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Effect of Saccharomyces boulardii CNCM-I 3799 and Bacillus subtilis CU-1 on Acute Watery Diarrhea: A Randomized Double-Blind Placebo-Controlled Study in Indian Children

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ABSTRACT

Purpose: To assess the effect of combination probiotic Saccharomyces boulardii CNCM-I 3799 and Bacillus subtilis CU-1 in outpatient management of acute watery diarrhea in children. Methods: A randomized double-blind placebo-controlled study was conducted in 180 participants aged six months to five years with acute mild to moderate diarrhea. All were enrolled from six centers across India and centrally randomized to receive S. boulardii CNCM-I 3799 and B. subtilis CU-1 or a placebo along with oral rehydration salts and zinc supplementation. Each participant was followed up for three months to assess recurrence of diarrhea. Results: The mean duration of diarrhea in the probiotic and placebo groups were 54.16 hours and 59.48 hours, respectively. The difference in the duration of diarrhea in those administered with probiotic or placebo within 24 hours of diarrhea onset was 25.21 hours. Furthermore, the difference in duration of diarrhea was 13.84 hours (p<0.05) for participants who were administered with probiotics within 48 hours. There were no significant differences in the stool frequencies between the two arms. After three months, 15% in the probiotic group and 18.5% in the placebo group reported episodes of diarrhea. The mean duration of diarrhea was considerably lower in the probiotic group, 31.02 hours versus 48 hours in placebo (p=0.017).

Conclusion: *S. boulardii* CNCM-I 3799 and *B. subtilis* CU-1 combination was effective in reducing the duration of diarrhea when administered within 48 hours of diarrhea onset.



 Received:
 Dec 22, 2020

 1st Revised:
 Mar 5, 2021

 2nd Revised:
 Apr 22, 2021

 Accepted:
 May 20, 2021

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Funding

Investigational products were provided by the sponsor of the study: Alkem Laboratories. However, they were not involved in the study design, protocol development, data collection, data analysis, interpretation and manuscript development.

Conflict of Interest

The authors have no financial conflicts of interest.

Similarly, it reduced recurrence of diarrhea and its intensity in the subsequent three months.

Keywords: Acute gastroenteritis; Diarrhea duration; Multi-strain probiotic; *Saccharomyces boulardii*; *Bacillus subtilis*; Stool frequency

INTRODUCTION

Probiotics are effective and have been widely used against acute watery diarrhea. Metaanalysis of several randomized controlled trials have demonstrated that certain probiotic strains with adequate dose exerted antidiarrheal effects in children [1]. The World Health Organization and European Society for Pediatric Infectious Diseases Evidence-Based Guidelines recommend active treatment with specific probiotic strains, in adjunct to oral rehydration salts (ORS) and zinc supplementation to reduce the duration and stool frequency of diarrhea [2].

The mechanism of action of probiotics is by colonizing in the intestinal wall to alter intestinal microflora. It competitively adheres to the intestinal mucosa and restore normal intestinal flora. Probiotics secrete antimicrobial products, intestinal mucin, and bacteriocins which inhibit pathogens and help to produce immunomodulation at the gut level to decrease duration of diarrheal symptoms.

The clinical effects and safety of one probiotic microorganism should not be extrapolated to others. The probiotic effect is strain specific and its efficacy and safety needs to be established. Furthermore, very few combination probiotics in the market have been studied extensively to establish their safety and clinical efficacy.

Saccharomyces boulardii has been extensively studied worldwide in different age groups of children for acute watery diarrhea. Studies also revealed a significant decrease of approximately 24 hours in the duration of diarrhea as well as stool consistency and frequency [3]. In a study conducted by Billoo et al. [4] with *S. boulardii*, besides reduction in the stool frequency and duration of illness, it also established 50% reduction in number of episodes for the subsequent two-month follow-up period as compared to the control treated with only ORS and nutritional support. Villarruel et al. [5] demonstrated that *S. boulardii* decreased the duration of diarrhea and reduced the risk of prolonged diarrhea in children less than 2 years old with mild or moderate acute diarrhea. The study also showed increased efficacy of *S. boulardii* when administered within the first 48 hours of the onset of diarrhea.

Bacillus subtilis CU1 is made of an exclusive and patented strain of *B. subtilis*, which is an effective probiotic for the prevention and treatment of enteric infections. Urdaci et al. [6] investigated the antidiarrheal action of *B. subtilis* CU1 on mice experimental models. They suggested that the antidiarrheal action may be through increasing the capacity of the colon to absorb water in diarrhea through an upregulation of sodium-hydrogene exchanger 3 (NHE3) and cystic fibrosis transmembrane conductance regulator (CFTR) expression, which was hypothesized to occur from an indirect mechanism on intestinal microbiota [6].

Horosheva et al. [7] demonstrated the efficacy of treating antibiotic associated diarrhea (AAD) with the administration of *B. subtilis*. Mehta et al. [8] also showed that *B. subtilis HU58* effectively improved stool consistency in AAD patients as compared to placebo [8].

The present study was designed with a multi-strain probiotic containing the yeast *S. boulardii* CNCM-I 3799 with 5 billion colony forming unit (CFU) and the spores of the bacteria *B. subtilis* CU-1 with 1 billion CFU which has been commercialized in India for acute diarrhea in children and adults. However, there is paucity of evidence regarding its effectiveness and tolerability for acute diarrhea treatment in infants and children.

This study aims to assess and compare the efficacy and safety between the probiotic and identical placebo arms in terms of a) duration of diarrhea (in hours) from product administration until the last abnormal stool consistency (loose or liquid) based on the 4-point Likert stool consistency scale (1: normal, 2: loose, 3: semi-solid, 4: liquid); b) stool frequency as number of times the subject passed stool every day; and c) tolerability using the 4-point Likert scale (1: excellent, 2: good, 3: fair, 4: poor). The exploratory endpoint was the number of acute diarrhea episodes in the subsequent 3-month period after treatment completion.

MATERIALS AND METHODS

The study was a multi-centric double-blind randomized placebo-controlled prospective study at six centres in India. The study protocol was approved by Institutional Ethics Committees of the six participating study sites. The trial was registered in Clinical Trials Registry of India CTRI/2018/06/014480 (Registered on: 08/06/2018). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval letters.

Children aged from 6 months to 5 years with acute watery diarrhea of duration less than 72 hours, without history of intake of any antibiotic were enrolled from the out-patient departments of the participating hospitals. Subjects with dysentery, severe dehydration requiring hospitalization or parenteral fluid therapy, ongoing or history of severe gastrointestinal diseases or intake of probiotics or antibiotics within the last three weeks, debilitated or seriously ill or immunocompromised, suspicion of an organic lesion of the digestive tract, or with undiagnosed abdominal pain or rectal bleeding ulcerative colitis, Crohn's disease, history of carcinomas of the bowel, malabsorption syndrome, intolerance to certain food types (lactose), functional diarrhea, and functional constipation were excluded. Written informed consent were obtained from all enrolled subjects' parent or legal guardian.

Subjects were randomized to probiotic or placebo treatments groups in a 1:1 ratio in a block size of ten. Site-specific randomization was done for each site before recruitment of the first patient. The codes were masked such that allocation of subsequent patients would not be revealed. Both groups received ORS, zinc, and their usual diet as part of their standard of care recommended by World Health Organization.

Each subject was issued a subject diary, which was designed to record the number of stools, stool color, consistency, and other symptoms such as vomiting or abdominal pain between days 1 to 5. All participants, caregivers, investigators, and site staffs involved in the study were blinded during the study. Each sachet had a combination of *S. boulardii* CNCM-I 3799 (5 billion CFU) in combination with *B. subtilis* CU-1 (1 billion CFU), manufactured by Swiss Garnier Biotech, which was dissolved in water upon consumption. The subjects were contacted telephonically on day 2 to enquire about their general well-being and time of last stool passed. On day 5, subjects were recalled to the study site, clinical examination was performed, and diary cards were collected and reviewed. Subjects were instructed to return





Fig. 1. Consort diagram.

to the study site after the 3-month follow-up wherein all episodes of diarrhea were recorded along with the stool frequency and consistencies (**Fig. 1**).

Tolerability to the study products was assessed based on a 4-point Likert scale (1: excellent, 2: good, 3: fair, 4: poor) and recorded by the caregivers in the subject diary at the end of treatment.

The sample size was calculated to detect a mean difference of six hours in duration of diarrhea between the two arms with a standard deviation of twelve hours within the group, a power of 90% at 5% level of significance and equal allocation ratio. The target number of evaluable subjects required in each arm was 86. In case of a 5% drop-out rate, 180 subjects were recruited with 90 subjects in each arm.

Continuous variables were tested using independent samples *t*-test or Mann–Whitney U (as appropriate based on the significance of Shapiro–Wilks test), and categorical variables using chi square test to detect differences between the two groups. p<0.05 was considered statistically significant, and 95% confidence intervals were constructed.

RESULTS

A total of one hundred eighty subjects (male 110, female 70) were randomized and enrolled from all participating study centers. The recruitment of patients began from June 2018 to

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Parameter	Probiotic group (n=91)	Placebo group (n=89)	<i>p</i> -value
Age (mo)	21.32±13.88	23.74±14.78	0.2595
Height (z-score)	-0.54±2.58	-1.03±2.63	0.2306
Weight (z-score)	-0.74±1.25	-0.75±1.30	0.9631
6–11 mo	28 (59.6)	19 (40.4)	0.6133
12–23 mo	35 (50.0)	35 (50.0)	
24-35 mo	15 (46.9)	17 (53.1)	
36-47 mo	6 (40.0)	9 (60.0)	

Table 1. baseline dermographic parameters

Values are presented as mean±standard deviation or number (%).

August 2019. The mean age group of the study population was 22.07±14.30 months (**Table 1**). The demographic profile and baseline clinical features of diarrhea were similar in both groups. A total of 16 patients (probiotic 9, placebo 7) were lost to follow-up between days 2 to 5. Additionally, three patients (probiotic 2, placebo 1) were withdrawn from analysis due to non-compliance of study product intake or discontinuation of treatment. Data from twenty-three (probiotic 13, placebo 10) patients could not be included for analysis due to inconsistencies in subject diaries. A total of one hundred sixty-one subjects were followed up in the exploratory phase of the study. Compliance to study products were recorded in the subject diaries. There were a total of 47 patients under 1 year of age (probiotic: 28 [59.6%], placebo: 19 [40.4%]) and 70 subjects between the age of 1–2 years (probiotic: 35 [50.0%], placebo: 35 [50.0%]).

The mean duration of diarrhea in the probiotic and placebo groups were 54.16 hours and 59.48 hours, respectively, with a difference in duration between groups of 5.32 hours. However, the difference between the groups were 25.21 hours when the IP was administered within 24 hours of onset of diarrhea (probiotic: 38.50, placebo: 63.71, n=17, *p*-value<0.05) and was 13.84 hours when the IP was administered within 48 hours of onset of diarrhea (probiotic: 48.55, placebo: 62.39, n=85, *p*-value=0.039) (**Table 2**).

The change in mean stool frequency from baseline to treatment end did not show a statistically significant difference between the two arms. However, there was a statistically significant difference in the mean change in stool frequency within 24 hours of probiotic administration as compared to placebo (**Table 3**).

A total of 161 patients (probiotic 80, placebo 81) came for follow-up visit after three months after treatment completion. Of these, 27 patients reported episodes of diarrhea: 12 patients

Table 2. Duration of diarrhea in relation to time of administration of probiotic group vs. placebo group (n=138)								
Time of onset	n	Probiotic group	Placebo group	<i>p</i> -value				
Less than 24 hours	17	38.50 (n=10)	63.71 (n=7)	0.161				
24-48 hours	68	51.50 (n=34)	62.12 (n=34)	0.361				
<48 hours	85	48.55 (n=44)	62.39 (n=41)	0.039				
More than 48 hours	53	66.50 (n=23)	55.50 (n=30)	0.547				

Table 3. Mean stool frequencies change from day-1 (between groups)

Difference	Probiotic group	Placebo group difference	Mean difference	p-value	95% CI	
	difference				Lower bound	Upper bound
Day-1 – Day 2	0.66	0.25	0.41	<0.05	0.39	0.45
Day-1 – Day 3	1.42	1.42	0.00	0.54	-0.033	0.017
Day-1 – Day 4	1.87	1.77	0.10	<0.05	0.071	0.12
Day-1 – Day 5	2.39	2.41	-0.02	0.054	-0.049	0.00047

CI: confidence interval.

(15.0%) in probiotic group and 15 patients (18.5%) in placebo group. The mean duration of diarrhea was significantly lower by 17 hours in probiotic group as compared to placebo group (probiotic 31.06 hours versus placebo 48 hours, *p*-value<0.05).

The tolerability to the study products as assessed by the 4-point Likert scale showed no significant difference between the two arms. The proportion of subjects' caregivers who rated the probiotic as "good" or "excellent" were 98.5% versus 98.7% in the placebo group.

Two serious adverse events in the form of severe dehydration requiring hospitalization were reported in the study. None of them were related to the study product. Both subjects recovered fully and had received placebo.

DISCUSSION

Probiotics have been established to modulate gut microbiota following dysbiosis due to disruption in the intestinal milieu. Despite lacking data on changes in the intestinal microbiome in cases of acute bacterial or viral gastroenteritis in humans, probiotics have shown to shorten the course of disease and ameliorate symptoms [9]. In a time series analysis characterizing the gut microbiota of children suffering from acute diarrhea and their recovery post-probiotic administration found that the microbiota composition seems to correlate with clinical improvement of diarrhea episodes [10].

In the meta-analysis conducted by Szajewska et al. [11] in 2007, probiotic administration in children with acute infectious diarrhea significantly reduced the risk of gastroenteritis lasting for more than 3 days as compared to placebo. A significant reduction in the mean duration of diarrhea was observed in patients treated with probiotics vs. placebo (–14.4 hours) [11]. In another meta-analysis in 2002, the difference in duration of diarrhea was between 13 to 26 hours when *S. boulardii* or *Lactobacillus GG* were used alone as compared with placebo [12].

Corrêa et al. [13] confirmed the efficacy of *S. boulardii* CMCM I-745 in reducing the duration of diarrhea if administered within 72 hours after the onset of the disease.

Vandenplas et al.'s study showed better efficacy if *S. boulardii* was administered within the first 24 hours of the onset of diarrhea, thus proving that earlier administration of *S. boulardii* for diarrhea could be more effective and hasten recovery [5]. The study also showed that the subjects in the *S. boulardii* arm had reduced incidence of diarrhea in the subsequent 3 months along with decrease in severity of diarrhea as compared to placebo.

In recent years, two randomized controlled trials regarding on the efficacy of probiotics in gastroenteritis have found that *Lactobacillus rhamnosus GG* alone or in combination with *Lactobacillus helveticus* were not effective in diarrhea resolution or improving vomiting in young children with gastroenteritis [14,15].

Although similar results were seen in stool frequency in this study, *S. boulardii* and *B. subtilis* combination when administered within 24 hours and 48 hours brought about a significant decrease in the duration of diarrhea (25.21 hours and 13.84 hours, respectively).

In our study, the recurrence of episodes of diarrhea after 3 months of treatment were found to be less in the probiotic group as compared to the placebo and mean duration of diarrhea was 31.02 hours as compared to 48 hours in placebo arm.

Since acute diarrhea is most often a self-limiting condition, it is the early response to therapy which has a significant clinical relevance in preventing dehydration and further complications. This finding of significant earlier recovery if probiotics were started within 24 hours as compared to placebo is paramount from clinical management perspective.

Based on meta-analyses, both European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) working group for prebiotics and probiotics, recommended *S. boulardii* and *Lactobacillus GG* in the management of children with acute gastroenteritis as an adjunct to rehydration therapy in 2014 [2].

In the 2020 updated recommendation of the working group of ESPGHAN and NASPGHAN for the use of probiotics in the management of acute gastroenteritis in children, new systematic literature would be considered for a particular probiotic strain if there were at least 2 well-designed randomized controlled trials of high quality for any strain which had benefits when used for treating acute gastroenteritis [16]. Despite a large number of studies, the Working Group had to make a weak recommendation for *S. boulardii* and *Lactobacillus GG*. Hence, the strain used has to be identified at the genus, species, and strain level and at least two similar trials in different centres needs to be done for being considered for recommendation [16].

Due to the paucity of Indian data, the Indian Society of Pediatric Gastroenterology Hepatology and Nutrition is yet to recommend any guidelines. The Indian Academy of Pediatrics guidelines 2006 on management of acute diarrhea recommended further trials on probiotics, which should have strains identified and conducted on Indian population with plausible endpoints to strengthen evidence [17].

There is hardly any double-blind controlled study using combination probiotics in acute diarrhea in children. It is suggested that there is a synergistic effect if more than one agent is used with different mechanism of action to control diarrhea. Apart from denying adhesion to pathogenic organisms, they release different toxins against them and also act through gut immune modulation producing immunoglobulin A. *S. boulardii* release enzymes 63 kDa proteases, alkaline phosphatase, and *B. subtilis* release 66 substances against pathogenic organisms. Trophic effect of polyamines prevents enterocyte damage and <1,000 Da proteins play anti-inflammatory role both produced by *S. boulardii*. Anti-Secretory molecules released by *B. subtilis* inhibit CFTR expression involving electrolyte transport, thereby reducing purging in mice models. Obviously, these anti-inflammatory properties could be playing a significant role during initial stages of infection. Therefore, certain benefits were observed when the candidate probiotics were started early [6,18].

The present study had a few limitations. Since participating centres were referral hospitals, most subjects referred from the clinics were prescribed antibiotics within 24 hours of diarrheal onset, thus delaying recruitment. There may be recall bias while reporting diarrhea episodes from days 2 to 5 and also during the three-month period following the end of treatment. Future studies evaluating effect of probiotic within early hours of diarrhea onset

and assess change in gut microbiota composition may be undertaken to study their long-term benefits, if any.

In conclusion, early administration of *S. boulardii* CNCM-I 3799 with 5 billion CFU and *B. subtilis* CU-1 with 1 billion CFU combination within the first two days of diarrhea onset is effective in significantly reducing duration of diarrhea and faster recovery. This study re-establishes the significance of early administration of strain specific probiotic in management of acute watery diarrhea. The administration of probiotic also reduces the number of episodes and severity of diarrhea if occurred during subsequent three months.

ACKNOWLEDGEMENTS

The authors would like to thank all the study subjects and their parents for participating in this study. The authors would like to acknowledge support of Medclin Research in the statistical analysis and manuscript development.

REFERENCES

- Guarino A, Guandalini S, Lo Vecchio A. Probiotics for prevention and treatment of diarrhea. J Clin Gastroenterol 2015;49 Suppl 1:S37-45.
 PUBMED | CROSSREF
- Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, et al.; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr 2014;58:531-9.
 PUBMED | CROSSREF
- Guarino A, Dupont C, Gorelov AV, Gottrand F, Lee JK, Lin Z, et al. The management of acute diarrhea in children in developed and developing areas: from evidence base to clinical practice. Expert Opin Pharmacother 2012;13:17-26.
 PUBMED | CROSSREF
- 4. Billoo AG, Memon MA, Khaskheli SA, Murtaza G, Iqbal K, Saeed Shekhani M, et al. Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. World J Gastroenterol 2006;12:4557-60.
 PUBMED | CROSSREF
- 5. Villarruel G, Rubio DM, Lopez F, Cintioni J, Gurevech R, Romero G, et al. Saccharomyces boulardii in acute childhood diarrhoea: a randomized, placebo-controlled study. Acta Paediatr 2007;96:538-41.
 PUBMED | CROSSREF
- Urdaci MC, Lefevre M, Lafforgue G, Cartier C, Rodriguez B, Fioramonti J. Antidiarrheal action of *Bacillus subtilis* CU1 CNCM I-2745 and *Lactobacillus plantarum* CNCM I-4547 in mice. Front Microbiol 2018;9:1537.
 PUBMED | CROSSREF
- Horosheva TV, Vodyanoy V, Sorokulova I. Efficacy of *Bacillus* probiotics in prevention of antibiotic-associated diarrhoea: a randomized, double-blind, placebo-controlled clinical trial. JMM Case Rep 2014;1:e004036.
 CROSSREF
- 8. Mehta DS, de Souza A, Jadhav SS, Devale M. A study of probiotic *Bacillus subtilis* HU58 for the management of antibiotic-associated diarrhoea in adults. Indian Pract 2020;73:22-8.
- Britton RA, Versalovic J. Probiotics and gastrointestinal infections. Interdiscip Perspect Infect Dis 2008;2008:290769.
 PUBMED | CROSSREF
- Dinleyici EC, Martínez-Martínez D, Kara A, Karbuz A, Dalgic N, Metin O, et al. Time series analysis of the microbiota of children suffering from acute infectious diarrhea and their recovery after treatment. Front Microbiol 2018;9:1230.
 PUBMED | CROSSREF

- Szajewska H, Skórka A, Dylag M. Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children. Aliment Pharmacol Ther 2007;25:257-64.
 PUBMED | CROSSREF
- Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics 2002;109:678-84.
 PUBMED | CROSSREF
- Corrêa NB, Penna FJ, Lima FM, Nicoli JR, Filho LA. Treatment of acute diarrhea with Saccharomyces boulardii in infants. J Pediatr Gastroenterol Nutr 2011;53:497-501.
 PUBMED | CROSSREF
- Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. N Engl J Med 2018;379:2002-14.
 PUBMED | CROSSREF
- 15. Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, et al.; PERC PROGUT Trial Group. Multicenter trial of a combination probiotic for children with gastroenteritis. N Engl J Med 2018;379:2015-26.

PUBMED | CROSSREF

- Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, et al.; Working Group on Probiotics and Prebiotics of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Use of probiotics for the management of acute gastroenteritis in children: an update. J Pediatr Gastroenterol Nutr 2020;71:261-9.
 PUBMED | CROSSREF
- Bhatnagar S, Lodha R, Choudhury P, Sachdev HP, Shah N, Narayan S, et al. IAP Guidelines 2006 on management of acute diarrhea. Indian Pediatr 2007;44:380-9.
- Moré MI, Vandenplas Y. Saccharomyces boulardii CNCM I-745 improves intestinal enzyme function: a trophic effects review. Clin Med Insights Gastroenterol 2018;11:1179552217752679.
 PUBMED | CROSSREF