Surg Endosc (2013) 27:1072–1082
DOI 10.1007/s00464-012-2560-5

Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study

Chao Li · Francesco Carli · Lawrence Lee · Patrick Charlebois · Barry Stein · Alexander S. Liberman · Pepa Kaneva · Berson Augustin · Mingkwan Wongyingsinn · Ann Gamsa · Do Jun Kim · Melina C. Vassiliou · Liane S. Feldman

Received: 18 May 2012 / Accepted: 21 August 2012 / Published online: 9 October 2012

Abstract

Background Patients undergoing colorectal cancer resections are at risk for delayed recovery. Prehabilitation aims to enhance functional capacity preoperatively for better toleration of surgery and to facilitate recovery. The authors previously demonstrated the limited impact of a prehabilitation program using exercise alone. They propose an expanded trimodal prehabilitation program that adds nutritional counseling, protein supplementation, and anxiety reduction to a moderate exercise program. This study aimed to estimate the impact of this trimodal program on the recovery of functional capacity compared with standard surgical care.

Methods Consecutive patients were enrolled in this pre- and postintervention study over a 23-month period. The postoperative recovery for 42 consecutive patients enrolled in the prehabilitation program was compared with that of 45 patients assessed before the intervention began. The primary outcome was functional walking capacity (6-min walk test [6MWT]). The secondary outcomes included self-reported physical activity (CHAMPS questionnaire) and health-related quality of life (SF-36). Data are expressed as mean ± standard deviation or median (interquartile range [IQR]) and were analyzed using Chi-square and Student's t test. All p values lower than 0.05 were considered significant.

Results The prehabilitation and control groups were comparable in terms of age, gender, body mass index (BMI) and American Society of Anesthesiology (ASA) class. There was no difference in walking capacity at the first assessment (6MWT distance, 422 ± 87 vs 402 ± 57 m; $p = 0.21$). During the prehabilitation period lasting a median of 33 days (range, 21–46 days), functional walking capacity improved by 40 ± 40 m ($p < 0.01$). The postoperative complication rates and the hospital length of stay were similar. The patients in the prehabilitation program had better postoperative walking capacity at both 4 weeks (mean difference, 51.5 ± 93 m; $p = 0.01$) and 8 weeks (mean difference, 84.5 ± 83 m; $p < 0.01$). At 8 weeks, 81 % of the prehabilitated patients were recovered compared with 40 % of the control group ($p < 0.01$). The prehabilitation group also reported higher levels of physical activity before and after surgery.

Conclusion In this pilot study, a 1-month trimodal prehabilitation program improved postoperative functional recovery. A randomized trial is ongoing (NCT01356264).

Presented at the SAGES 2012 Annual Meeting, March 7–March 10, 2012, San Diego, CA.

C. Li · L. Lee · P. Kaneva · M. C. Vassiliou · L. S. Feldman (✉)
Steinberg-Bernstein Centre for Minimally Invasive Surgery and Innovation, McGill University, Montreal, QC, Canada
e-mail: liane.feldman@mcgill.ca

C. Li · L. Lee · P. Charlebois · B. Stein · A. S. Liberman · M. C. Vassiliou · L. S. Feldman
Department of Surgery, McGill University, Montreal, QC, Canada

F. Carli · B. Augustin · M. Wongyingsinn · D. J. Kim
Department of Anesthesia, McGill University, Montreal, QC, Canada

A. Gamsa
Department of Psychology, McGill University, Montreal, QC, Canada

L. S. Feldman
McGill University Health Centre, 1650 Cedar Avenue, Room L9-303, Montreal, QC H3G 1A4, Canada

Keywords Functional recovery · Perioperative care · Prehabilitation · Preoperative exercise

In 2010, an estimated 100,000 new cases of colon cancer occurred in the United States [1]. Despite recent advances in surgical, anesthetic, and perioperative care for colon surgery, morbidity is significant, and patients are at risk for prolonged recovery. A large study identified colorectal resection as the general surgery operation with the greatest burden of adverse events and excess hospital stay [2]. With efforts focused on improving the quality of surgical care, awareness is increasing that major postoperative complications may be driven more by patient than by surgical factors alone [3].

The implementation of an enhanced recovery after surgery program ("fast-track surgery") reduces the hospital stay by 2 days after colorectal surgery [4]. However, patient-centered outcomes of functional capacity suggest that patients are not fully recovered even 6–9 weeks after major abdominal surgery [5, 6]. Poor preoperative physical fitness predicts mortality and major complications [7, 8] and delayed functional recovery after abdominal surgery [9].

Attempts to improve recovery have tended to focus on the intraoperative period (e.g., laparoscopic surgery, thoracic epidural) and the postoperative period (e.g., enhanced recovery pathways). However, intervening in the preoperative period to modify factors such as poor physical fitness contributing to morbidity and delayed recovery is an attractive strategy.

For cancer patients awaiting surgery, a 5-week preoperative exercise program was sufficient for measurable improvement of cardiorespiratory fitness and muscle strength [10]. Interventions designed to improve functional capacity in anticipation of an upcoming stressor such as surgery have been termed "prehabilitation" [11].

We previously reported a randomized study of an exercise-only prehabilitation intervention in colorectal surgery [12]. Patients were randomized to undergo either an intense exercise regimen based on daily biking (intervention group) or a "sham" intervention consisting of a recommendation to walk daily and do breathing exercises (control group). The primary outcome was walking capacity as measured by the 6-min walk test (6MWT). Adherence to the recommendations was low, with only 33 % improving during prehabilitation and 29 % deteriorating despite the intervention. An unexpected benefit resulted from the recommendation to increase walking and breathing; more people in the control group showed an improvement in walking capacity both before and after surgery. A reanalysis demonstrated that regardless of the exercise type received, patients who improved during the prehabilitation period were more likely to have recovered 9 weeks postoperatively [13].

Many factors may have influenced the results of our previous study. First, adherence to the intense stationary-bicycle-based exercise program was low, and the results were poor. Colorectal cancer patients can experience alterations in digestion from symptoms of the disease and changes to metabolism causing increased protein breakdown. Up to half of patients awaiting colon cancer surgery exhibit weight loss, and up to one in five is malnourished [14]. Adequate protein substrate is necessary to allow for successful muscle gain during a physical exercise regimen, but nutritional status was not assessed or subjected to control in this previous study.

Moreover, although anxious patients showed a greater improvement in functional capacity during the prehabilitation period, they were ultimately less likely to recover to baseline after surgery [13]. Finally, perioperative surgical care was not standardized by an enhanced recovery pathway. These results suggest that an intervention based on exercise alone may not have been sufficient to enhance functional capacity if factors such as nutrition, anxiety, and perioperative care were not taken into consideration during the program.

In view of this, we formulated a new prehabilitation intervention, adding nutritional and anxiety reduction interventions to a moderate exercise program. The goal of the nutritional intervention was to guarantee sufficient substrate to allow optimal effects of exercise.

Whey proteins are a by-product of cheese-making and serve as a highly nutritious supplement that can act synergistically with exercise to increase protein synthesis and muscle endurance [15, 16]. Participants in a 6-week exercise program were found to have significant increases in strength gained while taking 1.2 g/kg body weight in whey protein [17].

Whey proteins are also rich in essential and branched-chain amino acids and have shown both antiinflammatory and immune-modulating properties [18, 19]. The goal of the anxiety-reduction component was to allow patients to express their concerns to a psychologist and to become familiar with calming exercises used to reduce their perceived anxiety levels.

This study aimed to estimate the impact of our new trimodal prehabilitation program on functional recovery after colorectal cancer surgery in the setting of an enhanced recovery pathway.

Methods

Subjects

Consecutive patients awaiting elective surgery for primary colorectal cancer were assessed for enrollment in this prospective pre- and postintervention study from July 2009 to September 2011 at a university teaching hospital. The trimodal prehabilitation intervention was initiated in September 2010. The postoperative recovery of the patients enrolled in the trimodal prehabilitation program (intervention group) was compared with that shown by a cohort of 45 patients studied before initiation of the intervention (control group).

The inclusion criteria for the study specified adults with a colonic or rectal malignancy planned for resection. The exclusion criteria ruled out metastatic disease or any medical condition precluding the safe use of physical activity and any patient unable to understand English or French sufficiently for accurate completion of the questionnaires.

Care for the patients in both groups was provided by one of three fellowship-trained colorectal surgeons, and perioperative care was guided by a standardized enhanced recovery pathway established at our institution since 2008 [20]. Baseline patient characteristics, operative data, and postoperative complications were collected prospectively. The study was approved by the Research Ethics Board of the McGill University Health Centre.

Between July 2009 and September 2010, patients were approached at the preoperative center. After their consent, they were enrolled in the control group. They were assessed at three time points: at the time of recruitment (approximately 1 week before surgery), then 4 and 8 weeks after surgery. Starting in September 2010, the patients were referred from the colorectal clinic after a decision was made to proceed with surgery (Fig. 1).

At the initial visit, the prehabilitation program was explained, and informed consent was obtained. After a medical examination, the patients met with the kinesiologist, the nutritionist, and the psychologist for baseline measures to be obtained (see measures and interventions later). The patients then initiated the prehabilitation intervention at home.

The length of prehabilitation was determined by the wait time until surgery alone. As in the control group, the intervention group was reassessed 1 week before surgery at the preoperative center, then 4 and 8 weeks after surgery.

Prehabilitation intervention

Exercise

Exercise remained the mainstay of the prehabilitation program. Moderate aerobic exercise was combined with resistance training. A kinesiologist met with the patients for 1 h and planned an individualized exercise program and schedule. The patients were asked to walk or to use an aerobic exercise machine for 30 min three times a week. Target exercise intensity, set at half of the calculated maximal heart rate (220—age), was measured by the patient with a provided heart rate monitor. Resistance exercises consisted of calisthenics and elastic band movements performed three times a week to volitional fatigue.

Nutrition

The patients enrolled in the prehabilitation program were evaluated by a nutritionist during a 1-h visit. A subjective global assessment was carried out, and one or two modifiable dietary behaviors such as excess alcohol or fat intake were identified and discussed with the patient [21]. The patients were provided with whey protein isolate (Vitalus Nutrition Inc., Abbotsford, Canada), which was used as a nutritious food supplement to guarantee a daily intake of 1.2 g/kg body weight of protein. Recipes to make intake palatable were given. Patients were asked to consume protein preferably within 1 h of their exercise regimen.

Anxiety reduction

Preoperatively, patients were scheduled for a 90-min visit with a trained psychologist focusing on providing anxiety-reduction techniques such as relaxation exercises and breathing exercises. These exercises were mirrored on a compact disc for home practice. A primary goal of the psychological component was to enhance and reinforce patients' motivation to comply with the exercise and nutritional aspects of the intervention.

Outcomes and measures

The primary outcome of the study was functional walking capacity as measured by the 6MWT 8 weeks after surgery. The 6MWT evaluates the capacity to maintain a moderate level of walking and reflects the capacity to perform activities of daily living.

In the 6MWT, the patient is asked to walk along a 15-m stretch of corridor at a pace that makes him or her feel tired by the end. The total distance walked in 6 min is recorded in meters. Chairs are arranged along the corridor to allow for resting if needed, although any time spent resting is counted within the 6 min. Standard motivational messages are given at each minute as per American Thoracic Society guidelines [22]. Age- and gender-specific predicted distances can be calculated using the following formula:

$$\text{Predicted distance walked in 6 Min (m)} = 868 - (\text{age} \times 2.9) - (\text{female} \times 74.7),$$

where age is in years, and the value "1" is assigned for females [23]. The validity of the 6MWT as a measure of recovery after colorectal surgery is supported by evidence [24].

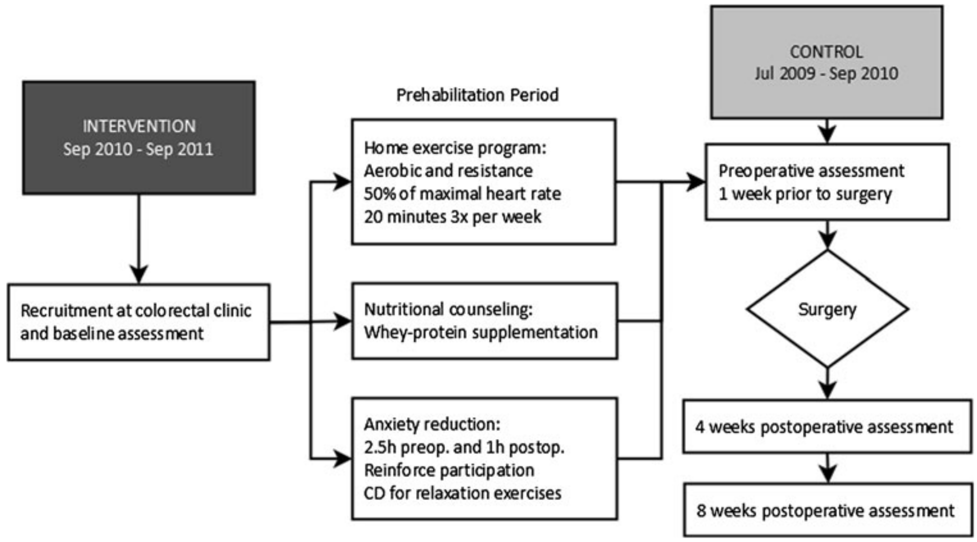

Fig. 1 Flow diagram showing timing of patient assessments and interventions. All assessments included walking capacity (6MWT), self-reported physical activity (CHAMPS questionnaire), and health-related quality of life (SF-36). *6MWT* 6-min walk test, *CHAMPS* Community Healthy Activities Model Program for Seniors, *SF-36* Medical Outcomes Study 36-Item Short-Form Health Survey

The secondary outcomes included complication rates, self-reported physical activity, and health-related quality of life. Complications were graded by severity using the Dindo-Clavien classification, in which grade 1 complications require bedside management, grade 2 complications require pharmacologic treatment, grade 3 complications require surgical or radiologic intervention, and grade 4 complications require intensive care treatment [25].

Self-reported physical activity was measured by the Community Healthy Activities Model Program for Seniors (CHAMPS) short-form questionnaire. Using the CHAMPS questionnaire, subjects estimate the number of hours spent performing listed activities of various intensities during the previous week. An estimate of the caloric expenditure associated with each activity is used to calculate weekly energy expenditure in kilocalories per kilogram per week. A 3 kcal/kg/week difference is equivalent to 1 h of moderate-intensity activity [26]. Available evidence supports the validity of the CHAMPS questionnaire as a measure of recovery of physical activity after elective surgery [27].

Health-related quality of life was measured using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). This survey assesses eight domains of health including physical function, role physical, role emotional, social functioning, bodily pain, general health, vitality, and mental health. Each domain is assessed on a scale of 0–100, with higher scores indicating better quality of life. Two summary scores—the physical component summary (PCS) and mental component summary (MCS)—have been standardized to have a mean of 50 and a standard deviation of 10. Canadian population norms are available [28].

Emotional health was measured using the Hospital Anxiety and Depression Scale (HADS) for patients undergoing the prehabilitation intervention. The HADS contains seven items, each scored from 0 to 3 points for anxiety and depression. It provides summary measures on a scale of 0–21, with scores exceeding 8 suggesting the presence of a mood disorder [29].

Statistical methods

To minimize potential bias from missing data (the 8-week 6MWT was missing for 5 patients in prehabilitation group), multiple imputation was performed, in which 20 imputations were created based on age, gender, comorbidities, complication profile, 6MWT results, and CHAMPS and SF-36 responses [30].

Functional data are presented as an aggregate of all imputations, taking into account variance between and within imputations using Rubin's rules. Continuous variables modeled by a normal distribution were reported as mean ± standard deviation and compared using an independent Student's t test. Non-normal data were reported as median (interquartile range [IQR]) and compared using a nonparametric Wilcoxon rank-sum test. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. For the elderly population, we used 20 m, considered to be the error of measurement for the 6MWT, to categorize change [31]. If a patient's 6MWT was within 20 m of his or her previous result, this change was not considered to be clinically meaningful.

Multiple linear regression was used on imputed data to evaluate the predictors of recovery of functional walking capacity 8 weeks after surgery. Standard errors accounted for variance both between and within imputations. A probability level less than 0.05 was considered significant. Statistical analyses were conducted using R version 2.14 (R Foundation, Vienna, Austria). Multiple imputation and analysis were performed using the Amelia II and Zelig packages, respectively [32, 33].

Results

Of the 52 patients assessed for eligibility to receive prehabilitation, 5 declined participation, and 1 did not have sufficient time for prehabilitation before surgery. Of the remaining 46 patients enrolled in the prehabilitation intervention, 3 did not have any postoperative visits, and 1 had benign disease shown in the final pathology. Thus, 42 patients were analyzed in the prehabilitation group and compared with the control group of 45 patients. Five patients in the prehabilitation group were lost to follow-up evaluation 8 weeks after the operation.

The patients who had missing data did not differ significantly from those who did not in terms of baseline and operative characteristics, complications, or functional data (data not shown). The prehabilitation and control groups were similar at the first assessment with respect to age, gender, body mass index (BMI), American Society of Anesthesiologist (ASA) classification, and location of tumor. At study enrollment, functional walking capacity did not differ from self-reported physical activity levels (Table 1).

In the intervention group, the median duration of prehabilitation was 33 days (range, 21–46 days). At the end of this period, 6MWT had increased by 42 ± 41 m ($p < 0.01$), and self-reported weekly physical activity energy expenditure had increased by a median of 14 kcal/kg ($p < 0.01$). Moreover, no patient deteriorated during the prehabilitation period, and 64 % of the patients improved by more than 20 m.

Serum albumin was measured in 17 patients and remained stable during the prehabilitation period (3.9 ± 0.5–3.8 ± 0.4 g/dL; mean change of –0.15 ± 0.3 g/dL; $p = 0.08$). Symptoms of anxiety and depression also decreased significantly by a median of 1 point during prehabilitation ($p = 0.04$ for anxiety and $p < 0.01$ for depressive symptoms). The control group was assessed only immediately before surgery, so changes during the preoperative period could not be assessed.

The perioperative variables are presented in Table 2. The most frequent operation was anterior or low anterior resection. The use of laparoscopy was routine in both the control group (93 %) and the intervention group (81 %). The proportion of patients receiving a stoma was similar between the two groups (44 % and 36 %). There were no differences in the incidence or severity of postoperative complications. The overall morbidity rates were respectively 44 % and 36 %, and very few were classified as grade 3 (2 % and 5 %). The median hospital stay was 4 days in both groups.

During the period of postoperative recovery, functional exercise capacity (6MWT) and self-reported physical activity were greater in the prehabilitation group than in the control group, at both 4 and 8 weeks after surgery (Table 3). The trajectory of change in functional walking capacity is illustrated in Fig. 2, which demonstrates its preservation in the prehabilitation group. Whereas the patients in the intervention group had returned to baseline by an average of 4 weeks postoperatively ($p = 0.21$), the control group remained below their preoperative level ($p < 0.01$). Moreover, at 8 weeks postoperatively, the patients who had undergone prehabilitation were 37 ± 70 m ($p < 0.01$) above their baseline values in functional walking capacity and 10 ± 48 kcal/kg/week ($p = 0.17$) above their baseline self-reported physical activity levels. A significantly greater proportion of the prehabilitated patients were recovered or above baseline at

Table 1 Patient characteristics at study enrollment

	Control ($n = 45$)	Prehabilitation ($n = 42$)	p Value
Age (years)	66.4 ± 12	67.4 ± 11	0.69[a]
Male gender	29 (64)	22 (54)	0.35[b]
ASA class			0.59[b]
1	6 (13)	3 (7)	
2	29 (65)	31 (74)	
3	10 (22)	8 (19)	
BMI at first assessment (kg/m^2)	26.9 ± 6	27.5 ± 4	0.61[a]
6-Min walk test (m)	402 ± 57	422 ± 87	0.21[a]
6-Min walk test (% predicted)	62 ± 9	66 ± 12	0.10[a]
Self-reported physical activity (kcal/kg/wk)	20 (9–32)	16 (10–36)	0.79[c]
SF-36 (Canadian norms, age 65–74 years)			
Physical function (75.7)	80 ± 24	82 ± 21	0.61[a]
Role physical (76.2)	58 ± 43	71 ± 42	0.18[a]
Bodily pain (74.0)	78 ± 29	78 ± 24	1[a]
General health (73.5)	69 ± 24	72 ± 17	0.47[a]
Vitality (67.7)	59 ± 23	64 ± 21	0.27[a]
Social function (87.0)	69 ± 44	88 ± 25	0.01[a]
Role emotional (80.3)	72 ± 26	83 ± 19	0.03[a]
Mental health (79.4)	70 ± 23	77 ± 17	0.13[a]
Physical component summary	47 ± 11	47 ± 10	0.93[a]
Mental component summary	45 ± 14	51 ± 10	0.01[a]
HADS Anxiety score		5 (2.3–8.8)	
HADS Depression score		2.5 (1–4)	

Data are expressed as mean ± standard deviation, n (%), or median (interquartile range [IQR])

ASA American Society of Anesthesiology, *BMI* body mass index, *HADS* Hospital Anxiety and Depression Scale

[a] Independent Student's t test

[b] Fisher's exact test

[c] Wilcoxon's rank-sum test

Table 2 Surgical information and outcomes

	Control ($n = 45$)	Prehabilitation ($n = 42$)	p Value
Surgery type			0.64[a]
Right hemicolectomy	9 (20)	12 (28)	
Left hemicolectomy	1 (2)	2 (5)	
Transverse colectomy	1 (2)	0	
Sigmoidectomy	3 (7)	5 (12)	
Anterior resection	11 (24)	5 (12)	
Low anterior resection	17 (38)	15 (36)	
Abdominoperineal resection	3 (7)	3 (7)	
Stoma	20 (44)	15 (36)	0.54[a]
Laparoscopic approach	42 (93)	34 (81)	0.11[a]
Surgery duration (min)	215 ± 74	203 ± 70	0.45[b]
Length of stay (days)	4 (3–6)	4 (3–6)	0.71[c]
Complication grade			0.67[a]
None	25 (56)	27 (64)	
I	10 (22)	6 (14)	
II	9 (20)	7 (17)	
III	1 (2)	2 (5)	

Data are expressed as mean ± standard deviation, n (%), or median (interquartile range [IQR])

[a] Fisher's exact test

[b] Independent Student's t test

[c] Wilcoxon's rank-sum test

Table 3 Functional outcomes (imputed data)

	Control ($n = 45$)	Prehabilitation ($n = 42$)[a]	p Value
6MWT (m)[b]			
Baseline		422 ± 87	0.21[b,c]
Preoperative	402 ± 57	464 ± 92	<0.01[c]
4 Weeks after surgery	356 ± 71	407 ± 111	0.01[c]
8 Weeks after surgery	375 ± 58	459 ± 101	<0.01[c]
Self-reported physical activity (kcal/kg/wk)[b]			
Baseline		17 (10–36)	0.69[b,d]
Preoperative	20 (9–32)	36 (19–74]	<0.01[d]
4 Weeks after surgery	3 (0–7)	18 (8–55)	<0.01[d]
8 Weeks after surgery	8 (0–30)	23 (11–52)	<0.01[d]
HADS anxiety score			
Baseline		5 (2.3–8.8)	
Before surgery		4 (2–6)	
4 Weeks after surgery		3 (0–6.8)	
8 Weeks after surgery		4 (1–7)	
HADS depression score			
Baseline		2.5 (1–4)	
Before surgery		1 (0–2)	
4 Weeks after surgery		2 (1–3.8)	
8 Weeks after surgery		2 (1–3.5)	

Owing to missing data, the number of observations ranges from 37–42

6MWT 6-min walk test, *HADS* Hospital Anxiety and Depression Scale

[a] Data are expressed as mean ± standard deviation or median (interquartile range [IQR])

[b] Compared with the first (preoperative) assessment in the control group

[c] Independent Student's t test

[d] Wilcoxon rank-sum test

8 weeks (81 %) compared with the control subjects (40 %). A post hoc power analysis examining the change in functional walking capacity from the first assessment to 8 weeks after surgery resulted in a power of 0.99.

Health-related quality of life (HRQL) is presented in Table 4. The general health, vitality, and mental health scores were higher in the prehabilitation group throughout the length of the study, including the enrollment scores. The prehabilitation intervention did not result in any clinically or statistically significant increases in any domains of HRQL.

A fully adjusted multiple linear regression analysis was performed on imputed data using the change in the 6MWT from enrollment in the study to the last evaluation as a measure of recovery from surgery (Table 5). After adjustment for a priori factors (age, gender, BMI, ASA classification, use of a stoma, low mental component summary score, and complications), the prehabilitation intervention remained a significant predictor of a positive change in functional capacity (average, +63 m; $p < 0.01$).

As expected, the patients with complications classified as grade 2 (–29 m; $p = 0.07$) or grade 3 (–96 m; $p = 0.02$) had a poorer functional recovery. A simplified model was selected using Bayesian Information Criteria, with no difference in point estimates compared with the fully adjusted model.

Discussion

The goal of prehabilitation is to enhance the functional capacity of patients during the waiting period for surgery. In the current study, a trimodal prehabilitation program consisting of moderate-intensity physical exercise supported

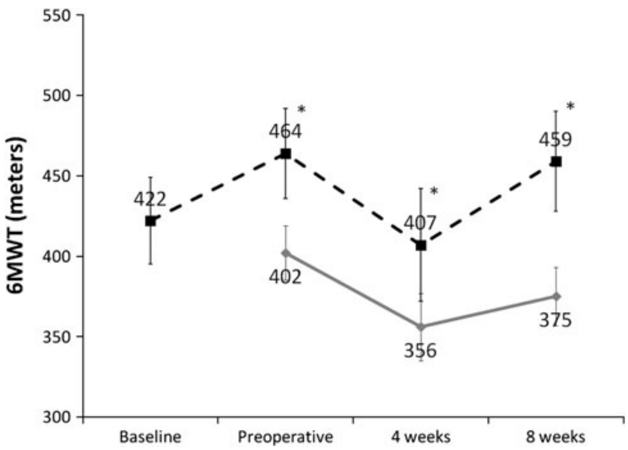

Fig. 2 Trajectory of change in functional walking capacity as measured by the 6-min walk test. Mean and 95 % confidence interval are displayed. The *dashed line* shows the intervention group, and the *grey line* shows the control group. $^{*}p < 0.05$

with nutritional supplementation and anxiety reduction techniques resulted in significantly improved functional walking capacity in the intervention group. The findings show that 64 % improved by more than 20 m, and no patients deteriorated while awaiting surgery. This improvement was associated with faster postoperative recovery in the intervention group than in the control group, with the great majority (81 %) of patients recovered by 8 weeks after surgery compared with only 40 % recovered in the control group. In a previous trial, despite an exercise-alone intervention, functional exercise capacity improved for only 33 % and actually decreased for 29 % of the patients during the prehabilitation period [12].

In the multivariate analysis, after adjustment for other confounders, the findings showed a benefit of 63 m independently attributable to participation in the trimodal prehabilitation program. This change was equivalent to approximately 15 % of the mean functional walking capacity at baseline. It is unclear whether this represents a clinically relevant change because no information exists on the minimal clinically important difference in 6MWT for surgical patients. However, in cardiopulmonary disease and in geriatric populations, a change of 50 m on the 6MWT is seen as clinically meaningful [34, 35].

At the first assessment, the HRQL measures were similar between the groups except for the role emotional and social function components. This may be explained by the fact that the questionnaire was based on a 4-week recall and the values for the prehabilitation group were taken just after the meeting with the colorectal surgeon, whereas the values for the control group were taken immediately before surgery. In the 4 weeks before their meeting with the colorectal surgeon, patients usually lead a relatively normal life, whereas in the 4 weeks coming up to a planned surgery, social and emotional function may be impaired.

The patients in this study tended to report better role physical and more feelings of vitality at completion of prehabilitation. However, the prehabilitation intervention itself did not significantly change the quality of life between baseline and preoperative values, and the two groups were comparable during the recovery phase. Quality of life may be too general a concept and the SF-36 questionnaire too generic to capture changes related specifically to our prehabilitation intervention.

The length of the prehabilitation period was the time from the first visit with the colorectal surgeon to the date of the operation, about 1 month. The prehabilitation program had no influence on the timing of surgery, and no attempt was made to tailor the length of the prehabilitation. The Canadian Society for Surgical Oncology recommends initiating treatment, including surgery, within 2 weeks after diagnosis [36].

During the last decade in Canada and the United States, wait times for colon cancer surgery have increased and likely will continue to lengthen due to increased volumes and specialization of care [37, 38]. Although little evidence exists to confirm that longer wait times have a direct impact on surgical outcomes, patients waiting for surgery do experience heightened levels of anxiety and frustration [39]. Exercise is associated with a reduction in anxiety and depression levels [40]. The inclusion of a psychological intervention focused on stress reduction was chosen in this study because it can also reduce anxiety levels during this emotionally difficult period.

Complications after surgery are related to a combination of surgical systems and patient factors. With an aging population, the comorbidities and characteristics of patients at the time of surgery pose significant challenges for quality improvement. Preoperative physical condition has been associated with postoperative complications [7]. For patients with cardiopulmonary disease, a 6MWT shorter than 350 m predicts mortality [34].

For colorectal surgery patients, we found that a baseline 6MWT shorter than 392 m predicts cardiopulmonary complications (unpublished data). However, unlike most other comorbidities, poor preoperative physical condition is a potentially modifiable risk factor and the main target for a prehabilitation intervention.

In the current study, for which all adult patients with colorectal cancer were eligible and patients with poor baseline physical capacity were not specifically targeted, the rate of major complications was relatively low and equal between the two groups. Whether targeting prehabilitation interventions specifically to patients with poor baseline functional walking capacity could prevent

Table 4 Health-related quality of life, as measured by the SF-36 questionnaire (imputed data)

Component (Canadian norms, age 65–76 years)	Control ($n = 45$)[a]	Prehabilitation ($n = 42$)[b]	p Value[c]
Physical function (75.7)			
Baseline		82 ± 21	0.61
Before surgery	80 ± 24	80 ± 22	0.94
4 Weeks after surgery	70 ± 28	64 ± 29	0.32
8 Weeks after surgery	71 ± 31	73 ± 25	0.76
Role physical (76.2)			
Baseline		71 ± 42	0.18
Before surgery	58 ± 43	74 ± 38	0.07
4 Weeks after surgery	37 ± 43	37 ± 43	0.93
8 Weeks after surgery	58 ± 40	58 ± 40	0.99
Bodily pain (74.0)			
Baseline		78 ± 24	1
Before surgery	78 ± 29	77 ± 23	0.81
4 Weeks after surgery	59 ± 24	67 ± 22	0.11
8 Weeks after surgery	72 ± 24	75 ± 24	0.55
General health (73.5)			
Baseline		72 ± 17	0.47
Before surgery	69 ± 24	75 ± 16	0.16
4 Weeks after surgery	65 ± 20	75 ± 18	0.02
8 Weeks after surgery	66 ± 18	69 ± 17	0.49
Vitality (67.7)			
Baseline		64 ± 21	0.27
Before surgery	59 ± 23	68 ± 20	0.05
4 Weeks after surgery	54 ± 22	61 ± 19	0.11
8 Weeks after surgery	58 ± 21	65 ± 17	0.09
Social function (87.0)			
Baseline		88 ± 25	0.01
Before surgery	69 ± 44	84 ± 27	0.06
4 Weeks after surgery	59 ± 47	59 ± 46	0.98
8 Weeks after surgery	75 ± 38	75 ± 36	0.93
Role emotional (80.3)			
Baseline		83 ± 19	0.03
Before surgery	72 ± 26	82 ± 21	0.07
4 Weeks after surgery	63 ± 32	72 ± 26	0.14
8 Weeks after surgery	71 ± 28	79 ± 22	0.10
Mental health (79.4)			
Baseline		77 ± 17	0.13
Before surgery	70 ± 23	77 ± 18	0.17
4 Weeks after surgery	69 ± 21	76 ± 18	0.11
8 Weeks after surgery	70 ± 21	79 ± 18	0.04
Physical composite score (50)			
Baseline		47 ± 10	0.93
Before surgery	47 ± 11	48 ± 8	0.69
4 Weeks after surgery	40 ± 9	40 ± 8	0.95
8 Weeks after surgery	44 ± 12	44 ± 11	0.99
Mental composite score (50)			
Baseline		51 ± 10	0.01
Before surgery	45 ± 14	50 ± 10	0.02
4 Weeks after surgery	44 ± 14	48 ± 13	0.12
8 Weeks after surgery	46 ± 11	51 ± 10	0.05

Data are expressed as mean ± standard deviation

SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey

[a] Due to missing data, the number of observations ranged from 41 to 45

[b] Due to missing data, the number of observations ranged from 37 to 42

[c] Independent Student's *t* test

complications is an attractive hypothesis that remains to be investigated.

It is not clear which component of the trimodal prehabilitation program had the greatest effect on enhancing functional capacity. It is, however, clear to us that a program based on exercise alone cannot be sufficient if other factors such as nutritional and psychological care are not taken into account, even if these components may only support the compliance and effectiveness of the exercise program.

We previously reported a limited impact of an intensive biking intervention on functional capacity. Only 16 % of the patients were fully compliant with the intensive biking intervention. The patients, especially the frail and elderly, may have been intimidated by the physical demands of the program or found the program to be too difficult [12]. With this in mind, we were more moderate with the recommended exercise intensity and decreased the frequency of aerobic exercise from daily to three times per week. We also allowed the patients to choose their preferred type of exercise, which also may have reinforced compliance by encouraging them to perform an exercise they already found enjoyable. According to weekly phone call logs, about 70 % of the patients reported exercising at least 2 days a week, with 45 % reporting full compliance during the prehabilitation period. There also was a significant increase in self-reported physical activity that persisted after the surgery. The exercise component may be an important adjunct to an enhanced recovery pathway, in which early ambulation is thought to play an important role.

In the current study, the goal of the nutritional component was to provide optimal protein intake in the context of an exercise regimen by supplementing the patients' diet with whey protein. The study patients did not show clinical signs of malnutrition when assessed by nutritional history, and the average albumin levels, when available, were normal at baseline and did not change during the prehabilitation period. Given the gains seen in functional walking capacity, the

Table 5 Fully adjusted and simplified models showing significant factors influencing recovery of functional walking capacity from first to last assessment (imputed data)

Variable	Model 1[a]		Model 2[b]	
	Estimate (β)	95 % CI[c]	Estimate (β)	95 % CI[c]
Intercept	–31.9	–78.2 to 14.4	–20.1	–35.8 to –4.5
Prehabilitation vs controls	63.6	39.5 to 87.7	65.5	43.5 to 87.5
Complication (Clavien grade) vs 0 or 1				
Grade 2	–28.5	–59.2 to 2.1	–27.7	–55.0 to –0.4
Grade 3	–95.6	–156.8 to –34.4	–97.7	–155.7 to –39.8

CI confidence interval

[a] Adjusted for other variables in the table and the following nonsignificant prognostic variables: age (referent is <75 years; ≥75 years 26 %, $\beta = -2.4$, CI = –30.8 to 26.0); gender (referent is female; male 59 %, $\beta = -1.2$, CI = –23.5 to 25.9); body mass index (referent is <30; ≥30 65 %, $\beta = -8.0$, CI = –33.6 to 17.7); stoma (referent is no stoma; stoma 40 %, $\beta = -9.0$, CI = –33.3 to 15.4); and SF-36 mental component summary (referent is ≥50; <50 45 %, $\beta = 9.0$, CI = –15.9 to 33.9)

[b] Simplified model selected according to Bayesian Information Criteria and adjusted only for other variables in the table

[c] Confidence intervals represent the variance within each imputation and between all imputations

addition of nutritional management and supplementation to exercise may have helped the patients to secure the adequate protein substrate for building muscle mass.

The preoperative period is a time of uncertainty for patients who often must face the unknowns of both cancer and surgery [39]. Preoperative psychological distress may have a negative impact on surgical recovery [41, 42]. Increased physical exercise has been associated with an improvement in depressive symptoms [43].

During the prehabilitation period in the current study, the patients showed a 1-point drop in both the anxiety and depression scores on the HADS questionnaire. This drop, although statistically significant, may not represent a large enough difference to have an impact on clinical symptoms. A single 1½-h session with a psychologist would not be sufficient for a patient to begin psychological therapy. This time rather allowed patients to gain the tools to take control of anxious or stressful moments they could have felt at home. The addition of this psychological component also served to reinforce the importance of participation and likely was a factor in boosting compliance with the physical exercise component.

Currently, little literature addresses preoperative psychological preparation by the use of anxiety-reduction exercises. However, we believe these exercises may be useful in allaying psychological distress by providing patients with strategies to deal with the stressful preoperative period.

This study had several strengths including the use of an enhanced recovery pathway for all the patients to minimize differences in perioperative care. A strength of the analysis was appropriate handling of missing data using multiple imputations instead of excluding observations with missing data, which decreases statistical power and may result in biased estimates of effect.

The study also had several important limitations. First, it was an observational study, and allocation to the two groups was not randomized. Also, whereas the intervention patients were enrolled directly from the colorectal clinic when the decision for surgery was made and then reassessed immediately before surgery, the control patients were enrolled in the preoperative clinic in the week preceding surgery and thus had only one preoperative assessment.

For the purposes of this study, we assumed that functional capacity did not change for the control patients during the wait time. Having this additional measure would have made baseline comparisons more accurate. It also would have enabled better quantification of the trajectory of functional capacity outcomes for untreated patients as they waited for surgery.

In conclusion, a short period of trimodal prehabilitation comprising moderate aerobic and resistance exercise, whey-protein supplementation, and anxiety reduction improved functional walking capacity and was associated with better postoperative recovery for patients undergoing colorectal cancer surgery.

Acknowledgments This research was supported by grants from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), Ethicon Endosurgery Canada, and the Department of Anesthesia, McGill University Health Centre. The Steinberg-Bernstein Centre for Minimally Invasive Surgery and Innovation is supported by an unrestricted educational grant from Covidien Canada.

Disclosures C. Li reports research support from the Surgeon Scientist Program, Department of Surgery, McGill University. L. S. Feldman reports research and fellowship support from Covidien and research support from Ethicon. L. Lee reports research support from the Canadian Association of General Surgeons and salary support from the Fonds de la recherche en santé du Québec (FRSQ) and the McGill Surgeon Scientist program. F. Carli, P. Charlebois, B. Stein, A. S. Liberman, P. Kaneva, B. Augustin, M. Wongyingsinn, A.

Gamsa, D. J. Kim, and M. C. Vassiliou have no conflicts of interest or financial ties to disclose.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Schilling PL, Dimick JB, Birkmeyer JD (2008) Prioritizing quality improvement in general surgery. J Am Coll Surg 207:698–704
3. Zingmond D, Maggard M, O'Connell J, Liu J, Etzioni D, Ko C (2003) What predicts serious complications in colorectal cancer resection? Am Surg 69:969–974
4. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ (2011) Fast-track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev (online): CD007635
5. Christensen T, Kehlet H (1993) Postoperative fatigue. World J Surg 17:220–225
6. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P (2002) Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology 97:540–549
7. Wilson RJT, Davies S, Yates D, Redman J, Stone M (2010) Impaired functional capacity is associated with all-cause mortality after major elective intraabdominal surgery. Br J Anaesth 105:297–303
8. Reilly DF, McNeely MJ, Doerner D, Greenberg DL, Staiger TO, Geist MJ, Vedovatti PA, Coffey JE, Mora MW, Johnson TR, Guray ED, Van Norman GA, Fihn SD (1999) Self-reported exercise tolerance and the risk of serious perioperative complications. Arch Intern Med 159:2185–2192
9. Lawrence V, Hazuda H, Cornell J, Pederson T, Bradshaw P, Mulrow C, Page C (2004) Functional independence after major abdominal surgery in the elderly. J Am Coll Surg 199:762–772
10. Timmerman H, de Groot JF, Hulzebos HJ, de Knikker R, Kerkkamp HEM, van Meeteren NLU (2011) Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer: a pragmatic study. Physiother Theory Pract 27:117–124
11. Carli F, Zavorsky GS (2005) Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metabol Care 8:23–32
12. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, Scott S, Mayo NE (2010) Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg 97:1187–1197
13. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, Stein B, Carli F (2011) Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. Surgery 150:505–514
14. Burden ST, Hill J, Shaffer JL, Todd C (2010) Nutritional status of preoperative colorectal cancer patients. J Hum Nutr Dietetics 23:402–407
15. Burd NA, Yang Y, Moore DR, Tang JE, Tarnopolsky MA, Phillips SM (2012) Greater stimulation of myofibrillar protein synthesis with ingestion of whey protein isolate v. micellar casein at rest and after resistance exercise in elderly men. Br J Nutr1–5
16. Aoi W, Takanami Y, Kawai Y, Morifuji M, Koga J, Kanegae M, Mihara K, Yanohara T, Mukai J, Naito Y, Yoshikawa T (2011) Dietary whey hydrolysate with exercise alters the plasma protein profile: a comprehensive protein analysis. Nutrition 27:687–692
17. Burke DG, Chilibeck PD, Davison K, Candow D, Farthing J, Smith-Palmer T (2001) The effect of whey protein supplementation with and without creatine monohydrate combined with resistance training on lean tissue mass and muscle strength. Int J Sport Nutr Exercise Metabol 11:349–364
18. Walzem RL, Dillard CJ, German JB (2002) Whey components: millennia of evolution create functionalities for mammalian nutrition: what we know and what we may be overlooking. Crit Rev Food Sci Nutr 42:353–375
19. Marshall K (2004) Therapeutic applications of whey protein: alternative medicine review. J Clin Therapeutic 9:136–156
20. Carli F, Charlebois P, Baldini G, Cachero O, Stein B (2009) An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery. Can J Anaesth (Journal canadien d'anesthésie) 56:837–842
21. Bauer J, Capra S, Ferguson M (2002) Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 56:779–785
22. American Thoracic Society (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166: 111–117
23. Gibbons WJ, Fruchter N, Sloan S, Levy RD (2001) Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehab 21:87–93
24. Moriello C, Mayo NE, Feldman L, Carli F (2008) Validating the six-minute walk test as a measure of recovery after elective colon resection surgery. Arch Phys Med Rehab 89:1083–1089
25. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications. Ann Surg 240:205–213
26. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS (2011) 2011 Compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exer 43:1575–1581
27. Feldman LS, Kaneva P, Demyttenaere S, Carli F, Fried GM, Mayo NE (2009) Validation of a physical activity questionnaire (CHAMPS) as an indicator of postoperative recovery after laparoscopic cholecystectomy. Surgery 146:31–39
28. Hopman WM, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C, Joseph L, Brown JP, Murray TM, Adachi JD (2000) Canadian normative data for the SF-36 health survey. Can Med Assoc J 163:265–271
29. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
30. Graham JW, Olchowski AE, Gilreath TD (2007) How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prevent Sci 8:206–213
31. Kervio G, Carre F, Ville NS (2003) Reliability and intensity of the six-minute walk test in healthy elderly subjects. Med Sci Sports Exerc 35:169
32. Honaker J, King G, Blackwell M (2011) Amelia II: a program for missing data. J Stat Softw 45(7):1–47
33. Imai K, King G, Lau O (2006) Zelig: everyone's statistical software. R package version 2.7–4
34. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE (2009) The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J 39:495–501
35. Perera S, Mody SH, Woodman RC, Studenski SA (2006) Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 54:743–749
36. Canadian Society for Surgical Oncology (2009) CSSO position statement. Retrieved 31 March 2012 at http://www.cos.ca/csso/policy.html
37. Simunovic M, Theriault ME, Paszat L, Coates A, Whelan T, Holowaty E, Levine M (2005) Using administrative databases to measure waiting times for patients undergoing major cancer

surgery in Ontario, 1993–2000. Can J of Surg (Journal Canadien de Chirurgie) 48:137–142
38. Bilimoria KY, Ko CY, Tomlinson JS, Stewart AK, Talamonti MS, Hynes DL, Winchester DP, Bentrem DJ (2011) Wait times for cancer surgery in the United States: trends and predictors of delays. Ann Surg 253:779–785
39. Moene M, Bergbom I, Skott C (2006) Patients' existential situation prior to colorectal surgery. J Adv Nurs 54:199–207
40. McHugh JE, Lawlor BA (2011) Exercise and social support are associated with psychological distress outcomes in a population of community-dwelling older adults. J Health Psychol
41. Scott JG, Mavros MN, Athanasiou S, Gkegkes ID, Polyzos KA, Peppas G, Falagas ME (2011) Do Psychological variables affect early surgical recovery? PLoS ONE 6:e20306
42. Linn BS, Linn MW, Klimas NG (1988) Effects of psychophysical stress on surgical outcome. Psychosom Med 50:230–244
43. Rimer J, Dwan K, Lawlor DA, Greig CA, McMurdo M, Morley W, Mead GE (2012) Exercise for depression. Cochrane Database of Systematic Reviews (Online) 7:CD004366