Randomized clinical trial

Randomized clinical trial of prehabilitation in colorectal surgery

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Background: **'Prehabilitation' is an intervention to enhance functional capacity in anticipation of a forthcoming physiological stressor. In patients scheduled for colorectal surgery, the extent to which a structured prehabilitation regimen of stationary cycling and strengthening optimized recovery of functional walking capacity after surgery was compared with a simpler regimen of walking and breathing exercises.**

Methods: **Some 112 patients (mean(s.d.) age 60(16) years) were randomized to either the structured bike and strengthening regimen (bike/strengthening group, 58 patients) or the simpler walking and breathing regimen (walk/breathing group, 54 patients). Randomization was done at the surgical planning visit; the mean time to surgery available for prehabilitation was 52 days; follow-up was for approximately 10 weeks after surgery.**

Results: **There were no differences between the groups in mean functional walking capacity over the prehabilitation period or at postoperative follow-up. The proportion showing an improvement in walking capacity was greater in the walk/breathing group than in the bike/strengthening group at the end of the prehabilitation period (47 *versus* 22 per cent respectively; $P = 0{\cdot}051$) and after surgery (41 *versus* 11 per cent; $P = 0{\cdot}019$).**

Conclusion: **There was an unexpected benefit from the recommendation to increase walking and breathing, as designed for the control group. Adherence to recommendations was low. An examination of prehabilitation 'responders' would add valuable information. Registration number: NCT00227526 (http://www.clinicaltrials.gov).**

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Introduction

Despite advances in methods of earlier detection, diagnosis, surgical technology, anaesthesia and perioperative care, which have made surgery safer, more effective and applicable to a wide range of the population, there is still a proportion of patients who undergo surgery with suboptimal recovery[1,2]. There is no 'gold standard' for measuring recovery, considering that this term means to get back to or regain a normal condition. Using this definition, it would follow that some aspects of preoperative function be included in the measurement of recovery[3–8]. When the impact of abdominal surgery was evaluated using measures of functional exercise capacity, two-thirds of people were shown not to have recovered to preoperative levels even 9 weeks after surgery[8,9].

Traditionally, efforts have been made to improve the recovery process by intervening in the postoperative period[10]. However, this may not be the most opportune time because many patients and surgeons are concerned about perturbing the healing process. In addition, patients may be depressed and anxious as they may be awaiting additional treatments for the underlying condition. The preoperative period may be a more emotionally salient time to intervene with regard to the factors that contribute to recovery as, beyond physical benefits, active engagement of the individual in the preparation process is likely to alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process.

The process of enhancing the functional capacity of the individual to enable him or her to withstand a stressful event has been termed prehabilitation[11,12]. Although several programmes have attempted to prepare patients for the stress of surgery and the postoperative recovery process through education and positive reinforcement[13–15], little has been developed systematically to enhance functional capacity before surgery[16,17]. Poor baseline physical performance capacity increases the risk of complications after major non-cardiac surgery[18,19] and prolongs recovery after abdominal surgery[20]. A recent review of the role of optimizing functional exercise capacity in the surgical population indicated that prehabilitation, before cardiac or abdominal surgery, may result in fewer postoperative complications, shorten the length of hospital stay, reduce disability and improve quality of life, in comparison with controls[21]. However, this review identified only one small non-randomized study enrolling patients undergoing abdominal surgery[16].

Recently, Jones and colleagues[22] reported on a single-arm study of a preoperative aerobic exercise programme for 25 patients scheduled for lung cancer resection; 18 patients completed the exercise programme and 13 had a postoperative assessment (mean 51 days after surgery). The primary measure of recovery was maximal oxygen uptake (VO_2); the 6-minute walk test (6MWT) was a secondary outcome. Mean maximal VO_2 increased by 17 per cent over baseline (2·4 ml per kg per min) and the 6MWT increased by 9 per cent (43 m). The impact of this improvement on postsurgical outcome was not reported. Nevertheless, these results indicate that even a relatively short period of preoperative physical training is a useful adjunct to reduce the negative impact of surgery.

The concept of using the preoperative period to prepare patients better to withstand the stresses of surgery is a new one, and there is a need to identify optimal prehabilitation programmes. The purpose of this exploratory study was to evaluate, in people scheduled for colorectal surgery, the extent to which a structured prehabilitation regimen (stationary cycling plus weight training) optimized the recovery of functional walking capacity following colorectal surgery in comparison with a simpler regimen (a recommendation to increase walking coupled with breathing exercises).

Methods

A stratified block-randomized trial was carried out. The study was approved by the McGill University Health Centre ethics board. The data for this study came from persons enrolled in a prehabilitation programme between January 2005 and December 2006 at McGill University Health Centre. A subset of this population was recruited into the trial. Data were collected at three time points: baseline, when the patient was scheduled for surgery; when arriving for surgery; and at postsurgical follow-up.

Participants were randomized to one of two types of intervention in preparation for the postoperative period: intensity-prescribed stationary cycling with weight training (bike/strengthening group), or recommendations to walk daily and perform foot and ankle exercises to enhance lower-extremity circulation as well as breathing exercises (walk/breathing group).

Persons were eligible to enter the prehabilitation programme if they were aged at least 18 years and were referred electively for resection of benign or malignant colorectal lesions, or for colonic reconstruction of non-active inflammatory bowel disease. Patients with American Society of Anesthesiologists (ASA) health status grade IV–V or co-morbid medical conditions interfering with the ability to perform exercise at home or to complete the testing procedures were excluded. Patients receiving preoperative chemotherapy or radiotherapy were not excluded, in order to maximize generalizability, as it was known that these subjects would have a scheduled delay to surgery of 3–6 weeks.

Procedures

Patients were identified for this programme by colorectal surgeons. They were screened by the medical research team for health conditions that would prohibit participation in the exercise programmes. The research coordinator contacted these patients and an appointment was made for the initial assessment. Once the study had been explained and consent obtained, subjects were tested on the 6MWT, followed by a 30-min rest period during which questionnaires were completed with the aid of the coordinator. A graded cycling exercise test was then carried out to volitional exhaustion using a standard protocol on an electronically braked cycle ergometer (Velotron Dynafit Pro; Racermate®, Seattle, Washington, USA). This was done with cardiac monitoring and medical supervision. Peak VO_2 was calculated as the mean of the three highest consecutive 20-s oxygen consumption readings during the test. The corresponding heart rate at peak exercise and the resting heart rate were used to set the level of exercise for the bike/strengthening group.

Both groups were instructed to follow their assigned programme daily, were visited at home at least once to verify the exercise programme, and telephoned weekly until surgery. During the week before the scheduled date of surgery, a second appointment was made to reassess participants on all measures. Postoperative reassessment was scheduled to coincide with a surgical follow-up visit 2–4 months after operation.

Interventions

Subjects in the bike/strengthening group were instructed to exercise initially at 50 per cent of their maximal heart rate; this was increased by 10 per cent each week, if tolerable. Weight training was to be carried out three times a week, to avoid muscle soreness. Patients were instructed to do push-ups, sit-ups and standing strides (lunges) until volitional fatigue, increasing this number to reach 12 repetitions. The weight chosen for strengthening of biceps, deltoids and quadriceps was based on what the person could lift to reach volitional fatigue with eight repetitions. Cycling was to start at 20 min per day, increasing to 30 min daily; weight-training exercises took 10–15 min per day. A fully adherent subject would do about 20–45 min per day for approximately 3·5 h per week, or 14 h over a 4-week period, the reference time for the physical activity questionnaire. A stationary cycle and weights were given to each subject for their use during the prehabilitation period, and afterwards if they desired.

Patients in the walk/breathing group were encouraged to walk daily for a minimum of 30 min. Breathing exercises consisted of practising deep breathing at full vital capacity as well diaphragmatic breathing, huffing and coughing for 5 min per day. In addition, 5–10 min of exercises to activate the circulation were prescribed, consisting of ankle rotations and pumping, static quadriceps contractions and bridging. The intervention was modelled on preoperative physiotherapy practices of the distant past[23].

All participants were visited once at home to demonstrate the programme and at least once to verify the exercise programme; they were also telephoned weekly until surgery. During the week before the scheduled date of surgery, a second appointment was made to reassess participants on all measures.

Measures

The primary outcome measure was the 6MWT, a measure of functional walking capacity[24–27]. Initially developed for patients with chronic obstructive pulmonary disease[24], the 6MWT evaluates the ability of an individual to maintain a moderate level of walking for a period of time, reflecting activities of daily living[28]. The test–retest reliability has been reported to range from 0·73 to 0·99 among a variety of populations, including the elderly[25,29–31]. In community-dwelling elderly persons, measurement error was estimated at 20 m[25,26], and this was used as the threshold value for determining true change. Subjects were instructed to walk back and forth, in a 20-m stretch of hallway, for 6 min, at a pace that would make them tired by the end of the walk; encouragement and feedback were given according to published guidelines[32]. They were allowed to rest during the test if needed, although this time was included in the 6 min. Reference equations are available for calculating the percentage of age- and sex-specific norms: predicted distance (m) = 868 − (age × 2·9) − (female sex × 74·7), where age is in years and the value '1' is assigned for women[27]. A recent paper has supported the validity of the 6MWT as a measure of surgical recovery[4].

As people awaiting surgery are often anxious and this may affect their ability to engage in the prehabilitation programme, emotional health was measured using the Hospital Anxiety and Depression Scale (HADS)[33,34]. Subjects were also asked to indicate the degree to which they felt their level of fitness before surgery was a factor affecting recovery. Postoperative complications were recorded and scored using the Clavien classification[35]. Subjects were asked to report on the frequency of physical and recreational activities over the study period using a standardized questionnaire[36,37] and this was used to infer adherence to the recommendations for exercise.

Statistical analysis

Baseline variables in the two groups were compared using *t* tests or χ^2 tests, as appropriate. Means and differences over time in the 6MWT and other outcome measures were calculated for each group. Observed differences were calculated for subjects with a 6MWT at all three time points. Change in the 6MWT, scored as a percentage of the baseline value, was calculated for each person at follow-up and, as this parameter was normally distributed, it was treated as a continuous outcome. Multiple linear regression was used to estimate the extent to which group randomization predicted change in functional walking capacity. Regression coefficients from this model were interpreted as the effect on the percentage change from baseline associated with being in the bike/strengthening group rather than the walk/breathing group. Both crude and adjusted estimates for group are provided; estimates were adjusted for age, sex, diagnosis (cancer or not), quartiles of baseline 6MWT, ASA, body mass index (BMI), complications at surgery (Clavien grade), HADS anxiety and depression scores, belief that fitness aids recovery, and length of prehabilitation period.

To minimize potential bias arising from missing data, multiple imputation was performed[38,39] on the longitudinal data for all outcomes with sufficient data. Imputation was based on the data arising from key measured variables, including 6MWT and 2MWT, peak VO_2, age, sex, BMI, diagnosis, and values on the health questionnaires. Twenty imputed data sets were chosen from a pool of 80 (to maximize data set independence). Multiple imputation provides estimates of the value of a missing variable that would have been recorded if the person had been assessed. The estimated values incorporate the data that are available, cross-sectionally and over time, as well as variation in the multivariable distribution of these existing data. In the analysis, both the estimate and the associated error, within and between imputed data sets, were used, and the model error term thus included the usual sources of error as well as error arising from imputation. Without this process, the *P* value tends to be underestimated and more likely to cross the conventional threshold for significance[38,39].

Both imputed and observed data are presented. All analyses were done using SAS® version 9.2 (SAS Institute, Cary, North Carolina, USA); analyses using imputed data incorporated the SAS procedure, PROC MIANALYSE.

Sample size

Sample size was estimated for an α level of 0·05 and 80 per cent power to detect a clinically important difference between groups at postsurgical follow-up of 32 m[31]; the estimate of variability (64 m) for the calculation was determined in the authors' earlier trial[8]. This yielded an effect size of 0·5, which required 64 persons per group.

Results

Figure 1 illustrates the flow of subjects through the study. A total of 133 subjects were randomized, 66 in the bike/strengthening group and 67 in the walk/breathing group. However, 21 subjects did not undergo colorectal surgery at the McGill University Health Centre, or at all, and were excluded from the analysis, resulting in a sample size of 112 (mean(s.d.) age 60(16) years). At the two follow-up periods, after prehabilitation and postsurgery, there were subjects who had discontinued participation in the study (14 patients) and those who had missing data for one or more of the outcomes. These subjects were kept in the analysis of the main outcome, and their data were imputed using multiple imputations.

Comparison of groups at baseline

Baseline distributions of patient and surgical variables were similar in the two groups (*Table 1*). The mean(s.d.) length

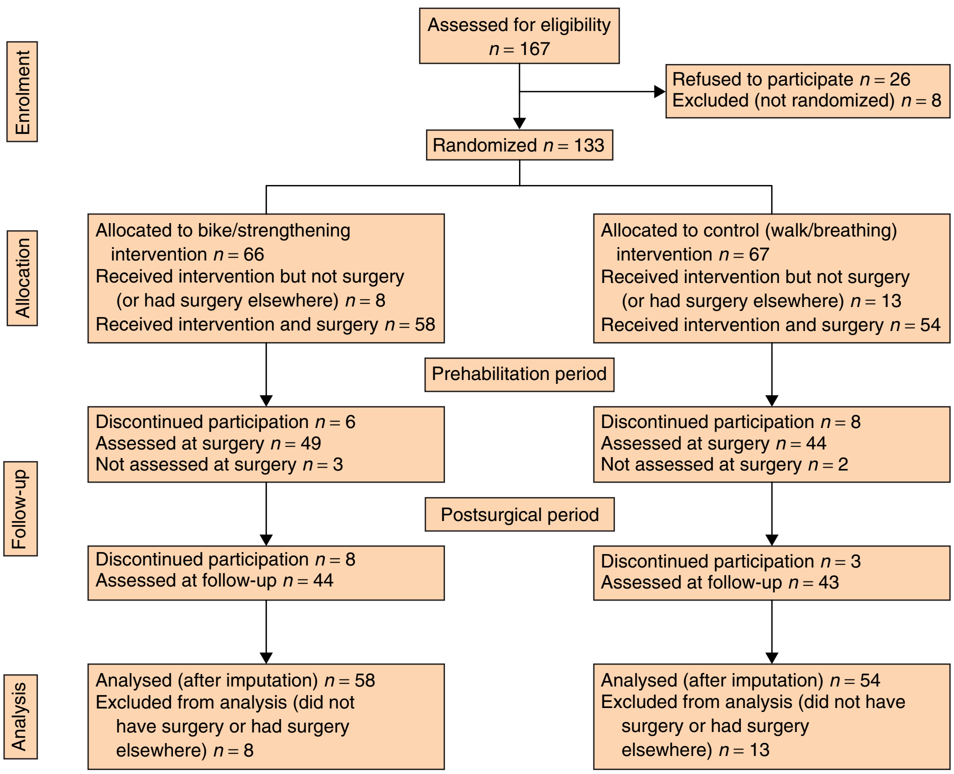

Fig. 1 CONSORT diagram for the trial

Table 1 Patient and surgical characteristics in the two groups at randomization before surgery

	Bike/strengthening group ($n = 58$)†	Walk/breathing group ($n = 54$)†
Age (years)*	61(16)	60(15)
Age < 65 years	32 (55)	31 (57)
Sex ratio (M : F)	34 : 24	31 : 23
Body mass index (kg/m^2)*	28(6)	27(5) ($n = 53$)
Belief that fitness aids recovery	36 of 51 (71)	37 of 49 (76)
Self-rated physical fitness (score 0–10)*	5(2) ($n = 51$)	5(2) ($n = 49$)
ASA grade		
I	3 (5)	4 (7)
II	42 (72)	39 (72)
III	13 (22)	11 (20)
Pathological diagnosis		
Cancer	35 of 56 (63)	31 of 51 (61)
IBD	9 of 56 (16)	9 of 51 (18)
Other	12 of 56 (21)	11 of 51 (22)
Surgical approach		
Laparoscopic	14‡ (24)	13 (24)
Open	44 (76)	41 (76)
Type of surgery		
Right hemicolectomy	17 (29)	14 (26)
Left hemicolectomy	6 (10)	4 (7)
Transverse colectomy	1 (2)	0 (0)
Sigmoid colectomy	3 (5)	4 (7)
Anterior resection	9 (16)	10 (19)
Low anterior resection	10 (17)	5 (9)
Abdominoperineal resection	4 (7)	6 (11)
Proctocolectomy	5 (9)	8 (15)
Small bowel resection	1 (2)	1 (2)
Ileorectal anastomosis	2 (3)	2 (4)
Postoperative analgesia		
Epidural	52 of 56 (93)	49 (91)
PCA	4 of 56 (7)	5 (9)
Length of prehabilitation (days)*	59·0(60·7)	45·4(37·9)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Numbers of patients are shown where sample size did not include whole group. ‡One converted to open approach. ASA, American Society of Anesthesiologists; IBD, inflammatory bowel disease; PCA, patient-controlled analgesia.

of the prehabilitation period in patients with cancer was 52(51) (median 38, interquartile range (i.q.r.) 22–60) days, with no statistically significant differences between the groups. For patients with cancer, the mean(s.d.) prehabilitation time was 43(30) (median 38) days. *Table 2* provides data to compare the two groups at baseline on the key outcomes. The bike/strengthening group was slightly disadvantaged at baseline on the 6MWT.

Table 2 Measures of exercise capacity, activity, anxiety and depression in the two groups at randomization before surgery

	Bike/strengthening group	Walk/breathing group
6MWT (m)	474(115)	496(114)
6MWT (% predicted)*	71(15)	74(15)
Peak V_{O_2} (ml/kg/min)	18(7)	19(6)
Peak V_{O_2} (ml/min)	1409(573)	1410(517)
HADS—anxiety (0–21)	6(4)	6(4)
HADS—depression (0–21)	4(3)	4(3)

Values are mean(s.d.). *Calculated from the regression equation using age and sex provided by Gibbons *et al.*[27]. 6MWT, 6-minute walk test; V_{O_2}, oxygen uptake; HADS, Hospital Anxiety and Depression Scale (each subscale is scored 0–21; higher values indicate more anxiety or depression, and a scores below 8 is considered to indicate emotional distress).

Outcomes

Table 3 presents the values on the 6MWT at baseline, after prehabilitation and at follow-up, as well as *P* values for within-group changes from baseline; both imputed data and data for completers alone are provided. The mean(s.d.) time to postoperative visit was 9·6(3·4) (range 4–27, i.q.r. 8–10) weeks postsurgery. For the bike/strengthening group, imputed data were lower than the data for completers alone at all assessment points, indicating that subjects with missing data had poorer results on the 6MWT. This was not the case for the walk/breathing group, where imputed data were similar to data for completers alone. Over the prehabilitation phase, the bike/strengthening group lost a mean of 10·6 m on the 6MWT, whereas the walk/breathing group gained a mean of 8·7 m; neither of these changes was statistically significant. Although the means for both groups at follow-up postsurgery were lower than at baseline, only the difference in the bike/strengthening group (−34·4 m) was statistically significant; changes in the walk/breathing group were within measurement error of baseline. This finding held even when the analysis was restricted to only those completing all three assessments. The values on the 6MWT were lower when missing data were imputed, indicating that dropouts had lower values than completers on the 6MWT.

Also shown for completers alone are the proportions of people in each group who had a change in the 6MWT beyond measurement error[25,26]. In the bike/strengthening group over the prehabilitation period, 22 per cent made a true gain in the 6MWT compared with 47 per cent in the walk/breathing group ($\chi^2 = 5·94$, 2 d.f., $P = 0·051$); after surgery, these proportions were 11 and 41 per cent respectively ($\chi^2 = 7·97$, 2 d.f., $P = 0·019$). Overall in

Table 3 Results of the 6-minute walk test over time

	Distance on 6MWT (m)	
	Bike/strengthening group	Walk/breathing group
Missing data imputed		
No. of patients	58	54
Baseline	474·3 (15·1)	494·1 (15·5)
At surgery	463·6 (18·5)	502·8 (15·8)
Change over prehabilitation period	−10·6 (7·3)	8·7 (6·8)
P†	0·148	0·203
Postsurgery	439·8 (18·6)	481·9 (18·5)
Difference from baseline	−34·4 (9·9)	−12·2 (10·9)
P†	< 0.001	0·266
Completers alone		
No. of patients	36	32
Baseline	495·6 (13·9)	494·6 (21·5)
At surgery	488·8 (16·1)	507·2 (21·4)
Change over prehabilitation period	−6·8 (7·0)	12·6 (7·2)
P†	0·343	0·091
Postsurgery	467·4 (15·6)	487·4 (23·6)
Difference from baseline	−28·1 (8·4)	−7·1 (11·5)
P†	0·002	0·540
Proportion of completers making clinically meaningful change*		
Over prehabilitation period‡		
> 20 m above baseline	8 (22)	15 (47)
Within 20 m of baseline	13 (36)	11 (34)
> 20 m below baseline	15 (42)	6 (19)
Postsurgery§		
> 20 m above baseline	4 (11)	13 (41)
Within 20 m of baseline	15 (42)	8 (25)
> 20 m below baseline	17 (47)	11 (34)

Values are mean (standard error, derived from multiple imputation) unless indicated otherwise; *values in parentheses are percentages. 6MWT, 6-minute walk test. †Paired t test. Between-group difference in proportions: ‡$P = 0{\cdot}051$, §$P = 0{\cdot}019$ (χ^2 test with 2 d.f.).

the two groups, almost one-third of subjects showed a deterioration in functional walking capacity while awaiting surgery (21 of 68 completers).

Physical activity

To understand changes in outcomes, the amount of time for which subjects performed exercises and physical activity, targeting walking, jogging, biking or weight training, was estimated for three time periods (*Table 4*). During the prehabilitation period, the mean(s.d.) time recorded for the 4 weeks before surgery for the bike/strengthening group was 8·3(6·2) (range 0·5–35) h, compared with 6·0(4·8) (range 0–20) h for the walk/breathing group ($P = 0{\cdot}054$). *Table 4* also shows the distribution of participation in exercise between the two groups: the proportion of patients with higher exercise participation was greater in the bike/strengthening group than in the walk/breathing group ($P = 0{\cdot}075$). In postoperative periods there were no significant differences between the groups.

Table 4 Exercise/physical activity before and after surgery

	Bike/strengthening group	Walk/breathing group
Baseline		
No. of patients	58	52
Exercise/activity (h)	4·2(4·9) (0–18)	4·5(5·5) (0–21)
Before surgery		
No. of patients	45	42
Exercise/activity (h)	8·3(6·2) (0·5–35)	6·0(4·8) (0–20)*
Distribution (h)†‡		
< 1	1 (2)	6 (14)
1 to < 6	15 (33)	18 (43)
6 to < 10	13 (29)	11 (26)
10 to < 14	9 (20)	4 (10)
≥ 14	7 (16)	3 (7)
To 4 weeks postsurgery		
No. of patients	30	36
Exercise/activity (h)	3·5(2·8) (0–13·5)	3·2(4·3) (0–20)
4–9 weeks (on average) postsurgery		
No. of patients	38	31
Exercise/activity (h)	6·1(4·3) (0·5–19·5)	5·4(3·9) (0–15)

Activities included walking for exercise or errands, brisk walking, jogging, biking, exercises, weight training. Values are mean(s.d.) (range) number of hours in the previous 4 weeks unless indicated otherwise; subjects with missing data were excluded. †Values in parentheses are percentages. *$P = 0{\cdot}054$ *versus* bike/strengthening group (t test); there were no significant differences between the groups postsurgery. ‡$\chi^2 = 5{\cdot}2$, 2 d.f. (10 to ≥ 14 h combined), $P = 0{\cdot}075$.

Other outcomes

Table 5 shows how the two groups changed over time on other outcomes relating to exercise capacity and emotional distress. Anxiety did not change in either group over the prehabilitation period but was considerably reduced after surgery. Depression improved over the prehabilitation period for the bike/strengthening group. Mean peak $\dot{V}O_2$ improved over the prehabilitation period in both groups: 134 ml/min ($P = 0{\cdot}003$) in the bike/strengthening group *versus* 112 ml/min ($P = 0{\cdot}007$) in the walk/breathing group. Too few people completed this test postsurgery for meaningful comparisons to be made.

Table 5 Other outcome measures over time (missing data imputed)

	Bike/strengthening group ($n = 58$)	Walk/breathing group ($n = 54$)
HADS—anxiety		
Baseline	5·4 (0·6)	6·0 (0·6)
At surgery	5·2 (0·5)	5·7 (0·6)
ΔBaseline to surgery	−0·3 (0·4)	−0·4 (0·5)
P‡	0·559	0·441
Follow-up	3·7 (0·5)	4·0 (0·5)
ΔBaseline to follow-up	−1·8 (0·7)	−2·0 (0·5)
P‡	0·007	< 0·001
HADS—depression		
Baseline	4·0 (0·5)	3·6 (0·4)
At surgery	3·2 (0·4)	3·4 (0·5)
ΔBaseline to surgery	−0·8 (0·4)	−0·2 (0·5)
P‡	0·045	0·703
Follow-up	3·2 (0·5)	3·2 (0·5)
ΔBaseline to follow-up	−0·8 (0·6)	−0·4 (0·5)
P‡	0·142	0·393
Peak $V\text{O}_2$ (ml/min)†		
Baseline	1395 (76)	1400 (71)
At surgery	1529 (88)	1511 (84)
ΔBaseline to surgery	134 (44)	112 (41)
P‡	0·003	0·007
Clavien complication grade*		
0	34 of 56 (61)	36 of 54 (67)
1	9 of 56 (16)	4 of 54 (7)
2	7 of 56 (13)	11 of 54 (20)
≥ 3	6 of 56 (11)	3 of 54 (6)
Postop. length of stay (days)	11·9 (34·6) ($n = 56$)	6·6 (3·6) ($n = 53$)
Less one outlier	7·4 (6·5) ($n = 55$)	6·5 (3·6) ($n = 52$)

Values are mean (standard error, derived from multiple imputation) unless indicated otherwise; *values in parentheses are percentages. HADS, Hospital Anxiety and Depression Scale; $V\text{O}_2$, oxygen uptake. †Too few people completed the peak $V\text{O}_2$ measurement at follow-up for meaningful analysis to be performed; none of the between-group comparisons of change were statistically significant (*t* test for continuous data, χ^2 test for Clavien grade). ‡Paired *t* test was used to compare within-group changes.

Regression models

To estimate the between-group effect taking time into account, the percentage change in the 6MWT after surgery from baseline values (before prehabilitation) was estimated for each subject as (postsurgery 6MWT − baseline 6MWT)/baseline 6MWT × 100, and a linear regression model was employed.

There was a strong potential for confounding in this type of behavioural intervention even with randomization, because randomization is effective only to balance groups at baseline, and with dropouts imbalance can occur. In addition, once the intervention has been put in place and time passes, the effect of the intervention on intermediate outcomes occurs and the unadjusted comparison on the main outcome may not provide full information about the relative effectiveness of the interventions. *Table 6* shows the estimate of the effect of group without, and with, adjustment. The unadjusted estimate indicates that assignment to the bike/strengthening group was associated with a poorer outcome (−5·9 per cent) on the 6MWT (modelled as percentage change from randomization), although the *P* value was 0·098. However, in the fully adjusted model, which included all significant ($P < 0{\cdot}100$) variables considered as potential confounders, the negative impact of the bike/strengthening regimen was reduced (−4·6 per cent; $P = 0{\cdot}192$). Variables that had a negative impact on recovery postsurgery were being female, aged 75 years or above, postoperative complications, lack of belief in fitness as influencing recovery, high baseline value on the 6MWT, and higher BMI.

Table 6 Results of linear regression models estimating the effect of prehabilitation group on the 6-minute walk test postsurgery

	β estimate	SE	*P*
Null model			
Group (bike/strengthening *versus* walk/breathing)	−5·9	3·6	0·098
Fully adjusted model			
Group (bike/strengthening *versus* walk/breathing)	−4·6	3·5	0·192
Sex (F *versus* M)	−7·7	4·3	0·073
Age (≥ 75 *versus* < 50 years)	−12·9	5·9	0·031
Clavien grade (2, 3 or 4 *versus* 0 or 1)	−15·5	4·5	< 0·001
Do not believe fitness aids recovery	−8·0	4·1	0·053
Lowest baseline 6MWT *versus* highest	15·8	7·4	0·033
BMI per unit kg/m^2	−0·9	0·5	0·088

All estimates shown were adjusted for one another and also for American Society of Anesthesiologists grade, diagnosis, duration of prehabilitation, categories of age, and Hospital Anxiety and Depression Scale anxiety and depression scores. SE, standard error; 6MWT, 6-minute walk test; BMI, body mass index.

Discussion

The principal finding of this study was that there was no difference, on average, at any time point between the two prehabilitation programmes on the primary outcome, functional walking capacity as measured by the 6MWT. To the authors' surprise the light exercise programme, which included walking and breathing activity, had a greater proportion of patients with a clinically meaningful improvement in walking capacity[25,26] in both the prehabilitation and the postoperative period. Considering that dropouts from the bike/strengthening group were more likely to be those with poorer outcomes, this difference may have been even greater had everyone agreed to be re-evaluated.

A number of explanations could underlie these findings, including chance, missing data and poor compliance. In addition, evidence for specificity of bike and treadmill training has long been known[40], so that those who walked for exercise might have been expected to show greater gains in the primary outcome, which was walking. The authors' premise for this study was that the walk/breathing regimen was a 'sham' intervention, with subjects advised simply to walk and to perform simple breathing and circulatory exercises. However, after the baseline peak VO_2 test, it was evident that subjects became very aware of their poor physical condition, and this may have provided an added incentive to subjects in the walk/breathing (sham control) group to do whatever they could to increase their conditioning by walking. Subjects in the bike/strengthening group knew they had been given a programme to deal directly with physical functioning, and perhaps felt things were being looked after. Even if the authors had opted for a no-intervention control, the informed consent and testing procedures would have been likely to increase awareness, and this alone would possibly have been sufficient to stimulate exercise adoption by some participants. Another explanation for the observed benefit of the walk/breathing group intervention is that the breathing exercises given before surgery to this group of mostly elderly and deconditioned patients may have been beneficial[23,41], whereas the more strenuous bike/strengthening programme may have been too aggressive and possibly harmful.

This study illustrates many of the challenges in conducting trials of behavioural interventions – principally, how to balance the groups to offset the impact of not being able to blind subjects to the type of intervention received. The authors opted for a sham intervention, but circumstances transformed it into a potentially potent intervention, which warrants further investigation. A no-intervention control group was not considered because the authors' previous randomized trial comparing two methods of anaesthesia for this same target group[8] indicated that with no active preoperative preparation the average decline at approximately 6 weeks after surgery was 34 m from baseline. Interestingly, the baseline 6MWT for the subjects in the previous and present trials was almost identical (around 480 m).

Poor adherence to the intense exercise programme probably contributed to its lack of benefit, as only 16 per cent of subjects in the bike/strengthening group were fully adherent to the protocol. In contrast to the easier walk/breathing group regimen, the more intense bike/strengthening group regimen may have been intimidating for some people, rendering it counterproductive, particularly in people with poor physical reserve at baseline. In this population, over 60 per cent of patients had cancer and more than 15 per cent had inflammatory bowel disease. It is also possible that lack of social support from family and friends, or the low belief in the benefits of fitness, may have impacted on their ability to participate in the more demanding prehabilitation programme. Finally, disease progression may have counteracted the benefits of physical exercise as a result of metabolic changes characterized by loss of muscle mass and anaemia.

As subjects conducted the exercises at home, lack of supervision may also have impacted on adherence. Jones and co-workers[22], using a similar exercise protocol to the present one but supervised in the laboratory, reported a mean increase of 40 m in the 6MWT distance during the prehabilitation period. The present authors decided on a home-based programme in order to increase patient acceptance, with the added advantage that the exercise could be performed at any time of the day. Daily attendance at a hospital laboratory would be costly, and a personal burden for these patients.

Exercise capacity as measured by peak VO_2 improved in both groups over the prehabilitation period, indicating that the subjects did in fact augment the amount of exercise or physical activity they did compared with the baseline. However, this increase in exercise/physical activity was minimal, with patients in the bike/strengthening group increasing activity by a mean of 4·1 h (about 1 h per week) and those in the walk/breathing group by a mean of 1·5 h (only 20 min per week). In the exercise programme prescribed for the bike/strengthening group, a fully adherent subject would have been expected to do approximately 14 h of exercise/physical activity over the 4-week period. In fact, only 16 per cent achieved this level and a further 20 per cent did 10 h or more (equivalent to 30 min daily for 4 weeks). Subjects in the walk/breathing group did less exercise than those in the bike/strengthening group (17 per cent did 10 h or more in the 4 weeks before surgery; $P = 0{\cdot}075$). Despite poor compliance, peak VO_2 improved in both groups over the prehabilitation period. The disparity between the increase in peak VO_2 and the absence of change in the 6MWT during the prehabilitation period might be explained by the fact that the two measures reflect different physiological outcomes, the former aerobic capacity, the latter functional walking capacity. The increase in peak $\dot{V}O_2$ is in agreement with that reported by Jones *et al.*[22] in patients undertaking a 3-week aerobic exercise before surgery for lung cancer, indicating that an increase in aerobic reserve can be achieved within a limited period of time.

Although regular exercise and physical conditioning is known to enhance physical performance in healthy individuals and to attenuate disease progression in patients with chronic medical conditions such as diabetes, hypertension, arthritis and some types of cancer, few studies have focused on presurgical exercise training. This may be due to the limited period of time between diagnosis and surgery constraining adequate physical preparation of the patient, and the more traditional approach of waiting for the postoperative period to start rehabilitation. In the present study, the period of time used for prehabilitation between the decision to proceed to surgery and the date of the operation was a mean of 52 (median 38) days; however, for those subjects scheduled for surgery for cancer the prehabilitation time was 9 days less (mean 43, median 38 days). Participation in the trial did not affect the waiting time.

In a multivariable model of predictors of recovery of walking capacity after surgery, prehabilitation group was non-significant; however, recovery was significantly poorer in women, subjects aged 75 years and above, those with complications and those reporting a lack of belief in the role of fitness in recovery. Subjects with low physical functioning at baseline showed recovery that was 15·8 per cent higher (β estimate) than that in subjects with good functioning, most likely because they could relatively quickly achieve recovery when measured as a percentage of baseline values.

The 6MWT was chosen as the primary outcome of this study because it is a functional test of walking capacity at a level required for activities of daily living and community mobility. It can be administered with minimal training and space, and does not rely on self-report of symptoms or activities by patients. This test incorporates not only a test of gait, but also muscular and aerobic endurance, coordination and skill. The recovery of normal ambulatory function after major surgery is a key component in patients who need to regain functional independence. The test has been validated in a similar surgical population[4]. In comparison with self-reported indices of recovery, the 6MWT can indicate exercise capacity and functional recovery quantitatively, and does not depend upon the perception of physical performance.

In this study, 47 per cent of people doing simple walking and breathing exercises before colorectal surgery improved their functional walking capacity over this period, compared with 22 per cent of subjects doing more strenuous exercise cycling and weightlifting ($P = 0{\cdot}051$); after surgery, the benefit of this simple prehabilitation programme remained. This result was surprising, as the authors had hypothesized that the bike/strengthening programme would be more effective; however, adherence to the more intense exercise programme was poor. Mean between-group differences in walking capacity were less striking than the differences in proportions. This is the first adequately powered trial in this field, and the lessons learned here will inform future research. Of note, almost one-third of subjects deteriorated in functional walking capacity while awaiting surgery (21 of 68 completers), supporting the need for future research to understand what can be done during this interval to offset the negative effects of waiting. For optimal management of the interval before scheduled surgery, it is important to determine whether there was any benefit to patients in either group who 'responded' to prehabilitation in comparison with that in patients who remained at the same level or who deteriorated while awaiting surgery.

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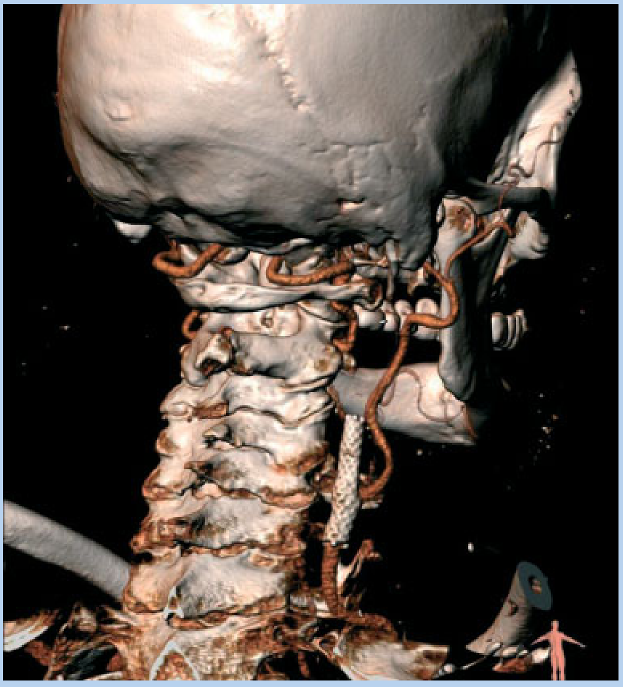
Carotid stent occlusion with persistent flow

A 77-year-old man presented with transient motory weakness of his left hand. Computed tomographic angiography (CTA) showed bilateral internal carotid artery (ICA) stenosis ≥ 70 per cent. The patient underwent successful stenting of his symptomatic right ICA stenosis with the stent covering the external carotid artery (ECA) origin.

Control CTA 1 month later revealed an asymptomatic ICA occlusion with patent flow through the common carotid part of the stent into the ECA. During 24 months of follow-up, the patient remained symptom-free.



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