INPLASY PROTOCOL

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Corresponding author:
Xueyan Wang

1406960652@qq.com

Author Affiliation:
Guizhou University of Traditional Chinese Medicine.

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None declared.

Intervention of oral microecological preparations on intestinal flora, adverse drug reactions and other outcome indicators in the perioperative period of colorectal cancer

Wang, XY[1]; Pan, LJ[2]; Wang, FQ[3]; Long, FX[4]; Yang, B[5]; Tang, DX[6].

Review question / Objective: **According to the PICOS acronym, the inclusion criteria were as follows: Participants (P): ① All cases included in the study must have pathologically confirmed CRC, and no metastases to the liver or other sites ② No microecological agents, antibiotics or laxatives within 1 month prior to surgery, have an indication for surgery and undergo radical CRC surgery ③ Approved by the hospital ethics committee, the patient and family understand and are informed, voluntarily participate in this study and sign the informed consent form ④ No restrictions by gender, race or country were found. Intervention (I) :Randomized controlled clinical trial of oral microecological preparations in the perioperative period for colorectal cancer and the content of the microecological preparations is not limited. Comparison (C) :On the basis of the control group, patients in the test group received oral microecological preparations. Outcomes (O) : Clinical efficacy and safety of microecological agents. Study design (S) : Randomized controlled clinical trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2023 and was last updated on 17 April 2023 (registration number INPLASY202340051).

INTRODUCTION

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Condition being studied: Colorectal cancer(CRC) is one of the top three causes of cancer deaths worldwide, and the number of cases and deaths are on the rise, and the incidence rate among young people (20-49 years old) has increased significantly, with CRC ranking third in incidence rate and second in mortality rate in 2020.

Microorganisms play a crucial role in human health and disease development, colonizing various parts of our body, and having different types of crosstalk with various organs, but the highest numbers are found in the intestine. Gut microbes interact with the immune system, providing signals to promote the maturation of immune cells and the normal development of immune function, which in turn is a major force in the regulation of cancer. Studies have shown that the occurrence of CRC is closely related to disorders of the intestinal microbiota.

CRC patients have significant ecological dysbiosis in their intestinal flora, and the various treatments that CRC patients receive during the perioperative period can cause changes in intestinal flora, and intestinal flora disorders can cause a series of adverse effects including increased intestinal inflammatory responses and harmful metabolites. In addition to preoperative mechanical bowel preparation, chemotherapy, radiotherapy, antibiotics and acid suppressants, CRC surgery itself and the stress response to surgery may also affect the intestinal flora and cause significant changes in the intestinal flora structure, which may affect postoperative recovery, short-term complications and long-term oncologic outcomes[10]In recent years, microecological preparations have been successfully used to improve the intestinal microbiota for the treatment of CRC and to mitigate treatment-mediated side effects. A large number of probiotic bacteria, their metabolites and other prebiotic components have been shown to influence CRC incidence and mediate intestinal immunity, while they also exhibit anti-inflammatory properties. And oral microecological agents, not only targeting systemic immunity, are also adept at managing mucosal immunity, thus addressing the inability of systemic immunity to affect the mucosal layer in the colon.

In this study, we conducted a systematic evaluation and meta-analysis of intestinal flora alterations, intestinal mucosal barrier-related factors, immune function-related indices, inflammatory factors, clinical efficacy and adverse effects produced after intervention with microecological agents in the perioperative period of CRC to provide a basis for the involvement of micro-ecological agents in the perioperative treatment of CRC.

METHODS

Participant or population: ① All cases included in the study must have pathologically confirmed CRC, and no metastases to the liver or other sites ② No microecological agents, antibiotics or laxatives within 1 month prior to surgery, have an indication for surgery and undergo radical CRC surgery ③ Approved by the hospital ethics committee, the patient and family understand and are informed, voluntarily participate in this study and sign the informed consent form ④ No restrictions by gender, race or country were found.

Intervention: Oral microecological agents in combination with conventional therapy or chemotherapy.

Comparator: Conventional treatment or chemotherapy.

Study designs to be included: Randomized controlled clinical trial.

Eligibility criteria: According to international diagnostic standards for colorectal cancer: ① All cases included in the study must have pathologically confirmed CRC, and no metastases to the liver or other sites ② No microecological agents, antibiotics or laxatives within 1 month prior to surgery, have an indication for surgery and undergo radical CRC surgery ③ Approved by the hospital ethics committee, the patient and family understand and are informed, voluntarily participate in this study and sign the informed consent form ④ No restrictions by gender, race or country were found.
Exclusion criteria: (1) non-randomized controlled trials (2) unclear dose and periodicity of microecological agents (3) incomplete test results (4) lack of sufficient data.

Information sources: Literature search in both international (Cochrane Library, PubMed, EMBASE, and Web of Science) and Chinese (CBM, CNKI, and Wan-fang Database) databases will be systematically searched for eligible studies from 2000 to February 2023, were independently conducted by two researchers.

Main outcome(s): The primary outcome included two efficacy measures: (I) changes in intestinal flora: mainly involving changes in the numbers of Lactobacillus, Bifidobacterium, Escherichia coli, and Enterococcus faecalis; and (II) adverse drug reactions, assessed by detecting hematologic toxicity (leukopenia), gastrointestinal reactions (nausea, vomiting, diarrhea, flatulence), infections (pulmonary, abdominal, urinary, intestinal, incisional), and anastomotic fistulas.

Additional outcome(s): Secondary outcome indicators included four efficacy measures: (i) short-term clinical efficacy objective response rate (ORR), disease control rates (DCR), short-term clinical efficacy according to the World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST), short-term tumor remission including complete response (CR), partial response (PR), stable disease (SD) remission, progressive disease (PD) remission, ORR, disease control rate ORR was defined as the sum of CR and PR, and DCR was the sum of CR, PR, and SD; (ii) immune function indicators CD4+,CD8+,CD4+/CD8+, and IgA, IgG; (iii) intestinal mucosal barrier detection indicators endotoxin, DAO, plasma D-lactate; (iv) inflammatory factors IL-6, TNF-α, CRP.

Quality assessment / Risk of bias analysis: Cochrane tools.

Strategy of data synthesis: Statistical analyses were performed using Review Manager 5.4 and R 4.2.2 software. The outcomes were mainly represented by risk ratio (RR) and standardized mean difference (SMD) with its 95% CIs. Two-tailed $p < 0.05$ was considered to be statistically significant. Cochrane's Q test and I2 statistics were used to assess heterogeneity between studies; $p \leq 0.1$ or $I2 > 50\%$ indicated the presence of statistical heterogeneity, and a random-effects model was used to calculate the results when statistical heterogeneity was not present, and a fixed-effects model (common effects model) was used when statistical heterogeneity was not present. Publication bias was tested using funnel plot tests when more than 10 studies reported the same results. Sensitivity analyses were performed by removing one study at a time from the pooled analysis to explore the effect of individual studies on the pooled results.

Subgroup analysis: Subgroup analysis was performed according to whether or not combined chemotherapy was administered.

Sensitivity analysis: Sensitivity analysis was performed in R 4.2.2 software to explore the impact of individual studies on the pooled results by removing one study at a time from the pooled analysis.

Country(ies) involved: China.

Keywords: Colorectal cancer, Perioperative period, Microecological agents, Meta-analysis.

Contributions of each author:

Author 1 - Xueyan Wang.
Email: 1406960652@qq.com
Author 2 - Lijun Pan.
Email: 13025640@qq.com
Author 3 - Feiqing Wang.
Author 4 - Fengxi Long.
Author 5 - Bing Yang.
Author 6 - Dongxin Tang.

Conceptualization: Xue-yan Wang; Methodology: Xue-yan Wang; Formal analysis and investigation: Xue-yan Wang, Li-jun Pan; Writing - original draft preparation: Xue-yan Wang; Writing - review and editing: Xue-yan Wang, Fei-qing Wang; Funding acquisition: Dong-xin Tang, Bing Yang; Resources: Xue-yan Wang; Supervision: Dong-xin Tang, Feng-xi Long and all authors commented on previous versions

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