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Review article

Effects of Enteral Administration of Bifidobacterium Breve on Dysbiosis Infants and Children: A Review

Yuichiro Yamashiro
Probiotics Research Laboratory, Juntendo University Graduate School of Medicine, Tokyo, Japan
*Corresponding author: Yuichiro Yamashiro, M.D., Ph.D,Probiotics Research Laboratory, Juntendo University Graduate School of Medicine, Hongo-Asakaz Bldg 3F, 2-9-8 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

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Introduction

Recent studies have shown that the trillions microorganisms that inhabit our gut influence our present and future health and could also account for the mounting incidences of various diseases that currently affect global populations including children, adults, and the elderly. It is strongly suggested that the fetus is already exposed to various bacteria by swallowing amniotic fluid [1]. At that point, infants begin a lifelong relationship with their gut microbiota, as demonstrated by the detection of live bacteria in the meconium of healthy term infants born vaginally. Interestingly, the meconium of Caesarean (C)-born infants is significantly less often colonized with Lactobacillus than vaginally born infants [2]. It has become clear that C-section results in abnormal gut microbiome composition in the newborn gut and may also account for the rising incidences of several serious health problems in children, including asthma, celiac disease, type 2 diabetes mellitus, and obesity [3]. Immediately after birth, bacterial colonization by both facultative and strict anaerobes of the gut proceeds rapidly within 1–2 weeks of birth. Our data indicated that the primitive microbiota core is predominated by facultative anaerobes including Proteobacteria, staphylococci, streptococci, and enterococci, whereas obligate anaerobes such as Firmicutes, Bacteroides, and Actinobacteria start prevailing during infancy [4]. Colonization continues through breastfeeding until weaning, with additional bacteria accumulating in a stepwise manner with the appearance of obligate anaerobes, predominantly Bifidobacterium, Bacteroides, and Clostridium, such that by 2–3 years of age, the microbiota resembles the extremely dense and complex microbial colonization of an adult [5]. Bifidobacterium remains a predominant component until the teenage years and subsequently decreases gradually through 80 years of age, but remains a predominant component [6]. B. breve, B. longum, B. infantis, B. bifidum, and B. catenulatum group are the primarily detected species. The proportion of Bifidobacterium detected during the first 6 months remains lower in C-section-born infants compared to vaginal-born infants [7]. B. breve is classified in the family Bifidobacteriaceae, order Bifidobacteriales, subclass Actinobacteridae, class Actinobacteria, and phylum Actinobacteria in the domain Bacteria. B. breve is a gram-positive, non-spore-forming, obligate anaerobe [8].

Description of bbg-01

BBG-01, a probiotic supplement provided by Yakult Honsha Co., Ltd. (Tokyo, Japan), is packaged as a freeze-dried powder, with corn starch, in a 1 g sachet containing more than 10^9 viable cells (colony forming units [CFU]/g dry weight) of B. breve strain Yakult. This article reviews data concerning the effects of clinical application of BBG-01 as a probiotic in infants and children.

Microbiota Establishment in Very Preterm Infants

Preterm infants are predisposed to serious short and long-term health complications. These effects are due to prematurity and nutrition affecting maturation of the gut microbiota, gastrointestinal tract, and immune system. These consequences of prematurity subsequently influence infant growth and development [9-11]. Therefore, preterm infants would benefit from enhanced weight gain, which affects growth and organ development. For this purpose, breast milk is the preferred source of nutrition for preterm infants [12,13]. Organic acids (short-chain fatty acids and lactic acid) are the end products of bifidobacteria fermentation, particularly of human milk oligosaccharides. In the gut, these organic acids can be absorbed into the circulation, where these acids serve as both microbiota-generated calories and important regulatory molecules; the host is estimated to receive 6–10% (or more in infants) of its energy from organic acids [14]. Bile acids are formed by the microbiota from host cholesterol, and these molecules also serve as signaling molecules that bind to distinct receptors [15] that have a major impact on metabolism.

We previously investigated the effects of Bifidobacterium supplementation concomitant with early feeding of mother's colostrum and breast milk in very preterm infants (VPIs), focusing on growth outcomes. We also analyzed fecal bacteria levels and related fecal parameters in these infants. We conducted a randomized controlled study on 35 VPIs, born between 24 and 31 weeks of gestation with birth weights <

1,500 g. Patients received either daily BBG-01 supplementation (Bifid group) or vehicle supplement only (placebo group). Parenteral nutrition was initiated with glucose, amino acids, and fatty acids for all infants soon after birth. Each infant received his/her own mother's colostrum within 24 h of birth and breast milk on subsequent days. Fecal bacteria, organic acids, pH, bile acids, and plasma fatty acids were analyzed.

Seventeen infants were allocated to the Bifid group and 18 infants were allocated to the placebo group. Birth weight and gestational age did not significantly differ between the two groups. Compared to the placebo group, the Bifid group showed significantly greater and earlier weight gain by 8 weeks and significantly higher total fecal bacterial counts, including bifidobacteria. The Bifid group also demonstrated higher levels of total fecal short-chain fatty acids, nominally (but not significantly) higher concentrations of plasma n-3 fatty acids, and lower levels of total fecal bile acid. Sepsis was observed in 3 infants (16.7%) in the placebo group and no infants in the Bifid group. No infants in either group developed necrotizing enterocolitis. Thus, BBG-01 supplementation of maternal colostrum and breast milk helped to establish a beneficial microbiota profile, leading to favorable metabolic responses that improved growth in VPIs [16].

Alleviation Therapy for Chemotherapy-Induced Mucositis in Children

Mucositis, also referred to as mucosal barrier injury, is one of the most debilitating side effects of chemotherapy [17]. Clinically, mucositis presenting with severe stomatitis and ulcers is associated with severe pain, appetite loss, diarrhea, high fever, bacteremia, and malnutrition. These complications often require total parenteral nutrition and intravenous infusion of broad-spectrum antibiotics. Chemotherapeutics have a detrimental effect on the intestinal microbial composition by drastically reducing the numbers of anaerobic bacteria, leading to bacterial translocation and intestinal mucosal damage [18].

To alleviate signs and symptoms of mucositis, we investigated the effect of BBG-01 administration in children with malignancy undergoing chemotherapy. A placebo-controlled trial was performed. Patients with malignancies admitted for chemotherapy (n=42) were randomized into one of two groups: BBG-01 or placebo. The effects of BBG-01 on infectious complications, natural killer cell counts, fecal microflora, fecal organic acid concentrations, and fecal pH were studied.

The frequency of fever and use of intravenous antibiotics were lower in the BBG-01 group than in the placebo group. BBG-01 administration enhanced the habitation of anaerobes. Disruption of the intestinal microbiota after chemotherapy, such as increase in population levels of Enterobacteriaceae, was more frequently observed in the placebo group than in the BBG-01 group. Concentrations of total organic acids were primarily maintained at normal levels. Fecal pH was persistently < 7.0 only in the BBG-01 group. Taken together, these results suggest that BBG-01 administration could yield clinical benefits in immunocompromised hosts by improving the intestinal environment [19].

Perioperative bbg-01 Administration to Improve Postoperative Morbidity and Mortality

Major surgical procedures can alter intestinal microbiota and disrupt intestinal barrier function, leaving the patient at risk of infection [20]. Although the efficacy of perioperatively administering probiotics has been reported in adults [21,22], the clinical value of probiotics in children requiring surgery is unclear. Therefore, we carried out a randomized, controlled trial to investigate perioperative changes in fecal and blood microbiota after oral administration of BBG-01 in pediatric surgical cases. BBG-01 was well tolerated without adverse effects, and postoperative infectious complications were significantly decreased. Fecal analysis showed increased Bifidobacterium and decreased Enterobacteriaceae, Clostridium difficile, and Pseudomonas. Fecal acetic acid concentrations were significantly increased, maintaining fecal pH at < 7.0. The incidence of detecting bacteria in blood was significantly reduced. BBG-01 improved the intestinal environment and may be implicated in suppressing bacterial translocation. Taken together, the findings indicate that perioperative administration of BBG-01 is safe, can improve the intestinal environment, and may help to suppress bacterial translocation [23].

Bbg-01 Administration in Neonates Undergoing Surgery for Congenital Heart Disease

Surgery for congenital heart diseases is performed in neonates worldwide with high success rates [24]. Infections and acute organ failure remain important complications and causes of reoperation, prolonged hospitalization, and intensive care, which significantly increase postoperative morbidity and mortality [25,26]. Neonates undergoing corrective or palliative cardiac surgery are at increased risk of mesenteric hypoxia due to oxygen desaturation and low cardiac output. These patients often receive antimicrobials for prophylactic or non-prophylactic indications. Moreover, the incidence of delayed enteral feeding due to respiratory or cardiovascular instability is high [26]. These factors, alone or in combination, may disrupt the intestinal microbiota and function of the intestinal barrier followed by bacterial translocation and associated disorders [27,28].The authors examined the effects of the perioperative administration of BBG-01 on the intestinal microbiota and clinical outcomes of neonates who underwent cardiac surgery.

In this study, 21 neonates undergoing surgery for congenital heart diseases at > 7 days after birth were randomly allocated to one of two groups: group A received 3×109 CFU/day of BBG-01, which was started 1 week before and terminated 1 week after surgery (n=10), and group B did not receive BBG-01 (n=11). Patient characteristics were similar in both groups. The number of postoperative days until fulfillment of the criteria for discharge from the PICU tended to be fewer in group A (8 [7–8] days) than in group B (9 [8–14] days) (p = 0.10). Likewise, the number of postoperative days to enteral nutrition or achievement of caloric goal tended to be fewer in group A than in group B. Bifidobacterium counts in fecal samples after

initiating BBG-01 in group A were significantly higher than that in group B. Enterobacteriaceae counts were significantly fewer in group A than in group B immediately (7.0 [3.9–7.7] vs. 8.5 [8.0–9.1] log10 cells/g) and 1 week (7.7 [7.0–8.1] vs. 9.3 [8.6–9.5] log10 cells/g) after surgery ($p < 0.05$ for both comparisons). Pseudomonas counts at 1 week after surgery was significantly lower in group A than in group B ($p = 0.04$). Concentrations of total organic and acetic acids were also significantly higher in group A than in group B. The postoperative course was uncomplicated, and all neonates were discharged alive from the PICU.

These results showed that perioperative administration of BBG-01 to neonates undergoing surgery for congenital heart disease was safe and significantly improved the intestinal environment. The positive effects of this treatment on clinically significant outcomes remain to be investigated [29].

Bbg-01 Use to Enhance Immunogenicity of an Oral Inactivated Cholera Vaccine

Oral vaccines, which are designed to stimulate intestinal mucosa immunity, are less immunogenic when given to children in developing countries compared to industrialized countries [30]. Probiotics are expected to enhance vaccine immunogenicity.

The protective efficacy of Dukoral® (SBL vaccine AB, Stockholm, Sweden), a commercially available oral cholera vaccine, is lower in children than in adults, demonstrating that there is a great need for an effective vaccine to protect children from the life-threatening consequences of cholera [31,32].

The authors evaluated BBG-01 for safety enhancement of immunogenicity of an oral inactivated cholera vaccine in a randomized, double-blind, placebo-controlled study. Bangladeshi children younger than 5 years received BBG-01 or placebo for 4 weeks with two doses of oral cholera vaccine. Serum/fecal antibodies and fecal bacterial flora were monitored. All adverse events were mild and transient, and no significant differences were observed between the two groups. Immunological responses were also similar between the two groups. A negative correlation between Bifidobacterium and Enterobacteriaceae in the probiotic group suggests the possible involvement of BBG-01 in alteration of the enteric bacterial flora. The results suggest that BBG-01 is well tolerated by children, although the post-vaccine immunostimulatory effect of BBG-01 was not evident [33].

Safety of bbg-01 in Preterm Infants

BBG-01 contains more than 109 powered viable cells of B breve. BBG-01 was first used in Japan in 1982 [33] and since then it has been used in pediatric patients for the treatment of clinical conditions such as infantile diarrhea [33] to prevent necrotizing enterocolitis [34], nutritional management of preterm infants and children with pediatric malignancy [19], and postoperative management of pediatric surgical patients [23].

Although the efficacy of BBG-01 has been widely reported, there is little information about adverse events related to its use. To trace adverse events seen by 109 doctors in 88 medical institutions in Japan where BBG-01 was used, the authors conducted a questionnaire survey of the number of occurrences and details of each case in Japan. Eighty-six clinicians (70 institutions) responded to the questionnaire (response rate, 78.9%). The number of respondents according to department of diagnosis (number of BBG-01-treated infants) was as follows: pediatrics, 29 respondents (10,938 patients); premature and newborn medicine, 26 (10,677 patients); obstetrics and gynecology, 1 (1,212 patients); and pediatric surgery, 22 (169 patients). More than 90% of all BBG-01-treated patients (23,092 patients) were seen in the departments of premature and newborn medicine and pediatrics, and BBG-01 had been used mainly in preterm infants and children with intractable diarrhea. Adverse events occurred in two extremely premature infants with functional ileus due to starch aggregates as vehicle and in two surgical neonates with bacteremia caused by B. breve strains genetically identical to BBG-01. However, no serious adverse events with poor outcomes were reported. Therefore, adverse events related to BBG-01 use appear to be rare and mild in severity, thus ensuring the superior safety of this preparation [35].

Conclusion

BBG-01 has been widely used in pediatric patients with increased susceptibility to infection, such as very preterm infants, children undergoing chemotherapy, pediatric surgical patients, and in the field of neonatology and pediatrics. Based on the results of studies described here B. breve (BBG-01) administration in infants and children has clinical benefits with good safety.

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