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Original Article

Saccharomyces boulardii and Lactulose for Childhood Functional Constipation: A Multicenter Randomized Controlled Trial

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Background/Aims
The effects of probiotics in children vary based on diseases and probiotic strains. We aim to investigate the effectiveness of *Saccharomyces boulardii* and lactulose for treating childhood functional constipation.

Methods
This open-label randomized controlled trial was conducted at 10 university hospitals in Korea. Children who were diagnosed with functional constipation were allocated to 3 groups (lactulose monotherapy, combination therapy, and *S. boulardii* monotherapy). The primary outcome was treatment success rate that was accordingly defined as ≥ 3 bowel movements without incontinence at week 12. The cumulative successful maintenance and drug maintenance rates without drug changes were calculated throughout the study period. We compared stool frequency, incontinence, consistency, and painful defecation at week 2 among the 3 groups.

Results
Overall, 187 children were assigned to the lactulose monotherapy (n = 69), combination therapy (n = 68), or *S. boulardii* monotherapy (n = 50) groups. The primary outcome was significantly higher in the lactulose monotherapy group (26.1%) or combination therapy group (41.2%) than in the *S. boulardii* monotherapy group (8.0%). The *S. boulardii* monotherapy group showed a significantly lower cumulative successful maintenance and drug maintenance rate than the other 2 groups. There were no significant intergroup differences in the frequency of defecation, incontinence, painful defecation, or stool consistency during the follow-up at week 2.

Conclusion
S. boulardii monotherapy was not superior to lactulose monotherapy or combination therapy and showed a higher drug change rate, supporting the current recommendation of probiotics in the treatment of childhood functional constipation.
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Key Words
Constipation; Microbiota; Pediatrics; Probiotics

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Introduction

Functional constipation (FC) in children affects neonates to adolescents, has a high prevalence, and tends to become chronic, accounting for a relatively high health care burden. Its prevalence varies from 0.7% to 29.6%, depending on the diagnostic criteria and age.[1]

Recent advances in 16S recombinant DNA gene sequencing have led to active research on the association between the gut microbiome and gastrointestinal diseases, including constipation, inflammatory bowel disease, and other allergic diseases, type 2 diabetes, and behavioral disorders.[2-4] A survey of pediatricians and pediatric gastroenterologists in the Netherlands revealed that the prescription rates of prebiotics or probiotics for the treatment of childhood FC were remarkably higher than those among United States physicians (32.0%). Both general pediatricians (27.0%) and pediatric gastroenterologists (19.0%) frequently prescribed prebiotics or probiotics.[5] According to a recent nationwide survey of the Korean Society of Pediatric Gastroenterology, Hepatology, and Nutrition, children with FC aged > 1 year were most commonly prescribed lactulose (59.1%), followed by polyethylene glycol (PEG) 4000 (17.7%), and 11.8% of respondents prescribed probiotics as the first-line maintenance treatment for these children.[6]

Although it is unclear how probiotics affect FC, some adult studies have reported that probiotics modulate colonic transit time and reduce functional gastrointestinal symptoms.[7,8] However, the effectiveness of probiotics in the treatment of childhood constipation remains controversial. Two recent systematic reviews of probiotics for childhood FC reported different conclusions.[9,10] One study showed no difference in treatment success between the probiotic and control groups,[9] while the other concluded that probiotics increased stool frequency and had other beneficial effects in Asian children.[10] In addition, most probiotic species used to treat FC belong to the genera *Lactobacillus* or *Bifidobacterium*.[9-15] Although several clinicians have demonstrated beneficial effects of *Saccharomyces boulardii* on acute and chronic gastrointestinal diseases, such as antibiotic-associated diarrhea, *Clostridium difficile* infection, acute diarrhea, *Helicobacter pylori* infection, inflammatory bowel disease, and irritable bowel syndrome,[16] no studies have evaluated the efficacy of *S. boulardii* in treating FC.

This study aims to investigate the effectiveness of *S. boulardii* versus lactulose monotherapy or combination therapy (lactulose plus *S. boulardii*) for the treatment of childhood FC.

Materials and Methods

Study Population

This randomized, open-label, multicenter study was conducted between July 2019 and November 2020. Pediatric gastroenterologists from 10 academic tertiary hospitals participated in this study. Patients aged 6 months to 10 years who were diagnosed with FC using the Rome IV criteria were eligible for inclusion. According to the Rome IV criteria, FC is defined as the presence of at least 2 of the following symptoms or signs for at least 1 month without an organic cause: ≤ 2 defecations per week, history of excessive stool retention, painful or hard bowel movements, presence of a large fecal mass in the rectum, history of large-diameter stools that could obstruct the toilet, and for toilet-trained children, ≥ 1 episode of incontinence per week.[17,18]

We excluded patients with organic causes of constipation such as Hirschsprung's disease, spina bifida, hypothyroidism, metabolic disorder, intellectual disability, or other gastrointestinal diseases, as well as those taking medications that could affect the gastrointestinal system, including oral laxatives or probiotics, for more than 2 weeks. The institutional review board of each hospital approved this study (2019GR0184). Written informed consent was obtained from the parents of each patient. This clinical trial was registered with the Clinical Research Information Service of the Korea Center for Disease Control and Prevention (KCT0004155).

Study Design, Intervention, and Randomization

The study was conducted over a treatment period of 12 weeks with 4 visits (baseline, 2 ± 1, 6 ± 2, and 12 ± 3 weeks). At the baseline visit, we included patients who met the inclusion criteria.

We randomly assigned the patients to the lactulose monotherapy, combination therapy, or *S. boulardii* monotherapy groups. We used Duphalac Easy syrup (JW Pharmaceutical, Seoul, Korea) containing 1.34 g/mL of lactulose and Bioflor 250 mg powder (Kuhnil Pharmaceutical, Seoul, Korea) containing 5×10^9 colony forming units of *S. boulardii* per sachet for monotherapy and combination therapy. The starting dosage of Duphalac Easy syrup was 1 mL/kg/day, and a dosage change was allowed according to any clinical improvement noted during the follow-up period. The dosage of *S. boulardii* was based on patient age (up to 2 years old, 2 sachets/day; over 2 years old, 3 sachets/day). The *S. boulardii* dosage was not adjusted according to clinical outcomes. Drug changes due to poor outcomes, poor compliance, or side effects were also recorded during the follow-up period. Patients were not permitted to use other laxatives or probiotics during the study period.

All patients received glycerin enemas for disimpaction before the intervention. Their parents were encouraged to keep stool diaries to enable the estimation of treatment effects, side effects, and interventional compliance. The stool diary included information on stool frequency per day, fecal incontinence frequency, stool consistency in terms of Bristol Stool Form Scale scores (7-point scale, 1 for separate hard lumps to 7 for watery stool),[19] frequency of painful bowel movements, and side effects such as abdominal pain, vomiting, abdominal distension, and diarrhea. During each visit, the physician checked patient compliance and the dosage of lactulose or *S. boulardii*.

Since there are no previous studies using a study regimen, data using *Lactobacillus* spp. were used for sample size estimation.[20] The sample size calculation formula was $n = [Z_{1-\alpha/2} + Z_{1-\beta}]^2 [p_1(1-p_1) + p_2(1-p_2)]/(p_1-p_2)^2$ with a difference of 30% and a power of 90% ($\alpha = 0.05$; $1-\beta = 0.90$). It was calculated as 56 in each arm, and we added 15% of the estimated drop-out. We added group 3 (*S. boulardii* monotherapy group) with the same numbers. Therefore, the estimated sample size was 65 per arm and a total of 195. The ratio of sample sizes was 1:1:1 for lactulose monotherapy, combination therapy, or *S. boulardii* monotherapy groups.

Randomization was implemented automatically using Random Allocation Software 2.0 (Informer Technologies, Inc, Dallas, TX, USA) with a random block size. Stratification was performed between the institutes.

Outcomes

Treatment success was defined as ≥ 3 defecations per week (and in toilet-trained children, no incontinence episodes) was calculated at each visit, and the treatment success rate at 12 weeks was considered as the primary outcome.

A drug change was defined as discontinuation of the administration of lactulose or *S. boulardii* and the addition of lactulose in the *S. boulardii* group. Drug changes were made when there was poor treatment outcome, poor compliance, and/or other side effects. Therefore, drug changes did not have the same meaning as treatment failure. We simply analyzed the drug change rate during the entire study period.

We investigated cumulative treatment outcomes throughout the study period using Cox regression analysis. The "cumulative successful maintenance rate" was defined as the success rate during the study period considering censored cases, and the "cumulative drug maintenance rate" was the maintenance rate of the original drug during the study period regardless of treatment success.

We compared other clinical outcomes such as stool frequency, consistency (Bristol Stool Form Scale score), frequency of fecal incontinence, and frequency of painful defecation at 2 weeks. We also compared the side effects, lactulose dosage, drug change rate, and follow-up loss rate.

Statistical Methods

Categorical variables, such as treatment success, were compared using the χ^2 test or Fisher's exact test. An analysis of variance was used to compare continuous variables such as defecation frequency, incontinence frequency, painful defecation frequency, and stool consistency. Repeated-measures analysis of variance was also performed to evaluate within-subject factors, treatment group factors, and between-subject factors. We used a *t* test to compare the successful dosage of lactulose between the lactulose monotherapy and combination groups. Analyses of the primary outcomes were performed on an intention-to-treat (ITT) basis, in which all participants in a trial were analyzed according to the intervention they were assigned regardless of whether they received it or not. We also used per-protocol (PP) analysis (including those patients who completed treatment) of the treatment success rate at week 2, clinical outcomes, and side effects.

Since the proportion of missing data was large, and higher drug change rates (up to 46.0%) were observed in the S. bouradii group, a simple treatment success rate at 12 weeks or imputation method could have bias. Therefore, we used the complete case analysis method for missing data.[21] We analyzed the cumulative successful maintenance rate and drug maintenance rate by Cox regression test to reflect follow-up loss and drug change during the study period. We adjusted for sex for the Cox regression analysis because there were sex differences among the 3 groups. The effect of the

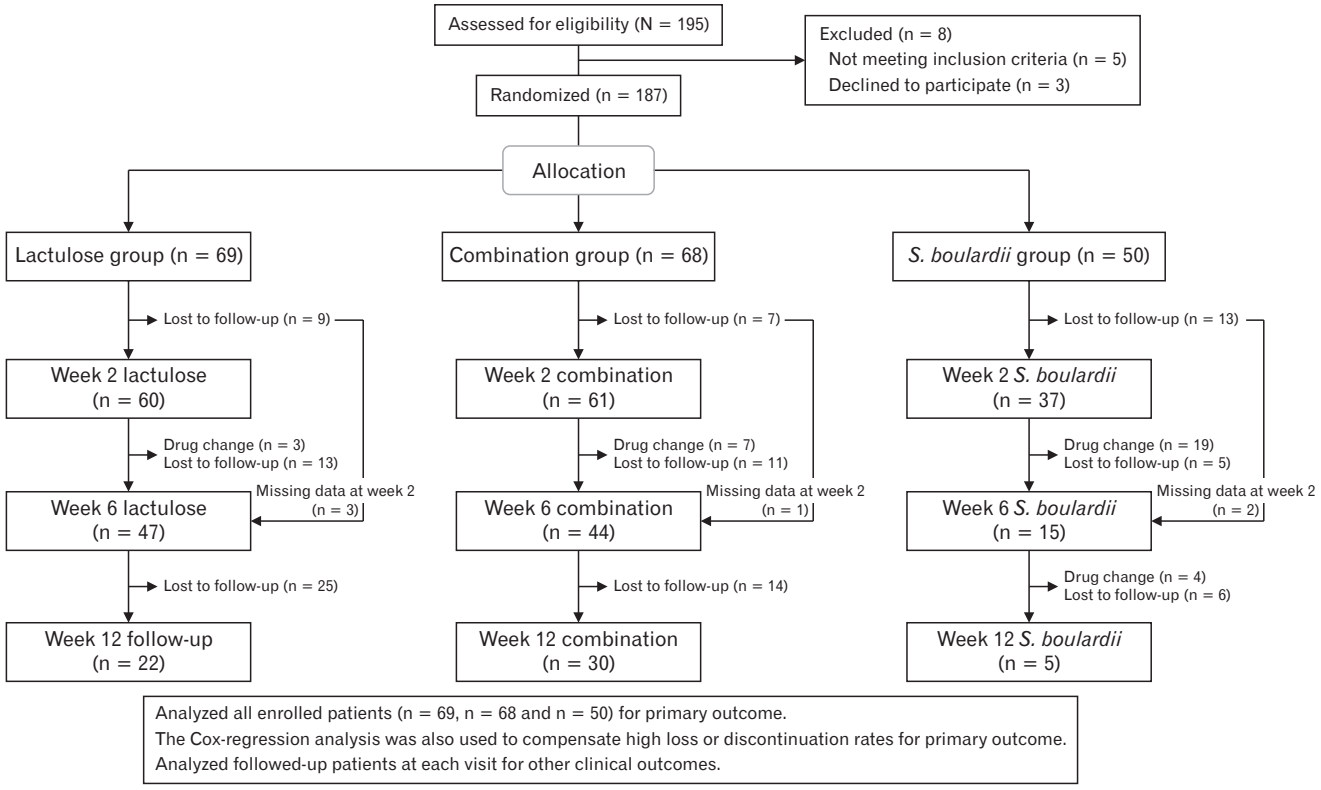


Figure 1. Study diagram. *S. boulardii, Saccharomyces boulardii.*

intervention on treatment failure and drug change through week 12 is expressed as a hazard ratio with 95% confidence interval (CI) derived from Cox regression. Treatment failure or drug change was coded as an event, and the final follow-up duration was used as the time period. Data were presented as the mean and standard deviation. The data were analyzed using SPSS version 21.0 software (IBM Corp, Armonk, NY, USA). Intergroup differences were considered to be significant at $P < 0.05$.

Results

Demographics

A total of 187 children with FC were randomly assigned to the lactulose monotherapy (n = 69 [36.9%]), combination therapy (n = 68 [36.4%]), and *S. boulardii* monotherapy (n = 50 [26.7%]) groups (Fig. 1). The patients' baseline characteristics and clinical characteristics are shown in Table 1. There were no differences in age, disease duration, or other clinical characteristics among the 3 groups. Approximately 17.4% of patients reported previously using laxatives, whereas 40.8% of the patients had previously used probiotics.

Primary Outcomes, Drug Change Rate, and Follow-up Loss Rate

The treatment success rate at week 12 was significantly higher in the lactulose monotherapy group (26.1%) or combination therapy group (41.2%) than in the *S. boulardii* monotherapy group (8%) ($P < 0.019$ and $P < 0.001$, respectively) (Table 2). These differences were also observed between the *S. boulardii* and combination therapy groups at weeks 2 and 6. The drug change rate during the study period was significantly higher in the *S. boulardii* monotherapy group (46.0%) than in the other 2 groups ($P < 0.001$). At week 2, medications were changed for 19 of 50 (38.0%) patients in the *S. boulardii* monotherapy group; lactulose addition was commonly used in this group (n = 17, 89.5%) following a change to PEG 4000 (n = 2, 10.5%). However, in the lactulose monotherapy and combination groups, the medication for most of the patients was changed to PEG 4000 (n = 3, 100.0%; n = 5, 71.4%). At week 6, the medication of 4 patients in the *S. boulardii* monotherapy group was changed to lactulose (n = 3) or PEG 4000 (n = 1).

The Cox regression analysis showed significant differences in cumulative successful maintenance and drug maintenance rates

Table 1. Patients' Baseline Characteristics

Clinical characteristics	Lactulose (n = 69)	Combination (n = 68)	*S. boulardii* (n = 50)	*P*-value
Male	33 (47.8)	24 (35.3)	29 (58.0)	0.047[a]
Female	36 (52.2)	44 (64.7)	21 (42.0)	
Age (mo)	42.3 ± 23.7	44.4 ± 23.6	38.6 ± 23.7	0.176
Disease duration (mo)	11.4 ± 11.3	7.6 ± 9.4	9.1 ± 11.2	0.109
Previous use of laxatives	9 (13.2)	17 (25.0)	7 (14.0)	0.178
Previous use of probiotics	27 (39.1)	28 (41.2)	21 (42.0)	0.970
Stool frequency/week	2.7 ± 1.8	2.9 ± 2.7	2.7 ± 2.2	0.883
Incontinency/week	1.2 ± 6.0	0.9 ± 3.0	3.0 ± 8.7	0.153
Stool consistency	1.7 ± 0.7	1.6 ± 0.8	1.9 ± 0.8	0.055
Painful defecation	66 (95.7)	63 (92.6)	49 (98.0)	0.396
Painful defecation/week	2.6 ± 1.8	2.3 ± 2.6	2.1 ± 1.3	0.484

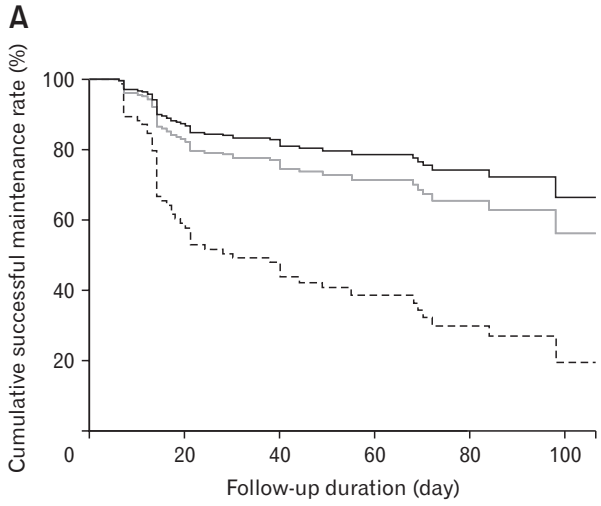
[a]Gender differences was observed between combination therapy group and *S. boulardii* monotherapy group.
S. boulardii, *Saccharomyces boulardii*.
Values are shown as n (%) or mean ± SD.

Table 2. Study Outcomes

Treatment outcomes	Analysis	Lactulose (n = 69)	Combination (n = 68)	*S. boulardii* (n = 50)	*P*-values		
					Lactulose vs Combination	Lactulose vs *S. boulardii*	Combination vs *S. boulardii*
Treatment success rates at each visit							
Week 12	ITT	18/69 (26.1)	28/68 (41.2)	4/50 (8.0)	0.086	0.019	< 0.001
Week 6	ITT	40/69 (58.0)	36/68 (52.9)	12/50 (24.0)	0.576	< 0.001	< 0.001
Week 2	ITT	39/69 (56.5)	42/68 (61.8)	19/50 (38.0)	0.799	0.087	0.018
	PP	39/60 (65.0)	42/61 (68.9)	19/37 (51.4)	0.702	0.206	0.091
Clinical outcomes at week 2		Lactulose (n = 60)	Combination (n = 61)	*S. boulardii* (n = 37)		*P*-values	
Stool frequency/week	PP	4.05 ± 2.49	4.57 ± 2.91	3.69 ± 2.60		0.264	
Incontinency/week	PP	0.53 ± 1.69	0.56 ± 1.66	0.96 ± 3.63		0.627	
Stool consistency	PP	3.38 ± 1.23	3.54 ± 1.32	2.92 ± 1.04		0.051	
Painful defecations/week	PP	0.48 ± 0.5	0.64 ± 0.97	0.68 ± 0.75		0.359	
Follow-up loss rate	ITT	9/69 (13.0)	7/68 (10.3)	13/50 (26.0)	0.616	0.072	0.025
Drug change rate during study period	ITT	3/69 (4.3)	7/68 (10.3)	23/50 (46.0)	0.511	< 0.001	< 0.001

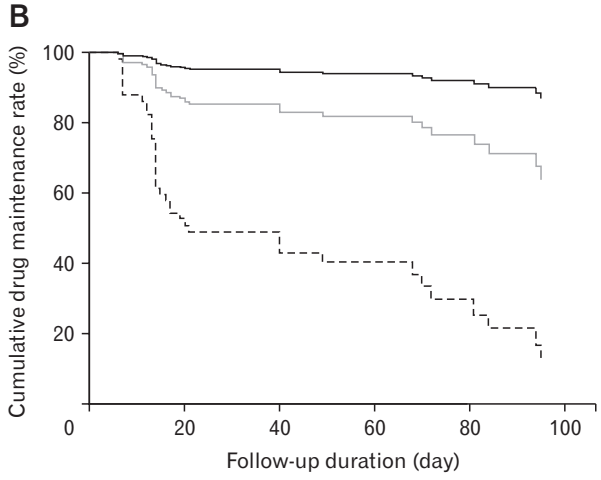
S. boulardii, *Saccharomyces boulardii*; ITT, intention-to-treat analysis; PP, per-protocol analysis.
Values are shown as n (%) or mean ± SD.

during the follow-up period after sex adjustment (Fig. 2). The *S. boulardii* monotherapy group showed a significantly lower cumulative successful maintenance rate than the lactulose monotherapy group (hazard ratio, 0.255; 95% CI, 0.143-0.456; $P < 0.001$) or combination therapy group (hazard ratio, 0.367; 95% CI, 0.210-0.639; $P < 0.001$; Fig. 2A). However, no differences were observed between the lactulose monotherapy and combination therapy groups (hazard ratio, 0.726; 95% CI, 0.392-1.347; $P = 0.310$). The *S. boulardii* monotherapy group showed a significantly lower cumulative drug maintenance rate than the lactulose monotherapy group (hazard ratio, 0.071; 95% CI, 0.024-0.205; $P < 0.001$) or combination therapy group (hazard ratio, 0.21; 95% CI, 0.102-0.434; $P < 0.001$; Fig. 2B). The combination therapy group also showed a significantly lower cumulative drug maintenance rate than the lactulose monotherapy group (hazard ratio, 0.27; 95% CI, 0.084-0.863; $P = 0.027$).



Risk ratio for treatemat failure	Risk ratio (95% CI)	*P* value
Lactulose monotherapy compared to *S. boulardii* monotherapy	0.255 (0.143-0.456)	< 0.001
Combination therapy compared to *S. boulardii* monotherapy	0.367 (0.210-0.639)	< 0.001
Lactulose monotherapy compared to combination therapy	0.726 (0.392-1.347)	0.310

Number at risk	Week 2	Week 6	Week 12
Lactulose monotherapy	58	34	11
Combination therapy	52	31	20
S. boulardii monotherapy	25	12	3



Risk ratio for drug change	Risk ratio (95% CI)	*P* value
Lactulose monotherapy compared to *S. boulardii* monotherapy	0.071 (0.024-0.205)	< 0.001
Combination therapy compared to *S. boulardii* monotherapy	0.210 (0.102-0.434)	< 0.001
Lactulose monotherapy compared to combination therapy	0.270 (0.084-0.863)	0.027

Number at risk	Week 2	Week 6	Week 12
Lactulose monotherapy	57	48	11
Combination therapy	52	46	15
S. boulardii monotherapy	25	12	3

Figure 2. Cumulative successful maintenance rate and drug maintenance rate during the study period by treatment group. (A) Cumulative successful maintenance rate during the study period. (B) Cumulative drug maintenance rate during the study period. Cox regression analysis was performed with gender adjustment. *S. boulardii, Saccharomyces boulardii*.

Other Clinical Outcomes and Adverse Events

There were no differences in the frequencies of defecation, incontinence, or painful defecation or stool consistency among the 3 groups at week 2 (Table 2). The follow-up loss rate at week 2 was significantly higher in the *S. boulardii* monotherapy group (26.0%) than in the combination group (10.3%, $P = 0.025$). However, there was no difference between the lactulose monotherapy and combination groups ($P = 0.616$).

Repeated-measures analysis of variance showed that treatment efficacy for these outcomes over time did not differ among the 3 groups: fecal incontinence ($P = 0.213$), defecation frequency ($P = 0.713$), painful defecation ($P = 0.769$), and stool consistency ($P = 0.534$).

Although the combination therapy group showed significantly lower successful doses of lactulose at week 2 compared to the lactulose monotherapy group (0.97 vs 1.11 mL/kg/day, $P = 0.014$), this difference was not maintained at weeks 6 (1.18 vs 1.41 mL/kg/day) and 12 (1.25 vs 1.33 mL/kg/day).

Abdominal pain was the most common adverse event (20.9%, 11.3%, and 1.8% at weeks 2, 6, and 12, respectively), followed by diarrhea (6.3% and 4.7% at weeks 2 and 6, respectively), abdominal distension (4.4% at week 2), and vomiting (1.3% at week 2). The frequency of adverse effects decreased from week 2 to week 12; no vomiting or distension was observed at week 6; and no vomiting, distension, or diarrhea was observed at week 12. There were no intergroup differences in the adverse events.

Discussion

To the best of our knowledge, this is the first study to evaluate the effectiveness of *S. boulardii* versus lactulose for treating FC. Although many studies have evaluated the beneficial effects of probiotics, especially *Bifidobacterium* and *Lactobacillus*, on FC,[9-15] no study has particularly investigated the effects of *S. boulardii* on FC.

S. boulardii, a non-pathogenic yeast discovered in 1923, effectively prevents and treats several acute and chronic gastrointestinal disorders by restoring intestinal barrier function.[16,22] Through multiple mechanisms, such as antimicrobial activity, antitoxin effects, cross-talk with normal microbiota, trophic action on the intestinal mucosa, and immune response regulation, *S. boulardii* benefits patients with acute and chronic intestinal diseases.[16] Some experimental studies demonstrated that *S. boulardii* affects intestinal permeability, suggesting its beneficial effects on inflammatory bowel disease and irritable bowel syndrome.[23-25] One study reported that constipation-induced dysbiosis could destroy intestinal barrier function.[26] A previous randomized controlled trial concluded that *S. boulardii* was helpful for abdominal pain severity, diarrhea, flatulence, and gurgling in irritable bowel syndrome patients, constipation symptoms were not relived,[27] However, there has been no study on *S. boulardii* for FC. Therefore, we investigated the effects of *S. boulardii* on childhood FC.

We report significantly different treatment outcomes between the *S. boulardii* monotherapy and lactulose monotherapy or combination therapy groups. The primary outcome of treatment success at week 12 was significantly lower in the *S. boulardii* group than in the other 2 groups, and this result was the same at week 6 by ITT analysis. However, there was no significant difference in treatment success rate between the lactulose monotherapy and combination groups during the study period. Furthermore, a significantly higher drug change rate was observed in the *S. boulardii* group than in the other 2 groups.

Unfortunately, a large amount of missing data occurred in our study, so we could not provide PP analysis at week 6 and week 12. Although the PP analysis provides a clear efficacy of a treatment intervention, this result does not reflect the real-world situation and usually shows overestimated treatment effects.[28,29] *S. boulardii* was discontinued and replaced by drugs during the early study period because of treatment failure or poor compliance. Our study also showed optimistic treatment effect of *S. boulardii* in PP analysis although only 5 (10.0%) patients were strictly adhered to the protocol in *S. boulardii* monotherapy group. As mentioned earlier, owing to the large proportion of missing data, the imputation method was not appropriate in our study.[21] Therefore, we only showed results of PP analysis for these clinical outcomes at week 2 because of the missing data that had the same problems.[28,29] Other clinical outcomes such as frequencies of defecation, incontinence, and painful defecation as well as stool consistency at week 2 were not different among the 3 groups by PP analysis. The reason why that there were no differences in these clinical outcomes was probably because the patients who did not improved were not followed up.

In our study, missing data were caused by several complex factors. A previous pediatric study also had a very low recruitment rate (23.8%) compared to the estimated sample size because pediatric FC is not a severe disease.[12] However, this may be a characteristic of childhood FC treatment in real-world practice. Furthermore, the coronavirus disease was a pandemic on March 11 2020,[30] and the Korean government declared social distancing rules. This situation made it difficult for our patients to visit our clinics. Lastly, the low efficacy of the study medication could be a reason for follow-up loss. Even considering the high follow-up loss rate, the sample size of our study was similar to or greater than that of other probiotic randomized controlled trials for childhood FC.[12,13,20,31,32]

We used Cox regression analysis to reflect missing data, which also showed inferior results for *S. boulardii* monotherapy versus lactulose monotherapy or combination therapy. The cumulative drug maintenance rate was higher in the lactulose monotherapy group than in the combination therapy group because of the discontinuation of *S. boulardii* in the combination therapy group. The only effect of *S. boulardii* observed was a lower successful dose of lactulose in the combination group (0.97 mL/kg/day) than in the lactulose monotherapy group (1.11 mL/kg/day) at week 2; however, this effect was not maintained until week 6 or 12.

A randomized study reported that children who consumed yogurt with *Bifidobacterium lactis* supplementation showed improved defecation frequency, but this increase was comparable to that of the control group.[33] In another study on *Lactobacillus casei rhamnosus* and *Lactobacillus reuteri* compared to placebo in children with FC, *Lactobacillus* was not superior to placebo.[32,34] One study compared the efficacy of *Lactobacillus rhamnosus GG* as an adjunctive therapy to lactulose in children aged 2-6 years with FC. The study showed no differences in treatment success, defined as ≥ 3 per week without incontinence, at 12 weeks and 24 weeks between the lactulose monotherapy and lactulose plus *L. rhamnosus GG* group.[15] However, other studies have reported beneficial effects of *L. reuteri* on defecation frequency in young infants[20] and *L. casei rhamnosus* resulted in higher defecation frequency and treatment

success than a placebo in Asian children with FC.[20]

Therefore, the effects of probiotics on pediatric constipation remain controversial.[9,10]

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition, and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition have developed guidelines for the evaluation and treatment of FC in children.[35] The guidelines recommended PEG as the first-line treatment for childhood FC with fecal impaction. Lactulose is also recommended if PEG is not available. However, they did not support the use of pre- or probiotics for the treatment of childhood constipation because of a lack of evidence. Many previous studies have reported the infectiveness of probiotics for treating childhood FC.[35]

The main limitation of our study was the high follow-up loss rate. We described parallel results of the ITT and PP analyses in addition to Cox regression analysis to allow readers to interpret the effect of our intervention. We also declare the pitfalls of the complete case analysis for dealing with missing data. Second, this was an open-label study, which may have biased the effects of the intervention.

The strength of our study is its prospective randomized design and appropriate sample size. We also conducted this study using *S. boulardii*, whose efficacy as an FC treatment has never been studied. Although it is well known that healthy gut microbiota shows beneficial effects on gastrointestinal disease, we did not find any beneficial effects of *S. boulardii* in the management of FC in children.

In conclusion, *S. boulardii* was not more effective than lactulose in treating childhood FC. Moreover, *S. boulardii* combined with lactulose showed no additional benefits. This result supports the current guidelines that do not recommend the use of probiotics in the treatment of childhood FC. Thus, appropriate evidence-based education is required for physicians in real-world practice.

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Conflicts of interest: None.

Author contributions: Kyung Jae Lee and Jung Ok Shim contributed to the study conception and design, and wrote and critically reviewed the manuscript; Ju Young Chung contributed to the study design and review; and Eell Ryoo, Yoo Min Lee, Jung Min Yoon, Hyo-Jeong Jang, So Yoon Choi, You Jin Choi, and Hyun Jin Kim collected data, discussed the results, and contributed to the final manuscript. All authors agree with submission of the final manuscript.

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