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Original Research Article

Comparative, randomized-controlled trial on efficacy and safety of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* in treatment of acute diarrhea in Indian children (COMPARE-GG trial)

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ABSTRACT

Background: Probiotics are routinely prescribed to boost gut health and reduce severity of diarrhea. This study aimed to compare the efficacy and safety of *Lactobacillus rhamnosus* GG (LrGG) and *Saccharomyces boulardii* as an adjunct treatment for acute diarrhea in Indian children aged 6–36 months.
Methods: In this single-center, open label, comparative, randomized controlled study, children were randomized into three groups (n=35, each) and provided either low osmolarity oral rehydration solution (ORS) and zinc (20 mg/day) alone or ORS+Zinc supplemented with one of the two probiotic preparations, LrGG ATCC 53103 or *S. boulardii* CNCM 1-745. Children were monitored every 8 hours after admission and the duration of diarrhea and hospital stay, and stool frequency were evaluated.
Results: Of the total 105 children enrolled in the study, majority were aged between 13–24 months (40%). LrGG significantly reduced the mean duration of diarrhea by nearly 19 hours, when compared to the control group (p=0.003), while reduction by *S. boulardii* was not significant. The mean hospital stay duration for control group was about 6 days, which was significantly reduced (p=0.0001) by nearly 23 hours by LrGG, and non-significantly by *S. boulardii*. On day 2, LrGG significantly reduced stool frequency by 32.31%, as compared to 27.44% reduction in control group. *S. boulardii* reduced stool frequency by 31.76%, which was not statistically significant compared to that in control group.
Conclusions: LrGG showed statistically significant reduction in duration of diarrhea and hospital stay, when compared against the group receiving ORS+zinc either alone or with *S. boulardii*.

Keywords: Acute diarrhea, Zinc, Probiotics, *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*

INTRODUCTION

Diarrhea is a common cause of morbidity and mortality across the globe and is the third leading cause of under-five mortality in India. According to the National Family Health Survey, the prevalence of childhood diarrhea has increased from 9% to 9.2% from 2016 to 2020 in India.[1] Acute diarrhea is the primary cause of dehydration among children. It mainly occurs in children under five years of age, and is most prevalent in children during their second year of life up to the age of three years.[2] Rotavirus infection is one of the most common causes of infectious diarrhea and acute gastroenteritis, and shows seasonal pattern in more temperate climates, showing seasonal epidemic peaks.[2]

Despite the self-limiting nature of diarrhea, appropriate treatment can positively reduce disease duration and rates of mortality. The primary goals of diarrhea management are the replenishment of lost water and electrolytes, along with providing adequate nutrition.[3] This prevents potential fatal complications, such as dehydration, electrolyte disturbance, sepsis, and metabolic acidosis.[2] The first-line therapy for managing diarrhea is oral

rehydration solution (ORS), supplemented with zinc. With rising awareness and acceptance of their benefits, probiotics have been implicated as an adjunct treatment for management of acute watery diarrhea and acute gastroenteritis, and for prevention of antibiotic-associated diarrhea and diarrhea due to nosocomial infections. Probiotics are live microorganisms that are routinely prescribed to boost gut health and reduce the duration and severity of diarrhea. Antibiotics are only used in cases of infectious diarrhea with a positive stool test for shigellosis, cholera, giardiasis, intestinal invasive amoebiasis, or campylobacter infection. The continuation of breastmilk remains important.[2] Multiple probiotic strains are available commercially, and several evidence-based recommendations and guidelines have been provided by global regulatory bodies for the selection of appropriate probiotic strains.[4]

The latest guidelines by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the Indian Academy of Pediatrics (IAP), published separately in 2022, positively recommend *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, which are also two of the most commonly prescribed probiotics in pediatric population.[5,6] Despite the recommendations, there is insufficient head-on comparative data on the efficacy of these two probiotics. In order to further reduce the ambiguity around choosing the probiotic strain in the Indian population, this study aimed to compare the efficacy of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* as an adjunct treatment for acute diarrhea in children aged 6–36 months.

METHODS

Study design

Study population

In this single-center, open label, comparative, randomized controlled study, a total of 105 children, aged 6–36 months, with acute diarrhea who were admitted to the Jaipur Golden Hospital, Institutional Area, Delhi, India from January 2019 to December 2020, were included and randomly assigned to one of the three treatment groups (A, B, and C; n=35 in each group) after obtaining written informed consent from their parents or legally acceptable representatives (LARs).

Children with a history of presence of blood or pus in stools, children with severe dehydration, children treated with antibiotics or probiotics within two weeks at time of enrolment, children with conditions known to produce immunodeficiency (such as, AIDS, congenital immunodeficiency syndromes, drug therapy with steroids and anticancer drugs), children with acute systemic illness, such as meningitis, sepsis and pneumonia, and children with persistent diarrhea were excluded from the study.

Methods

All children were provided WHO standard care of treatment for diarrhea, which included low osmolarity ORS and zinc (equivalent to 20 mg elemental zinc) per day. Children in group B and C were additionally given one of the two probiotic preparations, *Lactobacillus rhamnosus* GG ATCC 53103 and *Saccharomyces boulardii* CNCM 1-745, respectively. The details of intervention have been provided in Table 1.

After obtaining detailed demographic information from all children, the medication was randomly administered, and children were followed for diarrhea and monitored every 8 hours after admission till resolution. Primary outcomes included measurement of duration of diarrhea and duration of hospital stay. Secondary outcomes included measurement of stool frequency after starting medication.

Figure 1 depicts the overall study design. Total duration of diarrhea was calculated as time (in hours) from the time of admission to the hospital to the time the child passed the last abnormal (semisolid) stool.

Ethical considerations

This study was approved by the Institutional Ethics Committee of Jaipur Golden Hospital, Institutional Area, Delhi, India (JGH/DNB/EC/2018/6003).

Table 1: Grouping and study interventions.

Group	Standard care	Probiotic		
		Strain	Strength	Dose
Group A	ORS+zinc	-	-	-
Group B	ORS+zinc	*Lactobacillus rhamnosus* GG ATCC 53103	6 billion CFU per sachet	1 sachet twice daily for 5 days
Group C	ORS+zinc	*Saccharomyces boulardii* CNCM 1-745	250 mg per sachet	1 sachet twice daily for 5 days

ORS, Oral rehydration solution; group A, children receiving ORS + zinc; group B, children receiving ORS + zinc + *Lactobacillus rhamnosus* GG ATCC 53103; group C, children receiving ORS + zinc + *Saccharomyces boulardii* CNCM 1-745; CFU, colony forming units

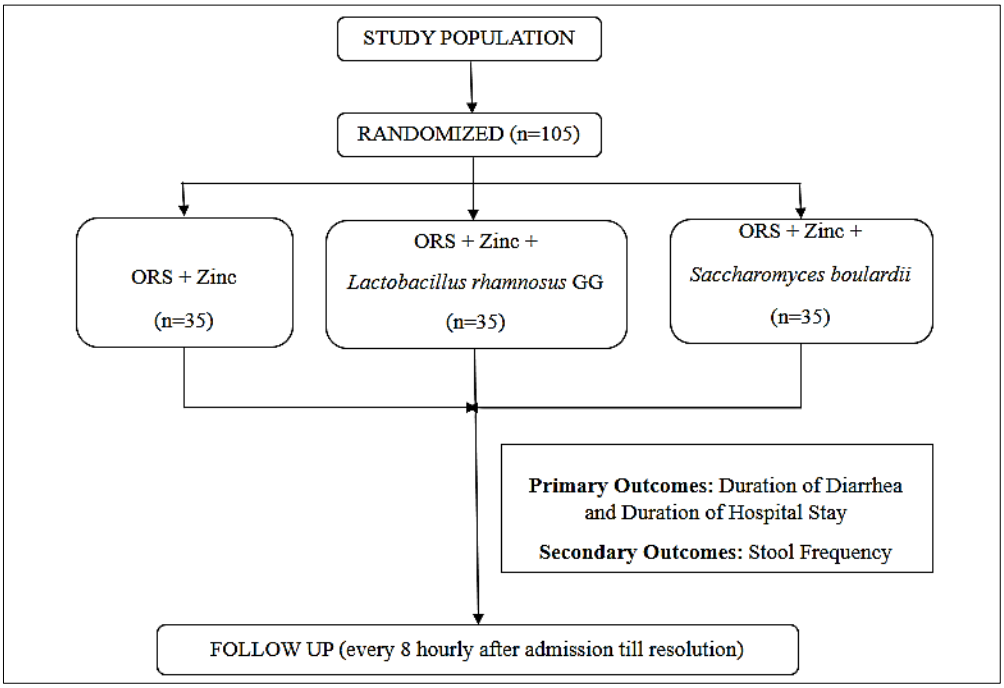

Figure 1: Overall study design.

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS) software version 25.0 (IBM, Chicago, USA). Continuous variables are expressed as mean±SD, and categorical variables are expressed as percentages or frequencies. Continuous variables were analyzed using student's t-test. Nominal categorical data was analyzed using the Chi-square test and non-normally distributed continuous variables were analyzed using the Mann-Whitney-U test. Statistical significance was established at $p<0.05$.

RESULTS

The baseline and demographic data have been given in Table 2. Of the total 105 children enrolled in the study, the majority were aged between 13–24 months (40%) followed by those more than 24 months of age (34%). No significant ($p>0.05$) difference was observed between the ages of children randomized to the three groups. The study enrolled subjects with a male-to-female ratio of 1:0.94, 1:1.69, and 1:0.84 in groups A, B, and C, respectively, which was not significantly different between groups ($p>0.05$). Out of 35 children in each group, 80% in group A, 77.14% in group B, and 80% in group C tested positive for rotavirus infection. The distribution of subjects with positive rotavirus status was comparable among the three groups ($p>0.05$).

The primary and secondary efficacy outcomes have been depicted in Figure 2. The mean duration of diarrhea (Figure 2a) in group B (80.23±17.41 hours) was significantly lesser than that in group A (96.91±20.6 h; $p=0.003$) and group C (94.4±23.43 hours; $p=0.015$). The difference in mean duration of diarrhea was not significant between groups A and C.

Table 2: Demographics and baseline parameters.

Parameter	Group A (n=35)	Group B (n=35)	Group C (n=35)
Age (n, %) (months)			
≤12	9 (25.71)	8 (22.86)	10 (28.57)
13–24	16 (45.71)	12 (34.29)	14 (40.00)
>24	10 (28.57)	15 (42.86)	11 (31.43)
Mean±SD	19±8.03	21.56±9.74	18.88±8.94
Gender (n, %)			
Female	18 (51.43)	13 (37.14)	19 (54.29)
Male	17 (48.57)	22 (62.86)	16 (45.71)
Rotavirus status (n, %)			
Positive	28 (80.00)	27 (77.14)	28 (80.00)
Negative	7 (20.00)	8 (22.86)	7 (20.00)

n, Number of patients; SD, standard deviation; group A, children receiving ORS + zinc; group B, children receiving ORS + zinc + *Lactobacillus rhamnosus* GG ATCC 53103; group C, children receiving ORS + zinc + *Saccharomyces boulardii* CNCM 1-745; ORS, oral rehydration solution

The mean duration of hospital stay (Figure 2b) of group B (4.74±0.78 days) was significantly reduced as compared to group A (5.69±0.83 days; $p=0.0001$) and group C (5.51±1.01 days; $p=0.001$). The difference in mean duration of hospital stay was not significant between groups A and C.

On day 1, the stool frequency was 19.17±2.26 for group A, 16.34±2.89 for group B, and 18.26±3.35 for group C. There was significant difference in stool frequency between groups A and B ($p=0.0002$), and between groups

B and C (p=0.019). On day 2, the stool frequency reduced to 13.91±1.93 for group A, 11.06±3.32 for group B, and to 12.46±2.65 for group C. There was significant difference in stool frequency between groups A and B (p=0.0001). However, stool frequency was not significantly reduced between groups A and C (p=0.077). On day 5, the mean stool frequency reduced to 3.36±2.79 in group A, 2.5±1.73 in group B, and to 3.58±2.54 in group C. No significant difference was observed in stool frequency between groups on days 3, 4 and 5 (Figure 2c).

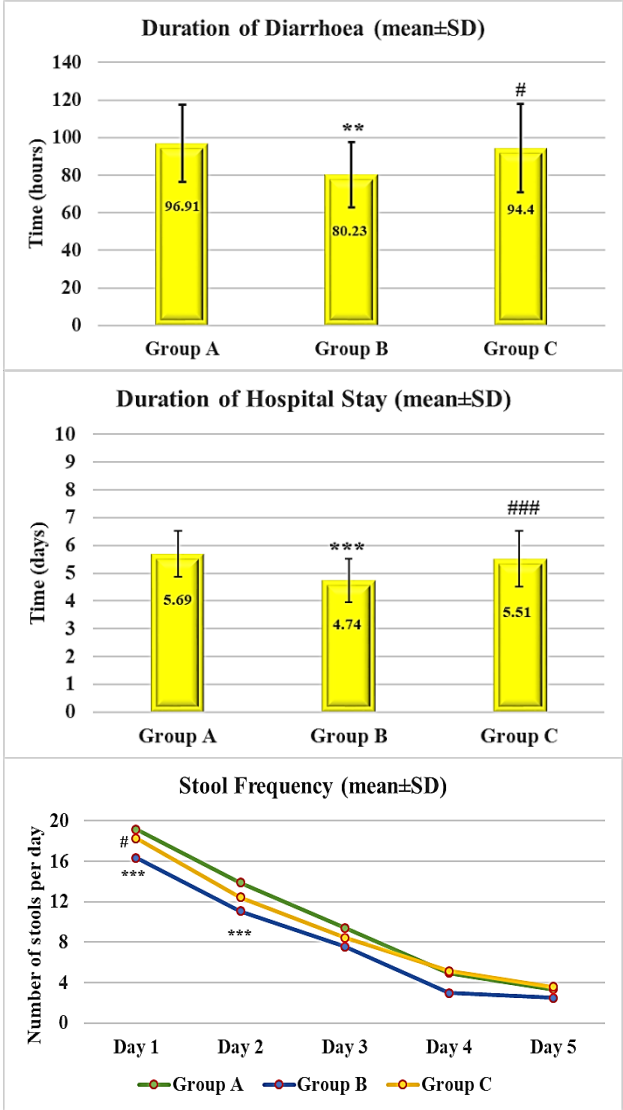

Figure 2: Primary and secondary efficacy outcomes (a) duration of diarrhea (the values are expressed as mean±SD, **p<0.01 versus group A, #p<0.05 versus group B), (b) duration of hospital stay (*p<0.001 versus group A, ###p=0.001 versus group B), and (c) stool frequency (***p<0.01 versus group A, #p<0.05 versus group B).**

SD, Standard deviation; group A, children receiving ORS + zinc; group B, children receiving ORS + zinc + *Lactobacillus rhamnosus* GG ATCC 53103; group C, children receiving ORS + zinc + *Saccharomyces boulardii* CNCM 1-745; ORS, oral rehydration solution

DISCUSSION

In 2008, ESPGHAN and the European Society for Pediatric Infectious Diseases (ESPID) introduced the usage of probiotics as adjunct management in acute diarrhea, and recommended LrGG and *S. boulardii*, which remain the widely recommended and used probiotics in pediatric settings till date. Therefore, it is crucial to generate clinical evidence of head-on comparison of the efficacy of both these probiotics in children.

The present study compared the efficacy of LrGG ATCC 53103 and *S. boulardii* CNCM 1-745 as an adjunct treatment in 105 children (aged 6–36 months) with acute diarrhea. A study conducted by Das *et al* compared the efficacy of *S. boulardii* to a placebo in 115 children aged 3–60 months.[7] In 2007, Canani *et al* evaluated the efficacy and tolerability of five probiotic preparations in 571 children with acute diarrhea in the outpatient setting.[8] In 2022, Kesavelu *et al.* studied the efficacy of three single-strain probiotics, LrGG (ATCC 53103), *Bacillus clausii* (O/C, N/R, SIN and T), and *S. boulardii* (CNCM 1-745) in 150 children with acute gastroenteritis aged 6 months to 16 years.[4]

Acute diarrhea is predominantly prevalent in children under five years of age during their second year of life. Mean age of children enrolled in present study was found to be between 18 to 22 months, with 13–24 months being the most common age group across all three experimental groups. The male: female ratio remained similar across all groups. The baseline characteristics of experimental groups matched that of control population, which ensured no selection bias occurred.

In children under the age of five years, diarrhea leads to hospitalization in order to prevent dehydration, failure of oral rehydration therapy (ORT), shock, severe vomiting, and neurological or surgical conditions. Studies by Nokes et al and Standeart et al report an average hospital stay duration of 5.2 and 7.62 days, respectively.[9,10] Similar results were found in our study with the mean hospital stay duration for control group as about 6 days. This duration was significantly reduced (p=0.0001) by nearly 23 hours in subjects receiving LrGG. However, *S. boulardii* reduced hospital stay duration by nearly 4 hours, which was not a statistically significant difference compared to control group. Similar results have been reported by Canani et al where LrGG significantly reduced duration of hospital stay by around 37 hours, while *S. boulardii* reduced the hospital stay by 10 hours, which was not statistically significant.[8] Guarino et al reported similarly reduced hospital stay duration in patients treated with LrGG.[11] Reports by Bhat et al and Kurugol et al showed significantly reduced duration of hospital stay in patients receiving *S. boulardii.*[12,13] The differences in findings may be attributed to differences in diarrhea etiology and patient population.

In our study, LrGG significantly reduced the mean duration of diarrhea by nearly 19 hours, when compared to the control group (p=0.003). However, *S. boulardii* reduced duration of diarrhea by nearly 4 hours, which was not statistically significant when compared to the control group. On day 2, LrGG significantly reduced stool frequency by 32.31%, as compared to 27.44% reduction in control group. *S. boulardii* reduced stool frequency by 31.76%, which was not statistically significant compared to that in control group. Further, from day 1 to day 5, the stool frequency was reduced by 80%, 83%, and 85% in patients receiving *S. boulardii*, ORS+zinc alone, and LrGG, respectively. The efficacy outcome was comparable among the three groups, with LrGG showing relatively better reduction in stool frequency.

These results are consistent with the reported literature. In a recent observational study using a large cohort (n=1900), Sanklecha et al reported an 80% reduction in stool frequency on day 5 of treatment with LrGG.[3] Niel et al reported that LrGG reduced diarrhea duration by nearly 17 hours (95% CI: 7.2–28.8 hours) and reported a reduction in stool frequency of 1.6 fewer stools on day 2 of treatment (95% CI: 0.7–2.6 fewer stools), when compared with patients receiving placebo.[14] Szymanski et al and Pant et al reported a reduction of 12 hours and 33.6 hours in the mean duration of diarrhea, respectively, in children receiving LrGG as an adjuvant treatment.[15,16] A systematic review by Ya-Ting Li et al further confirmed that administration of LrGG in doses $>10^{10}$ CFU significantly reduced duration of diarrhea (by 24 hours) and the stool number per day.[17] Contrastingly, Kesavelu et al reported a stool frequency reduction of 97% and 82%, in children receiving *S. boulardii* and LrGG, respectively.[4] Bhat et al also reported statistically significant (p=0.001, respectively) reduction in diarrhea duration upon treatment with *S. boulardii*.[12]

No adverse effects were reported in any groups in this study. However, this study had a few limitations. First, the sample size was low (n=35 in each group), which was mainly due to the pandemic situation, which made recruitment difficult. Second, being an open label study, there is theoretical possibility of incurring selection bias. Third, as a single center study, the findings may not represent the comprehensive effects of these probiotics in the community overall as the microbial colonization of gut differs with geography and ethnicity.

CONCLUSION

This study acts as additive evidence to the existing literature showing efficacy and safety of widely used probiotic strains, LrGG and *S. boulardii*, against a control group receiving only ORS+zinc. This study found that both probiotic strains were efficacious in reducing the duration of diarrhea, duration of hospital stay, and stool frequency. However, LrGG showed statistically significant reduction in duration of diarrhea and hospital stay when compared against the group receiving ORS+zinc either alone or with *S. boulardii*.

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