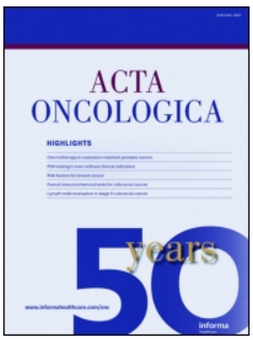

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Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience

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ORIGINAL ARTICLE

Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience

Enrico Maria Minnella, Guillaume Bousquet-Dion, Rashami Awasthi, Celena Scheede-Bergdahl and Francesco Carli

Department of Anesthesia, McGill University Health Center, Montreal, Quebec, Canada

ABSTRACT

Background: Multimodal prehabilitation is a preoperative conditioning intervention in form of exercise, nutritional assessment, whey protein supplementation, and anxiety-coping technique. Despite recent evidence suggesting that prehabilitation could improve functional capacity in patients undergoing colorectal surgery for cancer, all studies were characterized by a relatively small sample size. The aim of this study was to confirm what was previously found in three small population trials.

Material and methods: Data of 185 participants enrolled in a pilot single group study and two randomized control trials conducted at the McGill University Health Center from 2010 to 2015 were reanalyzed. Subjects performing trimodal prehabilitation (exercise, nutrition, and coping strategies for anxiety) were compared to the patients who underwent the trimodal program only after surgery (rehabilitation/control group). Functional capacity was assessed with the six-minute walk test (6MWT), a measure of the distance walked over six minutes (6MWD). A significant functional improvement was defined as an increase in 6MWD from baseline by at least 19 m. Changes in 6MWD before surgery, at four and eight weeks were compared between groups.

Results: Of the total study population, 113 subjects (61%) underwent prehabilitation. Changes in 6MWD in the prehabilitation group were higher compared to the rehabilitation/control group during the preoperative period {30.0 [standard deviation (SD) 46.7] m vs. −5.8 (SD 40.1) m, $p < 0.001$}, at four weeks [−11.2 (SD 72) m vs. −72.5 (SD 129) m, $p < 0.01$], and at eight weeks [17.0 (SD 84.0) m vs. −8.8 (SD 74.0) m, $p = 0.047$]. The proportion of subjects experiencing a significant preoperative improvement in physical fitness was higher in those patients who underwent prehabilitation [68 (60%) vs. 15 (21%), $p < 0.001$].

Conclusion: In large secondary analysis, multimodal prehabilitation resulted in greater improvement in walking capacity throughout the whole perioperative period when compared to rehabilitation started after surgery.

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Improving physical capacity is beneficial in almost all health and medical conditions, and strong evidence supports the relation between functional capacity and postoperative outcome [1,2]. Thus, enhancing cardiorespiratory fitness during the preoperative period has an intuitive appeal. In recent years, clinical trials have shown that increasing physical status before surgery is feasible in different settings, and through a wide spectrum of preoperative interventions [3,4]. A recent systematic review by Singh and colleagues on the impact of presurgical exercise demonstrated a potential benefit on postoperative short-term outcomes, such as muscle strength and physical fitness. Of 18 studies three were randomized controlled trials in patients with colorectal cancer fitting the criteria for inclusion in the study. Two studies used structured, home-based intense aerobic exercise together with resistance exercise before surgery, and the third one aerobic exercise only. In the former two studies the preoperative intense exercise protocol led to increased oxygen peak by 12%, but no improvement in functional walking capacity was shown after surgery. The authors also reported 16% compliance to the intense exercise. In view of these unexpected results these same authors subsequently conducted other trials using a multimodal prehabilitation protocol which included moderate structured, four-week, home-based aerobic and resistance exercise, nutritional counseling, and supplementation and psychological support, and they were able to demonstrate surgery significant improvement in pre- and postoperative functional capacity [5]. However, each of these studies included a small sample of patients.

The present study was therefore set up to reanalyze the result of three studies conducted over a period of five years in a single center using a multimodal prehabilitation.

CONTACT Francesco Carli franco.carli@mcgill.ca Department of Anesthesia, McGill University Health Center, 1650 Cedar Avenue, Room D10-144, Montreal, Quebec H3G 1A4, Canada

Supplemental data for this article can be accessed here.

The primary objective was to confirm that prehabilitation is associated with a better functional outcome before and after surgery in a large population undergoing colorectal surgery for cancer.

Method

Protocol design and study population

This study is a reanalysis of prospectively collected data from all consecutive participants enrolled in three consecutive studies: one published single group pilot study [4], followed by one published randomized control trial (RCT) [3], and subsequently by one recently completed RCT (GEN11-004). The trials were all approved by the institutional ethics board and conducted at the McGill University Health Center (Montreal, Quebec, Canada) over the period 2010–2015. Eligible patients were 18 years of age or older scheduled for resection of colorectal cancer at any stage. Exclusion criteria were morbid conditions that absolutely contraindicated exercise, severely impaired ambulation, simultaneously participation to a pharmacotherapy trial, and inability to provide an informed consent. Surgical interventions were performed by three fellowship-trained colorectal surgeons, and all patients were treated according to an enhanced recovery program (ERAS) as a standard of perioperative care [6]. Participants were assigned to receive the multimodal prehabilitation program either before (prehabilitation group) or after surgery (rehabilitation/control group). Functional capacity was assessed with the six-minute walk test (6MWT), which measures the distance walked over six minutes (6MWD). Changes in 6MWD in relation to baseline were compared between groups before surgery, at four and eight weeks after surgery. A clinically meaningful functional improvement has been defined as an increase in 6MWD from baseline by at least 19 m [7].

Prehabilitation program

The scientific rational and the detailed description of the program have been published previously [8]. Briefly, prehabilitation is a conditioning intervention that consists of three main components: exercise, nutritional care, and anxiety-coping intervention. Comprehensive history, physical assessment, and subsequent personalized training design were performed including aerobic, resistance, and flexibility static and dynamic balance exercises, either supervised or unsupervised. Endurance training was the core of the program, performed three days a week for 20–30 minutes per session. The intensity was set to achieve a moderate continuous training as defined with a Borg scale, a well validated index that rates the perceived exertion [9]. Resistance exercise was prescribed two times per week, and involved major muscle groups of lower body, chest and core body, and upper body. Stretching and strengthening exercises, warm-up and cool-down activities were performed in each training session. Patients' nutritional intake was assessed, and dietary changes and protein supplementation in order to achieve a total protein intake of 1.5 g/kg/day were prescribed, as recommended by the European Society of Nutrition and Metabolism [10]. A psychological consultation and basic relaxation techniques were provided. All the interventions were conducted by specialist professionals in the different fields, kinesiology, dietetics, and psychology. Prehabilitation lasted for four weeks before surgery, and continued after surgery for two months.

Control condition

Patients in the control group started the trimodal conditioning intervention (rehabilitation) after surgery, once they were discharged from hospital.

End point, measures, and assessments

The primary outcome was the 6MWD, recorded by a blinded assessor and following a standardized protocol [11]. Walk tests are routinely used by clinicians to evaluate aerobic capacity and therapeutic response for a wide variety of patients and settings. This test is very inexpensive and easy to administer as it requires minimal equipment, space, time, and expertise. Moreover, 6MWT has been shown to be strongly correlated with surgical outcome [12,13]. As the minimal important difference for the 6MWD (i.e. 'the smallest change in an outcome measure perceived as beneficial by patients or physicians') has been estimated at 14 m (95% CI 9–18 m) in colorectal surgical setting [7], we considered 19 m to be a meaningful change in functional ability throughout the perioperative period.

Assessments were performed four weeks before surgery (baseline), the day before surgery, and four and eight weeks after surgery. In addition to the 6MWT, a complete anthropometric evaluation was performed together with a self-reported physical activity as evaluated by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [14], well validated in surgical patients [7,15]. Assessment of compliance was based on the diary filled by the patient and the weekly structured telephone calls.

Surgical outcomes as total length of hospital stay and postsurgical complication, graded following Clavien-Dindo classification [16], were also analyzed.

All patients were undergoing standard clinical care according to an ERAS instituted since 2008, as previously described [17].

Statistical analysis

Statistical analysis was performed with SPSS, version 23 (IBM Corporation). We present descriptive statistics both for the pooled sample and stratified by study such that the reader can validate the appropriateness of the pooling of the data.

For all variables, variance homogeneity and normal distribution were tested with Kolmogorov-Smirnov tests. Data are presented as mean ± standard deviation (SD) or median (interquartile range). Data of the two groups were compared at the same time points using χ^2 or Fisher's exact test for categorical data, and Student's t-test or Mann-Whitney U-test for continuous data, as appropriate. The alpha level was set for all comparisons at a p value threshold of 0.05.

Results

Patients' characteristics

A total of 186 participants were enrolled in three prehabilitation trials from October 2010 to August 2015. One hundred and eighty-five patients (99%) completed the preoperative physiological assessment, and were included in this study, and of these 113 (61%) were in the prehabilitation group, 72 (39%) were in the control group.

The baseline demographic, oncological, and surgical characteristics of the patients were similar in the prehabilitation and the control group (Tables 1 and 2). However, a higher percentage of patients in the prehabilitation group were older than 75 years old. Moreover, despite the two group had a similar level of functional capacity (baseline 6MWD 428.0 ± 105 vs. 436.0 ± 94.6 m, $p = 0.600$), participants in the prehabilitation group had a lower self-reported physical activity [CHAMPS 22.3 (10.0–46.0) vs. 38.5 (14.2–61.6) kcal/kg/week].

Functional capacity over time

Functional capacity over time, as measured by 6MWD change in relation to baseline value, is shown in Figure 1. Walking capacity modifications were quantified for three time periods (Table 3). From the first assessment to the day before surgery, there was a statistically significant difference between groups, as the prehabilitation group improved their functional capacity by more than 30 m on average, whereas the control group stayed around baseline value.

At four weeks after surgery, participants in both groups decreased their physical status; however, the rehabilitation/control group experienced a significant higher reduction, more than 70 m on average. At eight weeks after surgery, the change in functional capacity was significantly higher in prehabilitation group, whereas the control group changed their functional capacity minimally. A significant preoperative improvement in physical fitness occurred in the prehabilitation group: 68 of 113 patients (60%) gain more than 19 m in 6MWD preoperatively versus 15 of 72 (21%) in the control group ($p < 0.001$). At four weeks after surgery, 37% in prehabilitation group (38/104, nine lost in follow-up) versus 19% (12/65, seven lost in follow-up) in the control one experienced a significant enhancement in walking capacity ($p = 0.015$).

The compliance to the multimodal program of the three studies ranged from 70 to 98% in the preoperative period,

Table 1. Demographic and surgical characteristics of patients.

	Prehabilitation (n = 113)	Control (n = 72)	*p* value
Age (years), mean ± SD	68.5 ± 11.8	66.6 ± 9.9	0.246
>75 years old, n (%)	40 (35)	13 (18)	0.012
Gender male, n (%)	69 (61)	46 (64)	0.757
BMI (kg/m^2), mean ± SD	27.4 ± 4.5	28.6 ± 4.2	0.076
Obesity (BMI ≥30), n (%)	35 (31)	28 (39)	0.271
ASA III–IV, n (%)	28 (24)	26 (36)	0.135
Charlson Comorbidity Index, median (IQR)	2.0 (2–3)	2.5 (2–3)	0.839
Cancer stage, n (%)			0.295
0–1	40 (35)	28 (39)	
2	33 (29)	21 (29)	
3	38 (34)	17 (24)	
4	2 (2)	6 (8)	
Laparoscopic approach, n (%)	94 (83)	53 (78)	0.434
Type of resection, n (%)			1.000
Colonic surgery	71 (63)	47 (66)	
Rectal surgery	42 (37)	25 (34)	
New stoma formation	29 (26)	15 (21)	0.721
Baseline 6MWD (meters), mean ± SD	428.0 ± 105	436.0 ± 94.6	0.600
Baseline self-reported physical activity (CHAMPS kcal/kg/week), median (IQR)	22.3 (10.0–46.0)	38.5 (14.2–61.6)	0.044

ASA: American Society of Anesthesiologists physical score; BMI: body mass index; CHAMPS: Community Healthy Activities Model Program for Seniors; IQR: interquartile range, Laparoscopic procedures converted into open were not considered in this category; SD: standard deviation; 6MWD: six-minute walk distance.

Table 2. Surgical characteristics and outcomes.

	Prehabilitation (n = 113)	Control (n = 72)	*p* value
Laparoscopic approach[a], n (%)	94 (83)	53 (78)	0.434
Type of resection, n (%)			1.000
Colonic surgery	71 (63)	47 (66)	
Rectal surgery	42 (37)	25 (34)	
New stoma formation	29 (26)	15 (21)	0.721
Length of hospital stay, median (IQR)	4 (3–5)	3 (3–6)	0.806
Grade of complication (Clavien-Dindo classification)[b], n (%)			0.752
Grade 0	68 (62)	45 (66)	
Grade I	20 (18)	11 (16)	
Grade II	15 (14)	8 (12)	
Grade III	6 (6)	2 (3)	
Grade IV	1 (1)	2 (2)	
Grade V	0(0)	0 (0)	

[a]Laparoscopic procedures converted into open were not considered in this category; [b]7 missing data.

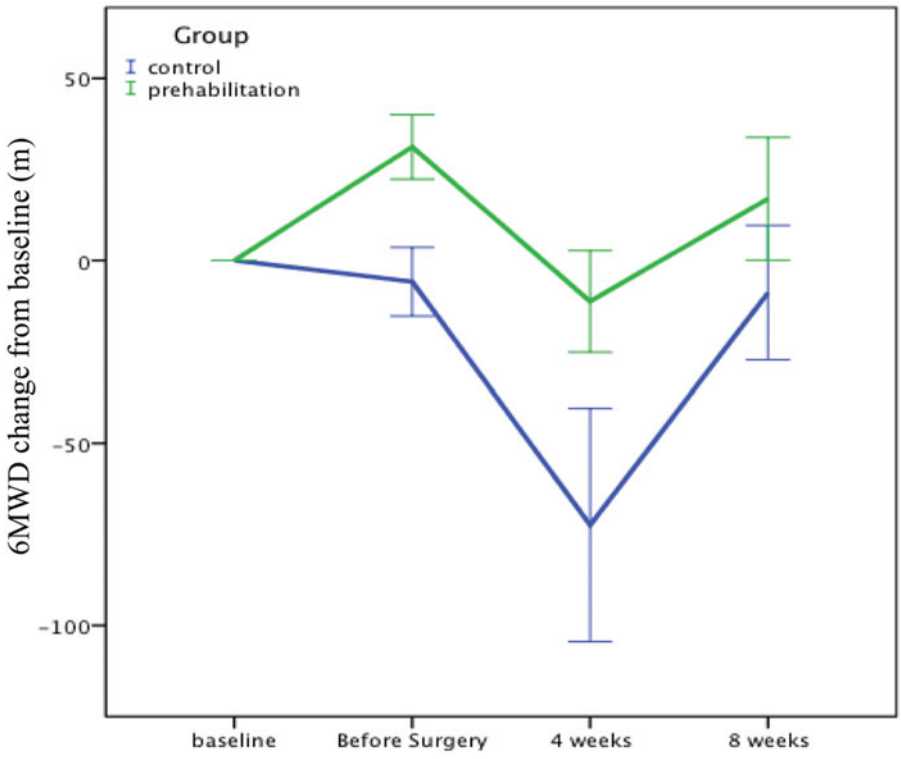

Figure 1. The trajectory of the changes in functional capacity through the perioperative period in the prehabilitation and the control groups. Error bars represent the 95% confidence interval. 6MWD: six-minute walk distance.

Table 3. Changes in walking capacity through the perioperative period.

	Prehabilitation (n = 113)	Control (n = 72)	*p* value
Preoperative change (in relation to baseline)			
Six-minute walk distance (meters), mean ± SD	+30.0 ± 46.7	−5.8 ± 40.1	<0.001
Four-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ± SD	−11.2 ± 72.0	−72.5 ± 129.0	<0.01
Eight-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ± SD	+17.0 ± 84.0	−8.8 ± 74	0.047

SD: standard deviation.

and 53–72% at four weeks and 53–82% at eight weeks. No adverse events were reported.

There were no differences in length of hospital stay or postsurgical complication (Table 2).

Descriptive characteristics by study are displayed in Supplementary Table S1, and shows that studies were relatively comparable in terms of age, gender distribution, body mass index and surgical procedures, but that baseline 6MWD was considerably longer in the second and unpublished trials compared to the single group pilot study and the first trial.

Discussion

This secondary analysis confirmed that a structured multimodal prehabilitation program improved walking capacity before and after surgery for colorectal cancer.

This demonstrates a possible role of enhancing physical fitness preoperatively in increasing the ability to deal with the stress of surgery, and to preserve or restore homeostasis throughout the postoperative period [18]. Indeed, patients in the prehabilitation group recovered their functional capacity faster after surgery, and more than one-third experienced a meaningful increase in their walking capacity one month after surgery.

Another element of interest in this study was the high rate of adherence to the preoperative exercise training. This could be due to the constant encouragement given by our research group to the patients, and weekly phone calls. Almost all patients (99%) returned the day before surgery to complete the preoperative assessment. Compliance to treatment declined after surgery (16 lost in follow-up), as a previous study has already shown [3].

Functional decline after surgery is one of the most known treatment-related adverse effects in medicine [19], strongly linked with the systemic inflammation induced by the stress response to surgery [18]. Indeed, both groups in this study tended to reduce their cardiorespiratory fitness one month postoperatively. This is a key period in cancer care, as the majority of complications occur within the first 30 days after surgery [20], and impact on functional and long-term outcome [21]. Although physical exercise has been shown to modulate positively inflammation in many chronic diseases

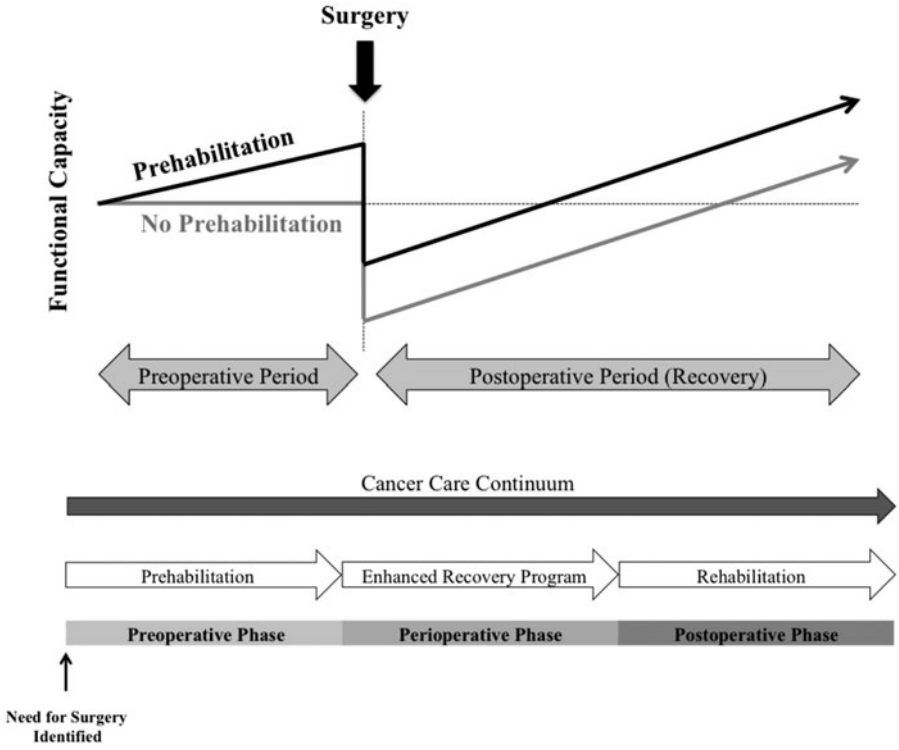

Figure 2. Prehabilitation in a continuum of cancer care.

[22], few studies addressed the potential role of preoperative exercise as a therapy for surgery-related functional impairment. Moreover, cancer and anticancer therapies are associated with varying degrees of side effects such as reduced muscle strength, decreased cardiorespiratory fitness, reduced lean body mass, bone loss, severe fatigue, depression, emotional distress, and anxiety [23]. Exercise has been suggested as a useful intervention to counteract both tumor and treatment-derived systemic effects, determined either by surgery or chemoradiotherapy [24,25]. In the present study functional capacity decreased after surgery in the prehabilitation group, but significantly less than in the control group implying that prehabilitation could have potential role in limiting the ailments associated with further cancer therapy. Future studies are needed to address volume, intensity, and type of exercise training, and whether the accelerated return to baseline function can facilitate the initiation of adjuvant chemotherapy

'Ideally, such interventions should be widely accessible to have the largest benefit for patients with varying age and functional status levels. Doubts have arisen about the feasibility of these programs in the surgical population, usually old, weak, and untrained. This is particularly true in patients with colorectal cancer, as a result of the high incidence of physical inactivity, nutritional disorders, and cardiovascular and metabolic comorbidities [26]. However, a recent study showed that unfit and old patients benefit the most from prehabilitation by increasing their functional capacity to a greater extent [27]. In this population functional walking capacity can be considered a proxy of independency and mobility, facilitating activities of daily living.

It is now commonly accepted that achieving full recovery after surgery does not only mean being discharged earlier and without complications. In fact surgery is only one step in cancer care, implying that every effort needs to be made to minimize the burden associated with further therapies. In colorectal cancer patients, a consistent body of evidence shows the negative role of physical inactivity and dietary disorder in cancer recurrence and survival [26]. Therefore, the perioperative period may be a key moment to address modifiable risk factors of cancer recurrence and treat surgery-related side effects by promoting prehabilitation integrated in cancer care (Figure 2). Further investigation on the possible impact of prehabilitation on postoperative complication and continuum of cancer care is required. Furthermore, this patient-centered, multidisciplinary, and integrated medical care program should start in the preoperative clinic where vulnerable patients are identified, risk stratified and adequately by an interdisciplinary team with the aim of improving surgical outcome and promoting health behavior throughout the continuum of cancer care.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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