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Review

The role of probiotics in gastrointestinal surgery

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ABSTRACT

The intestinal microbiota, which is a complex and dynamic population of different bacterial species, represents an important contribution to the health of the host. This microbiota plays a key role by promoting the integrity of the epithelial barrier and the development of mucosal immunity. However, under some stressful situations, such as after gastrointestinal surgery, infectious complications may originate from the intestinal microbiota of the patient. This phenomenon is known as the *gut origin of sepsis* hypothesis. However, the supply of probiotics has beneficial effects under similar conditions despite some controversial results. Therefore, it is important to carefully assess the efficacy of probiotics in the prevention and treatment of complications in surgical patients and to evaluate the safety of its use. This review provides an overview of the proposed mechanisms of probiotic action and the significant progress in this field, mainly concerning gastrointestinal surgery.

Introduction

The intestinal microbiota, which is a complex and dynamic population of different bacterial species [1], represents an important contribution to the health of the host. This microbiota plays a key role by promoting the integrity of the epithelial barrier and the development of mucosal immunity [2]. However, under some stressful situations, such as after gastrointestinal surgery, infectious complications may originate from the intestinal microbiota of the patient [3]. This phenomenon is known as the *gut origin of sepsis* hypothesis [4]. However, the supply of probiotics has beneficial effects under similar conditions despite some controversial results [5,6]. Therefore, it is important to carefully assess the efficacy of probiotics in the prevention and treatment of complications in surgical patients and to evaluate the safety of its use.

This review provides an overview of the proposed mechanisms of probiotic action and the significant progress in this field, mainly concerning gastrointestinal surgery. It is of utmost importance to verify whether there is sufficient evidence for the implementation of probiotics in daily practice to prevent complications in general surgical patients because surgical complications may affect overall mortality and health care costs.

Probiotics and their functions

Probiotics are defined as live microorganisms that have positive effects on human health when ingested in sufficient amounts [7]. These microorganisms are normally consumed in the form of yogurts, fermented milks, powder supplements, and capsules of freeze-dried organisms [8]. The most commonly used probiotics are lactic acid bacteria, *Bifidobacterium*, and other nonpathogenic strains such as *Streptococcus* species, *Enterococcus* species, and the yeast *Saccharomyces boulardii* [9]. Current evidence indicates that different probiotic strains exert their effects by different mechanisms of action [10].

The main functions of probiotics are related to increasing the intestinal motility to prevent bacterial overgrowth (modulation of the intestinal microbiota), improving the intestinal barrier function, and modulating the immune response.

Modulation of the intestinal microbiota

Probiotics promote a positive balance in the gut microbiota by increasing the concentration of beneficial microorganisms and antagonizing pathogenic bacteria. This antagonism occurs by several mechanisms, which include direct antimicrobial effects, such as the elaboration of bacteriocins [11], the increased release of defensins that are produced by Paneth cells [12], and the

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production of a physiologically restrictive environment. The restrictive environment is associated with pH, redox potential, and hydrogen sulfide production. Moreover, some probiotics compete for limited substrates that are required for fermentation [13] and inhibit the adherence of enteric pathogens to mucosal surfaces [11]. Probiotics enhance the secretion of the mucus layer overlying the epithelial lining of the gut [14,15] and have the capacity to obscure receptor binding sites [10] and directly bind to the pathogen [16].

Enhancement of barrier function

Enhancement of the barrier function has been observed in response to probiotic use and may represent an important mechanism in the host that benefits these microorganisms. To promote barrier integrity, probiotics induce alterations in mucus or chloride secretion [11], prevent bacterial adherence to the epithelial lining by competitive exclusion, inhibit pathogenic-induced alterations of epithelial permeability, and regulate enterocyte gene expression that is involved in the maintenance of the mucosa [17,18].

Immunomodulation

Modulation of the immune system is among the numerous beneficial effects of probiotics. Some probiotics inhibit the inflammatory response of the intestinal immune system by inhibiting nuclear factor-κB activation [19]. Probiotics increase the activity of the natural killer cells [20], induce the secretion of cytokines, and contribute to dendritic cell maturation [20]. Previous studies have reported that probiotics induce the secretion of immunoglobulin A [21].

Surgical complications and their origins

In recent years, advances in medicine and surgical techniques have lowered postoperative complications. However, infections after operations remain a factor affecting morbidity in surgical patients [22]. Among the main causes is disruption of the gut barrier, increased intestinal permeability, gut microbial imbalance, and immunologic compromise of the host with subsequent bacterial translocation [23,24]. Translocation is the passage of viable microbes from the gastrointestinal tract across the mucosal barrier to extraintestinal sites (normally sterile tissues such as the mesenteric lymph nodes and other internal organs) [22,25]. There is low translocation of indigenous microbiota, which are usually killed by host immune defenses during their passage through the lamina propria and in the mesenteric lymph nodes [26]. This physiologic phenomenon is necessary for the immunomodulatory function of the normal gastrointestinal microbiota. However, high bacterial translocation rates can become pathologic and trigger exaggerated or perpetuated immune responses that cause severe tissue damage and inflammation [27]. Furthermore, translocation is considered a pathophysiologic mechanism that is responsible for infectious complications in surgical patients [28]. A study of 927 patients undergoing laparotomy demonstrated that bacterial translocation occurred in 130 patients (14%) and was associated with an increased incidence of postoperative septic morbidity over a 13-y study period [23]. Another recent study detected bacterial translocation in 33% of patients with abdominal trauma undergoing laparotomy. This finding was significantly correlated with postoperative infections, because individuals with bacterial translocation presented with a rate of 41.6% compared with 12.5% of patients without bacterial translocation [29].

Based on the assumption that infectious complications in surgical patients may often originate from gut-derived microorganisms, manipulation of the intestinal microbiota may be a potential alternative to prevent or treat infection. Therefore, research on the ability of these microorganisms has significantly increased in recent years [30].

Current evidence from clinical trials

Recent evidence has indicated the potential role of probiotics in many types of gastrointestinal surgery (Table 1). Several studies on probiotics and liver resection have demonstrated positive effects, such as a decreased incidence of postoperative infections [32–35], improvement of patients' quality of life [36], shortened length of hospital stays, and antibiotic administration [35,36]. A recent study investigated whether probiotic supplementation influences liver function recovery by assessing the intraoperative risk, the type and frequency of intraoperative and postoperative complications, morbidity, intraoperative and early postoperative mortality, and the 1-y survival rate in patients undergoing hepatic resection due to hepatitis virus C–related cirrhosis. The investigators concluded that patients who used probiotics pre- and postoperatively had better and faster liver function recovery. These patients exhibited an improved acute immune response. As a consequence, intra- and postoperative complications were less frequent, leading to overall morbidity and mortality rates that were lower than those in patients who did not receive probiotics [35]. However, the basic mechanisms of probiotics on gut function and permeability in patients with liver disease have not been well elucidated.

With the exception of two studies by Rayes et al. [33,37], no other studies have evaluated patients undergoing liver transplantation.

Patients undergoing elective pylorus-preserving pancreatoduodenectomy (PPPD) are representative of patients undergoing major abdominal surgery [38]. Nomura et al. [39] studied 64 patients who were scheduled for PPPD. In this study, 30 patients were treated pre- and postoperatively with a probiotic mixture of *Enterococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A (BIO-THREE, Toa Pharmaceutical, Tokyo, Japan), and 34 patients did not receive any probiotics. The probiotic group exhibited a significant decrease of infectious complications compared with those in the control group (23% versus 53%), a shorter median length of hospital stay (19 versus 24 d), and a smaller percentage of patients with delayed gastric emptying (10% versus 20%).

A recent double-blinded study evaluated 80 patients who were enrolled after PPPD. All patients received early enteral nutrition through the nasojejunal route. Forty patients received a symbiotic cocktail with a combination of four different lactic acid bacteria *Lactobacillus plantarum*, *Lactobacillus paracasei* subspecies *paracasei*, *Leuconostoc mesenteroides*, and *Pediococcus pentosaceus* and β-glucan, resistant starch, inulin, and pectin (SYNBIOTIC 2000, Medipharm, Kagerod, Sweden). Another 40 patients received β-glucan, resistant starch, inulin, and pectin. In the group receiving the symbiotic cocktail, the incidence of nosocomial bacterial infections was significantly lower (12.5% versus 40%) compared with that in the control group, and only mild wound and urinary tract infections were observed [40].

Diepenhorst et al. [38] compared a standard treatment with a multispecies probiotic preparation (ECOLOGIC 641, Winclove Bio Industries, Amsterdam, Netherlands) with a standard treatment with selective decontamination of the digestive tract or a standard treatment alone in patients undergoing PPPD. The