The role of probiotics and synbiotics in preventing postoperative sepsis in gastrointestinal surgery

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Sepsis is a potentially fatal condition, accounting for over 1 million hospitalizations annually in the United States, with mortality rates as high as 40%. Patients undergoing gastrointestinal (GI) surgery are especially susceptible to sepsis, due to bacterial translocation secondary to surgical trauma and the use of antibiotics. Probiotics and synbiotics, which have been hypothesized to counteract disturbances in the intestinal flora and reduce pathogenic bacterial colonization, have been proposed for the prevention and treatment of a variety of GI conditions, including sepsis. Recent randomized control trials and meta-analyses evaluating the use of probiotic/synbiotic supplementation in elective surgical patients have demonstrated a significant reduction in the risk of developing postoperative sepsis in patients with the use of probiotic/synbiotics. Coupled with the prevention of numerous other GI symptoms, such as diarrhea, probiotics should be considered in all elective surgical GI patients.

Keywords: Probiotics; Synbiotics; Postoperative Sepsis; Gastrointestinal Surgery

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Sepsis, a potentially fatal condition with mortality rates as high as 40%, accounts for over one million hospitalizations and over $20 billion in healthcare spending each year in the United States (US) [1-3]. Surgical sepsis, accounts for nearly one-third of all cases, of which two-thirds are attributable to intra-abdominal surgeries [4]. Patients undergoing gastrointestinal (GI) surgery are especially vulnerable to the risk of bacterial translocation secondary to surgical trauma and the use of antibiotics. GI surgery impairs nutrient metabolism and immune regulation, severely disrupting the natural intestinal microbiome, leading to bacterial translocation from the GI tract to the systemic circulation, and ultimately resulting in sepsis [4].

Probiotics, first described by Fuller, are viable living microorganisms which have the potential to alter the host microbiota and result in beneficial health effects [5, 6]. A prebiotic is a non-digestible substance that stimulates the growth or activity of microorganisms within the GI tract [5, 6]. The combination of probiotics and prebiotics and its synergistic effects are referred to as synbiotics [6].
Recently, probiotics have been studied extensively for both the prevention and treatment of numerous GI conditions, including postoperative sepsis \(^7\) \(^-\) \(^9\). Although the precise mechanism remains unclear, it appears to be multifactorial. Probiotics compete for nutrients with pathogenic bacteria, preventing pathogen attachment and toxin activity, as well as suppressing pathogenic bacterial growth and invasion \(^10\) \(^-\) \(^11\). By inhibiting inflammatory cytokines such as interleukin-10 (IL-10) and increasing the secretion of IgA, neutrophils, and mucus, probiotics help maintain homeostasis and enhance innate immunity \(^11\) \(^-\) \(^12\). Probiotics also have a direct local effect on the intestinal mucosa by stimulating epithelial proliferation to act as a natural defense barrier \(^10\).

Various species of probiotics have been evaluated, with the Lactobacillus, Bifidobacteria, and Saccharomyces genus being the most common. Lactobacilli (L.), which is part of the natural GI microflora, produces bacteriocins as well as acetic and lactic acid, which act locally to prevent growth and invasion of pathogenic organisms, decrease the production of pro-inflammatory cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and IL-12, and stimulate the production of IgA \(^13\) \(^-\) \(^17\). Furthermore, Lactobacillus also increases mucin production, protecting the gastric epithelium and further suppressing pathogenic bacterial colonization \(^18\).

Bifidobacteria (B.), through a multitude of mechanisms, contribute significantly to the protective effect of synbiotics in elective surgery. For example, B. infantis 35624 stimulates an anti-inflammatory response within the host, prevents bacterial translocation, as well as inhibits growth of pathogenic organisms \(^19\). A Bifidobacterium-enhancing prebiotic (trans-galacto-oligosaccharide), enhances other Bifodobacterium, stimulating the immune system in elderly patients, while also reducing the incidence of traveler’s diarrhea \(^20\) \(^-\) \(^21\).

Saccharomycoses (S.) boulardii, a yeast, has been shown to augment the growth of probiotics in acidic environments. For example, S. cerevisiae EC-1118 significantly improved the viability of L. rhamnosus HN001 at pH levels of 2.5–4.0 \(^22\). Furthermore, S. boulardii interferes with pathogenic toxins, preventing pathogen activity and attachment \(^23\). S. boulardii also acts as an immune regulator, both systemically and locally within the lumen \(^23\).

A recent meta-analysis including 15 randomized control trials (RCT) and 1,201 patients evaluating the use of probiotics and synbiotics in patients undergoing elective GI surgery demonstrated a significant 38% risk reduction in postoperative sepsis (Relative Risk (RR) = 0.62; 95% Confidence Interval (CI), 0.52-0.74, \(p<0.001\)), with similar risk reductions seen for both probiotics (RR=0.63, 95% CI 0.52-0.77, \(p< 0.001\)) and synbiotics (RR= 0.57, 95% CI 0.39-0.83, \(p=0.004\)) \(^{24}\). When stratified by type of surgery, probiotics and synbiotics proved beneficial in nearly all types of GI surgery, including hepatopancreaticobiliary (RR = 0.27, 95% CI 0.09-0.80, \(p=0.019\)), liver transplants (RR = 0.44, 95% CI 0.23-0.85, \(p=0.015\)), and colorectal surgeries (RR = 0.65, 95% CI 0.53-0.80, \(p<0.001\)) \(^{24}\).

In addition to reducing the risk of postoperative sepsis, probiotics and synbiotics have been reported to reduce the risk of infections, diarrhea, nausea, and vomiting, with no significant change in hospital length of stay (LOS), intensive care unit (ICU) LOS, or mortality. He et al. (2013) published a review including 6 studies with 361 patients undergoing elective colorectal surgery, and reported a reduction in postoperative infections (Odds Ratio (OR) = 0.39; 95% CI, 0.22-0.68; \(p=0.001\)), diarrhea (OR = 0.29; 95% CI, 0.14-0.62; \(p=0.001\)), and symptomatic intestinal obstructions (OR = 0.39; 95% CI, 0.19-0.78; \(p=0.008\)) with the use of probiotics/synbiotics \(^{25}\). Similarly, Sawas et al. conducted a meta-analysis involving 4 studies and 246 patients undergoing liver transplantation surgeries and reported a reduction in infection rate (7% vs. 35%; RR = 0.21; 95% CI, 0.11-0.41; \(p=0.001\)), intraabdominal infection (2% vs. 11%; RR = 0.27; 95% CI, 0.09-0.78; \(p=0.02\)), as well as a shorter hospital LOS (Mean Difference (MD) = -1.41 days; \(p<0.001\)), ICU LOS (MD = -1.41 days; \(p<0.001\)), and duration of antibiotic use (MD = -3.89 days; \(p<0.001\)) with the use of probiotics/synbiotics, but no statistically significant difference in mortality (RR = 0.97; 95% CI, 0.21-4.47; \(p>0.05\)) \(^{26}\).

In addition to the direct benefits of probiotics and synbiotics in preventing postoperative infections, probiotics prevent numerous other GI symptoms such as diarrhea, which are beneficial for surgical recovery. A recent meta-analysis by Lau and Chamberlain (2016) concluded that probiotics significantly reduced the risk of developing Clostridium difficile-associated diarrhea by 59.5% among adults and 65.9% among children receiving antibiotics \(^9\).

Numerous studies have been published demonstrating the efficacy and potential side effects of probiotics and synbiotics. The Agency for Healthcare Research and Quality reviewed over 600 studies and published a review concluding that the majority of studies reported that probiotics were safe, and despite case reports of bacteremia and fungemia, such claims were inconsistent and not statistically significant when all available data was pooled together \(^{27}\).

Despite positive results in a majority of the published
RCTs and meta-analyses demonstrating significant reductions in postoperative sepsis, there are some limitations to take into account. In addition to the obvious differences in type of surgery and the indication for surgery, the demographics of patients varied including patient age, current health status, and comorbidities. Few studies included the elderly population, and further research into the safety and efficacy of probiotic use in this particularly vulnerable population is required. The use of antibiotics and preoperative bowel preparation received by the patients also differed, which may affect the risk of developing sepsis. Although studies have shown that probiotics reduce the risk of antibiotic associated nausea, vomiting, and diarrhea, these studies have included a variety of medications, and are mainly limited to medical patients while excluding surgical patients [9]. Furthermore, the specific species, dosage, route of delivery, and duration of treatment regimen also varied between studies, which limit the ability to comment on the optimal probiotic regimen.

Probiotic and synbiotic supplementation significantly reduces the risk of developing postoperative sepsis following GI surgery without significant adverse side effects. Given the high incidence of postoperative sepsis following GI surgery, probiotics and synbiotics should be considered as part of routine surgical patient care.

Conflicting interests

The authors have declared that no conflict of interests exist.

Author Contributions

All authors contributed to the conception and design of the project; acquisition, analysis, and interpretation of the data; as well as drafting and critically revising the manuscript.

Abbreviations

B: Bifidobacteria; CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; IFN: interferon; L: Lactobacilli; LOS: length of stay; MD: mean difference; OR: odds ratio; RCT: randomized control trial; RR: relative risk; S, Saccharomyces; TNF: tumor necrosis factor; US: United States.

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