The Effect of Perioperative Probiotics or Synbiotics on Postoperative Ileus in Patients Undergoing Abdominal Surgery: An Evidence-based Case Report

Helena Fabiani, Wiji Lestari**

*Department of Nutrition, Faculty of Medicine, Universitas Indonesia/
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:
Wiji Lestari. Department of Nutrition, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital. Jl. Salemba Raya No. 6 Jakarta, Indonesia. Phone +6221 31930208. E-mail: wijilestari.doc@gmail.com.

ABSTRACT

Background: *Postoperative ileus is a common postoperative complication following abdominal surgery. Perioperative probiotics or synbiotics may lower the risk of postoperative ileus. This study aims to evaluate the effects of perioperative probiotics or synbiotics on postoperative ileus in patients undergoing abdominal surgery.*

Method: *A literature search was conducted on four databases, PubMed, Cochrane, ProQuest, and Scopus, by using MeSH terms. The article selection process was undertaken by screening the titles or abstracts, reviewing the full texts, and determining their compliance with the inclusion and exclusion criteria. Two systematic review/ meta-analysis of randomized controlled trial were critically appraised for validity, importance, and applicability.*

Results: *Perioperative probiotics or synbiotics may contribute to recovery of gastrointestinal function, including reducing postoperative ileus in gastrointestinal cancer surgery. Supplementation of probiotics or synbiotics reduced overall postoperative complications in patients undergoing colorectal cancer surgery and did not cause any side effects. However, the administration of probiotics or synbiotics was not associated with postoperative ileus incidence.*

Conclusion: *Perioperative probiotics or synbiotics supplementation may be considered in promoting postoperative gastrointestinal function in abdominal surgery. However, their effect on reducing the incidence of postoperative ileus is still inconsistent.*

Keywords: *abdominal surgery, postoperative ileus, probiotics, synbiotics*

ABSTRAK

Latar belakang: *Ileus pascaoperasi merupakan komplikasi pascaoperasi yang umum terjadi pada pembedahan saluran cerna. Probiotik atau sinbiotik perioperatif dapat menurunkan risiko ileus pascaoperasi. Penelitian ini bertujuan untuk mengetahui efek probiotik atau sinbiotik perioperatif terhadap ileus pascaoperasi pada pasien yang menjalani pembedahan saluran cerna*

Metode: *Penelusuran literatur dilakukan pada empat pangkalan data, yaitu PubMed, Cochrane, ProQuest, dan Scopus menggunakan kata kunci MeSH terms. Seleksi artikel dilakukan dengan penapisan judul atau abstrak, telaah teks lengkap, dan menentukan terpenuhinya kriteria inklusi dan eksklusi. Dilakukan telaah kritis pada dua studi kajian literatur sistemik/meta-analisis dari uji acak terkontrol berdasarkan telaah validity, importance, dan applicability.*

Hasil: *Probiotik atau sinbiotik perioperatif dapat mendukung pemulihan dari fungsi saluran cerna, termasuk menurunkan komplikasi ileus pascaoperasi pada pembedahan kanker gastrointestinal. Pemberian probiotik atau sinbiotik mengurangi komplikasi pascaoperasi secara keseluruhan pada pasien yang menjalani pembedahan kanker kolorektal dan tidak menimbulkan efek samping. Namun, suplementasi probiotik atau sinbiotik tidak berhubungan dengan kejadian ileus pascaoperasi.*

Kesimpulan: *Pemberian probiotik atau sinbiotik perioperatif dapat dipertimbangkan untuk mendukung pemulihan fungsi gastrointestinal pada pembedahan saluran cerna, walaupun efeknya untuk menurunkan kejadian ileus pascaoperasi masih belum konsisten.*

Kata kunci: *ileus pascaoperasi, pembedahan saluran cerna, probiotik, sinbiotik,*

INTRODUCTION

Globally, there are 310 million major surgeries that performed each year. It is estimated that around 15% of the patients experience postoperative complications.[1] In the case of abdominal surgery, ileus is one of the most frequent complications, with an incidence of up to 30%.[2,3] In response to surgical procedures, postoperative ileus is defined with decreased or absence of gastrointestinal motility. In physiological condition, gastrointestinal function will recover as it was <72 hours after the surgery, but it is considered pathological if it occurs longer than 72 hours and can lead to complications. These complications include increasing the risk of abdominal discomfort, intestinal obstruction, also extending the length of stay and recovery time.[4,5]

Abdominal surgery can disrupt the gut microbiota due to surgical trauma. According to various studies, synbiotics and probiotics can lower the risk of postoperative gastrointestinal infections and increase gastrointestinal motility, reducing the incidence of postoperative ileus.[6,7] Probiotics are live microorganisms that can benefit the host when consumed in adequate amounts. Synbiotics are a combination of probiotics and prebiotics, precisely live microorganisms and substrates that are selectively used by host microorganisms that can provide health benefits for the host. Probiotics and synbiotics are widely used as adjuvant therapy for various gastrointestinal disorders.[8,9]

The effect of synbiotics or probiotics is still under debate due to inconclusive result. Therefore, this study is conducted to evaluate the effect of synbiotics or probiotics on the incidence of postoperative ileus in patients undergoing abdominal surgery.

CASE ILLUSTRATION

A 53-year-old male with chief complaint of hematochezia dan persistent abdominal pain for 3 months prior to admission. A mild right lower quadrant abdominal pain was present for the past 3 months, which intermittently worsen at night. He had frequent episodes of constipation, with frequency of defecation once every 5-7 days. He also complained of nausea, but not followed by vomiting. His appetite was reduced due to nausea, he could only eat half a portion of his usual intake. No other specific symptoms were present. Additionally, he experienced an unintentional weight loss over 10 kg weight. With regard to his past medical story, he had uncontrolled hypertension since the last 3 years. He also was a heavy smoker. He habitually consumed fried foods, red meat, and canned food and rarely consumed vegetables and fruits.

Blood pressure was 140/90 mmHg. Another vital signs were normal. Tenderness in right lower quadrant abdomen and the epigastrium were observed during the physical examination. Digital rectal examination showed hematochezia. He also met the criteria of malnutrition, such as reduced food intake, weight loss, low body mass index, and muscle wasting in temporal area, upper and lower extremities. His nutritional status was severe malnutrition, with a body mass index of 15.2 kg/m2. He also had anemia (hemoglobin level 10.5 g/dL). Inflammatory markers such as white blood cell count and C-reactive protein level were increased. Activated partial thromboplastin time was within the normal range. Abdominal imaging result indicated a small bowel obstruction. Colonoscopy and tissue biopsy indicated chronic colitis with dysplasia in ascending colon. He was diagnosed with ulcerative colitis with colon adenocarcinoma without any metastasis. Then he was planned for elective colon resection surgery. Medical nutrition therapy was given during hospitalization. Supplementation of probiotics or synbiotics in perioperative period was considered to reduce postoperative ileus complications.

METHOD

The clinical question was determined based on this research's population, intervention, comparison, and outcome (PICO). The clinical question for this research: Can perioperative probiotics or synbiotics supplementation reduce postoperative ileus risk in patients undergoing abdominal surgery?

P : Adult patients who undergoing abdominal surgery
I : Perioperative probiotics or synbiotics supplementation
C : Placebo
O : Postoperative ileus

The selected articles met the eligibility criteria using a systematic review, meta-analysis, and randomized controlled trials studies. The inclusion criteria include 1) patients undergoing abdominal surgery; 2) Adult patients (age ≥18 years); 3) Administration of probiotics or synbiotics in the perioperative period; 4) the results of the study are postoperative ileus symptoms; 5) systematic review/meta-analysis, randomized controlled trials (RCT); 6) publications within the last five years. Articles that are not written in English or do not have a full text will be excluded.

The literature search was conducted on 5th April 2023 using the Booleans *OR* and *AND* on four databases: PubMed, Cochrane, ProQuest, and Scopus. The strategy for reviewing the literature is shown in Table 1. The screening process was focused on the titles/abstracts using the MeSH terms adjusted to this study design and clinical question with search keywords including "probiotics," "synbiotics," "postoperative ileus," "gastrointestinal surgery," and "abdominal surgery." Therefore, another review with Mendeley was done afterward to exclude duplicate articles. Two studies were critically reviewed using the Oxford Center of Evidence-based Medicine (CEBM) critical appraisal tools for systematic review and meta-analysis studies by two authors. The review assesses the study's validity, importance, and applicability aspects.

RESULTS

Based on the literature search strategy, two articles met the eligibility criteria based on clinical questions. Both articles are systematic reviews/meta-analyses of RCT with level of evidence 1a (Table 2-4). The research subjects are postoperative patients receiving perioperative probiotics or synbiotics as interventions. Subjects underwent surgery for gastrointestinal cancer in the study of Tang et al.[10] Meanwhile the subjects underwent surgery for colorectal cancer in An S et al.[11] Study characteristics are shown in Table 3. It shows that Tang et al. does not meet one of the points of the validity criteria, precisely the similarity of study results, while An. S et al. does not meet two points of the validity criteria.

Table 1. Literature search

Database	Keywords in search	Hits
PubMed	("digestive system surgical procedures"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "digestive system surgical procedures"[All Fields] OR ("gastrointestinal"[All Fields] AND "surgery"[All Fields]) OR "gastrointestinal surgery"[All Fields]) AND (("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postop"[All Fields] OR "postoperative"[All Fields] OR "postoperatively"[All Fields] OR "postoperatives"[All Fields]) AND ("ileus"[MeSH Terms] OR "ileus"[All Fields])) AND ("probiotic s"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields] OR ("synbiotics"[MeSH Terms] OR "synbiotics"[All Fields] OR "synbiotic"[All Fields]))	11
Cochrane	#1 MeSH descriptor: [Gastrointestinal surgery] explode all trees #2 ("Gastrointestinal surgery"): ti,ab,kw #3 ("Digestive system"): ti,ab,kw #4 MeSH descriptor: [Probiotics] explode all trees #5 ("probiotics"): ti,ab,kw #6 ("synbiotics"): ti,ab,kw #7 MeSH descriptor: [Ileus] explode all trees #8 ("Postoperative ileus"): ti,ab,kw #9 #2 OR #3 #10 #5 OR #6 #11 #8 AND #9 AND #10	123
ProQuest	(Gastrointestinal Surgery) AND (Probiotics OR Synbiotics) AND (Postoperative ileus)	122
Scopus	TITLE-ABS-KEY (gastrointestinal AND surgery) AND (probiotics OR synbiotics) AND (postoperative AND ileus)	44

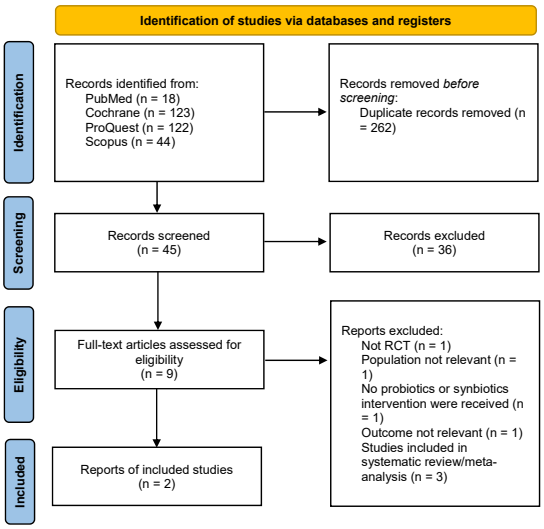

Figure 1. Prism flow chart in search strategy

Table 2. Validity criteria

Study	Validity								
	PICO	Review strategy	Study design	Study quality assessment	High quality	Results in tables/ forest plots	Similarity of study results	Result	Level of evidence
Tang G et al.[10]	+	+	+	+	+	+	-	A	1a
An S et al.[11]	+	+	+	+	+	-	-	B	1a

A: Significant results to reduce the incidence of postoperative ileus (RR, 0,47; 95% CI, 0,24, 0,91, P=0,02; I^2=9%, p=0.35).[10]

B: No relevancy in reducing the incidence of postoperative ileus (RR, 0,63; 95% CI, 0,39, 1.02).[11]

Table 3. Importance criteria

Study	Outcome	Notable research results
Tang G et al. (2022)	Time of first flatus, first defecation, days before first getting solid and liquid food, postoperative hospital stay period, the incidence of gastrointestinal distention, and incidence of postoperative ileus	- Shorter flatus time (MD, -0,53 days; 95% CI, -0,75, -0,30; p<0,00001; I^2=73%, p=0,0005) - Reducing time to first defecation (MD, -0,78 days; 95% CI, -1,27, -0,28; p = 0,002; I^2=86%, p<0,00001) - Shorten the waiting day for solid food (MD, -0,25 days; 95% CI, -0,39, -0,12; p=0,0002; I^2=0%, p=0,94) - Shorten the waiting day for liquid food (MD, -0,29 days; 95% CI, -0,47, -0,11; p=0,001; I^2=0%, p=0,83) - Reducing the postoperative stay in the hospital (MD, -1,43 days; 95% CI, -2,29, -0,58; p=0,001; I^2=67%) - Reduced incidence of gastrointestinal distension (RR, 0,62; 95% CI, 0,47, 0,81; p=0.0004; I^2=0%, p<0,97) - Reduced incidence of postoperative ileus (RR, 0,47; 95%CI, 0.24, 0.91, P = 0,02; I^2 = 9%, p=0,35)
An S et al. (2022)	Perioperative mortality, infection postoperative complications, side effects of probiotics, overall postoperative complications, length of stay, and postoperative quality of life	- Reducing postoperative infectious complications (RR, 0.45; 95% CI: 0,27, 0.76; I^2=38%;) - Reduction in overall postoperative complications (RR, 0.,47;95% CI: 0,30 to 0,74; I^2=8%) - No indication of side effects associated with the administration of probiotics (RR, 0,73, 95% CI, 0.45, 1,19; I^2=0%) - Did not reduce the length of postoperative care in the hospital (RR, 0,73, 95% CI, 0.45, 1.,9; I^2=0%) - Not associated with postoperative ileus (RR, 0,63; 95% CI, 0,39, 1,02)

MD, mean difference; RR, relative risk; CI, confidence interval.

Table 4. Applicability

Study	Population similarity	Possible interventions	Greater benefit than its risk
Tang G et al.[10]	+	+	+
An S et al.[11]	+	+	+

Table 5. Summary of studies

Articles	Study design	Intervention	Population	Outcome
Tang G et al. (2022)	A meta-analysis that included 21 RCTs with a total of 1776 subjects	Administration of probiotics alone in 12 studies and synbiotics in 9 other studies	Subjects with gastrointestinal cancer and undergoing surgery for colorectal, gastric, liver, gallbladder, esophageal, or periampullary cancer	Effects of probiotics or synbiotics on the return of postoperative gastrointestinal function in the form of shorter flatus time, first defecation, length of days until first getting solid and liquid food, reduced incidence of gastrointestinal distention, and postoperative ileus
An S et al. (2022)	A meta-analysis that included 20 RCTs with a total of 1763 subjects	Administration of probiotics or synbiotics in the perioperative period. Fourteen studies received probiotics, and six studies received synbiotics.	Patients were undergoing elective colorectal cancer surgery.	The impact of probiotics or synbiotics on perioperative mortality decreased postoperative infectious complications, decreased postoperative complications did not show side effects associated with giving probiotics, and did not reduce the length of stay in the hospital and postoperative quality of life.

RCT: *Randomized Controlled Trial*

DISCUSSION

Tang et al. conducted a meta-analysis study of 21 RCTs with 1776 subjects. Inclusion of the subjects in the research were patients with gastrointestinal cancer who underwent colorectal, gastric, liver, gallbladder, esophageal, or periampullary cancer surgery. The primary outcomes of this study were the time of first flatus, time of first defecation, number of days until first solid food, number of days until first liquid food, and length of stay after surgery. This study indicates that probiotics or synbiotics which given perioperatively can reduce the time of first flatus (MD, -0.53 days; 95% CI, -0.75, -0.30; p<0.00001) with high heterogeneity (I^2=73%, p=0.0005), time of first defecation (MD, -0.78 days; 95% CI, -1.27, -0.28; p=0.002) with high heterogeneity (I^2=86%, p<0.00001). the number of days until the first liquid food (MD, -0.29 days), the number of days to first solid food (MD, -0.25 days; 95% CI, -0.39, -0.12; p=0.0002) without low heterogeneity (I^2 =0%, p=0.94), and the length of postoperative stay (MD, -1.43 days; 95% CI, -2.29, -0.58; p=0.001; I^2=67%). In addition, probiotics and synbiotics supplementation also reduced abdominal distension incidence (RR, 0.62; 95% CI, 0.47, 0.81; p=0.0004) and postoperative ileus (RR, 0.47; 95% CI, 0.24, 0.91, p=0.02; I^2=9%, p=0.35). This result had low heterogeneity (I^2=0%, p< 0.97).[10]

An et al. used 20 RCTs with 1763 subjects that underwent colorectal cancer surgery. Both interventions in the studies are given orally with various types and dosages. The meta-analysis found that the probiotics could reduce postoperative complications subsequent to surgery related to colorectal cancer (RR, 0,47; 95% CI, 0,30, 0,74; I^2=8%). However, using probiotics in patients with gastrointestinal surgery was not associated with postoperative ileus (RR, 0,63; 95% CI, 0,39, 1,02). There was a slight difference in the administration of probiotics compared to placebo for the length of stay (MD, -1.06; 95% CI, -1.64, -0.47) with low heterogeneity (I^2=8%, p<0.97).[11]

A study conducted by Bajramagic et al. was in line with Tang et al.'s results. It is found in the study that postoperative ileus as a complication was significantly found (p<0,05) than other groups that did not get probiotics, where there was no sign of gastrointestinal peristalsis for more than six days postoperatively. After abdominal surgery, intestinal motility was impaired, so there was an increase in the amount of air and fluid in the intestine. This causes distension of the intestinal wall and impairs the intestinal circulation itself, exacerbating the loosening of the anastomosis. In addition, the impaired absorptive function of the intestine and the delay in the nutrients' delivery caused dysbiosis, exacerbating mechanical complications such as anastomosis leakage.[12] Consequently, it is expected that surgical procedures on the digestive system may potentially disturb the balance of the intestinal barrier, leading to both short-term and long-term consequences. Hence, the administration of probiotics or synbiotics could lower postoperative morbidity.[7]

The cause of postoperative ileus has not been fully understood. It is known to involve the interaction of various factors. The sympathetic nervous overstimulation induced by surgical treatment is the most critical factor. The enteric nervous system released nitric oxide that prolong postoperative ileus duration. Furthermore, the inflammatory cascade was stimulated by surgical trauma, releasing inflammatory mediators, such as interleukin-6, interleukin-1, monocyte chemoattractant protein-1, and cell adhesion molecule-1, which in turn interferes with the gastrointestinal muscles and inhibits the recovery of digestive tract function.

The study on the gut-brain axis found that gut microbiota, the immune system, the enteric nervous system, and the nervous system are interconnected and simultaneously control gut motility. Perioperative probiotics or synbiotics supplementation could modulate local and systemic immune system, suppressing the inflammatory response by reducing the release of inflammatory mediators. The gut microbiota is known to be able to interact with dendritic cells in the digestive tract so that probiotics or synbiotics can support the recovery of digestive tract function through the regulation of gut microbiota. However, most of the evidence comes from animal studies, and the effects on humans are still being determined because the research is still limited.[7,13] Meanwhile, the RCT study conducted by Rodriguez-Padilla et al. did not find a significant difference in the use of preoperative probiotics compared to placebo on the incidence of paralytic ileus (p=0.192).[14]

There is still no recommended strains and dosage of perioperative probiotics or synbiotics for abdominal surgery patients. The probiotics capsule consists of *Lactobacillus acidophilus* 1,75x10^9 cfu (colony forming unit), *Lactobacillus plantarum* 0,5x10^9 cfu, *Bifidobacterium lactis* 1,75x10^9 cfu and *Saccharomyces boulardii* 1,5x10^9 cfu was administered starting one day prior to surgery and 15 days postoperatively to patients undergoing colorectal surgery. The time until first bowel movement and the time until first defecation were shorter for intervention group

compared to placebo.[15] An enteral nutrition containing *Lactobacillus* and *Bifidobacterium*, combined with 25 g soluble dietary fiber was given 7 days consecutively after surgery in gastrointestinal surgery patients. The synbiotics group had a significantly shorter time of first flatus compared to placebo ($p<0,05$).[16] In colorectal surgery patients, Yang et al. showed significantly improvement of the time to first flatus ($p=0.0274$) and time to first defecation ($p = 0.0268$) compared to placebo after 12 days perioperatively administration of probiotics containing *Bifidobacterium longum* ≥1.0x10 7 cfu/g, *Lactobacillus acidophilus* ≥1.0x10 7 cfu/g, *Enterococcus faecalis* ≥1.0x10 7 cfu/g.[17]

The study conducted by Tang et al. has several strengths, including that only RCTs were included in this meta-analysis, and the strength of the results of this study was confirmed through sensitivity analysis. There are limitations to this study like some of the included studies had a small sample size, some of the outcomes were synthesized quantitatively based on the small number of studies, and there was significant heterogeneity in these studies, which may be related to significant differences in the type of abdominal surgery, probiotic strains or synbiotics, and the dosage of probiotics or synbiotics used.[10] Meanwhile, the study of An et al. has other limitations, like the incidence of postoperative ileus was not the primary outcome in the study, there was heterogeneity in the type and duration of probiotics administration in each RCT, the assessment of various infectious complications, the possibility of publication bias, and there were no large-scale studies involved. The strength of An et al.'s study has strengths, including subject screening, interventions, and more in-depth comparisons and data analysis using the Cochrane methodology and the application of GRADE in CoE evaluation.[11]

In the case illustration, a 53-year-old man with ulcerative colitis and colon adenocarcinoma was electively planned for surgery. The identity and diagnosis of the patient were similar to the identity and diagnosis of the study subjects discussed. Administering probiotics or synbiotics in perioperative period could help reduce overall postoperative complications, such as the duration of flatus and first defecation and reduce the incidence of postoperative ileus.

CONCLUSION

Perioperative probiotics or synbiotics supplementation may be considered to patients undergoing abdominal surgery in promoting postoperative gastrointestinal recovery, albeit the results shown are inconsistent. Although there is no definite recommendation strains and dosage for given probiotics and synbiotics, administering probiotics from the Lactobacillus and Bifidobacterium strains at a dose of $\geq 1.0 \times 10^7$ cfu/g, either alone or combination with prebiotics may provide benefits for gastrointestinal function. Further research is needed to evaluate the strains and dosage of preoperative probiotics or synbiotics on postoperative ileus undergoing abdominal surgery.

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