The Effect of the Nutraceutical "MICODIGEST 2.0" on the Colorectal Cancer Surgery With Curative Intent Complications Rate: A Study Protocol for a Placebo-Controlled Double-blind Randomized Clinical Trial

Cristina Regueiro, Laura Codesido, Laura García-Nimo, Sara Zarraquiños, David Remedios, Arturo Rodríguez-Blanco, Esteban Sinde, Catalina Fernández-de-Ana, Joaquín Cubiella

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Abstract

Background: Most of Colorectal cancer (CRC) diagnosed are candidates for surgical resection with curative intent, although colorectal surgery is associated with some complications that could be life-threatening. Antibiotic prophylaxis is commonly used for the prevention of postoperative complications. However, this intervention can change the composition of intestinal microbiota and promote adverse inflammatory outcomes in CRC patients. It seems that the combination of different fungal extracts could be beneficial because of their role in gut microbiota modulation and their anti-inflammatory activity.

Objective: Based on this hypothesis, we have designed a double-bind randomized clinical trial to evaluate the effect of the nutraceutical fungal extract MICODIGEST 2.0 on the complications of surgery for CRC resection.

Methods: CRC candidates for surgery will be considered for inclusion in the study. After evaluation in the multidisciplinary tumor board, patients who fulfill criteria will be screened, stratified according to the tumor location and randomly allocated to be treated with MICODIGEST 2.0 or placebo. Treatment will be continued until admission for surgery (4-6 weeks). Participants will also undergo a medical and clinical evaluation, which will include baseline and before admission quality of life, microbiome composition, inflammatory and nutritional status, adverse events and adherence. The main endpoint of the study is the surgery complication rate. We will evaluate them using the Clavien-Dindo classification. It would be necessary to recruit a total of 144 patients to find a relevant clinical difference. We will also evaluate the effect of the nutraceutical on microbiome composition, inflammatory response, nutritional status and quality of life, as well as the effect of these variables on the surgical complications.

Results: This study was funded in 2020 by the Center for Industrial Technology Development. The recruitment started in September 2021 and is expected to be completed in September 2022. Data will be analyzed and the results will be disseminated in 2023.

Conclusions: The results of this protocol study could help to reduce the surgery complications in patients with CRC. This study could also identify new features associated with colorectal surgery complications. In summary, this study trial could improve the management of CRC patients. Clinical Trial: Clinical Trials.gov. Identifier: NCT04821258. Registered on March 29, 2021.

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ABSTRACT

Background

Most of Colorectal cancer (CRC) diagnosed are candidates for surgical resection with curative intent, although colorectal surgery is associated with some complications that could be life-threatening. Antibiotic prophylaxis is commonly used for the prevention of postoperative complications. However, this intervention can change the composition of intestinal microbiota and promote adverse inflammatory outcomes in CRC patients. It seems that the combination of different fungal extracts could be beneficial because of their role in gut microbiota modulation and their anti-inflammatory activity.

Objective

Based on this hypothesis, we have designed a double-bind randomized clinical trial to evaluate the effect of the nutraceutical fungal extract MICODIGEST 2.0 on the complications of surgery for CRC resection.

Methods

CRC candidates for surgery will be considered for inclusion in the study. After evaluation in the multidisciplinary tumor board, patients who fulfill criteria will be screened, stratified according to the tumor location and randomly allocated to be treated with MICODIGEST 2.0 or placebo. Treatment will be continued

until admission for surgery (4-6 weeks)**.** Participants will also undergo a medical and clinical evaluation, which will include baseline and before admission quality of life, microbiome composition, inflammatory and nutritional status, adverse events and adherence. The main endpoint of the study is the surgery complication rate. We will evaluate them using the Clavien-Dindo classification. It would be necessary to recruit a total of 144 patients to find a relevant clinical difference. We will also evaluate the effect of the nutraceutical on microbiome composition, inflammatory response, nutritional status and quality of life, as well as the effect of these variables on the surgical complications.

Results

This study was funded in 2020 by the Center for Industrial Technology Development. The recruitment started in September 2021 and is expected to be completed in September 2022. Data will be analyzed and the results will be disseminated in 2023.

Conclusions

The results of this protocol study could help to reduce the surgery complications in patients with CRC. This study could also identify new features associated with colorectal surgery complications. In summary, this study trial could improve the management of CRC patients.

Trial registration

Clinical Trials.gov. Identifier: NCT04821258. Registered on March 29, 2021.

KEYWORDS

Colorectal Cancer, Sugery Complications, Gut microbiota, Inflammatory pattern, Nutritional status, Nutraceutical

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in western countries. In 2018, about half a million cases were diagnosed in Europe and 250000 of those affected died due to this disease (1). Most of the CRC diagnosed are candidates for surgical resection with curative intent. Cure rates after surgery vary between 92 % and 67 % depending on the tumor stage (2). However, colorectal surgery is associated with some complications that could be life-threatening. These complications are related to age, comorbidities, previous abdominal interventions, intervention urgency, tumor location and type of surgical approach. Post-surgical complications are detected in up to 40 % of patients during admission, 15 % in the month after discharge and 25 % in the first year

after surgery (3). The most common complications are suture failure, intra-abdominal sepsis, prolonged ileus, wound infection and systemic diseases decompensation (4). To assess the severity of surgical complications different scales are available, although the Clavien-Dindo classification is the most used in all parts of the world (5).

Some interventions have been proposed to reduce complications associated with colorectal surgery. Antibiotic prophylaxis is commonly used prior to the admission for the prevention of these postoperative complications. Several studies have shown that antibiotic administration reduces the risk of infections associated with surgery (6,7). Nevertheless, this intervention does not modify the mortality and severity of other complications detected (6,7).

There are also some studies analyzing the effect of prebiotics and symbiotics prior to the admission on surgery complications. The results show that the use of this dietary immunomodulation reduces the risk of infections associated with surgery and the admission duration without affecting other surgery complications or mortality (8). In addition, 34 randomized clinical trials evaluating the role of probiotics or symbiotics in surgery complications have been recently meta-analyzed. The results showed this administration reduces infectious complications during admission, without effect on mortality or noninfectious complications (9).

Human intestinal microbiota is a complex ecosystem that maintains homeostasis with the intestine and plays an essential role in wound healing and immune modulation (10). Consequently, microbiota alterations resulting from surgical stress and perioperative management may be associated with the presence of postoperative complications (11). Mechanical bowel preparation and antibiotic prophylaxis for colorectal surgery have a great impact on the diversity and composition of gut microbiota. It is known that mechanical preparation can both reduce the level of non-pathogenic bacteria like Bifidobacteria and Lactobacilli and increase pathogen bacterias like Escherichia coli and Staphyplococcus (12). Similarly, antibiotic prophylaxis and surgical stress can also impact the gut microbiota by causing changes in diversity and relative abundance (12, 13). Recent studies using animal models have shown significant alterations in the composition of intestinal microbiota after colon resection (14). Kong et al. evaluated the changes in gut microbiota using fecal samples from 43 CRC patients collected before and after surgery (15). After CRC surgery, the Bacteroidetes/Firmicutes ratio and the number of obligate anaerobes (including Bacteroides, Bifidobacterium, Faecalibacterium, Parabacteroides and Prevotella) decreased (16). Further, tumor-associated bacteria were eliminated and butyrate-producing bacteria (Bacillus, Bilophila, Barnesiella) were also reduced (16). On the contrary, conditionally pathogenic bacteria like Escherichia-Shigella, Enterobacteriaceae and Streptococcus increased (16). Therefore, all these alterations of gut micobiota could promote adverse outcome in CRC patients after surgery.

Fungal polysaccharides have attracted attention because of their role in gut microbiota modulation. It seems that this type of polysaccharides could reduce pathogen levels and stimulate the growth of beneficial

microorganism (17). As an example, some basidiomycetes like Ganoderma lucidum, Pleurotus eryngii or Hericium erinaceus have shown prebiotic activity in animal models (18-20). *In vitro* and *in vivo* studies have shown that polysaccharides from fungi can regulate the microbiota through the fermentation of polysaccharides into short-chain fatty acids (17). Human studies have also showed a stability for polysaccharides greater than 90 % and a capability for stimulate Lactobacillus greater than the capability described for other prebiotics (21). The beneficial of fungal polysaccharides is also shown by a randomized study comparing a diet for 10 days based on Agaricus bisporus or animal protein. As a result, patients receiving a diet based on fungi showed more Bacteroidetes and less Firmicutes (22).

The beneficial effects of fungal polysaccharides are not only consequence of their prebiotic activity. Additionally, anti-inflammatory activity has been described for fungal polysaccharides (20, 23). Polysaccharides isolated from Ganoderma and L. edodes have shown in colitis animal models immunomodulatory activity trough the production of nitric oxide, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (17). Another example are the effects of Basidiomycete extract on the immunological function of inflammatory bowel disease patients or the ability of Ganoderma lucidum to reduce the levels of pro-inflammatory cytokines in CRC patients (24, 25). Besides, some studies show that the combination of different fungal extracts is necessary to maximize the immunological function of different basidiomycetes (26, 27). Hence, it seems that this combination could send multiple stimuli to the immune system increasing intracellular reactions and interactions (28-30).

MICODIGEST 2.0 is a nutraceutical designed by the Hifas da Terra company, available since 2016 and without any adverse effect reported (Additional file 1). MICODIGEST 2.0 is composed of 9 fungal extracts: Ganoderma lucidum, Agaricus blazei, Grifola frondosa, Hericium erinaceus, Cordyceps sinensis, Inonotus obliquus, Pleurotus ostreatinus, Polyporus umbellae, and Polyporus Lepreatinella. Taking into account the beneficial effects of fungal polysaccharides, we hypothesized that the fungal extract nutraceutical MICODIGEST 2.0 could be used to reduce the complications after CRC surgery with curative intent.

METHODS

Primary objective

- To evaluate the effect of MICODEGIST 2.0 on the complications after surgery with curative intent for CRC.

Secondary objectives

- To evaluate the safety of MICODIGEST 2.0 in CRC patients.
- To evaluate the effect of MICODIGEST 2.0 on fecal microbiome composition and diversity.

- To evaluate the effect of MICODIGEST 2.0 on inflammatory pattern, nutrition status and quality of life.
- To analyze the effect of microbiome, inflammatory and nutrition status on complications after surgery.

Study design

We designed this study as a randomized, double-blind clinical trial. The study will be conducted at the Gastroenterology Department of Hospital Universitario de Ourense, Ourense, Spain, with the approval from the Clinical Research Ethics Committee of Galicia (2021/036). CRC candidates for surgery with curative intent will be considered for inclusion in the study. Patients who fulfill criteria will be screened and randomly allocated to be treated with MICODIGEST 2.0 or placebo previous to the admission. Additionally, we will stratify the included patients based on tumor location (distal or proximal to splenic flexure). The protocol includes a follow-up period of 4-6 weeks until surgery intervention. This study has been registered in ClinicalTrials.gov (ID: Identifier: NCT04821258) and has been developed in line with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (31).

Inclusion criteria

- CRC patients who are candidates for surgical treatment with curative intent (risk I-III).
- American Society of Anesthesiologists (ASA) physical status classification (ASA) <3.
- Patients aged between 18 and 85 years.
- Eastern Cooperative Oncology Group (ECOG) scale between 0-2.
- Patients with preserved cognitive function.
- Patient's authorization after reading the study information sheet.

Exclusion criteria

- Candidates for neoadjuvant therapy.
- Patients with concomitant carcinoma.
- Allergy to the supplied nutraceutical or presence of malabsorption syndrome.
- Presence of mental disorders
- Patient with active infection or antibiotic therapy in the last month.

- Previous colorectal surgery

Intervention

Patients will be randomized into two treatment groups:

1. Arm A (control): patient will be treated with placebo before surgery intervention in the same way and timing as the nutraceutical.
2. Arm B (experimental): patient will be treated with MICODIGEST 2.0 before surgery intervention.

Hifas da Terra company will provide MICODIGEST 2.0 as 30 capsules and 300 ml syrup with a syringe to measure doses. The drinkable syrup consists of organic extracts from Ganoderma lucidum, Agaricus blazei, Grifola frondosa, Hericium erinaceus, Pleutorus eryngii, Pleutorus ostratus, Myrciaria dubia, purified water, raw agave and natural aroma. The capsule contains clear vegetable capsule, L.brevis, L.plantarum, magnesium stearate, silicon dioxide and extract from Ganoderma lucidum. Additional file 2 summarizes all these constituents of MICODIGEST 2.0. This new treatment is a dietary supplement available since 2016 and without adverse effects reported (Additional file 1). The treatment will initiate with 10 mL/day and 1 capsule/day (before breakfast or before lunch) for 7 days, and rise to 20mL/day and 2 capsules/day (10mL + 1 capsule before breakfast and 10 mL + 1 capsule before dinner) until surgery admission (4-6 weeks).

In the same way, Hifas da Terra company will supply placebo as 30 capsules and 300 mL syrup with a syringe to measure doses. The drinkable syrup consists of purified water, natural aroma and agave nectar. This syrup also includes peptin and guar gumas as gelling agents, and potassium sorbate as preservative. The capsule contains hydroxypropyl methylcellulose and silicon dioxide as anti-caking agents and microcystalline cellulose as gelling agent. The treatment will initiate with 10 mL/day and 1 capsule/day (before breakfast or before lunch) for 7 days, and rise to 20mL/day and 2 capsules/day (10 mL + 1 capsule before breakfast and 10 mL + 1 capsule before dinner) until surgery admission (4-6 weeks).

The assigned study intervention will end if allergic reactions or any serious adverse events are reported. Additionally, patient withdrawal will be a criteria for discontinuing any intervention.

Randomization

We will randomize into the two parallel treatment arms using the distribution of a blinded treatment

kit containing test or placebo supplementation. The dietary supplement will be randomly assigned into the test or placebo groups at a 1:1 ratio according to a random number generated statistically. We will also achieve a stratified randomization to make sure an equal number of patients in the two groups based on tumor location (distal or proximal to splenic flexure).

Blinding

This is a double-bind clinical study so the patient and the trial staff will not know the arm of allocation. The trail staff will prepare treatment kits assigning them the identification codes following the randomization list. Only if it would be necessary for the safety of the patients, the kit code will be identified by the principal investigator of the study.

Preoperative nutritional supplementation

Nutritional supplementation will be carried out based on the risk of malnutrition and independently of the study protocol. To identify patients at risk of malnutrition, the Patient Generated Subjective Global Assessment generated by the patient (PG-SGA) will be used (32). In case of moderate or severe malnutrition we will refer patients to nutrition consultation.

Sample size

We designed the study on the basis that the complications rate in the non-intervention arm is 40 % and that a 50 % reduction would be clinically relevant. Assuming a 0.8 B error and an alpha error of 0.05, 64 patients should be included in each arm. By providing a dropout rate of 10 %, it would be necessary to include a total of 144 patients (72 patients in each group). The sample size calculation was performed with the Ene 3.0 statistical software. A medical doctor will explain to the patients at the digestive oncology consultation the benefits of participating in the study to reach the target sample size.

Study period

The subject's involvement in the study will end after 5-7 weeks. The schedule of this study will include the enrollment, the allocation, a weekly phone call and the close-out visit at the time of patient admission. Further, we will collect information after patient discharge. This study schedule is presented in Figure 1.

Visit 0: We will review inclusion and exclusion criteria in this visit. Patients who fulfill criteria will be informed about the study and will be assigned with an identification number. Principal

investigator will record and kept this number appropriately. Patient will receive the informed consent and a device to collect a fecal sample at home.

Visit 1: If patient agrees to participate in the study, we will perform randomization. We will also evaluate the nutritional status and the quality of life assessment. Previous medical history will be record and both fecal and blood samples will be collect. If malnutrition is detected, we will refer the patient to nutrition consultation. Additionally, patient will receive a device to collect the needed fecal sample at the end of the study.

Follow-up visits: Follow-up visits will be performed weekly for 4-6 weeks. We will used this weekly phone call to collect data about adverse effects and treatment compliance.

Close-out visit: Close-out visit will be at the same time of patient admission. The intervention will end at this time and the remaining treatment will be collected. We will also pick up fecal and blood samples and we will evaluate the nutritional status and the quality of life assessment again. Further, data about adverse effects will be collected at this visit.

End of the study: The end of the study will be defined by patient discharge. We will evaluate and classify the surgery complications at this time. Data collection will also include information about antibiotic prophylaxis used, admission duration, vital status, surgery performed and final staging of the CRC according to the TNM.

Figure 1. Study period at each visit in the clinical study.

TIMEPOINT	STUDY PERIOD				
	Visit 0	Visit 1	Follow-up visits	Close-out visit	Patient discharge
ENROLMENT:					
Inclusion/exclusion criteria review	X				
Informed consent	X	X			
Identification number	X				
Randomization		X			
INTERVENTIONS:					
Arm A (placebo)		X			
Arm B (experimental)		X			
Compliance			X	X	
ASSESMENTS:					
Nutritional evaluation		X		X	
Quality of life		X		X	
Medical history		X			X
Complication rate / Clavien-Dindo					X
Adverse effects			X	X	
Fecal and blood samples collection		X		X	

Outcomes and data collection

Medical history: Data regarding inclusion/exclusion criteria, demographic variables, tumor location, tumor stage, and type and duration of symptoms will be collected at first visit. At the time of patient discharge we will also recover data about type of intervention, admission duration, vital status and type and Clavien-Dindo classification (mild = 0-II, severe = III-V) of surgery complications.

Nutritional evaluation: We will use 4 anthropometric measures to evaluate the nutritional status: weight, height, body mass index (BMI) and body fat percentage. Nutritional status will be also based on PG-SGA survey, albumin, prealbumin, total lymphocytes and hemoglobin.

Quality of life: We will use the SF-36 questionnaire to evaluate the quality of life. This survey has

been already validated and it is frequently used to assess quality of life in CRC patients (33).

Treatment compliance: A staff study member will deliver treatment for 6 weeks at baseline visit. The researchers will ask fort compliance and quantity of treatment used will at follow-up visits. Patient will return the remaining treatment at close-up visit. This delivery option has been proposed to prevent too many visits at the hospital and to promote the retention and completion of follow-up.

Adverse effects: Adverse events and their severity will be collected using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (34). Principal investigator will be responsible for reporting adverse effects of interest or serious events to the sponsor. The sponsor must report immediately the possible serious events that may be related to the treatment.

Blood samples: Blood samples will be collected at baseline and at close-up visits. These samples will be stored at -20 ^{o}C until analysis. Laboratory analysis will include hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, albumin, prealbumin, C-reactive protein, creatinine, prothrombin time, neutrophil-lymphocyte ratio, IL-6, interleukin-10 and TNF-α.

Fecal samples: Fecal samples will be collect at baseline and close-out visits. Patient will have to pick up the samples at home and deliver them within a 4-hour time frame. Again, samples will be frozen at -20 ^{o}C until analysis. Fecal sample analysis will start with a high-quality DNA extraction. Then, the analysis will continue with the bacterial 16S ribosomal ribonucleic acid gene will be sequencing on an Illumina MiSeq. Finally, Metagenomic species and a database with > 200.000 strains will be used to define the microbiome composition.

Data Management

We will collect all the data in the electronic data notebook (eCRD). Additionally, principal investigator will keep a copy of all these data to ensure data entry security. Data integrity will be enforced using data rules and checks applied at the time of data entry. Moreover, all the modifications to the data written will be also documented. Missing visits or missing information will be also considered without meaning the loss of a patient. The principal investigator and all the staff members responsible for data collection and data analysis will have access to the final trial dataset.

Data Confidentiality

The trial staff will depersonalize all the information related to patients and will keep these data anonymous. Moreover, the results of the study will be always presented globally in order to preserve the confidentiality of the data. The promotor will contract a clinical trial insurance to cover physical injury or property which may occur during the study. This insurance will also cover the responsibilities of the promoter, the researcher, collaborators and the head of the center where the study is carried out.

Statistical analysis

Descriptive statistics: Descriptive analysis will be perform with IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp. We will use absolute numbers and percentages to describe qualitative variables. In contrast, we will use the median and interquartile range to describe quantitative variables.

Inferential statistics: We will apply inferential statistics to identify differences between both control and experimental groups. In general, dichotomous variables will be compared with Chi-square test, whereas qualitative variables with more than 2 categories will be compared with ANOVA test. Continuous variables will be compared with t-test for independent samples or with U of Mann-Whitney if they not meet normality. P values lower than 0.05 will be considered statistically significant. More specifically, to analyze the outcomes of the study the following statistical methodology will be performed:

- *Complication rate after surgery*: we will analyze the complication rate in the two intervention groups. We will base this analysis on severity and type of complication. After stratification by tumor location, we will use chi-squared test to identify significant differences between the two groups. Risk Ratio (RR) and 95 % confidence interval (CI) will be used to describe the found differences.
- *Adverse effects*: we will describe adverse events in each group. To find significant differences between the two groups chi-square test will be used after stratification by tumor location. RR and 95 % CI will be used to describe the found differences.
- *Gut microbiota*: diversity and composition of microbiota will be analyzed in the two groups. This analysis will include McNemar test and t-test to find significant difference between them.

- *Inflammatory pattern*: inflammatory differences between the two intervention groups will be analyzed with t-test if variables meet normality or Wilcoxon test if variables not meet normality.
- *Dietary pattern and quality of life*: differences in dietary pattern and quality of life will be analyzed with McNemar for qualitative variables or t-test for quantitative data.
- *Impact of microbiome, inflammatory and dietary pattern on complications after surgery*: We will perform an univariate analysis to identify any association with surgery complications. Then, we will carry out a multivariate regression model the found significant variables. In addition, the model fit will be assess with Likelihood Ratio Test (LR), Area Under the ROC Curve (AUC), Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). Finally, we will validate the designed model using Bootstrap method.

Ethics approval and consent to participate

The study has been designed according to the Declaration of Helsinki and the latest Good Clinical Practice guidelines. Ethical approval has been obtained from the Clinical Research Ethics Committee of Galicia, Spain (2021/ 036).

Informed consent will be obtained from all study participants. Any possible protocol modification will be communicated to the ethical committee and to all relevant parties. The staff study members will also inform participants that they can withdraw their consent to participate at any time and for any reason. Additionally, all the study patients will receive an information sheet. This informative document will include: objectives, methodology, interventions, action to be taken in case of forgetting treatment dose, benefits, risks and possible adverse events, voluntary participation and right to withdraw, confidentiality, action to be taken with the remaining treatment at the end of the study and information about principal investigator. A trained medical doctor will provide all these documents at the first visit.

RESULTS

This study was funded in 2020 by the Center for Industrial Technology Development with the project "Research in the modulation of microbiota and its effects on biomarkers associated with well-being and health (2/3)". Recruitment status is now active. Patient recruitment started in September 2021 and will be completed approximately in September 2022. Finally, we will analyze the data and will publish the results. The study findings will be disseminated in local and international journals and will be presented at conferences and clinical meetings.

DISCUSSION

The planned trial has been designed for evaluate the effects of a new dietary supplement on complications associated with surgery in CRC patients. The result, if positive, may provide a change in the current guidelines for preoperative care in CRC. Additionally, this study protocol will confirm the safety of MICODIGEST 2.0 supplement and will also evaluate the patient adherence to this new treatment. In sum, the results may provide a simple, safe, inexpensive and easy to adhere intervention to reduce surgery complications and, consequently, to improve the quality of life of CRC patients.

The protocol is necessary to be done not only to study the effects of MICODIGEST 2.0 but also to investigate patterns and features related to complications after surgery. The results may show clinical features, inflammatory patterns or nutritional status associated with postoperative complications. Moreover, the results could show new effects of gut microbiota on surgery complications. Therefore, the protocol designed could both define a more definite conclusion regarding risk factors for postoperative complications and help design new clinical studies to prevent CRC surgery complications.

The role of fungal polysaccharides in gut microbiota and immune regulation has been increased in last years. The results of this study may improve the knowledge about these biological functions describe for fungal polysaccharides. Further, this trial may help to define new health benefit of these bioactive polysaccharids and to design new studies about their use in CRC patients. Hence, the use of fungal polysaccharides as probiotics could introduce a new step in the prevention and treatment of CRC. Bioactive polysaccharides may improve the response to treatment, especially immunotherapies due to their immunomodulating activity. These polysaccharides could also increase the safety of the treatments commonly used in cancer and alleviate the adverse effects of these therapies. Additionally, the anti-inflammatory activity of fungal polysaccharides could have influence on carcinogenesis, progression and tumor metastasis.

In summary, the clinical trial designed may both provide a safe and effective treatment for CRC surgery complications and contribute to new study designs for the management of CRC patients candidates for surgical resection with curative intent.

DECLARATIONS

Funding

The trial has been funded by the Center for Industrial Technology Development with the project "Research in the modulation of microbiota and its effects on biomarkers associated with wellbeing and health (2/3)". This grant is partially financed by the European Regional Development Fund of the EU (FEDER). The funding source will not have any role during its execution, analyses or interpretation of the data.

Sponsor/Collaborators

Fundación Biomedica Galicia Sur is responsible sponsor for this clinical study. The sponsor had no role in the design of the trial and will not have any role during its execution, analyses, interpretation of the data or decision to submit results.

Competing interests

None declared.

Acknowledgements

None declared.

Authors' contributions

CR participated in the study design and drafted the manuscript. JC developed the study design and contributed to drafting the manuscript. LC participated in the study design. LGN participated in the study design and has the responsibility of clinical laboratory analysis. SZ and DR participated in the study design and were the medical overseers of the clinical protocol. ARB, ES and CFA participated in the study design and has the responsibility of providing the treatments. All authors provided the approval of the final version of this manuscript.

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LIST OF ABBREVIATIONS

CRC: Colorectal Cancer

TNF-α: Tumor Necrosis Factor alpha

IL-6: Interleukin-6

ASA: American Society of Anesthesiologists

ECOG: Eastern Cooperative Oncology Group

PG-SGA: Patient Generated Subjective Global Assessment

530 TNM: TNM classification of malignant tumors

531 BMI: Body Mass Index

532 CTCAE: Common Terminology Criteria for Adverse Events

533 RR: Risk Ratio

534 CI: Confidence Interval

Supplementary Files

Figures

Study period at each visit in the clinical study.

TIMEPOINT	STUDY PERIOD				
	Visit 0	Visit 1	Follow-up visits	Close-out visit	Patient discharge
ENROLMENT:					
Inclusion/exclusion criteria review	X				
Informed consent	X	X			
Identification number	X				
Randomization		X			
INTERVENTIONS:					
Arm A (placebo)		X			
Arm B (experimental)		X			
Compliance			X	X	
ASSESMENTS:					
Nutritional evaluation		X		X	
Quality of life		X		X	
Medical history		X			X
Complication rate / Clavien-Dindo					X
Adverse effects			X	X	
Fecal and blood samples collection		X		X	