Protocol for the PREHAB study—Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial

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ABSTRACT

Introduction: Frailty is a geriatric syndrome characterised by reductions in muscle mass, strength, endurance and activity level. The frailty syndrome, prevalent in 25–50% of patients undergoing cardiac surgery, is associated with increased rates of mortality and major morbidity as well as function decline postoperatively. This trial will compare a preoperative, interdisciplinary exercise and health promotion intervention to current standard of care (StanC) for elective coronary artery bypass and valvular surgery patients for the purpose of determining if the intervention improves 3-month and 12-month clinical outcomes among a population of frail patients waiting for elective cardiac surgery.

Methods and analysis: This is a multicentre, randomised, open end point, controlled trial using assessor blinding and intent-to-treat analysis. Two-hundred and forty-four elective cardiac surgical patients will be recruited and randomised to receive either StanC or StanC plus an 8-week exercise and education intervention at a certified medical fitness facility. Patients will attend two weekly sessions and aerobic exercise will be prescribed at 40–60% of heart rate reserve. Data collection will occur at baseline, 1–2 weeks preoperatively, and at 3 and 12 months postoperatively. The primary outcome of the trial will be the proportion of patients requiring a hospital length of stay greater than 7 days.

Potential impact of study: The healthcare team is faced with an increasingly complex older adult patient population. As such, this trial aims to provide novel evidence supporting a health intervention to ensure that frail, older adult patients thrive after undergoing cardiac surgery.

Strengths and limitations of this study

▪ Multicentre, randomised trial.
▪ Does not capture urgent or emergent patients with critical cardiac illness.
▪ Does not capture the very frail older patient.

has approved the study protocol V.1.3, dated 11 August 2014 (H2014:208).

Trial registration number: The trial has been registered on ClinicalTrials.gov, a registry and results database of privately and publicly funded clinical studies (NCT02219815).

INTRODUCTION

Owing to an ageing demographic, older and increasingly frail patients are now being referred for cardiac surgery. In fact, the proportion of patients aged 75 years and older undergoing cardiac procedures increased from 16% in 1990 to up to 25% in most recent estimates.3 The surgical process in this population is complicated by the multiple comorbidities in addition to the underlying cardiac dysfunction presented by these frail patients. Previous studies have demonstrated that frail patients, typically with higher levels of concurrent medical comorbidities, often experience higher rates of postoperative morbidity, mortality and prolonged hospital length of stay (LOS) with associated increased burden on the healthcare system.2–5

Frailty is a geriatric syndrome, defined as an increased vulnerability to stressors leading...
to a state of decreased physiological resistance. It is characterised by a “constellation of symptoms and signs [that] describe the heterogeneous response of older adults to physiological and metabolic challenges.”

While frailty is not necessarily synonymous with chronological age, it is more prevalent among the older adult population and is associated with up to a threefold increased risk of mortality or major morbidity postsurgery. A recent systematic review identified that frailty had a strong positive relationship with major adverse cardiac and cerebrovascular events in patients undergoing cardiac surgery (OR = 4.89). Thus, it has become critically important for healthcare systems to develop strategies designed to improve clinical outcomes in this high-risk population undergoing cardiac surgery.

Since the phenotype of frailty is characterised by reductions in muscle mass, strength, endurance and activity level, cardiac rehabilitation (CR) is ideally suited to counteract these impairments and improve an individual’s frailty status. A recent review of randomised trials concluded that multidisciplinary programmes were a promising therapeutic strategy for frail, older adults, although none of these specifically targeted these patients preoperatively. Thus, there is a strong biological and epidemiological rationale to investigate CR in this setting.

In Canada, when elective patients require cardiac surgery, they are placed on a waiting list for a period ranging from 1 to 4 months. While the wait period for elective patients is generally considered safe, it has been documented that patients on surgical waiting lists engage in very little physical activity as they wait for their procedure. A lack of physical activity can be problematic in an already deconditioned, frail cohort of patients because, at present, the current standard of care (StanC) does not provide a formal process to engage patients in physical activity during the waiting period. Therefore, the period of time prior to elective cardiac surgery presents a significant opportunity to optimise preoperative risk factors particularly in vulnerable patients, such as the frail, older adult population. The present study aims to reduce frailty in the high-risk, older adult patient to improve postsurgical outcomes of elective cardiac surgery.

CR has been shown to decrease morbidity and mortality in patients with established and unrepaired cardiac disease, and to be safe for patients who are elderly and suffer heart failure, in both hospital and community-based settings. A meta-analysis of randomised controlled trials reported that patients attending CR have a 20% and 26% relative reduction in all-cause morbidity and cardiac mortality, respectively, as compared with patients not attending CR. The proposed study has been designed according to the evidence-based, best practice guidelines published by the Canadian Association of Cardiac Rehabilitation, the recently published Canadian Cardiovascular Society Quality Indicators for CR, and the guidelines for exercise prescription in patients with cardiovascular disease according to the American College of Sports Medicine.

Although the benefits of postsurgical CR are well documented, less is known about the role that preoperative exercise may have in the trajectory of a patient undergoing heart surgery. A recent systematic review reported on the benefits of preoperative physical therapy in preventing postoperative pulmonary complications in patients undergoing cardiac surgery. Eight randomised controlled trials were included in the review, which found that preoperative physical therapy was effective in reducing postoperative pulmonary complications and length of hospital stay. However, the majority of the interventions used inspiratory muscle training and breathing exercises preoperatively and thus, did not address the potential benefit of exercise and education interventions in this population. In a seminal study by Arthur et al, 249 low-risk patients awaiting elective coronary artery bypass graft (CABG) surgery were randomised to an 8-week preoperative CR programme or to the StanC. Patients in the intervention group completed two exercise sessions per week and attended additional educational sessions on risk factor modifications. Following surgery, these patients experienced shorter intensive care unit (ICU) and hospital LOS postoperatively and an improved quality of life compared with controls. Notably, these promising results persisted for 6 months following surgery, indicating the potential long-term benefit of preoperative risk factor reduction. However, this particular study was conducted in relatively low-risk patients and thus, did not address the unique needs of frail, older adult patients that are now commonly being referred for cardiac surgery.

In a pilot, randomised control trial, 17 preoperative elective CABG surgery patients were randomised to StanC or to an exercise and health education intervention. The intervention involved a 2-day weekly programme consisting of exercise and education classes for 60 min per session. Walking distance was evaluated using a 6 min walk test (6MWT), while gait speed was evaluated using the 5 m gait speed test. Walking distance remained unchanged in the StanC group; however, the intervention group increased their walking distance by 132 and 145 m at the preoperative and 3 months postoperative assessments, respectively. Gait speed was improved in the intervention group, by 27% and 33% preoperatively and 3 months postoperatively, respectively, while remaining unchanged in the control group. This pilot, randomised controlled trial demonstrated the feasibility of implementing a preoperative exercise protocol to improve the patient’s functional capacity postsurgery; however, this study was performed for a relatively small number of younger patients and was designed as a simple feasibility and safety trial.

The Pre-operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery (PREHAB) study is a randomised control trial...
comparing a preoperative, interdisciplinary, exercise intervention and cardiovascular health promotion intervention to current StanC for the purpose of determining if the programme improves 3-month and 12-month clinical outcomes among a population of frail patients waiting for elective cardiac surgery. The primary objectives of the trial are:

1. To determine if the PREHAB intervention reduces the proportion of frail older adult patients requiring a prolonged hospital LOS greater than 7 days.
2. To determine if the PREHAB intervention influences frailty, exercise capacity, physical activity behaviour, in-hospital complications and health-related quality of life (HRQoL).

We hypothesise that the performance of an interdisciplinary programme preoperatively in patients awaiting elective cardiac surgery will reduce the proportion of frail, older adult patients requiring a postoperative hospital LOS greater than 7 days. We also hypothesise that the intervention will: (1) reduce frailty; (2) improve exercise capacity; (3) improve self-managed physical activity behaviour; (4) improve in-hospital outcomes; (5) improve clinical outcomes 3 months and 1 year postoperatively; and (6) improve HRQoL.

METHODS AND ANALYSIS

The PREHAB study is a prospective, randomised, open, blinded end point (PROBE)34 controlled trial using assessor blinding and intention-to-treat analysis. To date, no high-quality study has prospectively examined the impact of preoperative CR in the frail older adult population undergoing cardiac surgery. Thus, the PREHAB trial has been designed to address a noticeable knowledge gap in the current literature. The trial has been registered on National Institutes of Health ClinicalTrials.gov (NCT0219815). The study is funded by an Operating Grant from the Canadian Institutes of Health Research (326290), which was awarded following an independent peer-review process and supported by Technology Evaluation in the Elderly (TVN). We have used the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines in reporting this clinical trial.35

Setting

The PREHAB trial will be conducted in three centres across Canada: (1) Winnipeg, Manitoba; (2) Halifax, Nova Scotia and (3) Saint John, New Brunswick. The study will recruit a total of 244 patients or 122 per study arm. Surgical procedures in study participants will be conducted at two academic, tertiary care hospitals (Winnipeg, Manitoba and Halifax, Nova Scotia, Canada) and one non-academic hospital (Saint John, New Brunswick, Canada) that perform cardiac surgery. These study sites were strategically chosen based on similar patient demographics and comparable surgical waiting list time.36 37 Additionally, each of these hospitals are partnered with one or more community-based CR centres, which are certified medical fitness facilities dedicated to improving the health of the community through health promotion, disease prevention and rehabilitation services. These facilities offer expert guidance from certified professionals, innovative health enhancement programmes, and provide integrated medical, rehabilitative and fitness services. The CR centres will provide the infrastructure and programme expertise necessary for the implementation and delivery of the PREHAB intervention.

Participant selection

Inclusion criteria

1. Patients, aged 65 years or older, undergoing elective isolated CABG, aortic valve repair/replacement for moderate aortic stenosis or severe regurgitation, mitral valve repair/replacement for moderate stenosis or severe regurgitation, or combined/valve procedures.
2. Patients with Clinical Frailty Score (CFS) ≥4 (vulnerable) and <7 (8=very severely frail, approaching end-of-life or 9=terminally ill) at time of acceptance for cardiac surgery.
3. Patients with an estimated ≥6 week surgical waiting list time.

Exclusion criteria

1. Patients who have unstable or recent unstable cardiac syndrome as defined by:
   A. Severe heart failure (New York Heart Association Class IV) or angina (Canadian Cardiovascular Society Class IV) symptoms.
   B. Critical left main coronary disease.
   C. Hospitalisation for arrhythmias, congestive heart failure or acute coronary syndrome prior to randomisation.
2. Patients who have severe left ventricular (LV) obstructive disease as defined by:
   A. Severe aortic or mitral stenosis (aortic or mitral valve area <1.0 cm² or mean gradient >40 or >10 mm Hg, respectively).
   B. Dynamic LV outflow obstruction.
3. Patients who have demonstrated exercise-induced ventricular arrhythmias or have experienced a recent hospitalisation for arrhythmias.
4. Patients who have cognitive deficits that would preclude rehabilitation.
5. Patients who have physical limitations that would preclude rehabilitation.
6. Patients who are unable to attend the PREHAB programme.

Screening

Our strategy for rapid screening of frailty in the large numbers of incoming patients will utilise the nine-point CFS.38 We have defined a CFS of greater than or equal to 4 (classified as ‘vulnerable’) as an initial indicator of frailty. Following training, clinicians will complete a CFS
for every new cardiac surgery consult at each of the participating sites. Patients with a CFS of 4–6 will be eligible for enrolment and notification will be sent to the local site coordinator (see Figure 1 for patient flow). We will exclude severely frail patients with a CFS greater than or equal to 7 because of the physical limitations in these patients. Furthermore, we anticipate that this criterion will exclude less than 1% of the patients on the elective cardiac surgery wait list.

A medical director at each site will oversee all cases, and ensure patient eligibility and safety for programme initiation and throughout the duration of the study. All eligible and accepted patients will be evaluated at baseline for safety parameters and to ensure angina stability. Patients who are deemed appropriate for enrolment into the study will be randomised, following completion of the baseline data collection and confirmation of eligibility, to one of two trial arms—control (StanC) or treatment (PREHAB). All patients will undergo a baseline exercise stress test supervised by a cardiologist to ensure patient safety. Safety data, including new hospitalisation, worsening angina or heart failure and arrhythmias will be captured and all adverse events will be reportable to an independent data safety monitoring board (DSMB).

**Instrumentation**

Preoperative patient demographics, cardiac risk profile, procedure data, surgical risk scores (EuroSCORE II and STS-PROMM), medication profile, cardiac risk factors and cardiac illness severity are routinely collected for all patients in pre-existing site surgical databases. Each site will also collect covariates of comorbidities using the Charleston Co-morbidity Index, Functional Co-morbidity Index, Older Americans Resources and Services scale for activities of daily living (ADL) and instrumental ADL, as well as postoperative complications and postoperative hospital LOS. Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA). The Patient Health Questionnaire-9 (PHQ-9) will assess depressive
Objectively measured physical activity will be quantified using the International Physical Activity Questionnaire (IPAQ). Data collection package are cardiac-specific questionnaires—the Seattle Angina Questionnaire (SAQ), Kansas City Cardiomyopathy Questionnaire (KCCQ) and the International Physical Activity Questionnaire (IPAQ). Objectively measured physical activity will be quantified using multidirectional accelerometry (Actical Physical Activity Monitors) for a period of 7 days at each data collection time point. This technique is considered the gold standard for assessing daily physical activity accumulation. Patients will also undergo a standard 6MWT and will repeat the 6MWT at the preoperative time point in both the control and PREHAB groups to determine the impact of the intervention on physical capacity. The 6MWT was chosen because it requires minimal infrastructure and personnel to complete, has been demonstrated to be a valid prognostic tool for patient outcomes among cardiac surgery patients, and is comparable to an exercise stress test. The Modified Fried Criteria will be used to assess changes in frailty, in addition to secondary measures of frailty employing the Short Performance Physical Battery Test (SPPB).

Assessor blinding

Individuals performing the assessments preoperatively, 3 months postoperatively and 1 year postoperatively will be blinded to the study arm in which the patient was assigned. Additionally, hospital staff, including nurses and surgeons, will be blinded to the study arm in which the patient has been assigned.

Table 1 Comparison of PREHAB and standard care

<table>
<thead>
<tr>
<th>Standard care</th>
<th>PREHAB intervention</th>
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<tbody>
<tr>
<td>▶ Patient advised to rest and participate in light-intensity physical activity</td>
<td>▶ Patient will receive, in addition to standard care, 8-week exercise and education programme at community-based cardiac rehabilitation facility</td>
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<tr>
<td>▶ 1–2 weeks prior to the scheduled surgical date, patient attends single, 3 h cardiac assessment with nurse practitioner and cardiac anaesthesiologist</td>
<td>▶ Patient will undergo an intake health status assessment</td>
</tr>
<tr>
<td>▶ Patient receives counselling on basic healthy living behaviours</td>
<td>▶ Patient will be required to attend two supervised exercise sessions per week:</td>
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1. Warm-up of approximately 15 min including stretching
2. 10–30 min of aerobic exercise at 40–60% of heart rate reserve progressing to high-intensity interval training up to 85% of aerobic capacity, based on recommendations by cardiologist
3. 10 min cool-down period

▶ Patient will participate in four educational sessions covering a range of topics including risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, stress management and promotion of self-managed care

PREHAB, Pre-operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery.

Randomisation

Randomisation (with concealed allocation) will be stratified by study location and will occur on a 1:1 basis in permuted blocks.

Standard care

Currently, patients awaiting cardiac surgery receive StanC (see table 1) where they are at present given no specific, routine instruction while awaiting their procedure.

Intervention

Patients randomised to the intervention group will receive, in addition to the above StanC, an 8-week comprehensive exercise therapy and education programme at a CR facility (see table 1). This programme will target both the physical, and psychological and social cognitive aspects of cardiac disease and frailty. In brief, participants will be required to complete an intake health status assessment by the CR team, including a physiotherapist, cardiovascular nurse and dietitian, and complete a symptom-limited, graded exercise stress test according to the American College of Sports Medicine Guidelines for Exercise Testing and Prescription. This assessment will provide the basis for exercise prescription in our population, which will include an individualised, symptom-limited exercise programme. Intervention group patients will be required to complete at least two sessions of supervised, structured exercise sessions per week for a total period of 8 weeks. Attendance will be monitored by the local CR site. Participants will complete a warm-up programme of approximately 15 min at the beginning of each session. Subsequently, aerobic exercise will be prescribed at 40–60% of heart rate reserve (Karvonen Formula) based


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on baseline exercise stress test data.60 Aerobic exercise will be approximately 10–30 min in duration, depending on individual tolerance and current level of conditioning. Aerobic exercise prescription will progress to high-intensity exercise in the context of symptom-limited, interval training up to 85% of maximal aerobic capacity based on recommendations by a cardiologist and medical fitness facility staff.29 All individual sessions will be concluded with a 10 min cool down period. In addition to the prescribed exercise programme, patients will be required to participate in four educational sessions tailored towards self-management for CR and healthy living practices. These education sessions will be directly relevant to the patient population and will cover a range of topics, including risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, stress management and promotion of self-managed care. Principles of shared decision-making will be utilised with the PREHAB intervention, where training for providers and patients involved in the intervention will have shared control of treatment decisions.61–65

Data collection and management

All participants will meet with the research staff at five time points: (1–2) twice at time of enrolment after the patient is referred for a surgical procedure (ie, baseline preintervention); (3) 1 week preoperatively; (4) 3 months postoperatively and (5) 1 year postoperatively. Data collection will occur from both written and electronic medical record sources (ie, patient information systems, where applicable). Existing perioperative surgical, ICU and hospital data will be used to capture patient demographics, procedure urgency, intraoperative procedure and anaesthetic variables, cardiopulmonary bypass information, blood product utilisation, mechanical ventilation, delirium/coma, ICU and hospital LOS, major adverse events, infection and ICU, and hospital readmission are collected in institutional databases.

Local research staff will enter de-identified study data onto a trial-specific electronic case report form through REDCap, a secure, web-based application for managing online surveys and databases.64 The data will be housed on a secure server located at the University of Manitoba Faculty of Medicine.

Statistical analysis

The sample size calculation was based on the primary objective of the study—hospital LOS. Preliminary data collected by our group demonstrated the proportion of frail patients with a hospital LOS greater than 7 days to be 58.3%. For the intervention group, based on recommendations by a cardiologist and medical fitness facility staff.29 All individual sessions will be concluded with a 10 min cool down period. In addition to the prescribed exercise programme, patients will be required to participate in four educational sessions tailored towards self-management for CR and healthy living practices. These education sessions will be directly relevant to the patient population and will cover a range of topics, including risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, stress management and promotion of self-managed care. Principles of shared decision-making will be utilised with the PREHAB intervention, where training for providers and patients involved in the intervention will have shared control of treatment decisions.61–65

Objective 1: To determine if PREHAB reduces the proportion of frail older adult patients requiring a prolonged hospital LOS of greater than 7 days. A univariable analysis will be undertaken to determine if hospital LOS greater than 7 days is associated with frailty and other patient-level factors. A stepwise multivariable logistic regression model will then be developed to determine if PREHAB attendance is independently associated with a decreased risk of prolonged hospital LOS greater than 7 days. As a secondary analysis, hospital LOS will also be compared as a continuous variable between PREHAB and the StanC groups using a Mann-Whitney test. A multivariable model for hospital LOS will also be developed utilising generalised linear models with Poisson or Negative Binomial distribution.

Objective 2: Does attending PREHAB influence frailty, exercise capacity, physical activity behaviour, in-hospital complications, and HRQoL? The Modified Fried Criteria will be the primary frailty outcome over time from baseline to preoperative or from baseline to the long-term follow-up assessments. The primary measure of exercise capacity will be the 6MWT and will be analysed with univariable linear regression models to evaluate the association between the 6MWT and PREHAB attendance. Accelerometers will be used to objectively measure the number of minutes spent performing moderate to vigorous physical activity and the total physical activity per day for a period of 7 days and compared between groups. A composite outcome for a major adverse cardiac event (ie, in hospital stroke, myocardial infarction, renal failure requiring dialysis and death) and delirium will be compared between groups using a χ² or Fisher’s exact test. A multivariable logistic regression will be used to identify if PREHAB is independently associated with in-hospital delirium. The SF-12V2 and EQ-5D scores, after normative standardisation, will be analysed through use of a repeated measures analysis of variance to allow for a standardised group and group/time interaction effect estimation.

ETHICS

Ethics approval will be obtained at each individual study site. Any substantial protocol amendments will be sent to the local ethics committee for approval as per standard regulatory requirements at the institution. All study sites will then be informed of the amendments.

Informed consent

During an initial meeting with a cardiac surgeon, eligible and interested patients will be approached by a research assistant (RA) who will provide the patient with further details of the study. The patient will be informed about the trial by the RA and provided with a copy of
the patient information and consent form. Patients will be provided with adequate amount of time to consider their participation in the trial and will be given an opportunity to ask questions. If the patient decides to participate in the study, they will be asked to provide written consent, which will then be countersigned by the RA. All participants are free to withdraw from the study at any time, without any prejudice to future medical treatment.

End of trial
The trial will end when 244 patients have been enrolled and the final patient has completed their 1-year follow-up appointment.

Trial monitoring and oversight
The study management and steering committee is responsible for ensuring that the study meets the proposed milestones and deadlines. They will also be responsible for all aspects of the study design, management, ethical conduct, analysis and dissemination of results.

Safety data, including new hospitalisation, worsening angina or heart failure and arrhythmias, will be captured and all adverse events will be reportable to the DSMB. The DSMB is an independent group of experts that advises study investigators. They are responsible to periodically evaluate the study data for participant safety and study conduct, in addition to making recommendations concerning the modification and/or termination of the trial.

DISSEMINATION
Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators. Authorship will be determined based on internationally agreed on criteria and journal guidelines for authorship. A major component of the proposed project is to collect information that is appropriate to enable knowledge users to obtain the information they need to inform new initiatives within their own organisations. The integrated knowledge translation (iKT) approach enhances the likelihood that the PREHAB intervention will be implemented in the Canadian healthcare system and be sustainable over the long term. By using an iKT approach and best practice evidence to inform a model of care for frail elderly persons requiring cardiac surgery, it is anticipated that the project will influence the healthcare system in a variety of ways. The study protocol also includes a process for sharing study outcomes with participants. Specifically, study participants will have the option at the time of consent to indicate their interest in receiving a summary of study findings. This summary will then be sent to participants on completion of the study.

Trial status
The study is not yet recruiting patients. The first patient will be recruited in January 2015, and we expect recruitment to be complete in March of 2016. The expected completion date of the project, including all 1-year follow-up appointments, is May 2017.

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Competing interests
None.
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