as deemed appropriate. A typical regimen for these patients may include antiplatelet agents, B-blockers, ACE-inhibitors, and diabetic control agents. Patients will be advised to target a systolic blood pressure of ≤ 140 mmHg (≤ 130 mmHg if diabetic), LDL-C < 2.0 mmol/L and a HbA1c $\leq 7\%$. They will also be given information regarding engaging in exercise and physical activity three to five times per week. Patients will be asked to keep a log of their physical activity for the 12-week duration of the study. The patients will be provided with a log to record their physical activity.

Standardized Exercise Program Regimen

In addition to best medical therapy management, the patients randomized to the SEP arm of the trial will attend a supervised exercise program at a cardiac rehabilitation facility at least two times per week for 12 weeks. Programs will be designed and coordinated by an exercise physiologist. All patient expenses for the program will be covered by the study budget. There will be no financial burden placed on the participants.

MEASUREMENTS

General health metrics will be collected at the start and end of the 12-week intervention period. This includes height, weight, BMI, blood pressure and resting heart rate. We will record medications,

smoking history status, presence of diabetes, dyslipidemia, cardiovascular disease history including previous myocardial infarct (MI) and stroke/transient ischemic attack.

PRE/POST TESTING

Functional Capacity:

In order to assess functional capacity, we will measure walking performances at the first exercise session and after 12 weeks. Walking performance will be measured using a six-minute walk test (6MWT) (Guyatt et al, 1985) which has been validated in the functional evaluation of chronic disabling disease, more specifically in patients with PAD (Gardner, Montgomery, & Parker, 2012; McDermott et al., 2009). For this test, the patients will be made to walk on a flat surface for 6 minutes and total distance covered will be recorded by the test administrator. Patients will also undergo a graded treadmill test to evaluate maximum walking distance (MWD) and pain-free walking distance (PFWD). The treadmill is set at a constant speed of 3.2km/hr and starts at an incline of 0%, increasing by 2% every 2 minutes until an incline of 10% is reached or the patients stops the test (Gardner et al., 2012). This test is also commonly used and has been validated in PAD patients.

Quality of Life (QoL):

Validated generic and PAD-specific QoL questionnaires will be administered at the first and final visits. The Short Form 36 (SF-36) and VascuQoL. The SF-36 is a generic health status questionnaire, while the VascuQoL is a quality of life questionnaire validated for patients with PAD.

Given that this is a pilot study to assess the feasibility in exercise rehabilitation in this population that is considered end-stage PAD, we want to capture major challenges or barriers for these patients. As such, we will also perform an interview and survey at the mid-term and at the completion of exercise program for the SEP group to collect information around challenges associated with the rehabilitation.

Limb Hemodynamics:

Ankle brachial index (ABI) measurements will be recorded at initial assessment and 12 weeks as a measure of peripheral arterial blood flow. ABI is obtained by measuring the highest systolic pressure at the ankle over the highest systolic pressure in the arm. We will use a handheld Doppler probe and blood pressure cuff to collect these measurements. We will also use duplex arterial ultrasound at 2 weeks post intervention and again at 12 weeks to monitor patency of revascularization.

RANDOMIZATION

Microsoft Excel will be used to generate a block randomization sequence for Phase I (20 patients) followed by a block randomization sequence for Phase II (44 patients) of the study. Patients who are eligible to participate in the study will be stratified by sex and randomized to either SEP or BMT. Block sizes of 4 and 6 will be used to prevent anticipation of the randomization sequence.

ALLOCATION CONCEALMENT

Once the random block sequence has been generated, allocation cards will be created and sealed in sequentially numbered opaque envelopes. The envelopes will be stored in a secured filing cabinet in the vascular surgery research office. The envelopes will be opened sequentially after a patient consents to participate in the study.

DATA COLLECTION

No study data will be collected until patients have reviewed and signed the informed consent. Opportunity to ask questions and have time independent from study team will be provided.

Data will be recorded using Excel spreadsheets. Medical outcomes and complications will be tracked using Vascubase software. Data will be stored on Alberta Health Services computers to maintain patient confidentiality.

STATISTICAL ANALYSIS

Normally distributed data will be presented as mean \pm SD. Results at baseline and 12 weeks will be compared using a paired t-test. For data that is not normally distributed, comparisons will be performed using a non-parametric Mann-Whitney test. Comparisons will be accepted as statistically significant at 95% confidence level ($p \leq 0.05$). STATA software will be used for statistical analysis.

ETHICAL CONSIDERATIONS

Patients who are randomized to the SEP group will be provided with tri-weekly visits for supervised exercise guidance and support. Patients will receive reimbursement for travel to and from the exercise facility. This will include refunds for gas, parking or other required transportation (taxi, public transport, etc).

FOLLOW UP OF PATIENTS WITHDRAWN FROM STUDY

Patients who withdraw or do not complete the program will be contacted and interviewed at the end of the 12 week study period to understand why they were unable to complete the training program.

LIMITATIONS

One expected limitation of this study is the heterogeneity of the revascularization approach. Some patients will undergo endovascular treatment, while others will receive an open surgical bypass. Additionally, patients will not be stratified according to anatomical level of disease (aorto-iliac versus infrainguinal disease).

LONG-TERM FOLLOW-UP

This project is a pilot project with 12-week primary endpoint measures of functional capacity and quality of life. Given that we plan to extend to a broader randomized controlled clinical trial with long term follow-up, we will continue to follow the patients annually for five years. The annual follow-up will include QoL surveys, ABI measurements, ultrasound assessment for graft patency and any MALE. We will also monitor survival throughout this period.

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