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A New Acid-Resistant Seamless Capsule of Bifidobacterium Improves Chronic Constipation in Patients on Maintenance Hemodialysis

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Abstract

Objective: To assess the therapeutic efficacy of a new acid-resistant seamless capsule of Bifidobacterium supplements (Bs) for chronic constipation (Cc) in patients on maintenance hemodialysis (MHD).

Design: This was a prospective interventional study.

Setting: This study was performed in a tertiary care hospital.

Subjects: Sixtheen patients on stable MHD (mean ± standard deviation age, 70.4 ± 10.1; mean ± SD duration of dialysis, 10.2 ± 7.4 years) were enrolled. Patients with physical frailty or cognitive decline were excluded.

Intervention: Bs was added to the diet once daily for three months to assess whether it could achieve a beneficial effect on bowel habits in patients on MHD.

Main outcome measure: We used the constipation scoring system (css) and Bristol stool form scale (Bss) for objective assessment of Cc. In this system, the constipation score (cs) ranges from 0 to 30, with 30 being the worst. Bs ranges from 1 to 7, 1 being interpreted as a hard stool and 7 being classified as a liquid one: diarrhea. Results were obtained by patient questionnaire, and scores were calculated monthly.

Results: Compared with baseline, the mean cs improved significantly after the first month (from 10.7 ± 5.9 to 5.0 ± 4.0; $p<0.001$ by one-way analysis of variance with repeated measures). We also confirmed that the mean Bss changed significantly (from 3.4 ± 1.5 to 3.8 ± 1.0; $p<0.02$) after second month.

Conclusion: The results of our study suggest that this new type of Bs may have merit for improving Cc in patients on stable MHD without any adverse effects and is well tolerated.

Keywords: Bifidobacterium; Constipation; Oligosaccharide; Microbiota

Introduction

Chronic constipation (Cc) is widely known as a common health concern for patients on maintenance hemodialysis (MHD) [1]. Strict restriction of foods, such as fresh vegetables or dietary fiber, to avoid hyperkalemia or hyperphosphatemia could worsen the Cc of such patients [2,3]. Hence, nephrologists must find a better way to manage Cc. To date, several probiotics, including Lactobacillus and Bifidobacterium have been thought to be helpful, especially for the digestive system [4]. Hence, it is possible that probiotics may have merit for the improvement of Cc in patients on MHD.

A new acid-resistant seamless capsule of Bifidobacterium supplement (Bs) has recently become available in Japan (Morishita Jintan, Osaka, Japan). This product was developed specifically as a treatment option for Cc in patients on MHD. Thus, we wanted to investigate scientifically whether routine usage of the Bs had therapeutic efficacy for Cc. The aim of this study was to assess the therapeutic efficacy and safety of the Bs in the treatment of Cc in patients on MHD.

Material and Methods

This was a single-center study. We added the new acid-resistant seamless capsule of Bifidobacterium supplement (Bs) to the daily diet of our patients on MHD. In this product, "Bifidobacterium longum JBL01" a strain isolated from humans (2.0 × 109 colony forming units) is encapsulated in an acid-resistant seamless capsule along with an oligosaccharide (lactulose and raffinose). It is produced by Morishita Jintan, Osaka, Japan. It was developed especially for the better management of Cc in patients on MHD. We recognized that it was a type of small granule. According to the regimen, it can be taken

without water. Although that might be better for our patients, because patients on dialysis are usually under water-restriction, we were afraid that some patients would have a risk for mis-swallowing due to physical frailty. Consequently, we excluded patients who had difficulty swallowing. In addition, we excluded patients who were treated with stoma therapy, because it would have been difficult to analyze symptoms related to constipation, such as evacuation effort. In addition, we also excluded patients whose constipation score (details about constipation score were mentioned below) was 0.

The study period was three months. During this time, we carried out laboratory assessments and scored the condition of constipation monthly. In general, Cc has been considered to be a subjective symptom; therefore, we assessed the state of Cc based on the "constipation scoring system" (css) and Bristol stool scale (Bss) for the purpose of objective evaluation of Cc [5,6]. Although there were no commonly used assessment tools for constipation, we noticed that a previous study used the css and concluded that it would be appropriate for our investigation. The scoring system [5] was derived based on answers to the questions in a symptom questionnaire. It was composed of the following eight categories: frequency of bowel movements, painful evacuation effort, feeling incomplete, abdominal pain, minutes in lavatory per attempt, type of assistance, unsuccessful attempts for evacuation per 24 hours and duration of constipation (years). The score of each question ranged from 0 to 4 (zero being the best and 4 being the worst), with the exception of the "type of assistance". In that category, the score ranged from 0 to 2 (without assistance, 0; stimulant laxatives, 1; digital assistance or enema, 2). We summed the scores of these eight questions. In total, the best condition of bowel habit was interpreted as a score of 0, and the worst as a score of 30.

We also used a Bss to investigate whether the stool form could be affected by this Bs. Bss was known as a medical aid designed to classify the form of human feces into seven categories. The types of stool were type 1: separate hard lumps (hard to pass), type 2: sausage-shaped, type 3: like a sausage but with cracks on its surface, type 4: like a sausage or snake, smooth and soft, type 5: soft blobs with clear cut edges (passed easily), type 6: fluffy pieces with ragged edges, a mushy stool and type 7: watery, no solid pieces, entirely liquid. In summary, type 1 and 2 might indicate constipation, with 3 and 4 being the ideal stools (4 was much better) and type 5-7 tending towards diarrhea.

Besides, it had been reported that Bss was a useful surrogate measure of colon transit time, which was suggested to be associated with chronic constipation [7].

Taken together, we concluded that using these two scales to evaluate the state of Cc could be reasonable.

During the research period, we continued to prescribe necessary daily drugs, such as a phosphate binder or a laxative, as appropriate. Even though this Bs was not a drug but a kind of food, we recognized that our trial might be considered a prospective clinical trial; therefore, these methods were discussed and approved by the ethical committee of our hospital. We also obtained written informed consent to participate in the study from every enrolled patient.

Statistical analysis was performed with Stat View software version 5.0 for Windows. Data were expressed as mean ± standard deviation. The Wilcoxon signed-rank test and one-way analysis of variance (ANOVA) with repeated measures were used for the collected data. $P<0.05$ was considered statistically significant.

Results

The characteristics of the enrolled patients are summarized in Table 1. Two patients dropped out during the study period; consequently, 16 patients were enrolled. Our patients were elderly and under long-term hemodialysis. The mean ± standard deviation (SD) age was 70.4 ± 10.1 years, and the mean ± SD duration of dialysis was 10.2 ± 7.4 years. Laboratory data were obtained just before the first session of routine hemodialysis in a week.

Baseline characteristics of enrolled patiets (N=16)	
Age	70.2 ± 10.1
Duration of dialysis (year)	10.2 ± 7.4
Male/Female	11/5
Hb (g/dl)	10.7 ± 1.4
UA (mg/dl)	6.4 ± 1.5
BUN (mg/dl)	60.8 ± 9.7
Cr (mg/dl)	9.9 ± 2.7
*Ca (mg/dl)	8.8 ± 0.5
P (mg/dl)	5.2 ± 1.3
Alb (g/dl)	3.9 ± 0.3
Tchol (mg/dl)	186 ± 83
TG (mg/dl)	105 ± 52
nPCR (g/kg/day)	0.8 ± 0.2
GNRI	95.2 ± 6.5
Constipation Score	10.7 ± 5.9
Bristol stool scale	3.4 ± 1.5
Assistance for constipation (%)	50(8/16)

Table 1: Baseline characteristics of enrolled patients (N=16). Albumin-adjusted Ca concentration is indicated as *Ca.

Abbreviations: Alb, albumin, UA, uric acid, BUN, blood urea nitrogen, Hb, hemoglobin, TG, triglyceride, Tchol, total cholesterol, nPCR, normalized protein catabolic rate, GNRI, Geriatric Nutritional Risk Index.

The data are expressed as mean and standard deviation

The data were within recommended range, as described in the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guidelines [8]. To compare the nutritional status of the enrolled patients before and after the study, we used the GNRI (Geriatric Nutritional Risk Index) [9]. At baseline, the average constipation score (cs) of the participants was 10.7, and the median score was 12.5 (range, 1-18). Half of the patients needed assistance for constipation, such as laxatives or enemas. The average Bristol stool scare was 3.4, and the median was four (range, 1-5). Figure 1 shows the change in the cs (panel A) and Bss (panel B) during the study period. The cs improved significantly ($P<0.001$) after only one month since we had initiated the research. We could also ascertain that the cs was maintained to the end

of the study period. Besides, the Bss was also changed significantly ($p<0.02$) at second month.

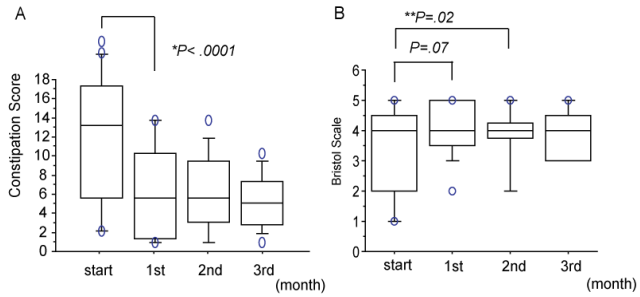

Figure 1: The constipation score for enrolled patients (panel A) and Bristol stool form scale (panel B) were measured monthly during the study period. Data are shown as box plot. Results of the statistical analysis are shown.

A comparison of GNRI and total-cholesterol is shown in Figure 2. There was no significant change in GNRI throughout the study. However, the total-cholesterol concentration was elevated significantly by the end of the study period (P=0.02).

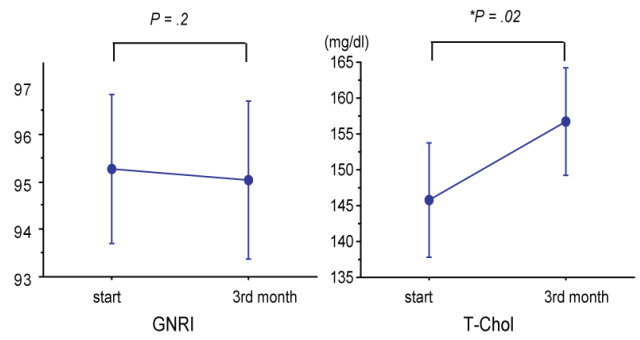

Figure 2: The comparison of results for changes in GNRI (Geriatric Nutritional Risk Index) and total cholesterol (mg/dl) concentrations over time. The data are expressed as mean and standard deviation. Results of the statistical analysis are shown.

Discussion

To our knowledge, this is the first study to assess the therapeutic efficacy of a specific Bs for Cc in patients on MHD. Hence, we consider our results to be of interest and worth reporting. We speculated that successful delivery of active bifidobacterium without being damaged by gastric acid could be necessary to improve the intestinal environment [10]. Besides, it had been reported that a kind of probiotics might contribute to improve bowel symptoms such as diarrhea or constipation by altering microbiota and insetinal flora. Thus, our Bs would be consistent with this concept [11-13].

It would be difficult to evaluate the clinical state of "constipation" in certain patients [14]. Moreover, it is difficult to initiate a quantitative research study about constipation in many patients due to lack of established consensus about the clinical definition of "constipation" or "improvement of constipation" [15]. However, to determine whether a probiotic supplement is effective for constipation, we needed to evaluate it based on an objective measure. As a result, we chose the css and Bss for the purpose of comparing the state or severity of constipation in this study.

As indicated in panel A in Figure 1, the cs improved significantly after the first month of Bs administration. This was much earlier than we had expected. In addition, we confirmed the effect of the Bs throughout the study period. In a correlation analysis, we found that the cs had strongest correlation with the score of "feeling incomplete" ($r=0.8$, $P=0.0004$). This symptom, an important factor of constipation, was also remarkably improved after the first month. In contrast, the score of "assistance for constipation" showed no significant change (data not shown). We interpreted the result as follows: Despite the fact that one of the annoying symptoms of their constipation had improved, some enrolled patients were reluctant to withdraw their laxative drugs. This might be reasonable, because the Bs was not a drug with immediate effects for constipation. The Bs was considered to be a kind of food with probiotics. Thus, we speculated that routine use of the Bs might gradually change the intestinal environment of the patients. Consequently, we could obtain a preferable result about "feeling incomplete". The result of Bss (panel B) might suggest that the form of the stool had been changed from slightly hard to soft. We could speculate that the form of stool might be closely associated with constipation. Hence, these two results could be consistent with each other. Taken together, we hypothesized that a dysbiosis of our MHD patients would gradually be altered with the aid of this Bs. To date, the interesting discussion about relationship between intestinal microbiota and complication of chronic kidney disease had been raised [16].

Our study had several limitations. First, it was a single-center study, and the number of enrolled patients was limited. Hence, the results must be confirmed in a larger study. Second, our patients were elderly; therefore, we need to obtain results from a different generation. Third, we tried to accomplish quantitative research about "constipation" in patients on MHD; however, our "constipation scoring system" was not a standard tool based on well-established consensus.

Moreover, we couldn't exclude the possibility that our result might be affected a by a placebo effect of this supplement.

Despite these limitations, we conclude that this new Bs was helpful and well tolerated for the improvement of Cc in patients on MHD in a larger study. Second, our patients were elderly; therefore, we need to obtain results from a different generation. Third, we tried to accomplish quantitative research about "constipation" in patients on MHD; however, our "constipation scoring system" was not a standard tool based on well-established consensus. Despite these limitations, we conclude that this new Bs was helpful and well tolerated for the improvement of Cc in patients on MHD.

Consequently, we concluded that assessing the detail mechanism of dysbiosis in our MHD patients might also be valuable.

In summary, we confirmed that the Bs would be effective for the improvement of Cc in patients with MHD.

We evaluated whether the patients' nutritional status was affected by comparing the GNRI; however, it was relatively stable (Figure 2). Interestingly, the concentration of total cholesterol increased significantly, while triglyceride concentrations did not change (data not shown). This could be a merit for the improvement of malnutrition frequently detected in MHD patients [17]. Nevertheless, other previous work reported a cholesterol-lowering effect of bifidobacterium [18,19]

therefore, we needed to carefully consider whether the result was acceptable. A detailed analysis of the relationship between Bs consumption and fat metabolism warrants further investigation.

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