

Effect of Home-based Prehabilitation in an Enhanced Recovery After Surgery Program for Patients Undergoing Colorectal Cancer Surgery during the COVID-19 Pandemic

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Research Article

Keywords: Prehabilitation, COVID-19, confinement, Body composition, Lean Mass and Fat Mass.

Posted Date: May 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-309905/v1>

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Abstract

Background

Surgery remains the first curative treatment for colorectal cancer. Prehabilitation seems to attenuate the loss of lean mass in the early postoperative period. However, its long-term role has not been studied. Lockdown due to COVID-19 pandemic has forced to carry out the prehabilitation program at home.

This study aimed to assess the effect of home prehabilitation on body composition, complications and hospital stay in patients undergoing oncological colorectal surgery.

Methods

A prospective and randomized clinical study was conducted in 20 patients operated of colorectal cancer during COVID-19 lockdown (13th March -21st June 2020) in a single university clinical hospital. Patients was randomly into two study groups (10 per group): Prehabilitation vs Standard Care. Changes in lean mass and fat mass at 45 and 90 days after surgery was measured using multifrequency bioelectrical impedance analysis.

Results

Prehabilitation managed to reduce hospital stay (4.8 vs 7.2 days, $p = 0.052$) and postoperative complications (20% vs 50%, $p = 0.16$).

45 days after surgery, the loss of lean mass decreased (1.7% vs 7.1%, $p = 0.17$). These differences in lean mass were attenuated at 90 days, however, the standard care group increased considerably their fat mass compared to the prehabilitation group (+ 8.72% vs -8.16%).

Conclusions

Home prehabilitation has proven its effectiveness achieving an attenuation of lean mass loss in the early postoperative period and a lower gain in fat mass in the late postoperative period. In addition, it has managed to reduce hospital stay and postoperative complications.

Registration number

This article is part of an ongoing, randomized and controlled clinical trial approved by the Ethics Committee of our Hospital and registered in ClinicalTrials.gov in August 2018 with registration number NCT03618329.

1. Introduction

Colorectal cancer (CRC) remains the third most common cancer diagnosis in Western countries, and tumor resection and regional lymphadenectomy form the basis of its treatment.^{1,2} In more advanced

stages and for tumors with poor prognostic factors, adjuvant chemotherapy in recommended cases has been shown to decrease recurrence and improve survival.³⁻⁶

However, many patient-dependent factors, such as malnutrition, sarcopenia or a deterioration in general status, have been associated with poorer perioperative outcomes and a delay in the start of adjuvant chemotherapy, with globally worse oncological outcomes being obtained.⁷⁻¹⁰ Adequate nutritional status with preservation of lean mass (LM) has become an important objective to be considered in the perioperative period of patients with CRC.¹¹⁻¹⁴

Prehabilitation aims to optimize the patient's health during the period between diagnosis and surgery, in order to reduce complications derived from surgery, thereby promoting an early recuperation of the patient's baseline condition. This is achieved by improving physical condition, optimizing nutritional status, and acting at the cognitive level to try to reduce stress and anxiety levels.^{15,16} Perioperative prehabilitation before and after surgery appears to attenuate LM loss in the early postoperative period, at 4-8 weeks. However, its long-term effect has not been studied to date.¹⁷

The COVID-19 pandemic has forced multiple countries worldwide to take exceptional measures such as limiting free movement of people and instating mandatory home confinement, restricting any out-of-home movements to purposes deemed essential; in our case, all prehabilitation had to be completed at home. After the period of peak COVID-19 prevalence, countries adopted de-escalation policies with a phased easing of measures, in some cases allowing people to leave their homes for daily physical exercise.

The primary objective of this study is to assess the impact of prehabilitation on the body composition of patients undergoing colorectal surgery enrolled in a home-based prehabilitation program versus Standard of Care (Enhanced Recovery After Surgery (ERAS) without prehabilitation) and its impact on postoperative outcomes in the home confinement context due to the COVID-19 pandemic.

2. Methods

This study is part of an ongoing randomized, controlled clinical trial with two study groups, the Prehabilitation (PH) group and the Standard of Care (SC) group (ERAS without prehabilitation). We analyzed a cohort of 20 patients affected by the consequences of COVID-19 pandemic, both in the Prehabilitation intervention group and the Standard of Care group.

Patients undergoing elective surgery for colon or rectal neoplasm during the mandatory home confinement period instated by Spanish government authorities from 13 March to 21 June 2020, were included consecutively. Patients with metastatic disease or nutritional supplementation at diagnosis and/or chemotherapy-radiotherapy prior to surgery were excluded. In addition, a minimum physical condition and/or autonomy allowing the patient to safely perform the program exercises was required.

The sample size was calculated to compare the incidence of complications postoperative in the control group (SC) versus to the intervention group (PH). With a confidence level of 95% ($\alpha=0.05$) and power of 80% ($\beta=0.2$) in a bilateral contrast, 11 subjects are required in the first group and 11 in the second to detect as statistically significant the difference between two proportions, which for the SC group is expected to be 0.35 and the PH group from 0.17, assuming 10% of losses.

During the preoperative consultation 24 patients were assessed for eligibility. The 20 patients who met the inclusion criteria were given the option to be included in the clinical trial, informed consent was obtained, and randomized into one of two groups: the SC group that followed the standardized ERAS perioperative care protocols, and the PH group, to which a prehabilitation intervention protocol was added.¹⁸ Block randomization was carried out by random sequence obtained previously. The patients in both groups underwent minimally invasive surgery performed by members of the colorectal surgery unit.

The primary study variables were changes in patient weight, LM and fat mass (FM). These measurements were taken in both groups at diagnosis, the day before surgery and 6 and 12 weeks after surgery using multifrequency bioelectrical impedance analysis with the Tanita[®] MC 780 device. Patients who received adjuvant chemotherapy treatment were excluded from the 12-week postoperative measurement. In addition, two criteria were established to determine whether the patient had suffered a deterioration in body composition: loss of LM greater than 2%, and patients who had not yet presented significant changes in their LM ($\pm 1\%$ change) but who experienced a gain in FM of more than 2%.

At the cognitive level, to assess patient anxiety and/or depression levels, determinations were made using a validated version of the *Hospital Anxiety and Depression Scale* (HADS).¹⁹

The clinical variables analyzed included age, gender, body mass index (BMI), major comorbidity, American Society of Anesthesiologists-Physical Status (ASA-PS) score, type of surgery, tumor stage, and use of anxiolytic and/or antidepressant medication. Time of hospital stay and postoperative complications occurring within the first 30 days were collected and divided into minor (classified as Clavien-Dindo I-II), which included low-risk events such as surgical wound infection or postoperative ileus, and major (Clavien-Dindo III-IV), which included life-threatening events and cases requiring radiological, surgical or endoscopic interventions to resolve them, such as anastomotic leaks, intra-abdominal collections, or pneumonia.²⁰

This study obtained the approval from the Ethics Committee of our hospital with registration number NCT03618329.

Trimodal prehabilitation interventions adapted to the COVID-19 pandemic situation.

The prehabilitation program was trimodal, with recommendations on physical exercise, nutritional supplementation and relaxation exercises to be performed at home for 30 days before surgery and the

first 30 days after hospital discharge.

The Canadian Study of Health and Aging Clinical Frailty Scale allowed us to subjectively assess the physical condition of the patient and personalize the type of physical exercise program to be performed and its objectives.²¹ The program was adapted so that patients could complete it at home every day using a video playlist with an approximate duration of 30-45 minutes. The videos included a combination of aerobic and muscular resistance training.

Nutritionally, all patients received dietary recommendations, highlighting the limitation of calorie intake so as not to gain weight and the reduction of toxic habits. In addition, high-protein nutritional supplementation, with high vitamin D and calcium- β -hydroxy- β -methylbutyrate (CaHMB) content, (Ensure Plus Advance, Abbott®) was administered to guarantee a minimum supply of 1.2 to 1.5 g of protein/kg/day.

In order to reduce perioperative anxiety, at the time of diagnosis, all patients received recommendations for relaxation and breathing exercises to be performed at least twice a week.

Patients in the SC group who agreed to participate in the study did not receive any education or recommendation on guidelines for physical activity, nutrition or relaxation, according to standard clinical practice.

Statistical analysis.

Data analysis was performed by comparing the Prehabilitation group to the control group using IBM SPSS Statistics software.

All continuous variables were analyzed using a t-test or Mann-Whitney U test from independent samples. All categories were described as percentages and were compared using a Chi-squared test or Fisher's exact test.

P-values <0.05 were considered significant.

3. Results

A total of 20 patients were included, 10 in the PH group and 10 in the SC group; 65% of them were males, with a median age of 65.5 years (SD = 9.2).

Table 1 presents the demographic data on age, gender, anthropometric parameters, comorbidities, ASA classification for anesthesia, tumor stage, type of surgery performed and postoperative complications. No statistically significant differences were found between the two study groups.

Table 1

Characteristics of patients in the study cohort and both groups.

	Study cohort (n = 20)	Prehabilitation (n = 10)	Standard care (n = 10)
Age median (years)	66 (61,8–71,5) SD = 9,4	66,5 (57,7–70) SD = 10,2	66 (64,7–75,5) SD = 8
Sex ratio (F:M)	7:13 (35%-65%)	4:6 (40%-60%)	3:7 (30%-70%)
Body mass index median (Kg/m²)	26,8 (24,5–28,8) SD = 4,3	27,5 (23,2,-30,9) SD = 5,6	25,8 (24,7–28,2) SD = 2,8
ASA			
1	5 (25%)	3 (60%)	2 (40%)
2	9 (45%)	5 (56%)	4 (44%)
3	6 (30%)	2 (33%)	4 (67%)
Co-morbidity			
Diabetes	3 (15%)	2 (67%)	1 (33%)
Smoker	6 (30%)	2 (33%)	4 (67%)
Hypertension (HBP)	5 (25%)	2 (40%)	3 (60%)
Type of surgery			
Right hemicolectomy	9 (45%)	3 (33,3%)	6 (66,7%)
Left hemicolectomy	1 (5%)	1	0
Sigmoidectomy	5 (25%)	4 (80%)	1 (20%)
Low anterior resection	5 (25%)	2 (40%)	3 (60%)
TNM staging system			
T0-T1-Tis	12 (60%)	7 (58,3%)	5 (41,7%)
T2-T3	7 (35%)	3 (42,9%)	4(57,1%)
T4	1 (5%)	0	1
N0	15 (75%)	8 (53,3%)	7 (46,7%)
N1	5 (25%)	2 (40%)	3 (60%)
Adjuvant chemotherapy	5 (25%)	2 (40%)	3 (60%)
Anxiolytic or depression treatment	6 (30%)	3 (50%)	3 (50%)

	Study cohort (n = 20)	Prehabilitation (n = 10)	Standard care (n = 10)
Global complications	7(35%)	2(20%)	5(50%)
Surgical site infections	3(43%)	0	3(30%)
Other complications	4(57%)	2(20%)	2(20%)

The mean duration of the prehabilitation period before surgery was 28.9 days (SD = 2.8). The postoperative follow-up of the patients in the short and long term occurred at 44.6 days (SD = 4.2) and at 90.6 days (SD = 6.9).

A total of 70% of PH patients experienced loss of LM before surgery, with a mean loss of 1.29% (SD = 4.2). However, in the early postoperative period, 45 days after surgery, LM loss was minimal. On comparing the PH patients with those in the SC group, the loss of LM from the time of diagnosis was 1.7% (SD = 2.32) versus 7.1% (SD = 7.7) in the SC group ($p = 0.17$). In addition, prehabilitation was shown to attenuate the deterioration of body composition as compared to the control group (20% vs 80%), according to the criteria, 45 days after surgery ($p = 0.001$).

On the other hand, the differences in LM were attenuated in the late postoperative period. At 90 days post-surgery, the PH group had an increase in LM from diagnosis of +0.15% (SD = 2.33) versus +1.45% (SD = 6.23) in the SC group. However, while in the SC group FM considerably increased by 8.72% (SD = 20.03), in the PH group, it decreased by 8.16% (SD = 15.09). With regard to body weight, patients in the PH group lost a mean of 1.46 kg (SD = 4.7) while those in the SC group gained 1.6 kg (SD = 2.97).

In the comparative analysis between the two groups, hospital stay was shorter in patients in the PH group, 4.8 days (SD = 1) versus 7.2 days (SD = 3.2) in the SC group ($p = 0.052$). Postoperative complications were also lower in PH patients (20% vs 50%, $p = 0.16$). In the SC group three patients had surgical site infections, one patient ileus and another one pneumonia. Complications in the PH group were one lower GI bleeding in the late postoperative period and one surgical wound bleeding.

No patient presented an anastomotic leak.

The means and standard deviations of the scores obtained in HADS-A and HADS-D are shown in Table 2.

Table 2
Mean score and standard deviation of HADS-A and HADS-D.

	Diagnosis	Surgery	45 days postoperative	90 days postoperative
HADS-A	6,4 SD = 3,5	6,6 SD = 3,9	6,1 SD = 2,5	5,3 SD = 4,36
HADS-D	3,6 SD = 4,2	3,4 SD = 4,2	4,1 SD = 1,9	4 SD = 4

In the anxiety sphere (HADS-A), it was found that 35% of patients had a pathological score at diagnosis, increasing to 40% at the time of surgery. During the postoperative period, these figures decreased from 30% at 45 days of follow-up to 25% at 90 days.

In the depression sphere (HADS-D), 15% of patients had a probably pathological score at diagnosis. These values remained stable at the time of surgery, as well as during the different postoperative measurements.

It was found that 30% of the patients in our sample were chronically taking some type of anxiolytic or antidepressant treatment before diagnosis. These same patients had higher HADS-A scores both at diagnosis ($p = 0.03$) and on the day of surgery ($p = 0.07$). Higher scores were also seen in the HADS-D questionnaire at long-term follow-up ($p = 0.02$).

Finally, patients who underwent adjuvant chemotherapy had higher values in both the HADS-A and HADS-D questionnaires in the early postoperative period ($p = 0.02$).

4. Discussion

To the best of our knowledge, this is the first project to evaluate the impact of outpatient prehabilitation during the mandatory home isolation period due to the COVID-19 health crisis.

As our results show, in terms of body composition, prehabilitation attenuates LM loss in the early postoperative period, 4–8 weeks after surgery.¹⁶ This could have a significant clinical and prognostic significance in prehabilitated patients, because a delay in the start of chemotherapy treatment beyond 8 weeks after surgery has been shown to have poorer oncological outcomes.^{7,8}

Moreover, loss of LM during adjuvant CT treatment in patients with metastatic CRC has been related to a poorer tolerance and a poorer response to treatment. Thus, any measure that results in a reduction in loss of LM will ensure greater treatment efficacy and a better long-term prognosis.^{22,23}

Furthermore, in our patients, prehabilitation had a protective effect on body composition during the period of immobility caused by the mandatory home confinement due to COVID-19, stabilizing weight gain and FM in long-term follow-up. Therefore, we have found that prehabilitated patients achieved better physical fitness with a faster recovery of their baseline activities of daily living after the end of the confinement period.

Bioelectrical impedance analysis makes it possible to calculate body composition by measuring the resistance to an electric current passing through the body. It is a valid, reliable, simple, inexpensive and safe method to assess fat-free mass in patients with non-metastatic CRC, and its use to evaluate

changes in body composition in prehabilitation programs has already been studied with good results.²⁴⁻²⁶

Prehabilitation in CRC surgery has helped improve the outcomes of ERAS protocols. The respective meta-analyses of Gillis et al. and Bolshinsky et al. showed that prehabilitation achieves a reduction in hospital stay by 2 days and a decrease in the rate of complications derived from surgery, outcomes that are similar to the data obtained in our study.^{27,28}

The lack of statistical significance is related to the small sample size, because the observation period or home confinement period was very short. However, the results of our study are promising and show the clinical importance of complying with the ERAS protocols and of systematically including prehabilitation in them, even if performed at home in times of movement restrictions or limitations.

Our study found that both diagnosis and surgery were life situations that induce high levels of stress. The mean HADS-A scores were higher than those obtained postoperatively, consistent with the published scientific evidence²⁹.

There are studies reflecting that between 25% and 50% of cancer patients present symptoms of depression during treatment.³⁰ *Satin et al* concluded that cancer patients suffering from symptoms of depression had an increase in mortality rate of 26%, and for those with major depression, the mortality rate increased to 39%.³¹ All of this underscores the importance of early detection of patients with symptoms of anxiety-depression and those most likely to suffer from them, of the implementation of preventive measures to avoid them, as well as of the importance of the implementation of therapeutic strategies to alleviate symptoms already present. Along these lines, we found that patients taking anxiolytic or antidepressant treatments prior to diagnosis had higher HADS-A values during the perioperative period. These patients would have possibly benefited from individualized treatment. In fact, there is evidence that in-person sessions with scheduled home exercises for self-control of symptoms achieve a significant reduction in those symptoms.³²

In addition, we found that there are other critical moments that can affect the emotional sphere of the patient, such as the need for postoperative adjuvant chemotherapy.

The follow-up of ERAS protocols results in shorter hospital stays and a lower incidence of postoperative complications, which is particularly valuable during the COVID-19 pandemic, where the availability of regular admission hospital beds and intensive care beds has been indispensable for the management of the healthcare crisis.³³⁻³⁵ Optimizing these resources during the pandemic allows us to perform cancer surgeries without excessive delays; said delays would lead to more advanced disease staging, together with a delay in the start of adjuvant chemotherapy, which in turn would result in poorer overall oncological outcomes. Similarly, the reduction in length of hospital stay has contributed to decreased exposure to the risk of in-hospital contagion of SARS-CoV-2, a perioperative nosocomial infection of which could have dire clinical consequences.³⁶ The COVID-19 era has forced us to change our diagnostic

and treatment strategies for patients with CRC.³⁷ Our study has shown that it is possible to carry out prehabilitation programs at home, achieving satisfactory results both in terms of preservation of patient body composition and in reducing complications and length of hospital stay.

As limitations of our work, we must highlight the low sample size, explained by the short observational period because of the duration of home-based confinement dictated by government authorities.

5. Conclusion

Home-based prehabilitation has shown to be effective, achieving an attenuation of loss of LM in the early postoperative period and decreasing the FM in the late postoperative period. In addition, its inclusion in ERAS protocols has reduced length of hospital stay and perioperative complications helping to fight against the health collapse caused by the COVID-19 pandemic.

In select cases, even in lockdown situations, prehabilitation can be carried out on an outpatient basis. More studies with a larger sample of patients will be necessary to confirm the benefits obtained in our study. Furthermore, outstanding issues as the cost-effective analysis of prehabilitation programs, the need to adapt and individualize these programs to the physical condition and body composition of patients, or the use of new technologies to monitor prehabilitation programs.

6. Declarations

-Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

-Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

-Availability of data and material: The datasets generated during and/or analysed during the current study are not publicly available due because de limitations of the law of data protections of our country but are available from the corresponding author on reasonable request.

-Code availability: N/A

-Author contributions

Francisco López-Rodríguez-Arias: Conceptualization, investigation and writing – Original Draft. **Luis Sánchez-Guillén:** Conceptualization, Writing -Review & Editing and Visualization. **Verónica Aranaz Ostáriz:** Writing -Review & Editing and investigation. **Daniel Triguero:** Investigation. **Cánovas Sandra Lario Perez:** Investigation. **Xavier Barber:** Formal analysis. **Francisco J Lacueva:** Writing -Review & Editing and Supervisión. **José M Ramírez:** Supervision. **Antonio Arroyo:** Conceptualization, Writing -Review & Editing and Project adminsitration.

-Ethics approval: Approval was obtained from the ethics committee of our hospital.

-Consent to participate: Informed consent was obtained from all individual participants included in the study.

-Consent to publication: The patients were informed that the data obtained during the study could be used for publications in scientific journals.

-Acknowledgements: We thank all the participants and the doctors who contributed to this project.

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Figures

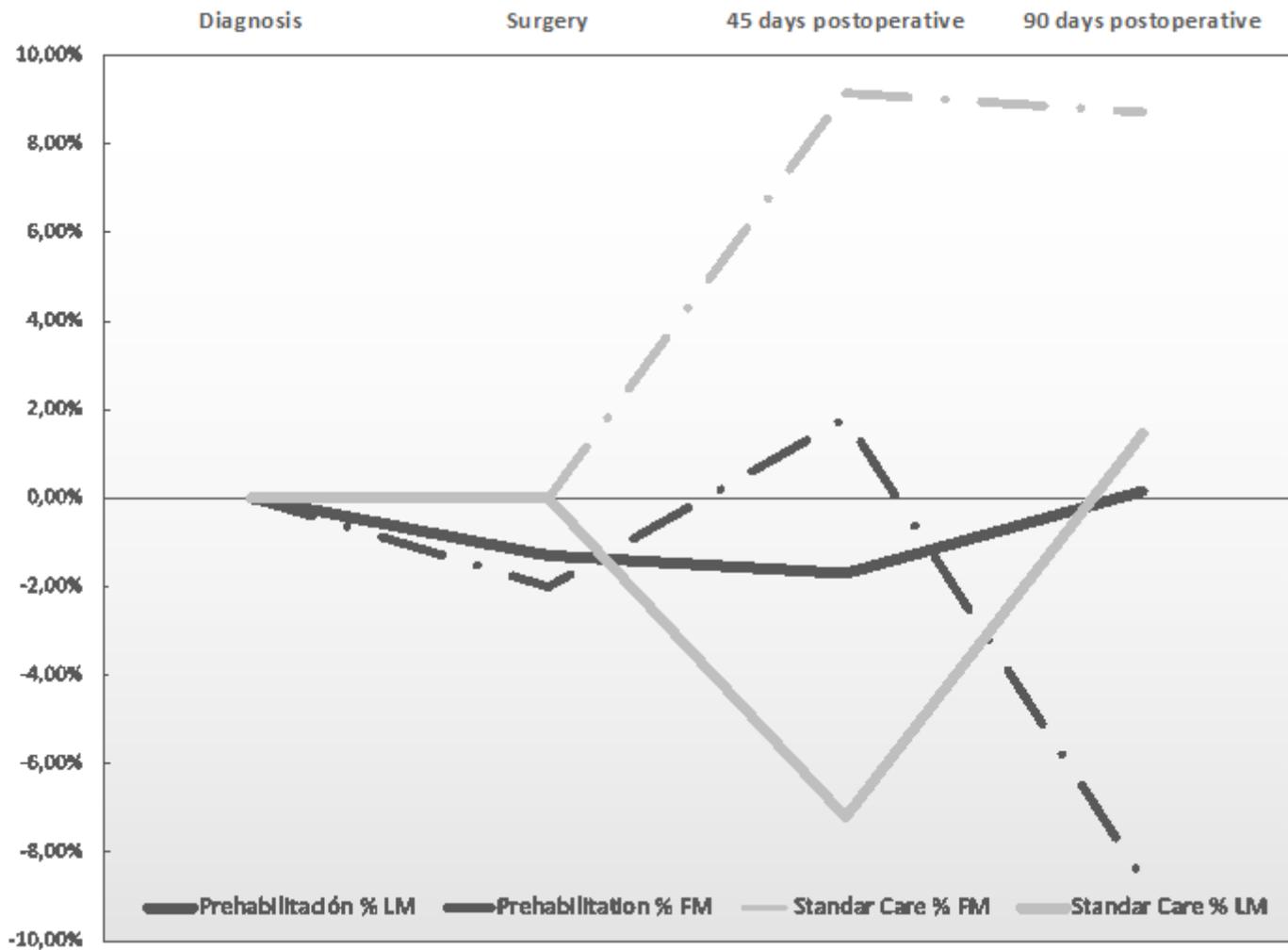


Figure 1

Evolution of changes in LM and FM in the PH and SC group since diagnosis.