Effectiveness of probiotics for antipsychotic-induced functional bowel disorders: A single-center retrospective observational study

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Research article

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Abstract

Background Probiotics have the potential to improve functional constipation, however, evidence is lacking regarding its recommendation related to gut microbiota. Constipation is highly prevalent and a serious side-effect in antipsychotic treatment. This study was to investigate the effects of probiotics supplementation on defecation in psychiatry.

Methods Subjects consisted of 31 male and 37 female inpatients who were co-administrated either of two probiotics: BIO-THREE or BIOFERMIN tablets. The medications that affect bowel movement including gastrointestinal drugs and antipsychotics in addition to their levels of chlorpromazine equivalent (CPeq) doses were compared between the two groups. Intestinal function was evaluated at baseline and one and two months using Bristol stool form scale. Sequential change of the three indices: average, constipation and diarrhea levels were compared within the group and analyzed to see any significant correlation against the CPeq levels.

Results There were no significant differences in the medical treatment between the groups. In both groups, the average and constipation levels increased, and the diarrhea levels decreased at two months from baseline; in particular, the constipation levels were significantly increased at two months from baseline in the BIO-THREE group (-9.6±1.0 vs -6.5±0.9, mean±se). In the BIO-THREE group, only the diarrhea levels were significantly negatively correlated with the CPeq levels at two months (r= -0.341), while no such correlations were found in the BIOFERMIN group.

Conclusions Probiotics supplementation may improve stool consistency, especially severe constipation and ameliorate diarrhea depended on antipsychotic dosage in psychiatric setting.

Background

Functional or chronic constipation is one of the most frequent conditions and major issues that is associated with impaired quality of life in primary care settings [1]. However, the definition and understanding of constipation vary widely among individuals and in some regions [2]. In the general population, the prevalence of constipation based on the Rome III criteria has been reported at varying levels around the world, from 8.2% to 32.9% [3, 4]. On the other hand, little epidemiological information is available regarding defecation habits and the prevalence of constipation in psychiatry [5].

Psychotic disorders and schizophrenia are severe mental disorders which often require long-term treatment with antipsychotics. In addition to their irregularity of dietary life, lack of exercise and serious mental condition, antipsychotics which possess dopamine blocking and anticholinergic effects can also induce constipation in psychiatric patients [6]. Moreover, schizophrenia as such and its treatment with antipsychotics could be accompanied with a higher discomfort or pain threshold, which could be a reason why these patients report somatic complaints later or less frequently [7, 8]. Cases of late detection or inadequate treatment of constipation have led to lethal complications such as paralytic ileus, bowel occlusion, perforation, and even death [9, 10].

The management of functional constipation remains challenging. Bulking agents, osmotic laxatives, stimulant laxatives, and stool softeners are commonly used [11]. However, half of patients are not completely satisfied with such treatments, with the main reasons being treatment efficacy, inconsistent symptom response, and concerns with regard to safety, adverse effects, taste, inconvenience, and cost [12]. Accordingly, patients with functional constipation commonly adopt self-management approaches, such as foods or nutraceuticals believed to exert a laxative effect.

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit to the host. The ability of gut microbiota to bidirectionally communicate with the brain, known as the gut–brain axis, in the modulation of human health is at the forefront of current research. Altered microbiota has been elucidated to link to neuropsychological disorders, metabolic disorders and gastrointestinal disorders [13]. Moreover, studies have also indicated that gut microbiota may be modulated with the use of probiotics, antibiotics, and fecal microbiota transplants as a prospect for therapy in microbiota-associated diseases [14].

A systemic review and meta-analysis of randomized control trials demonstrated that probiotics may improve whole gut transit time (WGTT), stool frequency, and stool consistency, however, do not yet provide sufficient scientific evidence to support a general recommendation about the use of probiotics in the treatment of functional constipation [15]. A recent study on the relationship between constipation and intestinal microbiota revealed that improving the intestinal flora is significantly useful for the treatment of chronic functional constipation, which has important potential for clinical application due to its safety, convenience and curative effect [16]. Based on current evidence, limited inferences can be made regarding the efficacy of probiotics in schizophrenia symptom, however, probiotics may have other benefits, for example to regulate bowel movement and ameliorate the metabolic effects of antipsychotic medications [17].

The aim of this study was to investigate the background factors and the effects of probiotics on defecation in hospitalized psychotic patients who were prescribed combination prebiotics under a real world clinical setting.

Methods

Subjects

Psychiatric inpatients treated with BIO-THREE tablets: mixture probiotics including *Streptococcus faecalis* 2×10^8 CFU/day, *Bacillus mesentericus* 1×10^7 CFU/day, and *Clostridium butyricum* 5×10^7 CFU/day (Toa Pharmaceutical Co., Ltd., Tokyo, Japan) or BIOFERMIN tablets: *Bifidobacterium bifidum* G9-1 （BBG9-1） 6×10^6～10^9 CFU/day (Biofermin Pharmaceutical Co., Ltd., Kobe, Japan) for two months or more were selected. Use of psychiatric medication such as antipsychotics, mood stabilizers, antidepressants, and antianxiety/hypnotics was permitted. Throughout the observation period, the exclusion criteria included undergoing treatment with probiotics and an alternation in psychiatric medication or any medical

treatment that directly affect the patient's defecation habit. Under these criteria, subjects were enrolled retrospectively from January 2017 to March 2018 at Kusatsu Hospital in Hiroshima, Japan.

Outcome measures

Among the treatment of gastrointestinal disorders, use of any type of laxatives (i.e. bulk-forming, hyperosmolar, saline and stimulant laxatives, and intestinal epithelial cell function transformation drugs), prokinetic agents, herbal medicine, and proton pump inhibitor (PPI) were checked in all subjects. We calculated the dopamine D2 receptor blockade of antipsychotic dose using the chlorpromazine equivalent scale that was expressed as CPeq.

To integrate time-sequential change in intestinal function after the initiation of probiotics, we used Bristol stool form scale [18] and gave the same number according to stool form type (e.g., 1=type1, 4=type4, 7=type7 and 'zero=0' on the day without evacuation) based on routine vital records in the present study. These scores were collected on seven consecutive days - the three days before, the day of, and the three days after – at each of three time points: baseline and one and two months following probiotics treatment, and categorized into three indices referred as 'average level', 'constipation level' and 'diarrhea level'. Specifically, the average level (A) was calculated from the total scores minus four time seven, the constipation level (C) from the sum of the score gap of 4 or less and the diarrhea levels (D) from the sum of the score gap of 4 or more, during seven consecutive days (e.g., 3, 6, 2, 4, 7, 1 and 5 in Bristol stool scale: (A) = 28-28 = 0, (C) = (-1)+(-2)+0+(-3) = -6, (D) = 2+0+3+1 = 6).

Statistical analysis

Between BIO-THREE and BIOFERMIN treated subjects, differences of age dived by gender, the levels of CPeq, and the levels of average, constipation and diarrhea were evaluated by unpaired, Mann-Whitney U test, and considered statistically significant at $p<0.05$. Distribution of antipsychotic and gastrointestinal pharmacological treatment status between BIO-THREE and BIOFERMIN treated subjects were analyzed using the chi-square test, to be considered statistically significant at $P<0.05$. Within BIO-THREE and BIOFERMIN treated subjects, multiple comparisons of the calculated levels at baseline and one and two months were performed with repeated-measured ANOVA, followed by post-hoc analysis using Boneferroni adjustment, and considered statistically significant at $P<0.05$. The data were analyzed to see whether there is any significant correlation between the Bristol stool form scale indices (average levels, constipation levels and diarrhea levels at baseline and one and two months in BIO-THREE and BIOFERMIN treated subjects, respectively) and the levels of CPeq using the Spearman's correlation coefficients method, and considered statistically significant at $p < 0.05$.

Results

Sample characteristics and treatment disposition

Subjects consisted of 22 men with a mean age of 59.6 years and 25 women with a mean age of 62.5 years in the BIO-THREE group; and 9 men with a mean age of 42.8 years and 12 women with a mean age of 52.0 years in the BIOFERMIN group. Within both gender, marginal difference was found in mean age between the two groups.

There were no significant differences in the use of antipsychotic and any medication for gastrointestinal disorders between the two groups. The levels of CPeq in the BIO-THREE group was lower than that in the BIOFERMIN group (271.3±42.7 vs 474.1±113.2, mean±se), although not significantly.

The clinical characteristics of subjects taking antipsychotics and gastrointestinal medications are summarized in Table 1.

Sequential changes of the Bristol stool form scale indices with follow up data and evaluation

At baseline, the levels of constipation were significantly lower in the BIO-THREE group than those in the BIOFERMIN group, while no differences were found in the levels of average and diarrhea.

In both groups, the average levels increased and the diarrhea levels decreased at two months from baseline, although not significantly. The levels of constipation were significantly increased at two months from baseline in the BIO-THREE group and not statistically increased in the BIOFERMIN group. The changes of the levels over time from baseline to one and two month are presented in Table 2, and those of constipation in the both groups are separately extracted from the database as Figure 1.

Correlation between the Bristol stool form scale indices and the chlorpromazine equivalent levels

In the BIO-THREE group, the diarrhea levels were significantly negatively correlated with the CPeq levels at two months, while there were no correlations between the average or the constipation levels and the CPeq levels throughout the observation period, and between the diarrhea levels and the CPeq levels at baseline and one month. Moreover, no such correlations were found in the BIOFERMIN group.

They are presented in Table 3, and the significant correlation is separately extracted from database as Figure 2.

Discussion

The results of the present study could be summarized as follows: 1) concomitant use of probiotics was effective to settle subject's defecation even when they have symptoms of chronic constipation and/or diarrhea, 2) probiotics, especially BIO-THREE treatment, improved the status of severe constipation, 3) BIO-THREE treatment led to soften stool form properly correlated with chlorpromazine equivalent.

There are several potential mechanisms of action by which probiotics may benefit functional constipation [19]. First, probiotics modify the gastrointestinal microbiota, intestinal permeability and the systemic immune response, which is known to be altered in constipation [20, 21]. Second, probiotic metabolites

may alter gut function, including suppression of stress induced visceral hypersensitivity [22] and regulation of irritable bowel syndrome [23]. Third, some probiotics increase the production of lactate and short-chain fatty acids (SCFAs), reducing luminal pH, which will enhance colonic peristalsis and shorten WGTT [24, 25]. The latest, the levels of proliferation of probiotics in the intestine correlates with the magnitude of host physiological responses, such as IgA production and mucin secretion modifying T-cell responses [26], and the manipulation of intestinal dysbiosis affect gut motility through regulation of serotonin biosynthesis [27].

Butyrate, one product of SCFAs, plays a strong regulatory role in microbial Toll-like receptors-dependent sensing, which is implicated in gut motility by secreting PYY and GLP-1 [28]. Ge X et al. reported that the butyrate levels were significantly lower in mice from slow-transit constipation (STC) donors than in mice from healthy donors. After supplementation with butyrate, the results of mice from STC donors were reversed in pellet frequency, water percentage, and colonic contractility. Therefore, fecal microbiota from STC donors might regulate gut motility by affecting the production of SCFAs [29].

In culture supernatants, BIO-THREE appeared to stimulate the Th1 immune response, downregulate pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and upregulate anti-inflammatory cytokine (IL-10), that is reasonable to speculate that BIO-THREE redirected the immune system toward an anti-inflammatory phenotype, rather than an aggressive immune response [30]. In clinical studies evaluating the effectiveness of Bio-Three for inducing remission in patients with ulcerative colitis (UC), the decrease in the UC disease activity index after treatment correlated with the decrease in the fecal butyrate concentration [31], and an increased butylate/asetae ratio resulting from decreased absorption of butyrate, an indicator of anti-inflammatory activity is associated with a higher risk of relapse in patients with UC [32].

There are few published studies of probiotic supplementation for patients with a primary psychiatric disorder. Dickerson FB et al. found that in schizophrenia patients receiving ongoing antipsychotic treatment, the probiotic supplemented (combined *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis strain* Bb12) group compared to placebo group was significantly less likely to develop severe bowel difficulty in a randomized, double-blind, placebo-controlled trial [33]. They also reported later that probiotic-induced alterations in the same group of subjects are related to regulation of immune and intestinal epithelial cells through the interleukin-17 (IL-17) family of cytokines, and hypothesize that supplementation of probiotics to schizophrenia patients may improve control of gastrointestinal leakage [34]. Thus, overlapping multiple these mechanism, probiotics may had a beneficial effect on stool consistency in psychiatric subjects.

As for the mechanism of psychotropic drug-induced chronic constipation, its anticholinergic effect on propulsive motility of the colorectum has been highlighted for many years. However, the central dopamine neurotransmission is important for bowel movement because the spinal dopamine system is involved in controlling the defecation reflex through the descending pain inhibitory pathways. In animal study, dopamine in the lumbosacral defecation center causes strong propulsive motility of the colorectum. The

effect of dopamine is a result of activation of sacral parasympathetic preganglionic neurons via dopamine D2 receptors of the descending pain inhibitory pathway [35]. Considering that the dopamine D2 blockade may reduce the stool frequency of schizophrenia patients dose-dependently, the beneficial effects of probiotics on stool consistency may be modulated by the chlorpromazine equivalent levels.

Psychobiotics are beneficial bacteria (probiotics) or support for such bacteria (prebiotics) that influence bacteria–brain relationships. Psychobiotics exert anxiolytic and antidepressant effects characterized by changes in emotional, cognitive, systemic, and neural indices. Bacteria-brain communication channels through which psychobiotics exert effects include the enteric nervous system and the immune system [36]. Therefore, a microbiome-mediated psychological or psychiatric effect sharing a signaling mechanism with psychobiotics should be investigated in an additional study.

There are several limitations to the present study. First, it was a single-center retrospective study design from one psychiatric hospital, and the duration of probiotic treatment was limited to just two months. Second, most of patients received several medications for the treatment of constipation, and lack of control subjects. Third, we used Bristol stool form scale as the only one simple method of assessing change in intestinal function, though change in WGTT from base line correlated with change in defecation frequency and with change in stool output but best with change in stool form as shown in previous study [18]. Finally, the fecal microbiota was not identified and luminal factors modulated by the microbiota such as SCFAs were not measured. So we could not evaluate these changes before and after probiotics supplementation.

Conclusions

Despite these limitations, our findings suggest that stool consistency were improved by probiotics supplementation in psychiatry. Further studies are needed to elucidate the effect of probiotics on gut microbiota using the technique of next generation sequencer.

Abbreviations

CPeq: chlorpromazine equivalent; GLP-1: glucagon-like peptide-1; IL-10: Interleukin-10; IL-17: Interleukin-17; PPI: proton pump inhibitor; PPY: peptide YY; SCFAs: short-chain fatty acids; STC: slow-transit constipation; TNF-α: tumor necrosis factor-α; UC: ulcerative colitis; WGTT: whole gut transit time

Declarations

Ethics approval and consent to participate

The ethics committee of Kusatsu Hospital, Hiroshima, Japan approved this study, and informed consent was obtained in the form of opt-out via an in-hospital bulletin board. All participants and guardians approved to analyze the stacked data during hospitalization. The personally identifiable information could not be specified throughout a research investigation.

Consent for publication

Not applicable.

Availability of data and materials

The data that supported this article are available in Tables 1 and 2 and Figs. 1 and 2. The data sets analyzed during the present study are available from the corresponding author on the reasonable request

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

Drs MN and TN contributed to the concept/design. Dr MN contributed to the data acquisition and the analysis/data interpretation. Drs MN and TN drafted this article. All authors read and approved the manuscript for publication.

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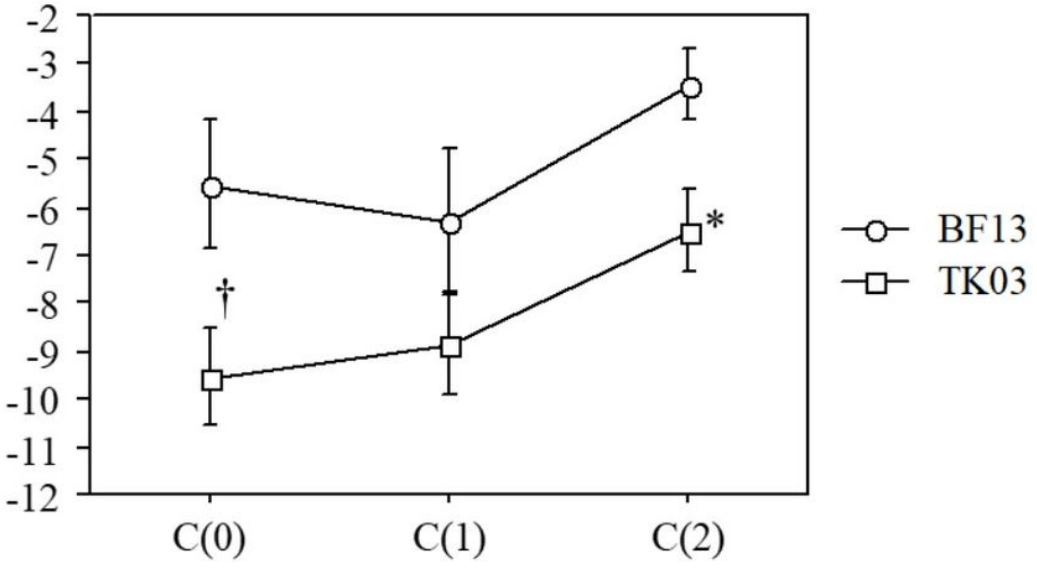
Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

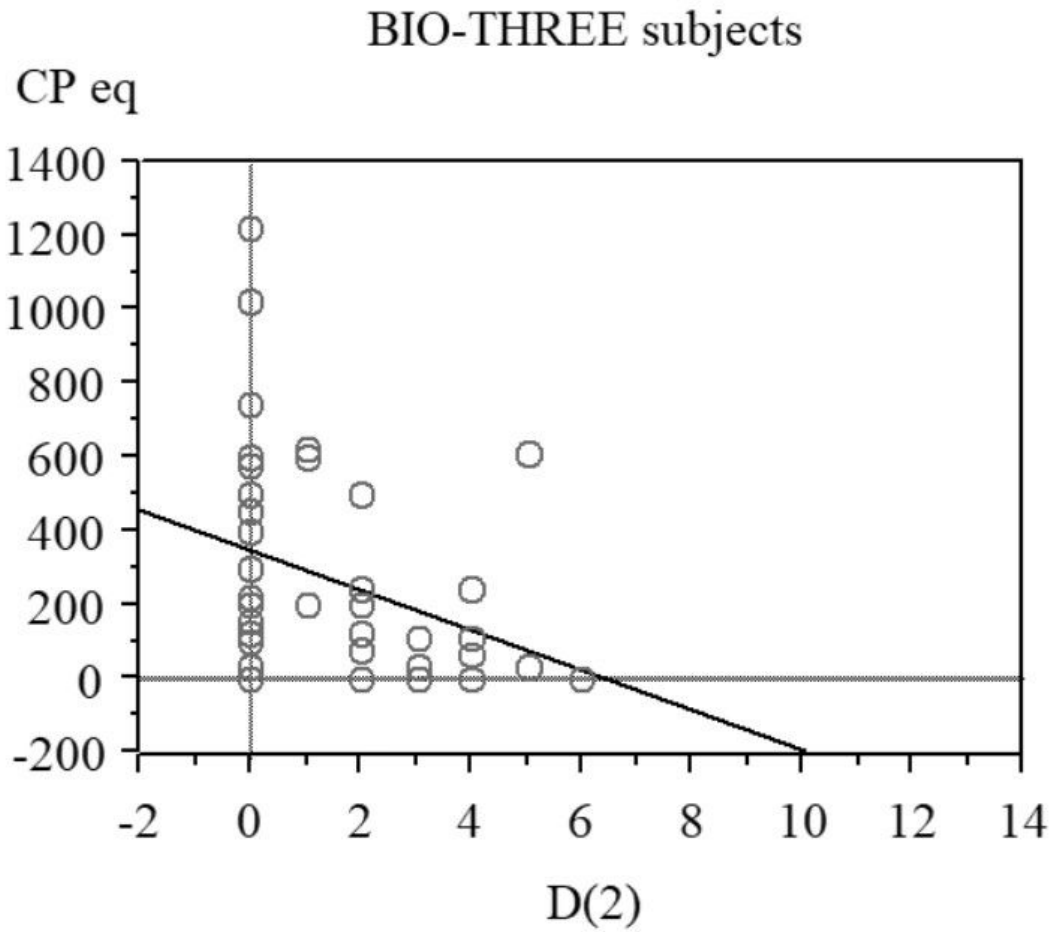


† P < 0.05, for within group comparisons at baseline
* P < 0.05, for intragroup comparisons for each time point relative to the baseline

Abbreviations: BF13 = BIOFERMIN subjects TK03 = BIO-THREE subjects, C = constipation, (0) = baseline, (1) = 1 month, (2) = 2 month

Figure 1

Changes in the levels of constipation at baseline and 1 and 2 months in BIO-THREE and BIOFERMIN subjects



Abbreviations: D = diarrhea, (2) = 2 month, CPeq = chlorpromazine equivalent

Figure 2

Correlation between the levels of diarrhea and the levels of chlorpromazine equivalent at 2 month in BIO-THREE subjects