Are preoperative oral antibiotics effective in reducing the incidence of anastomotic leakage after Colorectal cancer surgery: Study protocol for a prospective, multicentre, randomized controlled study

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Abstract

Introduction The optimal preoperative preparation for elective colorectal cancer surgery has been debated in academic circles for decades. Previously, many expert teams have conducted studies on whether preoperative mechanical bowel preparation and preoperative oral antibiotics can effectively reduce the incidence of postoperative complications, such as surgical site infections and anastomotic leakage. Most of the results of these studies have suggested that preoperative mechanical bowel preparation for elective colon surgery has no significant effect on the occurrence of surgical site infections and anastomotic leakage.

Methods/design This study will examine whether oral antibiotic bowel preparation (OABP) influences the incidence of anastomotic leakage after surgery in a prospective, multicentre, randomized controlled trial that will enrol 1500 patients who need colon surgery. The primary endpoint, incidence of anastomotic leakage, is based on 2.3% in the OABP ± mechanical bowel preparation (MBP) group in the study by Morris et al. The patients will be randomized (1:1) into two groups: the test group will be given antibiotics (both neomycin 1 g and metronidazole 1 g) the day before surgery, and the control group will not have any special intestinal preparation before surgery, including oral antibiotics or mechanical intestinal preparation. All study-related clinical data, such as general patient information, past medical history, laboratory examination, imaging results, and surgery details, will be recorded before surgery and during the time of hospitalization. The occurrence of postoperative fistulas, including anastomotic leakage, will be recorded as the main severe postoperative adverse event and will represent the primary endpoint.

Ethics and dissemination

Ethics and dissemination Ethics approval has been obtained from the Ethics Committee at the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200173). The results of this study will be disseminated at several research conferences and as published articles in peer-reviewed journals.

Trial registration: ChiCTR2000035550. Registered on 13 Aug 2020.

Introduction

The preoperative preparation of elective colorectal surgery has been debated in academic circles for decades. In 1973, Nichols et al conducted a prospective randomized controlled trial of mechanical bowel preparation (MBP) and MBP + oral antibiotic bowel preparation (OABP) and published a subsequent retrospective analysis [1, 2]. The results showed that the combined treatment programme can significantly reduce the incidence of postoperative complications. Since then, MBP and OABP have become part of preoperative preparation. Over the past decades, many expert teams have conducted various studies on whether preoperative mechanical bowel preparation and preoperative oral antibiotics can effectively reduce the incidence of postoperative complications, such as surgical site infections and anastomotic leakage. Most of the results of these studies have suggested that preoperative mechanical bowel preparation for elective colon surgery has no significant effect on the occurrence of surgical site infections and anastomotic leakage. On the other hand, preoperative oral antibiotics can effectively reduce the incidence of postoperative complications. Studies by Miettinen et al [4] in 2000, Patrick et al [3] in 2005, and Morris et al [8] in 2015 all showed no benefit of MBP in open colorectal surgery. Cannon et al [5] retrospectively studied 9,940 patients undergoing colorectal resection from 2005 to 2009 and concluded that preoperative oral antibiotics should be used as part of preoperative preparation for elective colorectal cancer surgery, while the use of preoperative oral antibiotics alone should be validated in randomized trials. Garfinkle et al [6] analysed data from adult patients undergoing elective colorectal surgery between 2012 and 2014 through the NSQIP in 2017 and concluded that OABP alone could effectively reduce the incidence of postoperative complications. In 2019, B Vadhvana et al [9] conducted a prospective single-centre randomized controlled study (RCT) to compare the prognostic effects of MBP and MBP + OABP in patients undergoing elective colorectal surgery. They

concluded that the preoperative strategy of MBP + OABP could significantly reduce the incidence of postoperative complications and accelerate the recovery of patients. The American Association of Colorectal Surgeons guidelines for bowel preparation in elective bowel surgery published in January 2019 also mentioned that the use of preoperative oral antibiotics alone is a low-grade recommendation based on low-quality evidence that still needs to be validated in randomized trials[7].

Currently, WHO guidelines do not recommend preoperative oral antibiotics alone or mechanical bowel preparation alone but require a combination of mechanical bowel preparation and oral antibiotics for elective colon surgery [12]. UK NICE has suggested that preoperative mechanical bowel preparation should not be a part of routine preoperative preparation[10]. In an online survey of surgeons, the European Colorectal Society reported that more than 60% of colorectal surgeries in Europe involve mechanical bowel preparation before surgery, while only 11% of surgeons give patients oral antibiotics before surgery[11]. This situation is quite different from the results of other domestic and foreign studies mentioned above. At the same time, the Chinese research on the correlation between preoperative oral antibiotics and the incidence of postoperative complications is still in its infancy.

To date, there remains a lack of large-sample, multicentre, randomized controlled trial studies on the effect of oral antibiotics before colorectal surgery on the incidence of postoperative anastomotic leakage in the international colorectal treatment field to establish relevant norms for preoperative preparation. Given this situation, we will use our experience and foundation in perioperative treatment in gastrointestinal cancer surgery to integrate advantages and resources to study this issue. We believe that our trial will further promote the establishment of and produce improvements in perioperative treatment norms around the world.

Methods/design

Study design

This study is a large-sample, multicentre, Superiority RCT in which 1500 patients will be randomly assigned to the test group or the control group in a 1:1 allocation ratio.figure 1 shows the trial flow chart.

Main Objective

By grouping 1500 patients who need colorectal cancer surgery according to the process shown in Fig. 1, we will explore whether oral antibiotics alone before surgery could effectively reduce the incidence of anastomotic leakage after surgery.

Inclusion and Exclusion criteria

1. Patients who have been diagnosed with colorectal tumors and are considered for elective surgery (including partial and total resection, with conventional laparotomy and two- or three-hole laparoscopic surgery) and have no obvious contraindications to surgery are eligible after the patients and their families agree to voluntarily participate in the clinical trial and sign the relevant informed consent after a conversation regarding informed consent and the clinical trial.

2. Patients meeting any of the following conditions will be excluded:

- Patients who take various antibiotics on their own or under medical orders for various reasons within the 2 weeks before surgery;
- Patients with previous or present diagnosis of inflammatory bowel disease;

- Patients with a diagnosis of acute intestinal perforation or acute small intestinal diverticulum;
- Patients with ischaemic colitis or infectious colitis included in the diagnosis;
- Patients who require two or more operations at the same time;
- Patients who have been diagnosed with acute or chronic peritonitis or other infectious diseases requiring perioperative anti-infective treatment;
- Patients with any acute physiological disorder indicating that the patient needs emergency, rather than elective surgery [e.g., requires preoperative mechanical ventilation or there is preoperative acute renal failure, preoperative systemic inflammatory release syndrome, sepsis or septic shock, etc.);
- Patients with ASA grade 5;
- Patients with immunodeficiency, immunosuppression or autoimmune diseases (e.g., patients undergoing allogeneic bone marrow transplantation within the last five years, taking immunosuppressive drugs, diagnosed with SLE, etc.);
- Patients who refuse to sign informed consent to participate in the trial;
- Patient who are unable to cooperate in a normal fashion with the doctor due to personal reasons or other circumstances in which the investigator considers participation in the experiment unsuitable;
- Patients who require single-port laparoscopic procedures, natural-port procedures, and various new procedures;

3.The terminating study criteria are as follows:

- Patients who violate the principles of treatment after enrolment (e.g., violate the criteria for enrolment and discharge or do not comply with the medication or surgical arrangement for the study duration);
- Patients who were unable to undergo surgery for various reasons after enrolment (reasons will be recorded);
- Patients experiencing non-study-related complications such as drug allergy after enrolment;
- Patients who the investigator does not consider appropriate for continuation (reasons for withdrawal need will be documented);
- Patients who develop severe complications or unacceptable adverse reactions;
- Patients who were unable to undergo elective surgery due to sudden aggravation or other reasons after enrolment.

Participating Entities

This clinical trial is a multicenter study, in which the leader unit is the First Affiliated Hospital of Air Force Military Medical University, and the participants are the Second Affiliated Hospital of Air Force Military Medical University, West China Hospital of Sichuan University, the First Affiliated Hospital of Xi'an Jiaotong University, Tumor Hospital of Tianjin Medical University, Zhongshan Hospital Affiliated to Shanghai Fudan University. These six hospitals are the top third-class A hospitals in China. All these hospitals have sufficient experience in the diagnosis and treatment of digestive tract tumors.

Assignment of interventions

The researchers of each sub center report to the team leader unit, and the specific researchers of the team leader unit use the network online grouping software for randomized grouping. Because the participants in the grouping did not participate in the specific implementation of the trial, and because the medication and other measures in this trial are clinical routine measures, and only the medication in the trial group, it is impossible to set a blind.

Treatment Protocols

All eligible patients with colorectal cancer will be randomly assigned to the test group or the control group in a 1:1 allocation ratio. The participants in both groups will undergo similar perioperative procedures with the exception that the test group will receive oral antibiotics before surgery. For the test group, antibiotics will be given (both neomycin 1 g and metronidazole 0.9 g) the day before surgery (at 1 pm, 3 pm and 10 pm). The control group will not undergo any special intestinal preparation, including oral antibiotics or mechanical intestinal preparation, before surgery (Table 1).

Table 1
shows the medication and usage in this experiment.

Time of Drug Administration				
Drug Name	Dose	13:00	15:00	22:00
neomycin	1g			
Metronidazole	0.9g			

Clinical Data

Clinical data from patients will be obtained by medical staff and recorded on an online electronic platform ([Http://www.medresman.org.cn](http://www.medresman.org.cn)) and in the CRF table. The sample will be coded, and the patient's identity will be known only by the attending physician. The clinical data will include the following: general patient information, past medical history, past surgical history, laboratory examination results, imaging results, surgery details, postoperative infection rate, incidence of postoperative complications, incidence of anastomotic leakage, and 30-day readmission rate after surgery. The timing and processing of the above recorded contents will all be reflected in the CRF table, and the laboratory examinations will mainly assess preoperative and postoperative routine blood and inflammatory indicators(Table 2).

A detailed description of the above data is shown in the CRF table .

Table 2
shows the test and data acquisition schedule for this experiment.

Trial Flow Chart										
stage	preoperative		Intraoperation	Postoperative						unplanned follow-up
Follow up period	2–3 days	1 day		1 day	3 days	5 days	14 days	30 days		
Baseline data collected	√	—	—	—	—	—	—	—	—	—
inclusion and exclusion	√	—	—	—	—	—	—	—	—	—
Sign informed consent	√	—	—	—	—	—	—	—	—	—
Group determination	√	—	—	—	—	—	—	—	—	—
Fill in the basic information	√	—	—	—	—	—	—	—	—	—
Physical examination	√	—	—	—	—	—	—	—	—	—
Imaging examination	√	—	—	—	If necessary	if necessary	√	if necessary	if necessary	if necessary
Blood routine examination	√	—	—	—	√	√	√	if necessary	if necessary	if necessary
Oral antibiotics	—	√	—	—	—	—	—	—	—	if necessary
Safety observation	—	—	√	√	√	√	√	√	√	if necessary
Operational observation	—	—	√	—	—	—	—	—	—	if necessary
Record adverse events	—	—	√	√	√	√	√	√	√	if necessary
Other works	√	√	√	√	√	√	√	√	√	if necessary

Sample Size Estimate And Statistical Analysis

Because there is a lack of international studies on the correlation between use of oral antibiotics alone and the incidence of anastomotic stoma after surgery, we can only refer to the correlation data between oral antibiotics before surgery and the incidence of total complications in the previous literature to estimate the sample size. Based on the data in the study by Morris et al [5], the anastomotic leakage rate in this trial was defined as 2.3%, and there is minimal literature available on the comparison between OABP alone versus no preparation. To verify whether OABP is effective in reducing the incidence of anastomotic leakage after colorectal surgery, we designed a superiority test with a superiority margin of 1% ($\alpha = 0.01$, $\beta = 0.01$, 99% power). With a standard error of 0.01 and a confidence interval of 99%, a sample size of 1232

was needed. To minimize sampling error and account for the rate of loss to follow-up for various reasons, we determined the sample size to be 1500. Standard descriptive statistics will be used to analyse qualitative and quantitative variables such as relative and absolute frequencies, frequency tables, means, medians, standard deviations, ranges, and quartiles. A 99% confidence level will be considered appropriate for analysis. Descriptive statistics will also be used to describe the most relevant clinical parameter measurements. Association of categorical variables will be performed by two-sample t-tests or Fisher's exact test. The causes of anastomotic leakage after surgery are very complex, and infection is only one potential cause. If there is no significant difference in the infection rate between the two groups in this test and there is a significant difference in the incidence of anastomotic leakage after operation, then the result will be negative, that is, the difference is not related to whether antibiotics are used before operation; otherwise, there is a relationship.

Efficacy Assessment Indicators

The main efficacy indicators will be the percentage incidence of anastomotic leakage after surgery. Anastomotic leakage will be defined as the breakdown of the connection and subsequent leakage of digestive system fluid from a surgical anastomosis of digestive system structures. If postoperative anastomotic leakage is clinically suspected, digestive tract radiography will be performed to diagnose the leak. Usually, sufficient abdominal drainage is the most effective treatment.

The secondary efficacy indicators are postoperative recovery, as follows: (1) postoperative complications (n) at 30 days according to the Clavien-Dindo classification, which includes incisional infection, abdominal abscess, intraperitoneal haemorrhage, anastomotic bleeding, postoperative intestinal obstruction, pancreatitis, pulmonary complications, and other organ complications; (2) inflammation index at 1, 7 and 14 days after the operation; (3) re-hospitalization rate within 30 days after operation (days); and (4) incision healing.

Adverse events refer to adverse medical events that occur in clinical trial patients after receiving the medications. In this study, an adverse event will be considered regardless if it is related to the therapy from the time when patients sign the informed consent form to 1 month after the end of treatment. Assessing the nature and determining the severity of adverse events will be conducted in accordance with "expert consensus on diagnostic criteria for postoperative complications of gastrointestinal cancer in China". To assess the adverse events and its causal relationship to therapy, the investigator will evaluate the possible associations between adverse events and trial medications. The following five criteria will be used to determine the results: the time of occurrence of adverse events coincide with the time of administration, adverse events are related to known adverse reactions of the medication, adverse events could not be explained by other reasons, adverse events disappeared after discontinuing therapy and adverse events are reproduced after medication administration. The results documented as positive, relevant and possibly related will be deemed to be adverse reactions. The incidence of adverse reactions will be calculated accordingly. To record, process and report adverse events, the investigator will document any adverse events. Records of adverse events will include a description of adverse events and all related symptoms, time of occurrence, severity, duration, measures taken, results and final outcomes. The reporting methods and treatment measures for severe adverse events will classify as severe adverse events if they meet one or more of the following criteria: death, life-threatening (eg, immediate risk of death), prolonged hospitalization or hospitalization, permanent or severe disability, congenital malformations or defects, some events that has not yet caused death, danger to life or hospitalization; but will consider a severe adverse event by a physician if they cause harm to the patient or require medication or surgical treatment to avoid the above situation. For any severe adverse events during the clinical trial, the investigator will file a report of severe adverse events within 24 hours and report in writing to the Ethics Committee, the superior authorities and the sponsor. The written report will include the time, severity, duration, measures taken and outcomes of serious adverse events.

Data Collection And Observation Indicators

The baseline data (Collected medical history and demo- graphics including patient gender, age and contact number; Detailed medical history, treatment history, body mass index (BMI); Blood routine; inflammation index; Coagulation test (Prothrombin time (PT), activated partial thrombo- platin time (APTT), thrombin time (TT), fasting blood glucose (FBG), D-dimer, international normalized ratio (INR)) will be recorded. Pre- medication imaging assessment test (CT/MRI) included enhanced CT or MRI of the chest, abdomen and pelvis will be completed within 2 days before medication administration. All suspected lesions will be evaluated by imaging test.

Follow-up

The follow-up phase will start from the first day after surgery. The patients who did not recover from the adverse reactions will be treated and followed up closely until they return to the first level or complete recovery specified in the "expert consensus on diagnostic criteria for postoperative complications of gastrointestinal cancer in China". Follow-up tests include: Incision condition, RBC, WBC, hemoglobin, lymphocyte, neutrophils, eosinophils, CRP, calcitonin, TNF- α , IL-6, image test (enhanced CT or MRI of the chest, abdomen and pelvis). In addition, the quality of life will also be assessed.

Patient Protection/written Informed Consent Forms

Both parties ensure the protection of the patient's personal records. Except for documents required by law, patient names are not included in any form in tabular reports, publications or any type of research publication document. Informed consent will be formulated in strict accordance with Chinese laws and regulations. Written informed consent, including all changes made throughout the study, must be pre-approved by the Internal Review Board/Independent Ethics Committee before inclusion in the study. Medical staff at each centre will obtain a signature with written informed consent from each patient (if the patient is unable to make their own decision for various reasons, the immediate family will decide on their behalf) prior to any specific activities related to the study. Researchers at each centre will submit and keep original copies of all written informed consent forms signed by patients and provide additional copies to patients or their immediate family members for their records.

Monitoring Of The Study

Before the start of the study, the personnel of the project unit will visit the research centre and discuss with the researcher (and/or other research-related personnel) the responsibility of the researcher for the research programme and the responsibility of the project undertaking unit or representative.

During the study period, the project undertaker or the supervisor representing the project undertaker will regularly contact the research centre, for a number of reasons including the following: providing information and technical support; establishing randomized grouping as required; confirming that the investigator complies with the study plan, the data on the CRFs are accurately recorded, and the dosage of drugs being used is checked; and carrying out original data analysis (e.g., the data on CRFs are related to the records of patients in the hospital, and the research will compare these with other records). This requires direct access to the original records of each patient (e.g., clinical charts)

Representatives authorized by project undertakers, regulatory departments, and independent ethics committees may visit the centre for inspections, including to verify the original data every half year. The purpose of the inspections of the site and personnel is to systematically and independently examine all research-related behaviours and documents, to

determine that these behaviours have been managed and that the data have been analysed, recorded and accurately reported in accordance with the research programme, GCP, ICH guidelines and other regulatory requirements.

Patient And Public Involvement

Patients or the public will not be involved in the design, or conduct, or reporting or dissemination of our research.

Ethical approval and consent to participate

This trial is a prospective, large sample size, multicentre, collaborative, randomized controlled study designed to explore the best strategy for preoperative preparation for colorectal surgery. This study will strictly abide by all legal requirements, regulations and general principles formulated by international agencies concerning ethical conduct in human biomedical research and by the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Beings. This study protocol was approved by the Chinese Registered Clinical Trial Ethics Committee (Hong Kong Center, China Clinical Trial Registry, Kowloon Pond Baptist University Road, Hong Kong Special Administrative Region, China, Approval No. ChiECRCT20200173, Resolution 19 July 2020). Information about any adverse events (AEs) will be reported to the Ethics Committee until reaching a stable situation. The Ethics Committee has the duty to periodically evaluate the progress of this trial.

Consent Form For Data Publication

All participants signed a consent form for data release.

Abbreviations

OABP

oral antibiotic bowel preparation

MBP

mechanical bowel preparation

RCT

randomized controlled study

NSQIP

National Surgical Quality Improvement Program

WHO

World Health Organization

UK NICE

National Institute for Health and Clinical Excellence

ASA

American Society of Anesthesiologists

CRF

Case Report Form

ERAS

enhanced recovery after surgery

Declarations

Funding

No funds were used during the process of this trial.

Availability of data and materials

Data sets used and/or analysed in this study are available from the corresponding authors on reasonable request.

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Author Contributions

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Survey and Data Summary GR-Q, WW-D, YP-F

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Writing - Draft GR-Q

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All authors approved the final version of the manuscript

Competing interests

The authors declare that they have no competing interests.

Abbreviations

OABP: oral antibiotic bowel preparation

MBP: mechanical bowel preparation

RCT: randomized controlled study

NSQIP: National Surgical Quality Improvement Program

WHO: World Health OrganizatioSn

UK NICE: National Institute for Health and Clinical Excellence

ASA: American Society of Anesthesiologists

CRF: Case Report Form

ERAS: enhanced recovery after surgery

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Figures

Figure 1

This is the whole flow diagram of the test.

Supplementary Files

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- [Checklist.doc](#)