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Synbiotics, Surgical Infection and Colonization Resistance

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Abstract

In our recent randomized controlled study to assess the effect of perioperative oral administration of synbiotics on surgical outcome in patients undergoing laparoscopic colorectal resection, the efficacy of synbiotics as a treatment to reduce the incidence of infectious complications was not validated. However, this study incorporated molecular-based methods and a large sample size, and microbiological examinations showed that dysbiosis induced by surgery was greatly improved by perioperative synbiotic treatment, resulting in the decrease of potentially pathogenic bacteria, such as *Clostridium difficile*. This study also provided novel evidence that could explain, in part, the mechanisms whereby probiotics enhance colonization resistance in the gastrointestinal tract.

Keywords: Postoperative complication; Probiotics; *Bifidobacterium*; *Clostridium difficile*; Bacterial translocation; Short chain fatty acids

Description

The gut microbiota performs a wide range of beneficial functions for human health and homeostasis, maintaining nutrition, strengthening the immune system and improving colonization resistance. There is also increasing evidence that gut microbial imbalances (dysbiosis) are associated with various intestinal-related diseases such as inflammatory bowel diseases and irritable bowel syndrome, as well as infectious complications after surgery [1-4].

Probiotics are defined as live microorganisms that have positive effects on human health when ingested in sufficient amounts. The therapeutic effects of probiotic administration on disorders presumably associated with dysbiosis have been extensively examined [1-3,5-7]. Several randomized controlled trials, including pancreatoduodenectomy, hepatobiliary resection and liver transplantation, demonstrate that the use of probiotics in patients undergoing abdominal surgery is a promising approach to the prevention of post-operative infectious complications [8-11]. Nevertheless, the effectiveness of probiotics treatment for prevention of infectious complications after colorectal surgery remains inconclusive [1,3,12-21], possibly due to differences in patient groups, varying preparations of probiotics, and heterogeneity in the quality of methods. Whether or not beneficial bacteria actually survive in the intestine also remains unclear.

We recently published the results of a randomized controlled study to assess the effect of perioperative oral administration of synbiotics, a combination of probiotics (*Lactobacillus casei* strain Shirota and *Bifidobacterium breve* strain Yakult) and prebiotics (dietary supplement of probiotics), on surgical outcome in patients undergoing laparoscopic colorectal resection [22]. In this study, surgical site infection (SSI) occurred in 17.3% of synbiotics group patients and in 22.7% of control group patients (OR 0.761, 95%CI 050-1.16; p=0.20). Overall, the rate of postoperative complications, including anastomotic leakage, did not differ significantly between groups. The efficacy of perioperatively administered synbiotics was not validated as a treatment to reduce the incidence of infectious complications after surgery. In previous studies of hepatobiliary, pancreatic, and esophageal surgery, usefulness of synbiotics/probiotics as prophylaxis has been described in the context of bacterial translocation (BT), associated with an altered intestinal barrier and immune function [8-11,23-25]. The conditions for use of prophylactic agents in the colon and rectum may, however, be different. In these organs BT plays a less prominent role and the potential risk of intraoperative contamination appears far greater.

In contrast to our results, some recent randomized controlled studies showed a considerable reduction of infectious complications after open radical colorectal surgery with a combined probiotic formula over placebo [15,21,26]. It is not likely that the inconsistent results may attribute to the difference in administered probiotics, because our formula was shown to distinguishingly improve microbial imbalance as well as reduction in organic acids induced by surgery. Rather, the colorectal resections with open laparotomy may have elicited greater surgical stress or systemic inflammatory response, in which effects of probiotics protecting against BT could emerge more prominently, compared with our laparoscopic surgery.

In the same series of patients, microbiological examinations using molecular-based methods with a large sample size provided novel and precise evidence that significant changes in fecal bacterial composition occur following laparoscopic colorectal resection [22]. Such microbial imbalance induced by mechanical bowel preparation [27], surgical stress or manipulation of the intestine was improved by perioperative synbiotic treatment whereby decreases of potentially pathogenic bacteria, such as *Clostridium difficile* (CD) (4% in synbiotics group vs. 13% in control group), and increases in beneficial bacteria were observed. These results also indicate that the administration of synbiotics restores the diminished fecal organic acids and rise in pH level elicited by surgical procedures.

Protection of the host intestines from exogenous pathogens by commensal bacteria is termed colonization resistance. Disruption of the barrier function (e.g. induced by antibiotic treatment) is associated with an increased risk of CD infection and/or flourish of multi-resistant bacteria. Various possible mechanisms have been proposed to

explain how the indigenous microbiome constitutes colonization resistance, including direct interactions between microbes as well as indirect mechanisms mediated by stimulation of the mucosal immune system by members of the health-associated microbiota [4,28-30]. An interesting aspect of our study is that positive correlations were observed among administered probiotics, the number of *Bifidobacterium* species and the concentrations of short chain fatty acids, which are closely associated with decreases in potentially harmful species, including CD. This finding from human samples may help explain the mechanisms whereby probiotics reduce colonization of pathogenic organisms through enhanced colonization resistance in the gastrointestinal tract; it may also support the view, proposed by Fukuda et al, that *Bifidobacteria* can protect against enteropathogenic infection through production of acetate [31,32].

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