Review Article

Probiotics Used for Postoperative Infections in Patients Undergoing Colorectal Cancer Surgery

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Objective. The objective of this study was to conduct a systematic review and meta-analysis about probiotics to improve postoperative infections in patients undergoing colorectal cancer surgery. Methods. The PubMed and the Web of Science were used to search for appropriate randomized clinical trials (RCTs) comparing probiotics with placebo for the patients undergoing colorectal cancer surgery. The RevMan 5.3 was performed for meta-analysis to evaluate the postoperative infection, including the total infection, surgical site infection, central line infection, pneumonia, urinary tract infection, septicemia, and postoperative leakage. Results. Our meta-analysis included 6 studies involving a total of 803 patients. For the incidence of total postoperative infection (odd ratios (OR) 0.31, 95% confidence interval (CI) 0.15–0.64, \( I^2 = 0\%\)), surgical site infection (OR 0.62, 95% CI 0.39–0.99, \( I^2 = 11\%\)), central line infection (OR 0.61, 95% CI 0.15–2.45, \( I^2 = 65\%\)), pneumonia (OR 0.36, 95% CI 0.18–0.71, \( I^2 = 0\%\)), urinary tract infection (OR 0.26, 95% CI 0.11–0.60, \( I^2 = 26\%\)), septicemia (OR 0.28, 95% CI 0.17–0.49, \( I^2 = 10\%\)), and postoperative leakage (OR 0.45, 95% CI 0.06–3.27, \( I^2 = 68\%\)), the results showed that the incidences of infections were significantly lower in the probiotics group than the placebo group. Conclusions. Probiotics is beneficial to prevent postoperative infections (including total postoperative infection, surgical site infection, pneumonia, urinary tract infection, and septicemia) in patients with colorectal cancer.

1. Introduction

The postoperative complications of colorectal cancer surgery result in increased ventilation days, hospital stay days, mortality, and cost. Postoperative infection is a major factor affecting the morbidity of the patients. Bacterial translocation is defined as transmitting the bacteria from the gastrointestinal tract to normally sterile tissues. A large number of studies have shown that the bacterial translocation plays a significant role in increasing the incidence of postoperative infections [1, 2].

The probiotics therapy, which was introduced by Lilly and Stillwell [3], could lead to positive clinical and laboratorial outcomes for patients undergoing gastrointestinal surgery. Probiotics are live microorganisms and it is known that probiotics benefit to the host as they can stabilize the intestinal microbiological environment. Nowadays, probiotics have been proved to treat several diseases, such as chronic inflammatory bowel disease [4], hepatic encephalopathy [5], and atopic disease [6]. Horvat et al. [7] showed us his interesting finding that preoperative administration of probiotics in elective colorectal surgery had the same protective effect in preventing a postoperative inflammatory response as mechanical bowel cleaning.

Probiotics study is very important in recent year, there is a recent paper discussing about the importance of probiotics in the prevention and treatment of colorectal cancer. So we want to conduct a meta-analysis to integrate all this interesting studies to guide clinical practice, as meta-analysis has the higher quality than common RCTs if we only include high quality RCTs. We try to explore the incidence of post-operative infections, including the incidence of the total infection and subgroup infection, such as surgical site infection, central line infection, pneumonia, urinary tract infection, septicemia and postoperative leakage.
2. Methods

2.1. Search Strategy. Two investigators independently searched the articles in the databases (PubMed, the Web of Science). The reference lists of eligible studies and relevant papers were also manually searched and reviewed. Searching terms included “probiotics”, “colorectal cancer”, and “surgery”. Searching terminal date was 2019/1/10. Firstly, we found 407 articles after duplications excluded, and then 307 of them were excluded by reading the title and abstract. Finally, 6 articles were left after reading the whole articles [8–13] (Figure 1).

2.2. Inclusion and Exclusion. Inclusions contain: (1) randomized controlled study comparing probiotics with placebo, (2) outcome: various kinds of infections, (3) only be published in English.

Exclusions contain: (1) review, retrospective research, case report, (2) insufficient data in the articles.

2.3. Data Elected. Two authors (Chongxiang Chen, Tianmeng Wen) independently reviewed the identified abstracts and selected articles to full review. The third reviewer addressed the discrepancies (Qingyu Zhao). For each selected publication, the following baseline and study characteristics were extracted: first author, publication year, country, participant characteristics, patient age, dosage form of probiotics groups, experimental durations, and the baseline characteristics of these studies were concluded (Table 1). The risk of bias of the included studies is shown in Figures 2 and 3. Efficacy outcome measures were the total infection, surgical site infection, central line infection, pneumonia, urinary tract infection, septicemia, and postoperative leakage.

2.4. Risk of Bias Assessment. The risk of bias of trials included in this meta-analysis was assessed according to the recommendations of the Cochrane Handbook of trials in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (http://handbook.cochrane.org). Jadad scale was used to calculate the quality of every enrolled study.

2.5. Statistic Analysis. We pooled data and used mean deviation (OR, with 95% confidence interval) for dichotomy outcomes: the total infection, surgical site infection, central line infection, pneumonia, urinary tract infection, septicemia, and postoperative leakage. We would use a fixed-effect model
| Study                  | Type  | Jadad scale (randomization + concealment of allocation + double blinding + withdrawals and dropouts) | Time (published) | Country               | Participant | Total number (probiotics vs. placebo) | Age (probiotics vs. placebo) | Probiotics                                                                 | Duration                                                                 |
|-----------------------|-------|------------------------------------------------------------------------------------------------|------------------|------------------------|-------------|----------------------------------------|-----------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Kotzampassi et al.    | RCT   | $1 + 1 + 2 + 1 = 5$                                                                                 | 2015             | Greece                 | One center  | 164; 84/80                            | $65.9 \pm 11.5$ vs. $66.4 \pm 11.9$ | One capsule (Lactobacillus acidophilus LA 5, Lactobacillus plantarum, Bifidobacterium lactis BB 12 Saccharomyces boulardii) twice a day | The day of operation and for the next 14 days                              |
| Liu et al.            | RCT   | $2 + 1 + 2 + 1 = 6$                                                                                 | 2012             | China (Taiwan)         | One RCC     | 150; 75/75                            | $66.06 \pm 11.02$ vs. $62.28 \pm 12.41$ | Encapsulated bacteria (Lactobacillus plantarum; Lactobacillus acidophilus; Bifidobacterium longum) patients in probiotics group received 2 g/d, at a total daily dose of $2.6 \times 10^{14}$ CFU | 6 days preoperatively and 10 days postoperatively                          |
| Liu et al.            | RCT   | $2 + 2 + 2 + 1 = 7$                                                                                 | 2015             | China                  | One ICU     | 134; 66/68                            | $66.62 \pm 18.18$ vs. $60.16 \pm 16.20$ | Encapsulated probiotics (Lactobacillus plantarum; Lactobacillus acidophilus; Bifidobacterium longum) patients in probiotics group received 2 g/d, at a total daily dose of $2.6 \times 10^{14}$ CFU | Intervention period lasted 16 days, 6 days preoperatively and 10 days postoperatively; Detailed records were recorded for up to 30 days after surgery For 7 days before the operation and from postoperative day 5 for 10 days |
| Sadahiro et al.       | RCT   | $1 + 1 + 0 + 1 = 3$                                                                                 | 2013             | Japan                  | One ICU     | 195; 100/95                           | $67 \pm 9$ vs. $66 \pm 12$           | Three Bifidobacteria tablets orally after each meal three times daily | For 3 days (days −5 to −3) before surgery                                          |
| Zhang et al.          | RCT   | $1 + 1 + 2 + 1 = 5$                                                                                 | 2011             | China                  | One center  | 60; 30/30                             | $61.5 (46-82)$ vs. $67.5 (45-87)$      | 3 oral bifid triple viable capsules (Enterococcus faecalis; Lactobacillus acidophilus; Bifidobacterium longum), 3 times a day | For 3 days (days −5 to −3) before surgery                                          |
| Liu et al.            | RCT   | $2 + 2 + 2 + 1 = 7$                                                                                 | 2010             | China                  | One center  | 100; 50/50                            | $65.3 \pm 11.1$ vs. $65.7 \pm 9.9$    | Encapsulated bacteria (contain: Lactobacillus plantarum; Lactobacillus acidophilus; Bifidobacterium longum) patients in placebo group received probiotics 2 g/d, total daily dose of $2.6 \times 10^{14}$ CFU | 6 days preoperatively and 10 days postoperatively                          |

RCT: randomized controlled trial; ICU: intensive care unit; RCC: respiratory care center.
showed that heterogeneity testing significantly lower in probiotics group (odds ratios (OR) 0.31, 95% confidence interval (CI) 0.15–0.64). Heterogeneity testing showed that \( I^2 = 11\% \), indicating low heterogeneity (Figure 5).

3.3. Central Line Infection. For the results of the incidence of central line infection, our study enrolled 2 studies, including a total of 284 patients, central line infection (OR 0.61, 95% CI 0.15–2.45, \( I^2 = 65\% \)) reflected no significant difference in two groups. Heterogeneity testing showed that \( I^2 = 65\% \), indicating high heterogeneity (Figure 6).

3.4. Pneumonia. For the incidence of pneumonia, our study enrolled 4 studies, including a total of 508 patients, and the result showed that probiotics was significantly lower than the placebo (OR 0.36, 95% CI 0.18–0.71, \( I^2 = 0\% \)). Heterogeneity testing showed that \( I^2 = 0\% \), indicating low heterogeneity (Figure 7).

3.5. Urinary Tract Infection. For the result of the incidence of urinary tract infection, our study included 3 studies and a total of 448 patients, and the result reflected significant difference in groups (OR 0.26, 95% CI 0.11–0.60, \( I^2 = 26\% \)). Heterogeneity testing showed that \( I^2 = 26\% \), indicating low heterogeneity (Figure 8).

3.6. Septicemia. For the result of the incidence of septicemia, our study enrolled 4 studies, including a total of 509 patients, and the result showed that probiotics was significantly lower than the placebo (OR 0.28, 95% CI 0.17–0.47, \( I^2 = 10\% \)). Heterogeneity testing showed that \( I^2 = 10\% \), indicating low heterogeneity (Figure 9).

3.7. Postoperative Leakage. For the result of the incidence of postoperative leakage, our study enrolled 3 studies, including a total of 419 patients, and the result did not show that probiotics was significantly lower than the placebo (OR 0.45, 95% CI 0.06–3.27, \( I^2 = 68\% \)). Heterogeneity testing showed that \( I^2 = 68\% \), indicating high heterogeneity (Figure 10).

Potential publication bias of probiotics used for surgical site infection was performed and shown as funnel plot (Figure 11).

4. Discussion

Several RCTs showed that the use of probiotics in patients with abdominal surgery was a promising approach to the prevention of postoperative infectious complications and well tolerated by patients with minor side effects [14]. However, in abdominal surgery, some investigators reported that there was no evidence supporting any benefit of a preoperative use of probiotics in patients with critical illnesses and undergoing elective abdominal surgery with increased risk of mortality [15, 16], and that in some cases, there was even an increased risk of mortality.

In our meta-analyses, the results showed that probiotics could effectively decrease the rate of postoperative infections, such as pneumonia, surgical site infection, and urinary tract infection.
surgery markedly improved intestinal microbial populations and significantly decreased the incidence of further infectious complications. The mechanism of the action of probiotics may be related with either the earlier bowel movement preventing bacterial translocation from the gut or the modulation of the innate immune responses.

Gastrointestinal microbiota may be modulated by probiotics. Our study demonstrated that the use of probiotics improved the capacity of the gut ecosystem to survive from surgically induced injury, resulting in fewer postoperative infections. Not only the incidence of infections but also the quality of life is improved in these studies, which shortens the duration of postoperative hospital stay and the antibiotics administration period. Furthermore, probiotics are considered to generate antitumor agents, which have chemo-preventive effects against colorectal cancer [17]. In addition, probiotics can improve immune function [18].

It is shown that probiotics protect epithelial barrier function. The outcomes probably result from the balance of the enteral bacteria environment. The use of probiotics after surgery markedly improved intestinal microbial populations and significantly decreased the incidence of further infectious complications. The mechanism of the action of probiotics may be related with either the earlier bowel movement preventing bacterial translocation from the gut or the modulation of the innate immune responses. Gastrointestinal microbiota may be modulated by probiotics. Our study demonstrated that the use of probiotics improved the capacity of the gut ecosystem to survive from surgically induced injury, resulting in fewer postoperative infections.
**Table**

| Study or subgroup | Probiotics Events | Probiotics Total | Control Events | Control Total | Weight | Odds ratio M–H, Fixed, 95% CI | Odds ratio M–H, Fixed, 95% CI |
|-------------------|-------------------|-----------------|---------------|---------------|--------|-----------------------------|-----------------------------|
| Liu 2012          | 4                 | 75              | 12            | 75            | 49.5%  | 0.30 [0.09, 0.96]            |                             |
| Liu 2015          | 7                 | 66              | 6             | 68            | 50.5%  | 1.23 [0.39, 3.86]            |                             |
| **Total (95%CI)** | **141**           | **143**         |               |               | **100.0%** | **0.61 [0.15, 2.45]**     |                             |

**Figure 6:** Incidence of postoperative Central line infection.

**Table**

| Study or subgroup | Probiotics Events | Probiotics Total | Control Events | Control Total | Weight | Odds ratio M–H, Fixed, 95% CI | Odds ratio M–H, Fixed, 95% CI |
|-------------------|-------------------|-----------------|---------------|---------------|--------|-----------------------------|-----------------------------|
| Kotzampassi 2015  | 2                 | 84              | 9             | 80            | 30.4%  | 0.19 [0.04, 0.92]            |                             |
| Liu 2012          | 3                 | 75              | 10            | 75            | 32.4%  | 0.27 [0.07, 1.03]            |                             |
| Liu 2015          | 6                 | 66              | 8             | 68            | 24.2%  | 0.75 [0.25, 2.29]            |                             |
| Zhang 2011        | 1                 | 30              | 4             | 30            | 13.0%  | 0.22 [0.02, 2.14]            |                             |
| **Total (95%CI)** | **255**           | **253**         |               |               | **100.0%** | **0.36 [0.18, 0.71]**     |                             |

**Figure 7:** Incidence of postoperative pneumonia.

**Table**

| Study or subgroup | Probiotics Events | Probiotics Total | Control Events | Control Total | Weight | Odds ratio M–H, Fixed, 95% CI | Odds ratio M–H, Fixed, 95% CI |
|-------------------|-------------------|-----------------|---------------|---------------|--------|-----------------------------|-----------------------------|
| Kotzampassi 2015  | 4                 | 84              | 6             | 80            | 24.1%  | 0.62 [0.17, 2.27]            |                             |
| Liu 2012          | 2                 | 75              | 10            | 75            | 40.0%  | 0.18 [0.04, 0.84]            |                             |
| Liu 2015          | 1                 | 66              | 9             | 68            | 35.9%  | 0.10 [0.01, 0.82]            |                             |
| **Total (95%CI)** | **225**           | **223**         |               |               | **100.0%** | **0.26 [0.11, 0.60]**     |                             |

**Figure 8:** Incidence of postoperative urinary tract infection.

**Table**

| Study or subgroup | Probiotics Events | Probiotics Total | Control Events | Control Total | Weight | Odds ratio M–H, Fixed, 95% CI | Odds ratio M–H, Fixed, 95% CI |
|-------------------|-------------------|-----------------|---------------|---------------|--------|-----------------------------|-----------------------------|
| Kotzampassi 2018  | 1                 | 85              | 4             | 80            | 6.7%   | 0.23 [0.02, 2.07]            |                             |
| Liu 2012          | 41                | 75              | 55            | 75            | 40.9%  | 0.44 [0.22, 0.87]            |                             |
| Liu 2015          | 39                | 66              | 60            | 68            | 39.7%  | 0.19 [0.08, 0.47]            |                             |
| Zhang 2011        | 1                 | 30              | 8             | 30            | 12.7%  | 0.09 [0.01, 0.82]            |                             |
| **Total (95%CI)** | **256**           | **253**         |               |               | **100.0%** | **0.28 [0.17, 0.47]**     |                             |

**Figure 9:** Incidence of postoperative septicemia.
Data Availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon request.

Consent

All authors have agreed to the publication of this manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Chongxiang Chen designed the study. Chongxiang Chen, Qingyu Zhao designed the search strategy and performed the search. Chongxiang Chen, and Tianmeng Wen performed abstract screening, full text screening, data extraction, and risk of bias assessment. Chongxiang Chen and Qingyu Zhao drafted the manuscript. All authors revised the manuscript, as well as reading and approving the final manuscript.

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