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ORIGINAL ARTICLE

Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial*

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ABSTRACT

Background: Prehabilitation has been previously shown to be more effective in enhancing postoperative functional capacity than rehabilitation alone. The purpose of this study was to determine whether a weekly supervised exercise session could provide further benefit to our current prehabilition program, when comparing to standard post-surgical rehabilitation.

Methods: A parallel-arm single-blind randomized control trial was conducted in patients scheduled for non-metastatic colorectal cancer resection. Patients were assigned to either a once weekly supervised prehabilitation (PREHAB+, $n = 41$) or standard rehabilitation (REHAB, $n = 39$) program. Both multimodal programs were home-based program and consisted of moderate intensity aerobic and resistance exercise, nutrition counseling with daily whey protein supplementation and anxiety-reduction strategies. Perioperative care was standardized for both groups as per enhanced recovery after surgery (ERAS®) guidelines. Functional exercise capacity, as determined by the 6-minute walk test distance (6MWD), was the primary outcome. Exercise quantity, intensity and energy expenditure was determined by the CHAMPS questionnaire.

Results: Both groups were comparable for baseline walking capacity (PREHAB+: 448 m [IQR 375–525] vs. REHAB: 461 m [419–556], p=.775) and included a similar proportion of patients who improved walking capacity (>20 m) during the preoperative period (PREHAB+: 54% vs. REHAB: 38%, $p = .222$). After surgery, changes in 6MWD were also similar in both groups. In PREHAB+, however, there was a significant association between physical activity energy expenditure and 6MWD ($p < .01$). Previously inactive patients were more likely to improve functional capacity due to PREHAB+ (OR 7.07 [95% CI 1.10–45.51]).

Conclusions: The addition of a weekly supervised exercise session to our current prehabilitation program did not further enhance postoperative walking capacity when compared to standard REHAB care. Sedentary patients, however, seemed more likely to benefit from PREHAB+. An association was found between energy spent in physical activity and 6MWD. This information is important to consider when designing cost-effective prehabilitation programs.

Abbreviations: ERAS: enhanced recovery after surgery; RCT: randomized control trial; PREHAB+: prehabilitation with supervised exercise sessions; REHAB: rehabilitation; 6MWD: 6-minute walk test distance; CHAMPS: Community Healthy Activity Model Programme for Seniors; METS: metabolic equivalents; GEE: generalized estimating equations; HADS: Hospital Anxiety and Depression Scale; ACS: American Cancer Society

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Introduction

Fatigue [1] and low functional capacity have been reported [2] in cancer patients following treatment, such as surgery, chemotherapy and radiotherapy [3]. Emerging evidence indicates that a multimodal prehabiltation program improves preoperative functional reserve and, subsequently, helps patients to better tolerate the side effects of surgery [4]. In a randomized controlled trial, conducted by Gillis et al., it was demonstrated that 80% of patients who received a multimodal prehabilitation program prior to colorectal cancer resection recovered their baseline functional capacity by 8 weeks post-surgery compared to a 40% recovery rate in a historical control that received post-operative rehabilitation only [5]. The multimodal prehabilitation program implemented in the Gillis study consisted of a home-based, unsupervised exercise program (moderate-intensity aerobic and resistance

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training), nutritional counseling, protein supplementation and anxiety easing techniques that was initiated approximatedly 28 days prior to surgery and continued for 8 weeks into the postoperative period. Despite the overall benefits attributed to the prehabilitation program, there remained a 30% decline in functional capacity- as determined by 6-minute walking distance (6MWD) – during the first month post-surgery, which was attributed to either exercise of an insufficient intensity or low adherence to preoperative exercise.

Supervised exercise sessions increase functional recovery after cardiac [6] and orthopedic surgery [7], as well as improving long-term maintenance of physical activity [8] and degree of exercise progression [9]. Also, supervision of exercise by a qualified professional can promote patient confidence and determination in achieving recommended exercise goals [10].

In an attempt to further mitigate the decline that occurs in the immediate postoperative period [5], the goal of this randomized control trial (RCT) was to determine whether the addition of a once-a-week supervised exercise session to our current prehabilitation program would further enhance recovery when compared to standard care rehabilitation, thus promoting an accelerated return to baseline physical function. The design was based on a previously published study where a prehabilitation group was compared to a control that received a similar program but offered as rehabilitation only [4].

We hypothesized that patients who received a prehabilitation program that included a once-a-week supervised exercise session in the preoperative period will enhance their walking capacity prior to surgery when compared to the rehabilitation group. In addition, this improvement will subsequently aid in mitigating the postoperative decline in physical function and promote an earlier return to baseline functional capacity when compared to a rehabilitation-only group.

Methods

Subjects

The study was approved by the Research Ethics Board of the McGill University Health Center (11-004-GEN), Montréal, Québec, Canada and registered on ClinicalTrials.gov (NCT02586701). Participants were enrolled from December 2013 to August 2015 at a single tertiary care center affiliated with McGill University in Montréal, Québec, Canada. Consecutive adult patients, scheduled for colon or rectal cancer resection, were approached at the initial visit with their surgeon. Participants were deemed ineligible for this study if they had metastatic cancer, did not speak English or French or had concurrent medical conditions that contraindicated exercise. Surgical care for study participants followed the enhanced recovery after surgery (ERAS®) guidelines which has been the standard of surgical care at our institution since 2008 [11,12].

Study design

The study was conceived as a single-blind parallel-arm RCT and was based on the design of previously published studies where efforts were made to minimize the potential bias of offering an exercise intervention to only one group [4,5].

Preoperative phase

Group assignment

Once recruited and consented for the study, each participant was scheduled for a baseline assessment by a kinesiologist, nutritionist and a psychology-trained research team member. At the baseline evaluation, patients were randomly assigned on a 1:1 ratio by computer-generated random numbers in sealed envelopes to receive either the supervised prehabilitation (PREHAB+) or the rehabilitation (REHAB) program. This assessment was performed approximately 4 weeks before the scheduled surgery date, with participation in this study having no affect on surgical waiting time (see Figure 1).

Prehabilitation

Patients assigned to the PREHAB + group were prescribed a multimodal home-based exercise program to be commenced immediately after the baseline assessment (see Figure 1). In addition, during the pre-surgical period, these patients were required to attend once a week in-laboratory exercise sessions that were supervised by a trained kinesiologist. Post-surgery, PREHAB + patients recommenced their exercise prescription while still in the hospital (after nurse-led mobilization) and, upon discharge, were instructed to continue their home-based program (minus the supervised sessions) for an additional 8-week period. The details of the home-based program, supervised sessions and in hospital exercise are presented in the following sections.

Rehabilitation

At time of group assignment, the REHAB patients were provided with pre-operative information that is a normal part of ERAS® protocol (walking, ankle rotation, breathing exercises, see Figure 1). Two days prior to surgery, REHAB patients were provided with an 8-week multimodal post-surgical rehabilitation program that was identical to the home-based program prescribed to the PREHAB + group. Again, as in the PREHAB + group, exercise also commenced as soon as the patient was mobilized by the unit nurse. The primary differences between the study groups were that PREHAB + had the pre-operative exercise, as well as the supervised sessions.

Exercise intervention

The home-based component

At baseline, participants in both study groups were assessed by a staff kinesiologist and prescribed exercise following the guidelines of the American College of Sports Medicine [13]. The whole-body exercise prescription consisted of aerobic and resistance training, which was personalized to each participant's fitness level. Aerobic exercise intensity was prescribed based on the rate of perceived exertion (Borg scale) and from the 6MWD measurements obtained at baseline. The resistance exercises prescribed

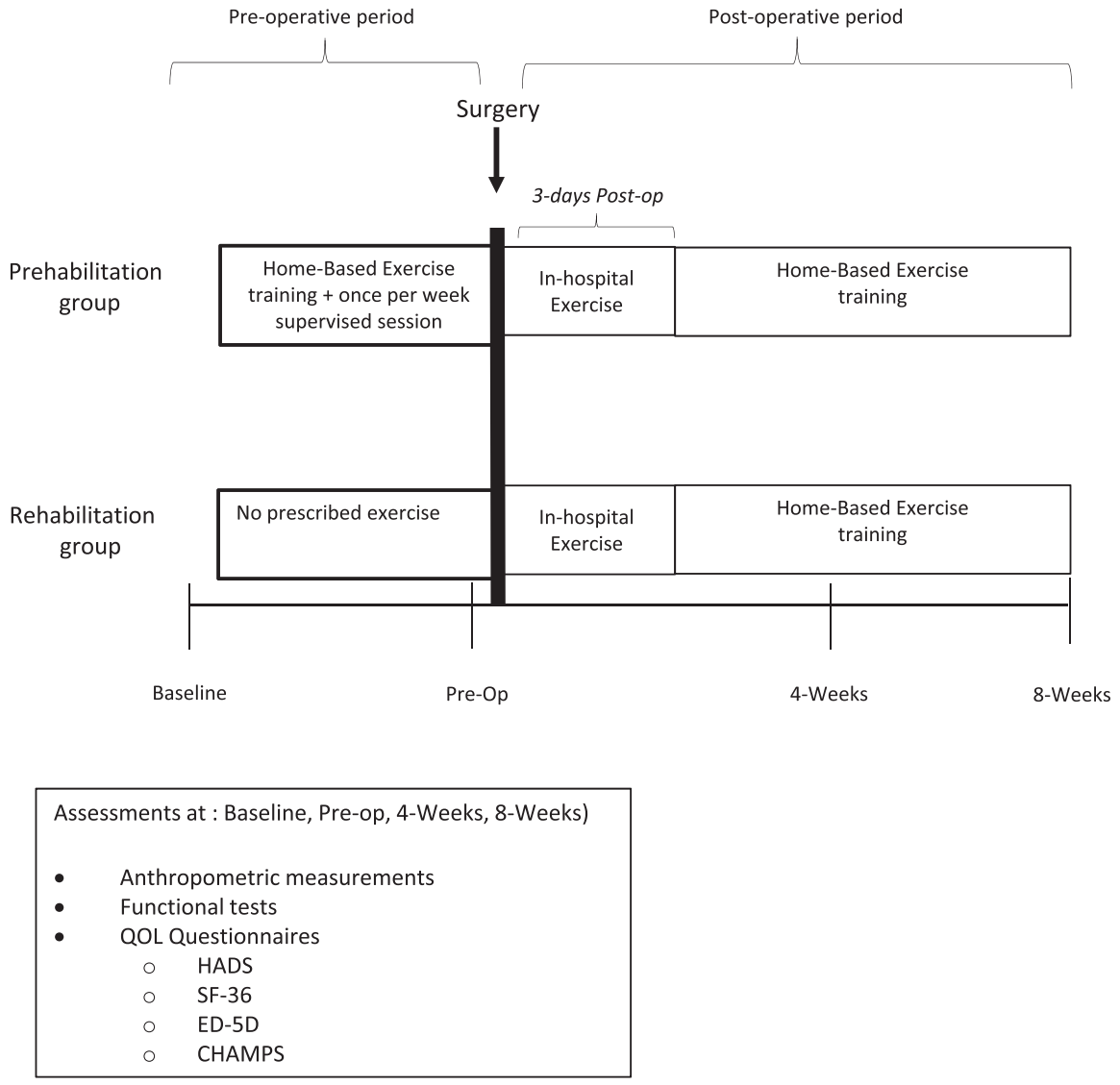

Figure 1. Study design.

were based on eight repetitions maximum test, which provides a submaximal estimation of the patient's maximal strength. Participants were prescribed to perform 3–4 days per week 30 minutes of moderate intensity aerobic activity (60–70% of maximal heart rate calculated from the Karvonen formula, after verification that the patient was not on any drug that could affect the heart rate response) consisting of either walking, cycling or jogging (according to patient abilities and preference). The resistance training consisted of eight exercises targeting major muscle groups of the core, upper and lower limbs and to be performed 3–4 times per week in up to two sets of a range of 8–15 repetitions, dependent on volitional fatigue. The Borg scale was provided to the patients in an information booklet in order to assist in the determination of appropriate exercise intensity at home. Patients were given an elastic resistance band (Theraband®) that was matched to their fitness level, as well as a pedometer to encourage them to participate in daily walks. This component was started by the PREHAB + group prior to surgery and by the REHAB group after discharge from the hospital.

The supervised exercise component

During the preoperative period, participants in the PREHAB + group were required to return once a week to the hospital exercise laboratory where they trained under a kinesiologist's supervision on either a NuStep® T5 (NuStep Inc., Ann Arbor, MI) recumbent stepper [14] that mimicks the walking motion or a standard treadmill, as per subject preference and physical ability. In addition, they also performed their resistance exercise program in this supervised session. Feedback was provided and resistance training was progressed (increasing intensity) when patients could complete the routine with perceived mild exertion (defined as 12 or less on the 20 point Borg scale). Each supervised session consisted of 30 minutes of moderate aerobic exercise, including a 5-minute warmup, and 25 minutes of resistance exercises followed by five minutes of stretching [13].

The in-hospital exercise

Patients in both study groups were encouraged to start in-hospital exercise as soon as cleared for mobilization by the nursing

staff. At this point, the patients in the REHAB group were able to review the exercise program with the kinesiologist, in order to ensure that they were both confident and comfortable with performing the exercises after discharge. The PREHAB + group recommenced their exercise program, with kinesiologist feedback and modification, if required.

Nutritional intervention

At baseline, all participants had their nutritional status assessed and were counseled accordingly by a registered dietitian. Nutritional status was evaluated using the Subjective Global Assessment (SGA) and the Nutritional Risk Screening tool NRS2002 [15]. The SGA gives letter scores to patients based on their degree of malnourishment; A = well nourished, B = mildly to moderately malnourished, or suspected malnutrition, C = severely malnourished. The NRS2002 attributes for risk factors such as nutritional status, the severity of disease and age, and patients with scores $\geq$3 are considered at nutrition risk. Participants were asked to complete a three-day food diary from which carbohydrate, fat and protein quantities were estimated using food exchange lists and composition tables. Macronutrient intake was evaluated based on Dietary Reference Intake Values [16], and food choices were compared to Eating Well with Canada's Food Guide recommendations [17]. Protein requirement in the healthy adult is 0.8 g/kg of body weight per day, but requirements in the surgical patients are higher at 1.2 g/kg of body weight (or adjusted body weight in obese patients) as per European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [18]. If the patient did not meet the protein requirement by diet alone, they were provided with whey protein supplementation to match ESPEN guidelines (Immunocal®; Immunotec Inc., Vaudreuil, Canada). Patients were instructed to ingest protein and/or the supplements within one hour of their exercise training to make use of the 'anabolic window', the moment at which muscle protein synthesis is the highest [19]. Further nutritional counseling was given to help with bowel movements regularity, body composition optimization and glycemic control.

Anxiety-reduction strategies

Each patient received a 60-minute session under the supervision of a psychology-trained member of the research team who provided personalized techniques to alleviate anxiety, such as relaxation exercises based on visualization, along with breathing exercises [20]. Patients were provided with a compact disc with an audio track containing the instructions to help them perform the exercises at home two to three times a week. The coping strategies of each patient were also assessed, and suggestions were given to support them in the management of their anxiety or depression symptoms.

Instruction booklet and follow-ups

All patients were provided with an information booklet containing the instructions, the Borg scale to gauge intensity, as well as figures depicting each element of the program. The booklet also included a diary in which patients were required to record all activities related to the program in order to assess adherence to the program. To reinforce compliance to the program, patients were contacted on a weekly basis by telephone and were asked a standardized set of questions. Information on the frequency, intensity and duration of exercises, additional physical activity performed, the quantity and frequency of whey protein supplementation taken and the use of the relaxation techniques was collected. Based on this information and the diary in the patient booklet, compliance was calculated as a percentage of each element of the program.

Outcomes and measures

Primary outcomes

The primary outcome was functional walking capacity, as assessed by 6MWD. The test evaluates the ability to walk at a moderate intensity and is associated with the capacity to perform activities of daily living. It has been validated in a surgical population [21,22] and is linearly correlated to oxygen consumption at peak [23] and at anaerobic threshold [24]. It integrates strength, endurance and balance and is easily reproducible. The walking distance is calculated in meters by counting how many times participants can walk back and forth between cones placed 15 m apart in a hallway in six minutes. Participants were allowed to rest if needed while the six minutes continued to elapse. Standardized feedback was given to the patients every minute as per guidelines of the American Thoracic Society [25]. A 2-minute walking test was done as a practice before the 6MWD. A change of at least 20 m was considered to be the minimal clinically meaningful difference and is the estimated measurement error of the test [26]. The 6MWD was performed at baseline, before surgery and at 4 and 8 weeks after surgery. The assessor, using a standardized protocol and script during the tesing, was blinded to group assignment. Personal 6MWD prediction, based on age and sex, was calculated with the formula: predicted value = 868 – (age $\times$2.9) – (74.7 if female), where age is in years [27].

Secondary outcomes

The Community Healthy Activity Model Programme for Seniors (CHAMPS) [28] questionnaire was used to estimate the weekly energy expenditure of participants, based on intensity and frequency of the activity. Participants were asked to report all physical activities, categorized as either light (1–3 METS), moderate (3–6 METS) or vigorous (>6 METS) intensity. Based on their responses, participants were also categorized as either meeting or not meeting the recommended weekly time spent performing moderate to vigorous physical activity as per the American Cancer Society (ACS) guidelines. The ACS recommends 150 minutes per week of moderate or 75 minutes per week of vigorous physical activity [29]. For this study, participants were considered

to be active if they met these recommendations and inactive if they did not.

Other measurements performed

i. *Body composition* was measured at baseline with an inBody320® (Biospace, Ottawa, Canada) scale which uses bioelectrical impedance analysis to determine weight, body fat percentage and lean body mass.
ii. *Grip strength* was measured at baseline using a grip dynamometer. Measurements were performed twice on each arm and the highest value was reported.
iii. *Administrative data*, including length of stay, emergency department visits, hospital readmission and complications, and severity at 30 days after surgery were collected prospectively. Complications were defined as any deviation from the optimal post-operative course. Complication severity was graded with the Clavien–Dindo classification [30] according to their associated usage healthcare resources; grade I complications are managed at the bedside or with medications of specific therapeutic categories, grade II complications require treatments such as blood transfusion, antibiotics, anticoagulants or total parenteral nutrition, grade III complications require a surgical, radiological or endoscopic intervention and grade IV complications require intensive care treatment.
iv. *Compliance* was defined as attendance to the preoperative supervised exercise sessions and recorded.
v. *The patient's psychological status* was assessed through the use of the Hospital Anxiety and Depression Scale (HADS) [31]. The scale contains 14 questions, seven assessing stress and seven assessing depression, scored from 0 to 3. A score greater than 8 in either category is suggestive of a mood disorder.

Statistical analysis

In the protocol, the sample size and power calculations were based on the inputs provided from two studies previously conducted by the same group [5,32]. Based on the mean changes in the 6MWD between baseline and eight weeks (control group = 25(±66)); prehabilitation group = 35(±68)), a sample size of 80 patients (40 per group) was estimated to detect these differences with a power of 80% and a two-tailed alpha of 0.05 [4].

Normality of the data distribution was assessed with the Shapiro–Wilk test. Continuous variables were compared with the two-sided Student *t* test or the Mann–Whitney *U* test, as appropriate. Categorical variables were compared using Pearson's Chi-Square test or Fisher's Exact test. The effect of the interventions was assessed by calculating the mean difference on the 6MWD compared to a baseline of all subsequent measurements and the proportions of patients who increased ≥20 m, which represents those patients who experienced clinically significant improvement.

Logistic generalized estimating equations (GEE) were used to assess whether prehabilitation predicted clinically significant improvement in 6MWD. Crude and adjusted odds ratios were calculated to reveal the longitudinal association with physical activity.

Analyses were performed with IBM SPSS Statistics for Macintosh, Version 23.0 (IBM Corp., Armonk, NY) and STATA 14.1 (StataCorp, College Station, TX).

Results

Participants

From the surgical clinic, 88 patients scheduled for colorectal cancer resection consented to partake in this study. Between the time of consent to the time of randomization, eight patients were exluded. The remaining 80 patients, at the time of their first laboratory visit for baseline assessments, were then randomized to either the PREHAB + or REHAB study groups. Of the patients who were randomized to REHAB, a further seven patients were excluded without altering the baseline characteristics of the participants. After surgery, a total of 10 patients were subsequently lost to follow up (four in the PREHAB + group and six in the REHAB group). The data of 37 participants from the PREHAB + group and 26 from the REHAB group were then analyzed. All details are presented in the CONSORT diagram in Figure 2.

Baseline demographic and clinical characteristics were similar between the two groups and are presented in Table 1. Patients in the REHAB group tended to be younger ($p = .05$) compared to the PREHAB + group. The proportion of patients aged ≥75 years old was also lower, but not to a significant extent, in the REHAB group (23% vs. 43%, $p = .098$). Overall, there were no significant differences between the two groups in all demographics and clinical measurements (see Table 1). Median time to surgery was comparable between the two groups (32 days (IQR 25–48) for the PREHAB + group and 20.5 days (IQR 15–32) for the REHAB group).

Functional walking capacity

The participants completed the 6MWD at all four assessment points (see Table 2). At baseline, mean values were 448 m (SD 118 m) in the PREHAB + group and 461 m (SD 109 m) in the REHAB group. Both groups improved walking capacity over the preoperative period: PREHAB + had a mean increase of 21 m (SD 47 m) while REHAB had a mean increase of 10 m (SD 30 m). No significant differences were detected between the groups, either before or after surgery. Over the pre-surgial period, 54% of PREHAB + increased walking distance by more than 20 m, as compared to 38% of REHAB ($p = .261$). At 4 weeks after surgery, there was a a decrease in walking capacity from baseline by an average of 8 m (SD 67 m) in PREHAB + and 17 m (SD 85 m) in REHAB. At this time point (4 weeks), 50% of participants in both groups had recovered to their baseline walking capacity. At 8 weeks after surgery, both the PREHAB + and the REHAB group had walking distances above baseline values, with mean gains of 20 m (SD 54 m) and 11 m (SD 58 m), respectively. Although 74% of patients in PREHAB + had recovered walking capacity

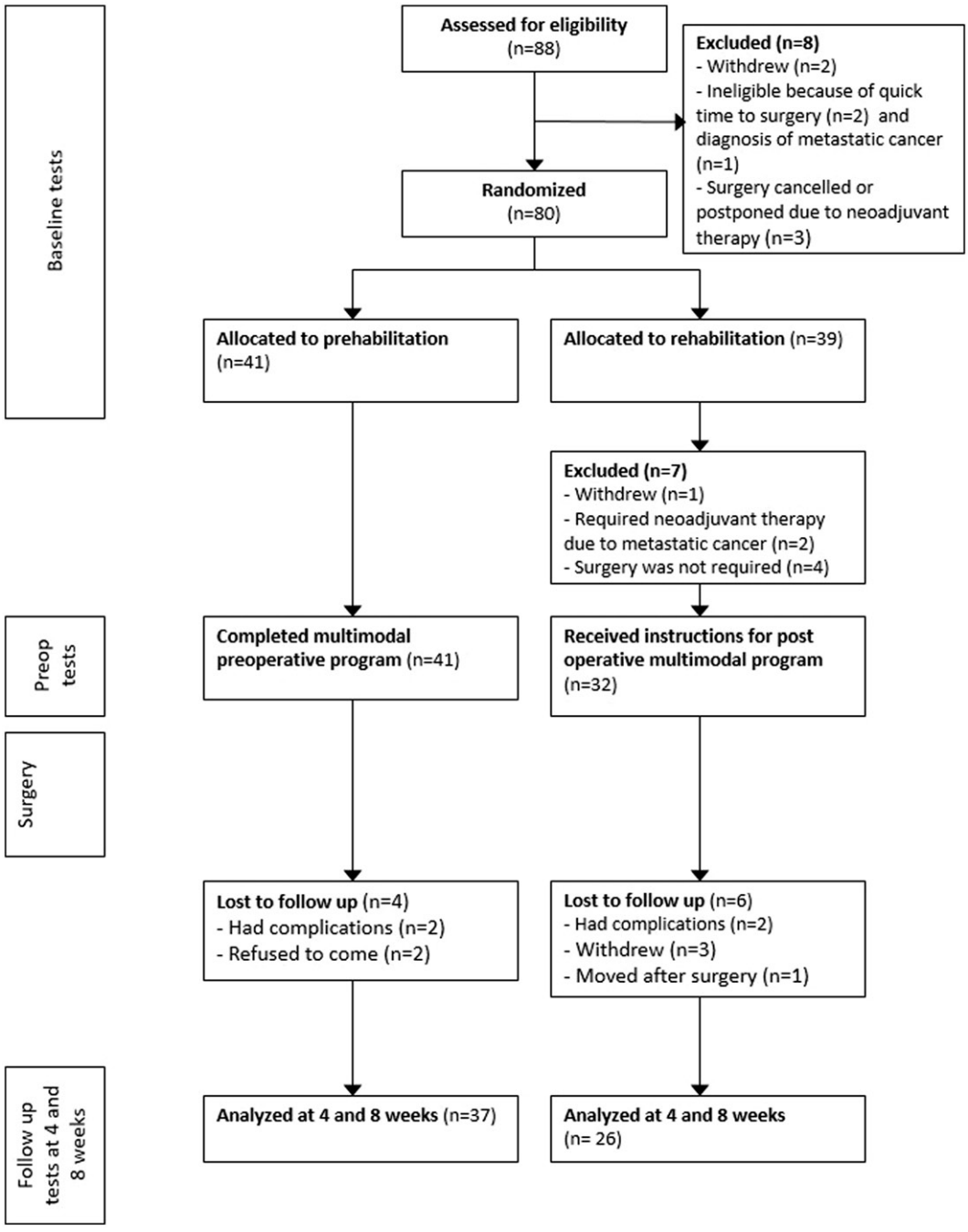

Figure 2. CONSORT diagram for the trial.

vs. 65% in REHAB, there was no detectable difference between the groups.

Secondary outcomes

Self-reported physical activity

The CHAMPS questionnaire was filled out by each patient at all 4 assessment points. Physical activity was analyzed as total energy expenditure in kcal/kg/week and separated in energy spent on light and moderate to vigorous physical activities (see Table 2). The total amount of energy dedicated to light activities (1–3 METS) was similar between groups at all assessment points. In contrast, the amount of energy spent on moderate and vigorous physical activities (>3 METS) was significantly higher in the PREHAB + group compared with the REHAB group at the preoperative assessment ($p = .021$) and at 8 weeks after surgery ($p = .04$). Similarly, the number of patients who met the ACS recommendations for physical activity (150 minutes per week of moderate or 75 minutes per week of vigorous physical activity) was significantly higher in the PREHAB + group at the preoperative visit (PREHAB+ = 32 patients [86%] vs. REHAB = 15 [58%]) and at 8 weeks after surgery (PREHAB+ =29 patients [78%] vs. REHAB = 13 patients [50%]) (see Table 3). We estimated the median difference of 6-minutes walking distance separately among those who met the recommendations of the ACS guidelines (active) and those who did not (inactive), and found statistically significant differences at the follow-ups: Pre-operation (Ranksum test

Table 1. Patient demographics and clinical measurements.

Variable	PREHAB+ $N = 37$		REHAB $n = 26$	
Age (years)				
Median, IQR	74	[67.5–78]	71	[54.5–74.5]
Age ≥75 years				
n, %	16	43%	6	23%
Sex-Male				
n, %	30	81%	16	62%
Weight (kg)				
Mean, SD	80	14	81	13
BMI (kg/m^2)				
Mean, SD	27.5	4.1	28.6	4.5
ASA status				
1				
n, %	1	3%	3	12%
2				
n, %	23	62%	11	42%
3+				
n, %	13	35%	12	46%
Comorbidities				
Diabetes				
n, %	10	27%	4	15%
COPD				
n, %	2	5%	4	15%
CAD				
n, %	2	5%	4	15%
HTN				
n, %	23	62%	11	42%
PVD				
n, %	2	5%	1	4%
AF				
n, %	4	11%	1	4%
Tumor stage				
0				
n, %	4	11%	4	15%
1 and 2				
n, %	22	59%	11	42%
3 and 4				
n, %	11	30%	11	42%
Neoadjuvant therapy				
n, %	5	14%	4	15%
Adjuvant therapy within 8 weeks of surgery				
n, %	2	5%	2	8%
Laparoscopic procedure				
n, %	31	84%	21	81%
Site of resection				
Colon				
n, %	25	68%	19	76%
Rectum				
n, %	12	32%	6	24%
New stoma				
n, %	6	16%	4	16%
6 minute walking distance				
Meters				
Mean, SD	448	118	461	109
Percentage predicted				
%		69		71
Number of patients <400 m				
n, %	9	24%	5	19%
CHAMPS				
Physical activity (kcal/kg/week)				
Median, IQR	37.5	[15–65]	38.5	[10–58]
Number meeting ACS requirements				
n, %	18	49%	13	50%
Grip strength				
Right (kg)				
Median, IQR	36	[25.0–40.5]	32	[21–44.4]
Left (kg)				
Median, IQR	34	[23.8–42.5]	31	[20–42.1]
Fat-free mass (kg)	56	[51.1–64.2]	55	[42.4–62.9]
Fat percentage (kg)	29	[25.2–34.1]	31	[28.4–37.3]
Albumin (g/L)	40	3	40	3
CRP (mg/L)	3	[0.9–7.3]	3	[1–7.2]
HbA1C (%)	6	0.5	5.9	0.4
Charlson score	2	[2–3]	3	[2–4]

(*continued*)

Table 1. Continued

Variable	PREHAB+ N = 37		REHAB n = 26	
CR-POSSUM				
Physiological score				
Median, IQR	9	[9–11]	9	[7.5–10]
Operative score				
Median, IQR	7	[7–10.5]	7	[6–8.5]
HADS				
Suggestive of anxiety (score >7)				
n, %	13	35%	6	23%
Suggestive of depression (score >7)				
n, %	4	11%	5	19%

BMI: body mass index; ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; HTN: hypertension; PVD: peripheral vascular disease; AF: atrial fibrillation; CHAMPS: Community Healthy Activity Model Programme for Seniors; CRP: C-reactive protein; HbA1C: glycated hemoglobic; HADS: Hospital Anxiety Depression Scale; IQR: inter-quartile range.

$p = .0165$), at 4-weeks ($p = .0087$) and at 8-weeks ($p = .0005$) (see Table 3). Furthermore, patients who were considered to be inactive were more likely to significantly improve their functional exercise capacity if they were in the PREHAB + group (OR 7.07 [95% CI 1.10–45.51]) (see Table 3). According to GEE binomial analysis, age was not a factor in whether the patients were considered to be inactive, however, women were almost 15 times (OR 14.65 [95% CI 1.86–1115.26]) more likely to not meet ACS guidelines than their male counterparts (see Table 3).

Compliance with the program

In the PREHAB + group, compliance to the program, including the supervised exercise sessions, was 98% (see Table 2). After surgery, compliance to the prescribed program was similar between both groups, which was over 70% at any time point during the study.

Post-operative outcomes at 30 days after surgery

The length of first stay, emergency department visits and complications rate was similar between both groups (see Supplementary Data). Hospital readmission and the total duration of hospitalization tended to be higher in the PREHAB + group, but not when analyzed in an intention-to-treat fashion, in which we considered patients who were excluded after surgery due to missing 6MWD at follow-ups (see Supplementary Data).

Discussion

The present results show that, contrary to our original hypothesis, both PREHAB + and REHAB groups increased their walking capacity during the pre-operative period and no difference was found between the two groups. Patients who were assigned to the supervised multimodal prehabilitation program improved their walking capacity by an average of 21 m in the preoperative period, and over 50% walked over 20 m, a measure of functional capacity considered clinically significant [26]. The amount of energy spent on moderate and vigorous physical activities increased from 10 to 24 kcal/kg/week and the proportion of patients who met the current ACS recommendations of performing 150 minutes per week of moderate to vigorous physical activity [29] increased from 49% (95% CI = 37–78%) to 87% (95% CI = 55–97%). A dose–response relationship was observed between high energy expenditure of physical activities and 6MWD achieved [4]. Compliance with the supervised sessions was 98% and over 90% in the home-based component. It is interesting to note that, within the inactive patients, those who received prehabilitation were seven times more likely to improve their walking distance in a significant fashion than those who received rehabilitation alone.

In contrast, the REHAB group increased their 6MWD by 10 m and 38% of these patients improved their walking capacity over 20 m. No changes in physical activity were shown, highlighting the low proportion of patients who met the ACS recommendations.

We had hypothesized that one day per week of supervised exercise, when added to the home-based program in the pre-surgical period, would have further improved functional capacity and, subsequently, attenuating the postoperative drop in 6MWD distances that we have previously reported in our prehabilitation studies [4,5]. Although compliance to the supervised exercise sessions was 98%, the increase in the 6MWD was of a similar magnitude to that previously shown in the Gillis study [4] where no supervised exercise sessions were provided. The reasons for the lack of effect are not clear but could be due to a high motivation to perform exercise in the Gillis study or that – in this study – a higher exercise intensity and/or greater amount of supervised exercise sessions is required to attenuate the immediate post-operative decline.

The lack of preoperative difference in 6MWD between the PREHAB + and REHAB groups was mostly unexpected. This could be due to various reasons such as the relatively small sample size, the initial fitness level of the REHAB group (as indicated by their baseline 6MWD results), the lower proportion of subjects over the age of 75 years in the REHAB group (23%) compared with 43% in the PREHAB + group or, again, an insufficient number of supervised sessions or intensity of exercise . It is also possible that, by participating in a study on the effect of exercise on the postoperative outcome, some of the patients in the REHAB group had become active,

Table 2. Clinical outcomes.

Assessment	Baseline		Preop		4 weeks		8 weeks	
	Prehab	Rehab	Prehab	Rehab	Prehab	Rehab	Prehab	Rehab
6 MWD								
Walking distance in meters, mean (SD)	448 (118)	461 (109)	470 (118)	471 (108)	441 (120)	444 (116)	468 (118)	472 (108)
Mean change compared to baseline, *n* (%)			21 (47)	10 (30)	−5 (67)	−17 (85)	20 (54)	11 (58)
No. of patients who improved 6MWD compared to baseline								
Improvement, change ≥20 m, *n* (%)			20 (54%)	10 (38%)	11 (30%)	9 (35%)	17 (46%)	12 (46%)
No improvement, change <20 m, *n* (%)			17 (46%)	16 (62%)	26 (70%)	17 (65%)	20 (54%)	14 (54%)
Self-reported physical activity, CHAMPS (kcal/kg/week)								
Light (kcal/kg/week)	10 [5–27.5]	13.8 [5.3–35]	10 [5–21.3]	10 [5–35.6]	5 [1.9–18.1]	10 [1.3–25]	12.5 [3.8–25]	13.8 [8.4–25.6]
Moderate to vigorous (kcal/kg/week)	10 [2.5–44.3]	11.3 [0–33.9]	24 [12.4–47.3]*	13.8 [0–27.4]	13 [1.8–25.6]	12 [4.9–18.8]	30.5 [13.5–52.9]*	14 [2.7–31.1]
Total (kcal/kg/week)	37.5 [15.3–64.5]	38.5 [10–58.3]	45 [19.1–69.3]	31.1 [7.8–70.8]	25.1 [11.7–39.9]	23 [11.5–37.3]	46.8 [26.3–85.1]	28.4 [15.1–58]
Number of patients meeting ACS physical activity recommendation, *n* (%)	18 (49%)	13 (50%)	32 (86%)*	15 (58%)	20 (54%)	15 (58%)	29 (78%)*	13 (50%)
Mean compliance to multimodal program since previous assessment								
Exercise			98%		72%	79%	82%	75%
Nutrition			100%		91%	84%	92%	83%

6MWD: 6 minute walking distance; CHAMPS: Community Healthy Activity Model Programme for Seniors; light physical activity: defined as 1–3 METS or metabolic equivalents; moderate to vigorous physical activity: defined as >3 METS or metabolic equivalents; ACS: American Cancer Society.
$^*p < .05$.

Table 3. 6MWD change in patients categorized by physical activity levels (GEE binomial).

Variable	Patients who did not meet ACS requirements (inactive) Adjusted OR (95% CI)	Patients who met ACS requirements (active) Adjusted OR (95% CI)
Change in 6MWD		
<20	1	1
≥20	7.07 (1.10–45.51)	1.86 (0.55–6.30)
Age	0.96 (0.86–1.07)	0.94 (0.89–1.00)
Sex		
Male	1	1
Female	14.65(1.86–115.26)	1.35 (0.27–6.63)
Body mass index	1.07 (0.90–1.26)	1.05 (0.91–1.21)
Glycated hemoglobin (HbA1C)	0.10 (0.01–0.48)	0.48 (0.18–1.32)

or more active, in light of their upcoming surgery. In fact, 38% of these patients increased their 6MWD over 20 m, indicating that bias in the form of contamination is also possible. In the light of their baseline assessment, some patients assigned to this group may have sought outside help or guidance to improve their pre-operative physical condition. However, as indicated in Table 2, there was no significant increase in their self-reported physical activity. As their mean walking capacity was already high, with their predicted 6MWD over 70%, and with a low proportion of patients walking less than 400 m in 6 min, it could be interpreted that this group was in better baseline physical condition than the PREHAB + group.

Training supervision has been studied extensively in the context of rehabilitation after cardiac surgery and myocardial infarction, which consists mainly of aerobic physical activity [6]. In a recent Cochrane review, both home-based vs. traditional center-based forms of cardiac rehabilitation were observed to be equally safe and effective at improving clinical outcomes in low-risk heart failure and coronary heart disease patient [33]. However, a degree of supervision is still maintained through follow-up visits, phone calls by healthcare professionals or self-monitoring diaries. A systematic review of 25 RCTs that studied exercise programs in patients with peripheral vascular disease demonstrated the benefits of a supervised training intervention on walking capacity [34]. The addition of supervised sessions to a partially home-based exercise program has also been shown to provide better motivational outcomes in patients who were post-cancer therapy. Namely, breast cancer survivors who participated in a 12-week exercise program, including twice weekly supervised sessions, were more active and motivated to remain active for a period up to 5 years post-intervention than those who were unsupervised [8]. Similar benefits from supervised training sessions were observed in lung cancer survivors [10]. It remains to be seen whether the frequency of exercise sessions is more important than the intensity of the training, although recent studies seem to indicate a role for higher intensity training to achieve greater effect [35].

After surgery, there was no difference in postoperative functional capacity between the REHAB and PREHAB + groups, and the proportion of patients returning to baseline 6MWD at 4 and 8 weeks was also similar. This can be explained by either the patients in the REHAB group

tending to be younger ($p = .05$) with a lower proportion of patients over 75 years (23% vs. 43%) or they had a higher baseline 6MWD (mean 461 m vs. 448 m). In addition, the effect of in-hospital exercise training might have motivated the REHAB group to become more involved in the program once they reached home.

Although PREHAB + did not result in either a greater difference in 6MWD than the REHAB group or mitigating the drop in immediate post-surgical functional capacity, it was successful in shifting a greater number of patients to perform more moderate to vigorous physical activities. Importantly, this change in physical activity also meant that a greater number of patients met physical activity recommendations, as put forth by the ACS, both preoperatively and at 4 and 8 weeks after surgery. To determine this, the CHAMPS questionnaire – a validated measurement of surgical recovery that correlates with physical function – was used, thus further contributing to the clinical significance of this observation [28]. This is particularly relevant in assessing the progress of patients who participate in the prehabilitation program, such as the frail and sedentary who start with a low CHAMPS score [36].

In the present study, previously inactive patients – and, in particular, previously inactive women – who received prehabilitation were also more likely to significantly improve their functional capacity. Such observation confirms previous findings whereby patients whose baseline 6MWD was less than 400 m increased by an average of 45 m if involved in prehabilitation [37]. This provides important insight as to which patients should be specifically targeted to receive a such as this.

Conclusions

This study demonstrated that one supervised exercise session per week for 4 weeks did not futher increase further the preoperative functional capacity in colorectal cancer patients from what we have previously reported in studies using a home-based multimodal prehabilitation program alone. Despite this, patients who were considered to be the most inactive significantly increased their degree of physical activity before surgery and, importantly, accelerated their recovery of functional capacity after surgery. This was particularly true for previously inactive women. Our results need careful interpretation as our estimates, based on the small change, could represent random fluctuations. For these reasons, we consider the data presented here as more exploratory in nature than confirmatory. Further research is required in order to identify optimal strategies to increase preoperative physiological reserve in anticipation of surgery. It is also important to consider, in light of current restraints in both clinical settings and financial costs, which patients might benefit the most from interventions such as this.

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Ethics approval: The study was approved by the Research Ethics Board of the McGill University Health Center (11-004-GEN), Montréal, Québec, Canada and registered on ClinicalTrials.gov (NCT02586701). Participants were enrolled from December 2013 to August 2015 at a single tertiary care center affiliated with McGill University in Montréal, Québec, Canada. Informed consent was obtained from all study participants.

Availability of data and material: The dataset supporting the conclusions of this article is available in the Open Science Framework repository at http://osf.io/khf94.

Disclosure statement

The authors report no conflict of interest.

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