Prevention of postoperative microbial infection by synbiotics

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Prevention of infectious complications after major surgeries including those for cancer has been a major concern in the clinical field. To overcome this problem, probiotics and synbiotics (combination of probiotics and prebiotics have recently been introduced for post-operative treatment. Clinical application of synbiotics in severe cases, such as severe pediatric surgical cases, acute pancreatitis, liver transplantation, and biliary cancer, has been reported. The present article deals with the clinical effect of such synbiotic therapies for the patients under emergency medical care, and discusses the possible mechanism of action and prospect of synbiotic therapy.

Keywords: Microbial infection, Postoperative infection, Prebiotic, Probiotic, Synbiotic

Conceptually, probiotics are microorganisms that exhibit beneficial effects for hosts by improving balance of intestinal flora. However, the joint expert meeting (2001) held by the Food and Agriculture Organization (FAO) of the United Nations and World Health Organization (WHO) has proposed a new definition for it as ‘microorganisms that exhibit beneficial health effects for hosts when a sufficient amount of them are ingested’. Reports on diverse functions of probiotics indicate that they not only improve the balance of intestinal flora but also improve abnormal immunological conditions of hosts. In addition, prebiotics have been introduced as indigestible food components that contribute to host health by activating the proliferation and function of beneficial intestinal bacteria, with short-chain sugars, such as oligosaccharides, serving as a specific nutrient source for probiotics, represented by Bifidobacterium and lactic acid bacteria. Use of combination of probiotics and prebiotics is called synbiotics.

Prevention of infectious complications after major surgeries including those for cancer is a major concern in clinical field. Based on past experiences of the spread of antibiotic-resistant bacteria, such as methicillin resistant Staphylococcus aureus (MRSA), due to the massive postoperative and long-term administration of antibiotics, refraining from the use of antibiotics as much as possible is the basic attitude of those in the surgical field. To overcome this problem, probiotics and synbiotics have recently been introduced. For example, the clinical application of synbiotics for severe cases, such as cases of severe pediatric surgical diseases, acute pancreatitis, liver transplantation, and biliary cancer, has been reported. This report reviews the clinical effects of such synbiotic therapies, introduces recent reports on application of synbiotic therapy for patients in poor states under emergency medical care, and discusses the possible mechanism of action and prospect of synbiotic therapy.

Synbiotic therapy in pediatric surgery—Kanamori et al. have reported efficacy of long-term synbiotic therapy in pediatric patients under surgery for short-bowel syndrome that showed repeated episodes of refractory enteritis and bacteremia since birth and tracheoesophageal fistula. For probiotics, live bacterial preparations of Bifidobacterium breve strain Yakult and Lactobacillus casei strain Shirota were used and galactooligosaccharides were supplemented as prebiotics. A high viable probiotic bacterial content was detected in the patients’ faeces, the intestinal bacterial flora was improved and the titre of harmful microorganisms, Pseudomonas aeruginosa and Candida, were reduced. As the intestinal bacterial flora was improved by synbiotic therapy, intestinal peristalsis recovered, intestinal expansion was reduced, and the nutritional condition improved as reflected by gain in body weight.

Synbiotic therapy in digestive organ surgery—Rayes et al. compared postoperative complications among groups treated with- (a) antibiotics for intestinal bacterial eradication; (b) synbiotics and (c)
killed lactic acid bacteria, in patients with liver transplantation. \textit{Lactobacillus plantarum} 299 as a probiotic and oats as a prebiotic were administered to the synbiotic therapy group for 12 days. The incidence of postoperative infections by discharge was 48, 13 and 34\% in (a), (b) and (c) group, respectively, showing that the incidence was significantly lower in the synbiotic group than in the intestinal bacterial eradication group. When 4 species of lactic acid bacteria and 4 types of fiber were combined in synbiotics after liver transplantation, the incidence of postoperative infections was further reduced to 3\% (only 1 of 33 patients) suggesting that synbiotic therapy was capable of reducing the incidence of postoperative infection that could not be completely checked by antibiotics treatment for control of intestinal bacteria. Olah et al. have compared the incidence of infectious complications between treated (synbiotics + enteral nutrition) and control (killed lactic acid bacteria + enteral nutrition) groups of patients with acute pancreatitis in which \textit{Lactobacillus plantarum} 299 and oats were administered for 1 week as probiotic and prebiotic, respectively. The incidence of infectious pancreatic necrosis and abscess was 30.4\% (7/23 in the control group), but it was significantly reduced to 4.5\% (1/22) in the synbiotic group.

Kanazawa et al. have compared the incidence of postoperative infection between groups with and without synbiotic administration in patients with biliary cancer. Two types of live bacterial preparation, \textit{Bifidobacterium breve} strain Yakult and \textit{Lactobacillus casei} strain Shirota, were administered as probiotics, and galactooligosaccharides were added to postoperative enteral nutrition as prebiotics. The incidence of postoperative infectious complications was 52\% (12/23 in the non-synbiotic treatment group), while it was significantly reduced to 19\% (4/21) in the synbiotic treated group (Table 1). On comparison of intestinal flora, the count of \textit{Bifidobacteria} and \textit{Lactobacilli} was significantly increased in synbiotic treated group than non-synbiotic group, whereas those of etiologic bacteria of opportunistic infection, such as \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa}, and \textit{Candida}, were significantly reduced (Fig. 1). Considering the preoperative oral ingestion of synbiotics, in addition to postoperative synbiotic therapy, may effectively prevent infections, a randomized controlled study was performed with a preoperative and postoperative synbiotic ingestion group and control group with the postoperative ingestion of synbiotic alone (synbiotic group: 41 patients, control group: 40 patients). \textit{L. casei} strain Shirota-fermented drink (containing 40 billion or more live bacteria of \textit{L. casei} strain Shirota) and \textit{B. breve} strain Yakult-fermented drink (containing 10 billion or more live bacteria of \textit{B. breve} strain Yakult) were selected for postoperative synbiotics, and 55\% of galactooligosaccharides solution as a prebiotic. Preoperative synbiotic ingestion for 2 weeks (one each bottle of probiotics per day and 15 g of galactooligosaccharides solution per day significantly elevated the peripheral blood NK activity and total

| Table 1—Prevention of postoperative infectious complications by synbiotics |
|-----------------------------|-----------------------------|
|                            | Untreated control (n=23)    | Synbiotics (n=21) |
| Wound infection            | -                          | -               |
| Bacteremia                 | -                          | -               |
| Intra-abdominal abscess    | -                          | -               |
| Pneumonia                  | -                          | 0               |
| Patients with infectious complications | 12 (52\%) | 4 (19\%) |

Infectious complications were recorded up to 30 days after hepatectomy in biliary cancer patients.

Fig. 1—Improvement of disrupted faecal bacterial flora by synbiotics after hepatectomy. (A) Numbers of beneficial bacteria \[\bullet, \text{Bifidobacteria in synbiotics}; \bigtriangleup, \text{Bifidobacteria in control}; \bigtriangledown, \text{Lactobacilli in synbiotics}; \blacktriangle, \text{Lactobacilli in control}]. (B) Harmful bacteria in faeces before and after hepatectomy were examined \[\circlearrowleft, \text{Enterobacteriaceae in synbiotics}; \circlearrowright, \text{Enterobacteriaceae in control}; \triangle, \text{Candida in synbiotics} \blacktriangle, \text{Candida in control}; \bigtriangleup, \text{Pseudomonas in synbiotics}; \bigtriangledown, \text{Pseudomonas in control}]. *\(P < 0.05\) between synbiotics and control.
The incidence of systemic infectious diseases, such as enteritis, pneumonia, and sepsis, was also lower than the group without synbiotic treatment. The condition of patients admitted to the emergency care unit needs immediate treatment/improvement, but improvement has been observed by synbiotic therapy.15

Mechanism of action of synbiotic—Bacterial translocation (BT) is defined as transfer of viable intestinal bacteria from the intestinal lumen to lamina propria mucosae, then to mesenteric lymph nodes (MLN) and other organs via intestinal mucosa.17,18 It has recently been interpreted as the passage through the anatomically normal mucosal barrier of viable and dead bacteria and bacterial cell components such as endotoxin including all microbial translocations. There are 3 factors which are considered to induce BT: (1) Abnormal bacterial growth in the gut; (2) Impairment of the barrier function of the digestive tract wall and (3) Failure of host defense mechanism against invading bacteria. An increase in intestinal organic acid production by synbiotic therapy may improve host resistance to the above 3 factors of BT in postoperative infections of digestive organs. As shown in the above examples, improvement of intestinal bacterial flora by improving the intestinal environment may be particularly important.

Inhibition of abnormal growth of pathogenic bacteria in intestine by synbiotic has been reported in animals. Asahara et al.19 have reported that administration of B. breve strain Yakult inhibits intestinal growth of and fatal host invasion by Salmonella typhimurium in a mouse S. typhimurium infection model.19 (Fig. 2). These effects pronounced by supplementing synbiotic in combination with galactooligosaccharides. A similar infection-preventive effect of B. breve strain Yakult has also been observed in an entero-hemorrhagic Escherichia coli O157 intestinal infection model. In these experimental models, B. breve strain Yakult improves the intestinal environment particularly by normalization of intestinal organic acid level by acetic acid production and inhibition of infection induced intestinal pH elevation.20 On the other hand, augmentation of host defense system against
infections has been reported by treatment of synbiotic\textsuperscript{3,21,22}. Patients with severe stress, such as those undergoing surgery for biliary cancer and SIRS described above, are typical compromised hosts, and compensation for deteriorated host defense mechanism against infections seems to be important.

Prospects of synbiotic therapy—There are several essential aspects of regarding synbiotic therapy which should be considered carefully. Firstly, synbiotic must be safe since patients undergoing major surgeries will be under anesthesia for taking more than 10 hours and those admitted for emergency and critical care are very weak, synbiotics. Secondly, verification of the efficacy and reliability of synbiotics by clinical organizations is necessary because clinical reports are lacking. Recently, a meta-analysis of prevention of infectious complications (proportion of patients with nosocomial infection, proportion of patients with pneumonia, hospital mortality, and length of ICU stay) by probiotics and synbiotic therapy in adult patient under intensive care unit did not conclusively demonstrate their efficacy\textsuperscript{21}. It could be due to variation among probiotics and patients and also too small number of analyzed cases. To make an accurate assessment, more clinical data is necessary.

Clarification of mechanism of action by animal studies such as those described above is necessary. Basic studies on defense against infections focusing on -(1) Intestinal environment (bacterial flora, pH, and organic acid concentration; (2) Activation of the host defense system and (3) Elucidation of factors determining bacterial strain-specific effects. Regarding point (1) investigation of the colonization resistance mechanism of indigenous bacterial flora from the viewpoint of quorum sensing is one method; point; (2) investigation of details of cross-talk between intestinal microorganisms and intestinal mucosa epithelial cells may clarify the mechanism of involvement of intestinal bacterial flora in abnormal host immune reactions; and for point (3) elucidation of bacterial strain-specific metabolic systems and signal transduction pathways in bacterial cells is important. Regarding immunoregulatory function, the investigation of responsible bacterial strain-specific structures is important because killed probiotics also exhibit their function\textsuperscript{22}. These analyses may clarify adequate methods concerning the use of synbiotics (administration methods corresponding to pathological conditions, such as timing, amount, and combination of probiotics and prebiotics).

Importance of nutritional management of patients has recently been emphasized. Adequate nutritional management for individual patient is called nutrition support\textsuperscript{23}. The concept of the nutrition support team (NST), originated in USA, has rapidly spread in Japan. NST aims at adequate nutritional management of patients by establishing a cross-occupational team in each medical institution, mainly consisting of physicians, nurses, pharmacists, dietitians, and administrative support, based on the concept that adequate nutritional management leads to improvement of prognosis of patients. To prevent infectious complications in patients in emergent states such as those described above, this concept may be very important. Symbiotic therapy is expected to be widely incorporated as a part of nutrition support.

References


