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LITERATURE REVIEW

Probiotics administration as a prevention for postoperative infectious complications in colorectal cancer patients: A literature review

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Abstract

Background Colorectal cancer is the third leading cause of death from cancer in adults in the United States, with increasing prevalence in other countries. Radical resection is the gold standard of treatment in most cases of colorectal cancer, with a high rate of postoperative complications. Perioperative probiotics can improve the immune response and the postoperative intestinal microbiota environment. Although several studies have shown the benefits of probiotics in preventing postoperative complications of infection, the administration of perioperative probiotics in colorectal cancer patients is still controversial.

Objective. The purpose of this critical appraisal is to know the effectiveness of administering probiotics to prevent infectious complications in colorectal cancer patients.

Methods. Literature research using Pubmed, Cochrane, and EBSCOhost was carried out and 2 articles were obtained in the form of meta-analysis using STATA v11 and Revman v5.2 that was critically examined using the FAITH method. A comprehensive search for all studies was done to find all relevant studies using both MeSH terms and text words. The article should describe the assessment of quality and criteria used in method section, also provide information on the quality of individual studies in result section to minimize bias. The result section should state whether heterogeneity exists and mention possible reasons.

Results. Based on 2 meta-analyses that have been critically examined, which each consisting of 13 and 7 studies, giving probiotics can reduce the overall infection rate after colorectal cancer surgery. One meta-analysis showed an odds ratio (OR) of 0.51 (95% CI: 0.38 – 0.68, p = 0.00). Probiotics, such as *Lactobacillus acidophilus* and *Bifidobacterium longum* can also reduce the incidence of surgical site infections (OR = 0.59, 95% CI 0.39 – 0.88, p = 0.01) and pneumonia (OR = 0.56, 95% CI 0.32 – 0.98, p = 0.04). Probiotics did not provide statistically significant benefits in preventing urinary tract infections, leakage of anastomosis, and duration of postoperative pyrexia compared to the control group. Seven articles analyzed in the second meta-analysis showed probiotics to be useful in preventing postoperative infections with OR 0.5388 (95% CI, 0.4058-0.7154, P <0.0001).

Conclusions. Combination of more than one strain of probiotics such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections in patients undergoing colorectal cancer surgery.

Keywords colorectal cancer, probiotics, lactobacillus, postoperative infection

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Introduction

Cancer is one of the major health problems throughout the world and is the second leading cause of death in the United States. Colorectal cancer is the third leading cause of death from cancer in adults in the United States.[1] In China, colorectal cancer ranks fifth for cancer deaths.[2] In Indonesia, based on the 2018 Basic Health Research, the prevalence of cancer increased compared to 2013 from 14 to 18 per 10,000 lives with the highest prevalence at the age of 55-64 years.[3]

Radical resection is the gold standard of treatment in most cases of colorectal cancer, although patients with colorectal cancer who undergo surgery often experience complications of postoperative infections. Postoperative infections can cause negative impact on long-term prognosis because they increase the morbidity and mortality of patients. Postoperative morbidity in colorectal cancer reaches 15-23.2%.[4-6] Postoperative infections in colorectal cancer patients occur due to intestinal dysbiosis caused by perioperative stress, inflammatory responses and intestinal mucosal atrophy due to perioperative fasting and ischemia of the intestinal tract which induces translocation of intestinal microbiota into the intestinal mesenteric lymph glands to other organs.[7-9]

Prevention of postoperative infections including restoration of normal intestinal microbiota and prevention of bacterial translocation must be undertaken to minimize postoperative complications.[10] Probiotics are beneficial microorganisms in regulating homeostasis of microbiota, immunity and maintaining intestinal mucosal barrier. Administration of oral probiotics, such as *Lactobacillus* and *Bifidobacterium* is reported to be able to reach the colon and rectum in an active form to form colonies in the intestinal mucosa.[11,12] The use of preoperative combination of several probiotics, such as *Lactobacillus* and *Bifidobacterium* can enhance the immune response and improve the postoperative intestinal microbiota environment. Although several studies have shown the benefits of probiotics in preventing postoperative complications of infection, the administration of perioperative probiotics in colorectal cancer patients is still controversial. Synbiotics are essentially a synergistic combination of probiotics and prebiotics. Research by Anderson, et al.[13] concluded that the administration of synbiotics against the protection of the intestinal mucosal barrier did not produce meaningful results. Another research conducted by Consoli, et al.[14] showed that administration of *Saccharomyces boulardii* can reduce levels of IL-23 and IL-10 and inhibit T-cell activation, strengthen the intestinal barrier, and inhibit proinflammatory cytokine production. Research done by Gianotti, et al.[15] showed that administration of *Lactobacillus johnsonii* (La) and *Bifidobacterium longum* (BB536) in colorectal cancer patients before surgery was able to reduce the number of intestinal pathogenic bacteria and modulate local immune responses.

Research on the benefits of probiotics includes specific strains and doses that are adequate for cancer patients has not yet achieved conclusive results. Based on the literature, combination of more than one probiotic such as *Lactobacillus* and *Bifidobacterium* can improve the intestinal microbiota environment, the immune system and prevent complications, especially postoperative infections. For this reason, a literature study and critical study are needed to assess the benefits of probiotics in colorectal cancer patients in preventing complications of postoperative infections.

Clinical scenario

A male patient aged 51 years came to the hospital with complaints of lower left abdominal pain arising and subsiding in the last 9 months. The patient also complained of difficulty defecating, small round hard, blackish-colored feces. CT scan results showed the patient had a tumor in the large intestine. The patient lost 15 kilograms in 1 year. Patient claimed to often consume grilled foods from a young age and rarely consume vegetables and fruits. The patient's blood pressure 120/80 mmHg, the pulse rate 84 times/minute, the respiratory rate 20 times/minute, the temperature 36^0C.

The conjunctiva anemic, the abdomen flat with normal bowel sounds. The patient's body weight 59 kg, his body height 169cm, and body mass index 20.6 kg/m^2. Laboratory tests showed that Hb was 7.4 g/dL, hematocrit 23%, leukocytes 2,900/μL, platelets 645,000/μL. The results of a large bowel

biopsy showed a sigmoid colon adenocarcinoma. From the surgical department, the patient is planned to have a colon resection and colostomy. Therefore, a critical study will be conducted on the effectivity of administering probiotics to reduce complications of postoperative infections.

Clinical question

P: Adult colorectal cancer patient
I: Patients receiving perioperative probiotics supplementation
C: Patients who have not received perioperative probiotic supplementation
O: Postoperative infectious complication

Methods

The literature search was done on 3 databases (PubMed, Cochrane, and EBSCOhost) using advanced search on December 22, 2019.
Critical review is carried out using the FAITH method (Find, Appraise, Include, Total Up, Heterogeneity).[16]

Eligibility criteria

Article selection was based on the inclusion and exclusion criteria, which addressed the clinical question. The inclusion criteria were: 1) colorectal cancer patients over 18 years old; 2) patients got perioperative probiotics; 3) the study design used was a Randomized Controlled Trial, Cohort, or Case-control. The exclusion criteria were: 1) research in the form of reviews, comments, conference abstracts, letters, sections in a book or non-clinical study; 2) research that did not include the dose of probiotics used; 3) provision of probiotics used in combination with prebiotics or as synbiotics; 4) research that was not done in humans; 5) research that did not mention the odds ratio (OR) or the difference in the standard mean difference (SMD); 6) research that did not include probiotic strain.

Critical appraisal of Ouyang et al. [17]

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) as a guide. The method section describes the search strategy by taking relevant studies from the Pubmed, Embase, Cochrane, and CNKI databases, but does not include data collection from relevant and unpublished studies. One of the weaknesses of this meta-analysis is that it only includes English and Chinese studies so that it is possible to lose important data in other language studies. Thirteen studies have been assessed as having complete, unbiased, and not selective data in their reporting. Twelve studies were also carried out by blinding. The study included in this meta-analysis has a low risk of bias involving 12 articles which are RCT design studies and 1 study which is a controlled clinical trial. The types of probiotics involved in this study varied greatly in terms of species, dosage, and duration of administration. The type of probiotics used are *B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii* either given alone or in combination with a dose range of $10^6 – 10^{11}$ CFU/day. Probiotics were given 2-4 times per day with a range of administration varies from 8 days before to 14 days postoperatively. The results of the meta-analysis study are presented in the form of a summary table and Forest plot. Heterogeneity tests have been carried out and no heterogeneity was observed among studies on the effects of preventing probiotics on postoperative infection rates ($p = 0.60$, $I^2 < 0.01$). Forest plots evaluate the preventive effects of probiotics on overall postoperative infections. Data from 13 studies were collected to calculate pooled OR. The analysis model showed a pooled OR for overall infection was 0.51 with 95% CI 0.38 to 0.68. This meta-analysis concludes that the use of probiotics can prevent infections in patients undergoing CRC surgery and improve surgical recovery.

Critical appraisal of Calaca et al.[18]

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a guide. The research was taken from 5 databases namely Pubmed, Science Direct, Scielo, Scopus, and LILACS systematically from 2005 to 2016. The search was not limited to English-language studies, but also involved studies published in Spanish and Portuguese. The studies included in this meta-analysis are studies published

in leading journals, in the form of seven RCTs published from 2010 to 2016 and sample sizes ranging from 20 to 161 (average 90.1). The results of the meta-analysis study are presented in the form of a summary table and forest plot. Seven articles were analyzed to assess the effect of probiotics on infectious complications with $I^2 = 14.3\%$ (DF = 25, p = 0.2338) in the infection group. The type of probiotics used are *B. longum, B. bifidum, L. johnsonii, L. acidophilus, L. plantarum, E. faecalis, C. butyricum* either given alone or in combination with a dose range of $10^7 – 10^{11}$ CFU/day. Probiotics were given 2-4 times per day with a range of administration varies from 7 days before to 12 days postoperatively. Overall, the assessment of heterogeneity in this systematic review shows low heterogeneity. Two studies showed positive effect on probiotics for infectious complications with OR = 0.5388 (95% CI, 0.4058 – 0.7154, p <0.0001). This systematic reviews and meta-analysis show that the combination of more than one microorganism such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections.

Discussion

Complications of postoperative infections, including surgical site infections, urinary tract infections, sepsis and pneumonia resulted in increased length of stay and morbidity in patients. The two meta-analyses obtained from literature research and critical study are systematic reviews that are well-prepared and meet critical reviews using the FAITH method. Both of meta-analyses, shown that combination of probiotics, such as *Lactobacillus* and *Bifidobacterium* play an important role in preventing infections after colorectal cancer surgery including overall infections, surgical site infections, and pneumonia.

From the two systematic reviews conducted, it was found that four studies were similarly involved in both of meta-analyses. The probiotics used in these studies were *E. faecalis, C. butyricum, B. mesentericus, B. bifidum,* and *L. plantarum*.[17] The meta-analysis conducted by Calaca, et al.[17] involved 7 studies and was published in 2017. One of the studies in the meta-analysis conducted by Calaca et al[17] was RCT research conducted by Liu et al.[19] Research by Liu, et al.[19] shows that administration of perioperative *Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacterium longum* can reduce the inflammatory response and decrease the length of stay in patients following colorectal cancer surgery. Microbial dysbiosis due to stress and inflammatory responses after colorectal cancer surgery improves with the administration of *Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacterium longum*.

Analysis using the Forest plot found that the benefits of probiotics in preventing surgical site infections were only found in one out of 4 studies, so the results of the analysis were not statistically significant (OR 0.6538, 95% CI 0.3951 – 1.0817).[8] The results of the analysis of the effectivity of the administration of probiotics to the detection of bacteria in the blood taken from 4 articles gave significant results with OR 0.4069 (95% CI, 0.2662 – 0.6222, P <0.0001). Seven articles analyzed to assess the benefits of probiotics in preventing postoperative infections gave significant results with OR 0.5388 (95% CI, 0.4058-0.7154, P <0.0001).

A meta-analysis carried out by Ouyang, et al.[17] involving 13 studies showed that the preventive effect of probiotics (*B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii)* on anastomotic leakage and urinary tract infections did not show significant results, possibly because collection of more updated researches may lead to the main differences this meta-analysis compared to previous meta-analysis. An evaluation using the Forrest plot showed that probiotics (*B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii)* had an overall preventive effect on postoperative infections (OR 0.51, 95% CI 0.38 – 0.68). Preventive effects of probiotics on surgical site infections in 9 studies showed significant results with OR 0.59 (95% CI 0.39 – 0.88) as well as against pneumonia prevention (OR 0.52 with 95% CI 0.32 – 0.98).[17]

There are several weaknesses to be noted in this meta-analysis. First, this study only took data from published research without taking data from other unpublished studies and therefore could result in loss of data in other relevant studies. Secondly, this study only analyze the individual effects of

probiotics without involving research with prebiotics or as synbiotics that might affect the results of the analysis even though the role of prebiotics or synbiotics in the prevention of postoperative infections is also still not conclusive. Third, some important data such as serum antibody concentration and inflammatory factors are only available in a number of studies so no in-depth analysis is performed. Fourth, the probiotics strain and doses in several studies collected were not consistent with each other. Several studies that combined probiotics with other treatment should be excluded so that they might not induce confounding factor in this meta-analysis.[17]

Conclusion

Combination of more than one strain of probiotics such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections in patients undergoing colorectal cancer surgery which provides benefits in post-surgical recovery and decreases the length of treatment. The dose that can be given ranges from $10^6 – 10^{11}$ CFU/day with the frequency of administration 2-4 times per day and range of administration varies from 8 days before to 14 days postoperatively. The administration of probiotics must still be adjusted to the patient's condition and the therapy given. Further research is needed to determine the best type of probiotic strain along with the optimal dosage and duration of administration to prevent complications of postoperative infections in colorectal cancer patients.

Table 1. Terminology

Database	Terminology	Hits
PubMed	Search ((prevent[Title/Abstract] OR treat[Title/Abstract]) AND (probiotics[Title/Abstract] OR probiotics[MeSH Terms] OR lactobacillus[MeSH Terms] OR lactobacillus[Title/Abstract])) AND ((colon cancer[Title/Abstract] OR rectal cancer[Title/Abstract]) OR colorectal cancer[Title/Abstract])	71
Cochrane	ID Search #1 (prevent):ti,ab,kw OR (treat):ti,ab,kw (Word variations have been searched) #2 (lactobacillus):ti,ab,kw OR (probiotics):ti,ab,kw (Word variations have been searched) #3 (colon cancer):ti,ab,kw OR (rectal cancer):ti,ab,kw OR (colorectal cancer):ti,ab,kw (Word variations have been searched) #4 #1 AND #2 AND #3	71
EBSCOhost	Search Alert: ("probiotics” OR “lactobacillus”) AND ("treat" OR "prevent") AND ("colon cancer" OR "rectal cancer" OR “colorectal cancer”) Research Article	50

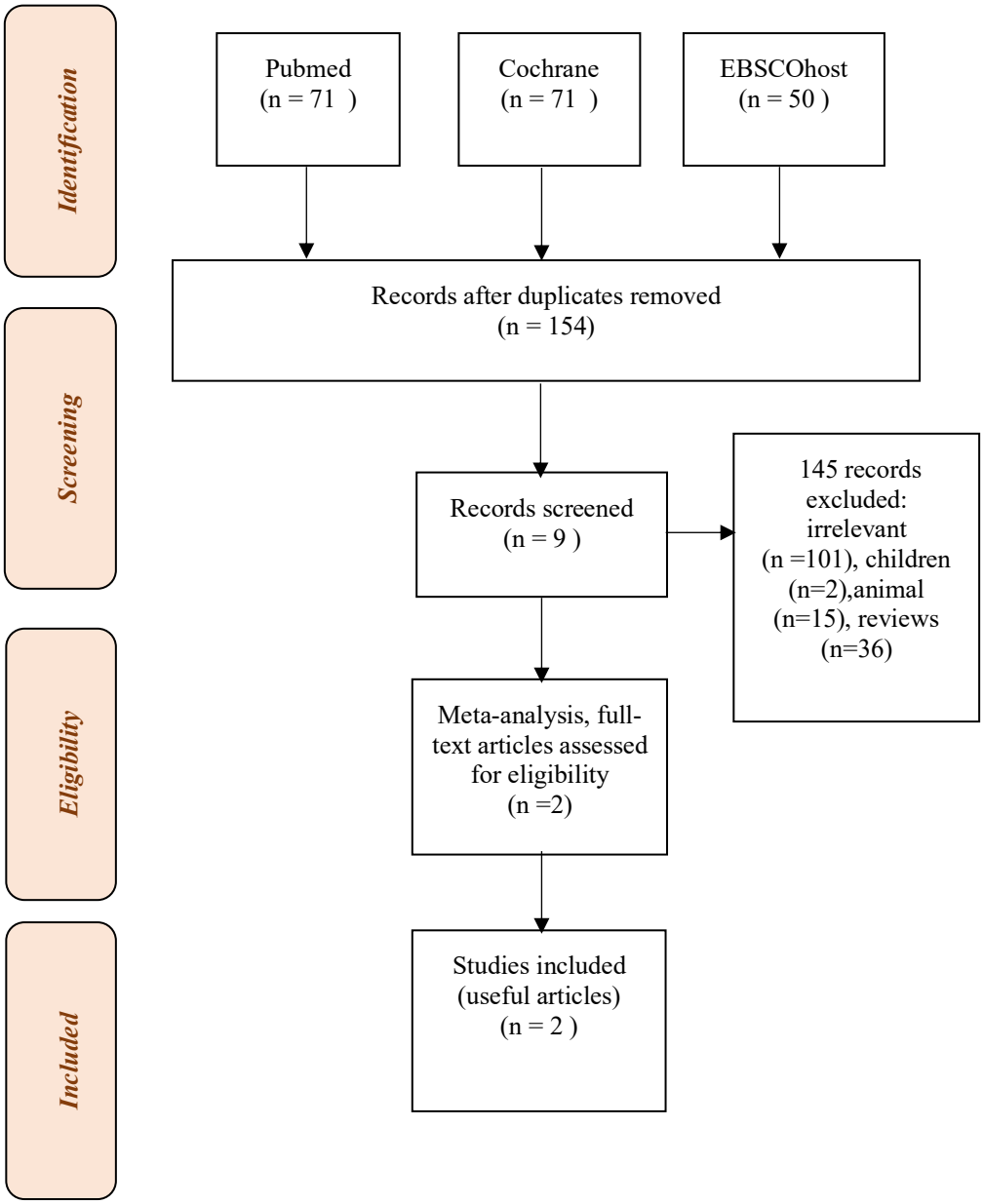

Figure 1. PRISMA Flowchart

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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