Original Article

Effectiveness of *Lactobacillus rhamnosus* GG as an Adjunct in the Treatment of Enteric Fever in Children: A Double-Blinded Randomized Controlled Trial in Southern India

Ramya Rajamanickam, Aparna Jayaraman, Shobhana Sivathanu
Department of Paediatrics, ESICMC and PGIMSR, Chennai, Tamil Nadu, India

Abstract

Introduction: A probiotic used as an adjunct in *Salmonella typhi* infection along with antibiotic is postulated to interfere with the virulence and growth of Salmonella. To determine the effectiveness of *Lactobacillus rhamnosus GG* (LGG), as an adjunct with intravenous ceftriaxone, compared with a placebo in defervescence and toxemia resolution in children with enteric fever. **Settings and Design:** This hospital-based randomized double-blinded controlled trial was conducted among 56 study participants who were children below the age of 12 years, admitted as inpatients with fever and whose blood culture grew *S. typhi*. **Materials and Methods:** Study participants were equally allocated into intervention or control group by simple randomization. The intervention group received injection ceftriaxone and oral LGG (probiotic) for 7 days while the control group received an injection ceftriaxone and oral placebo for 7 days. **Statistical Analysis:** Kaplan–Meier curves and mantel cox log-rank test were used to compare the duration for defervescence and toxemia resolution after treatment initiation. **Results:** Mean duration for defervescence in the intervention and control groups was 3.87 (1.57) days and 3.35 (1.19) days, respectively. The mean time taken for the resolution of toxemia was 3.00 (1.15) days in the intervention group and 2.64 (0.87) days in the control group. **Conclusions:** The addition of oral LGG at a dose of 3×10^9 colony-forming units for 7 days to the standard antibiotic therapy for enteric fever did not show a significant reduction in the time taken for defervescence ($P = 0.099$) or resolution of toxemia ($P = 0.148$).

Keywords: Enteric fever, *Lactobacillus rhamnosus* GG, probiotic

Introduction

The annual burden of enteric fever is estimated as 11–20 million cases which results in about 128,000–161,000 deaths per year according to the World Health Organization reports. Populations with inadequate sanitation and lack of access to safe water are at a higher risk for enteric fever. The advent of newer antibiotics and better living conditions has drastically reduced the morbidity and mortality due to enteric fever in industrialized countries. However, the disease continues to be a significant public health problem in developing areas of countries such as Africa, South-East Asia, and the Western Pacific regions.[1] South Asia has the maximum number of patients with enteric fever in the year 2017 accounting for 71.8% of global cases of typhoid fever.[2]

Probiotics have shown efficacy in treating and preventing various medical conditions associated with the gastrointestinal tract in children.[3] Probiotics confer a health benefit on the host when administered in adequate amount.[4] Probiotics act through various mechanisms like immunomodulation, antibacterial action, and competitive exclusion. Antibacterial action is by the production of antibacterial substances by which it acts against pathogens such as Salmonella species, Clostridium difficile, and *Escherichia coli*.[5] Data is supporting the use of certain probiotics as an adjunct in treating acute viral gastroenteritis, and for preventing gastrointestinal diseases.[6] One of the

Address for correspondence: Dr. Ramya Rajamanickam, Department of Paediatrics, ESICMC and PGIMSR, Chennai, Tamil Nadu, India.
E-mail: docramyraj@gmail.com

Submitted: 07-Feb-2023 **Revised:** 25-Apr-2023
Accepted: 23-May-2023 **Published:** 28-Jun-2023

Access this article online

Quick Response Code:

Website: www.actamedicainternational.com

DOI: 10.4103/amit.amit_13_23

How to cite this article: Rajamanickam R, Jayaraman A, Sivathanu S. Effectiveness of *Lactobacillus rhamnosus* GG as an adjunct in the treatment of enteric fever in children: A double-blinded randomized controlled trial in Southern India. Acta Med Int 2023;10:52-8.

best studied among probiotics is *Lactobacillus rhamnosus GG* (LGG).[3] Several researches have shown the efficacy of probiotics in reducing the duration of acute viral infectious diarrhea and also reduction in length of hospitalization, in both severely malnourished and well-nourished children with minimal side effects.[7-12]

A research study by Abdel-Daim *et al*. has demonstrated that twelve *Lactobacillus plantarum* isolates inhibit *Salmonella typhi in vitro* by interference with its growth and virulence.[13] The LGG-derived soluble proteins act by various mechanisms like LGG adherence to the intestinal epithelium and it also protects them from cytokine-mediated injury by regulation of several signaling pathways. Seven different peptides which were isolated from LGG-conditioned media, showed anti-Gram-positive and anti-Gram-negative bactericidal activity.[14]

Enteric fever is an important cause of mortality and morbidity in both adult and pediatric patients.[15] Fever spikes can persist for 5–7 days even with effective antibiotic therapy in enteric fever and it usually takes at least 36 h of therapy for defervescence.[16] A probiotic used as an adjunct along with antibiotic could cause early resolution of symptoms by various mechanisms. There is a possibility that LGG could protect against *S. typhi* infection by various mechanisms like interference with its virulence and growth through, cytotoxicity, invasion, and adherence.[13]

Although several studies related to the effect of probiotics on gastrointestinal infections are available, data on the effect of probiotic on enteric fever is very limited. With this background, the present research was undertaken and the objectives of this study were, to determine the effectiveness of LGG, as an adjunct with intravenous ceftriaxone, in comparison to a placebo on (1) defervescence of fever in children with enteric fever and (2) resolution of toxemia in children with enteric fever.

Materials and Methods

Study design, study setting, and study duration

This double-blinded, randomized controlled trial (RCT) was done in the pediatric inpatient ward of a tertiary care hospital in southern India for 1 year from October 2020 to August 2021. This parallel design of RCT was conducted with 1:1 allocation ratio. This clinical trial was conducted and analyzed and reports were prepared as per the CONSORT guidelines.

Study participants

Children below the age of 12 years, who were admitted with fever and whose blood culture grew *S. typhi,* and whose parents consented were included as the study participants. Children who were immunocompromised, had other coinfections, critically ill were excluded from the study.

Sample size calculation

The "*n*" n Master version 2.0 (BRTC, CMC, Vellore, India.) was used for sample size calculation. Defervescence takes at least 36 h of treatment and fever can persist for 5–7 days even with effective antibiotic therapy in enteric fever.[16] Szymański *et al*. reported *L. rhamnosus* reduced the duration of rotavirus diarrhea compared to placebo (76 ± 35 h vs. 115 ± 67 h) ($P = 0.03$).[17] As *in vivo* studies on the effectiveness of LGG in enteric fever were limited, it was expected that LGG when given along with the antibiotic would cause defervescence in enteric fever on an average in 3 days while the placebo-antibiotic combination would require 7 days. Hence, the expected difference between the treatment group and the control group was assumed to be 4 days with a standard deviation (SD) of 1.5 days. This trial was conducted as a superiority trial against a placebo and was conducted as a parallel design RCT with equal allocation in the treatment and control groups. With a 5% level of significance (α), 95% confidence level and 80% power (1−β), the sample size was calculated keeping the superiority margin (δ) as 3 days; expected difference (μ_T-μ_C) as 4 days and SD (σ) as 1.5 days. The minimum sample size required in each group (*n*) was calculated as follows

$$n = \frac{2\sigma^2(Z_{1-\alpha} + Z_{1-\beta})^2}{((\mu_T - \mu_C - \delta)^2}$$

$$= \frac{2 \times (1.5)^2 \times (1.64 + 0.842)^2}{(4 - 3)^2} = 28 \text{ in each group}$$

Randomization and allocation concealment

Prior informed consent and/or assent from the parents were obtained and the study subjects were randomized into either the intervention or control group. A simple randomization technique was followed for the allocation of cases into intervention and control groups by the generation of random numbers from Rand Corporation random numbers table. The randomization was done by the co-investigator and allocation concealment was done using sequentially numbered opaque sealed envelopes. Randomization and allocation concealment were done by the statistician.

Intervention

All enteric fever patients participating in the study were treated with intravenous ceftriaxone for 7 days. The intervention group received injection ceftriaxone (75 mg/kg/day in 2 divided doses for 7 days) and 1 g of oral LGG (probiotic) containing 3×10^9 colony forming units (CFU) in a blinded powdered sachet once daily for 7 days. The control group received injection ceftriaxone (75 mg/kg/day in 2 divided doses for 7 days) and 1 g of oral placebo in a blinded powdered sachet once daily for 7 days. These regimens were started on the same day of confirmation of enteric fever by blood culture.

The oral probiotic or placebo was given to the patient by the coinvestigator, who also confirmed the intake of the drug by the patient. The probiotic or the placebo was dissolved in 50 ml of water and consumed immediately. The dose of LGG or placebo was repeated if the patient vomited within half an hour of intake of the drug.

Blinding

The placebo used was similar in appearance and taste compared

to the probiotic used. The parents/guardian and the principal investigator were blinded to the intervention received by the patient.

Data collection methods

The baseline characteristics, focused history, relevant clinical examination, investigations, and other data were collected in the proforma by the principal investigator by direct interview, observation, examination of the patient, and laboratory reports. The progress of the patient's condition was collected daily by the principal investigator till the discharge of the patient. The patients were also monitored for any adverse events in both the groups. On completion of intravenous therapy and defervescence of fever, the patients were discharged on oral antibiotics to complete a 14-day course of antibiotics. The day of defervescence of fever after initiating the intervention was taken as the desired primary outcome and the day of resolution of toxemia was recorded as the secondary outcome. Symptoms like improvement in anorexia, general well-being, improvement in dehydration, and improvement in coated tongue were considered for resolution of toxemia.

Statistical analysis

Data were entered into Microsoft office excel worksheet. Statistical analysis was done using SPSS version 28.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics such as mean, median, SD, and proportions were used to describe the socio-demographic characteristics, symptoms on admission to hospital, laboratory investigation and treatment outcomes of study subjects in intervention and control groups. Inferential statistics like 95% confidence interval, independent *t*-test, Chi-square test, and Fisher's exact test were used for comparison between intervention and control groups. Kaplan–Meier curves and Mantel cox log-rank test were used to compare the duration for defervescence after treatment initiation and to compare the duration for resolution of toxemia

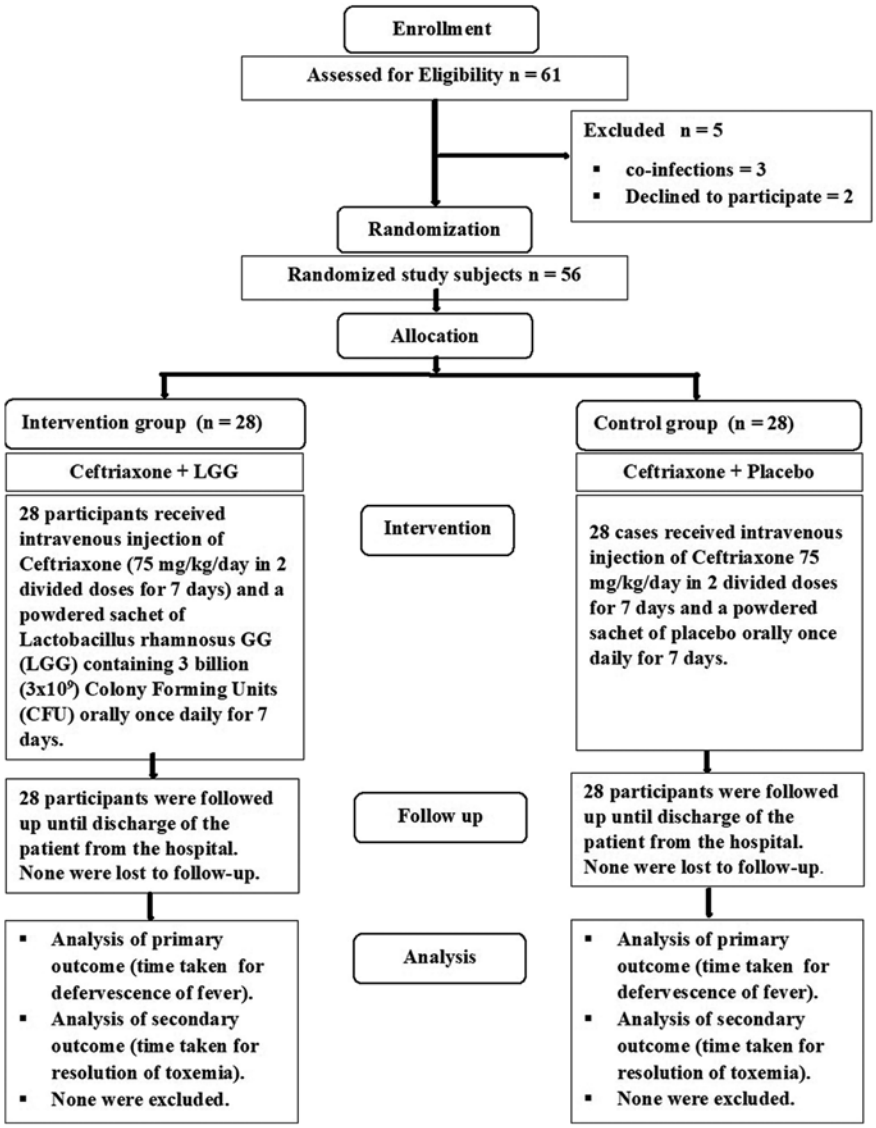

Figure 1: Flow chart for enrollment and follow-up of study participants

after treatment initiation between the intervention and control groups. At 95% confidence level and 5% level of significance, a $P \leq 0.05$ was considered to be statistically significant.

Ethical issues

Prior approval from the Institutional Ethics Committee was obtained to conduct the study (reference no. IEC/2019/1/02). The objectives of the study, details of investigators, procedures involved in the study, side effects, right to withdrawal from study and maintenance of confidentiality of their personal details were explained in the regional language to the parents and their children who satisfied the inclusion criteria. Written informed consent from parents and assent from children aged above 7 years were obtained before their inclusion as study participants. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000048048 (Available from: http://www.umin.ac.jp/ctr/index.htm). The research followed the guidelines laid down in the Declaration of Helsinki.

Results

Among 61 patients who were assessed for eligibility, 3 of them were excluded due to coinfections such as urinary tract

Table 1: Distribution of sociodemographic characteristics of study subjects

Parameters	Intervention group (n=28), n (%)	Control group (n=28), n (%)	P
Age of children (years)			
Upto 5	10 (35.7)	7 (25.0)	0.081
6–10	10 (35.7)	10 (35.7)	
>10	8 (28.6)	11 (39.3)	
Sex			
Male	17 (60.7)	15 (53.6)	0.394
Female	11 (39.3)	13 (46.4)	
Socioeconomic status (as per B.G Prasad Scale)			
Upper class	4 (14.3)	2 (7.1)	0.625
Upper middle class	13 (46.4)	12 (42.9)	
Lower middle class	10 (35.7)	11 (39.3)	
Upper lower class	1 (3.6)	3 (10.7)	
Typhoid immunization status			
Not vaccinated	28 (100.0)	28 (100.0)	-
History of consumption of food prepared outside home			
Present	19 (67.9)	21 (75.0)	0.384
Absent	9 (32.1)	7 (25.0)	
Sanitary latrine facility			
Available	28 (100.0)	27 (96.4)	0.500
Not available	0	1 (3.6)	
Hand hygiene practices			
Present	28 (100.0)	27 (96.4)	0.500
Absent	0	1 (3.6)	
Boiling of drinking water			
Present	11 (39.3)	5 (17.9)	0.069
Absent	17 (60.7)	23 (82.1)	
History of enteric fever in family members			
Present	3 (10.7)	4 (14.3)	0.600
Absent	25 (89.3)	24 (85.7)	
Nutritional status of children aged above 5 years according to IAP growth charts (n=11)			
Normal	10 (55.6)	17 (80.9)	0.202
Thinness	1 (5.6)	2 (9.5)	
Overweight	2 (11.1)	0	
Obese	5 (27.8)	2 (9.5)	
Nutritional status of children aged up to 5 years according to WHO growth charts (n=17)			
Normal	10 (100.0)	7 (100.0)	0.281
Moderate or severe acute malnutrition	0	0	
Co-morbidities			
Present	2 (7.1)	0	0.245
Absent	26 (92.9)	28 (100.0)	

Chi-square-test, Fisher's exact test. IAP: Indian Academy of Pediatrics, WHO: World Health Organization

infection, dengue, and malaria. Of the 58 participants enrolled for the study 2 of them did not consent. Finally, 56 of the study subjects were randomized and allocated into either intervention or control groups. All the 56 study subjects completed their treatment as per the protocol and none left the study before occurrence of the primary and secondary outcome. None of the study participants encountered any adverse events following the intervention. A flowchart of the study participants is depicted in Figure 1.

As shown in Table 1, there were no statistically significant differences between the intervention and control group study participants in socio-demographic characteristics, environmental and nutritional factors. The age group of study subjects ranged from 2 to 12 years in the intervention group and between 1 and 12 years in the control group. The mean age in years (SD) of study subjects in intervention and control groups were 7.8 (3.6) years and 8.2 (3.7) years respectively. Although 100% of the subjects in the intervention group and 96.4% of the subjects in the control group utilized the sanitary latrine at home and had practiced hand hygiene measures, only 39.3% of the study subjects in the control group and 17.9% of them had boiled their drinking water before consumption. Almost 75% of the study subjects in the control group and 67.9% of subjects in the intervention group had a history of consumption of food prepared outside their home. None of them were vaccinated against enteric fever in the past. Among the two patients who had comorbidities, one of them had Rheumatic heart disease and the other had Asthma. Both of them were in the Intervention group.

There was no significant difference in the clinical features and examination findings between the two groups on admission as shown in Tables 2 and 3. Fever was the major symptom among the study participants. The mean (SD) duration of fever in the intervention and control group were 6.7 (2.5) and 6.6 (2.3) days, respectively. Majority of them had continuous types of fever in both the groups. As shown in Table 2, other prominent symptoms on hospital admission were vomiting, diarrhea, abdominal pain, and anorexia. A few of them had chills and rigor, headache, and myalgia. The majority of them had coated tongue and hepatomegaly in both the groups.

No significant difference was noted in the laboratory investigations between both the groups as shown in Tables 4 and 5. 35.7% of children had anemia in both the intervention and control groups. All the study subjects had elevated C-reactive protein and majority of them had eosinopenia. Only a few of them had thrombocytopenia in both the groups.

Table 6 shows the comparison of treatment outcome between the intervention and control groups. When the primary outcome was considered, the mean duration of defervescence of fever after the initiation of treatment in the intervention and control group was 3.87 (1.57) days and 3.35 (1.19) days respectively. This difference was not statistically significant ($P = 0.171$). On considering the secondary outcome, the mean time taken for the resolution of toxemia was 3.00 (1.15) days in the intervention

Table 2: Distribution of study subjects based on their symptoms on admission

Symptoms	Intervention group ($n=28$), *n* (%)	Control group ($n=28$), *n* (%)	*P*
Fever duration (days)			
Upto 5	12 (42.9)	11 (39.3)	0.163
6–10	13 (46.4)	17 (60.7)	
>10	3 (10.7)	0	
Type of fever			
Continuous	16 (57.1)	17 (60.7)	0.500
Intermittent	12 (42.9)	11 (39.3)	
Chills and rigor	3 (10.7)	2 (7.1)	0.500
Head ache	3 (10.7)	4 (14.3)	0.500
Myalgia	3 (10.7)	3 (10.7)	0.665
Anorexia	7 (25.0)	12 (42.9)	0.129
Loss of weight	0	1 (3.6)	0.500
Vomiting	17 (60.7)	14 (50.0)	0.296
Diarrhoea	10 (35.7)	13 (46.4)	0.294
Constipation	2 (7.1)	0	0.245
Abdominal pain	9 (32.1)	9 (32.1)	0.612
Abdominal distension	0	1 (3.6)	0.500

Chi-square-test, Fisher's exact test

Table 3: Distribution of study subjects based on their general and systemic examination

General and systemic examination	Intervention group ($n=28$), *n* (%)	Control group ($n=28$), *n* (%)	*P*
Dehydration	12 (42.9)	10 (35.7)	0.392
Coated tongue	18 (64.3)	14 (50.0)	0.209
Pallor	4 (14.3)	3 (10.7)	0.500
Abdominal tenderness	1 (3.6)	0	0.500
Hepatomegaly	21 (75.0)	16 (57.1)	0.129
Splenomegaly	8 (28.6)	3 (10.7)	0.089

Chi-square-test, Fisher's exact test

Table 4: Distribution of study subjects based on their laboratory investigations

Blood investigation	Intervention group ($n=28$), *n* (%)	Control group ($n=28$), *n* (%)	*P*
Anemia	10 (35.7)	10 (35.7)	0.219
Thrombocytopenia	5 (17.9)	4 (14.3)	0.266
Leukopenia	2 (7.1)	3 (10.7)	0.204
Leukocytosis	1 (3.6)	4 (14.3)	0.204
Eosinopenia	24 (85.7)	23 (82.1)	0.500
Abnormal LFT	6 (21.4)	5 (17.9)	0.500
Elevated CRP	28 (100.0)	28 (100.0)	-

Chi-square test, Fisher's exact test. Anemia: Hemoglobin <11 g/dL, Thrombocytopenia: Platelets <1.5 lakhs/mm^3, Leukopenia: TLC <4000 cells/mm^3, Leukocytosis: TLC >10,000 cells/mm^3, Eosinopenia: Eosinophils <24 cells/mm^3, Abnormal LFT: AST/ALT >45 IU/L, elevated CRP >6 mg/L. LFT: Liver function test, CRP: C reactive protein, TLC: Total leucocyte count, AST: Aspartate transaminase, ALT: Alanine transaminase

Table 5: Comparison of laboratory investigation of study subjects in intervention and control groups

Blood investigation	Intervention group ($n=28$)		Control group ($n=28$)		*P*
	Mean±SD	95% CI	Mean±SD	95% CI	
Hemoglobin (mg/dL)	11.03±1.61	10.40–11.65	11.30±1.51	10.71–11.89	0.519
TLC (/mm^3)	6815.71±2161.65	5977.51–7653.91	6838.21±2857.04)	5730.37–7946.06	0.974
Platelet count (/mm^3)	2.39±0.83	2.06–2.71	2.25±0.77	1.95–2.55	0.512
CRP (mg/L)	33.71±25.22	23.93–43.49	32.48±18.51	25.30–39.67	0.837

Independent *t*-test. SD: Standard deviation, TLC: Total leukocyte count, CRP: C-reactive protein, CI: Confidence interval

Table 6: Comparison of treatment outcomes of intervention and control groups

Treatment and outcomes (days)	Intervention group ($n=28$)		Control group ($n=28$)		*P*
	Mean±SD	95% CI	Mean±SD	95% CI	
Duration of intravenous antibiotic treatment	10.07±2.22	9.21–10.93	9.39±2.33	8.49–10.30	0.270
Duration for defervescence after treatment initiation	3.87±1.57	3.26–4.48	3.35±1.19	2.89–3.82	0.171
Duration for resolution of toxemia after treatment initiation	3.00±1.15	2.55–3.45	2.64±0.87	9.21–10.93	0.197
Duration of hospital stay	11.29±2.12	10.46–12.11	10.36±2.07	9.55–11.16	0.104

Independent *t*-test. SD: Standard deviation, CI: Confidence interval

group and 2.64 (0.87) days in the control group. This difference was not statistically significant ($P = 0.197$).

Duration for defervescence after treatment initiation

Kaplan–Meier curves were used for comparing the probability of resolution of fever from initiation of treatment in intervention and control groups [Figure 2]. The median duration for defervescence in intervention group and control group was 4 days and 3 days respectively. This difference in duration for defervescence was not statistically significant (log rank test [mantel cox], $P = 0.099$).

Duration for resolution of toxemia after treatment initiation

Kaplan–Meier curves were used for comparing the probability of resolution of toxemia from initiation of treatment in intervention and control groups [Figure 3]. The median duration for resolution of toxemia in the intervention group and control group was 3 days and 2 days, respectively. This difference in duration for resolution of toxemia was not statistically significant (log-rank test [mantel cox], $P = 0.148$).

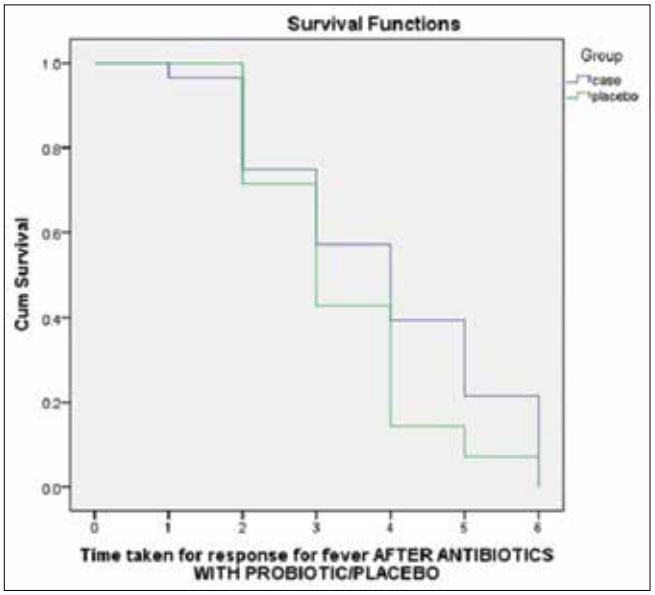

Figure 2: Comparison of duration for defervescence after treatment initiation between intervention and control groups

Discussion

The results of this study show that the addition of the probiotic LGG at a dose of 3×10^9 CFU for 7 days, to the standard antibiotic regime has no effect on reducing the duration of fever or toxemia, in enteric fever. Probiotics are used in the treatment of gastroenteritis, worldwide. However, the results of RCTs are conflicting even for this indication. Szymański *et al*. found a significant decrease in the duration of rotaviral diarrhea when *L. rhamnosus* strains were used in the management of affected infants. However, this probiotic did not show a significant effect on other causes of diarrhea.[17] A major systematic review published in Latin America concluded that probiotics were found useful and hence recommended in acute infectious diarrhea, especially of viral origin.[3] This systematic review and another by Szajewska *et al*. showed that probiotic use was however not beneficial in bacterial diarrhea.[3,18]

A Cochrane database review, in 2010 concluded that probiotics have some benefits in the treatment of acute diarrhoea.[9] However, the 2020 Cochrane database review showed no benefit of probiotic in diarrhea.[19] So even for the most widely used indication, namely diarrhea, the benefit of probiotic use is inconclusive. Several *in vitro* and animal studies have found probiotics to be effective in the elimination of salmonellosis, in addition to standard antibiotic therapy.[13,20,21]

However, this effect could not be replicated in human subjects in our study. To the best of our knowledge, ours is the first study to assess the efficacy of probiotics in enteric fever in humans. Although the results are not encouraging, it might still be worthwhile to consider conducting more such studies before concluding that probiotic use is not beneficial for this

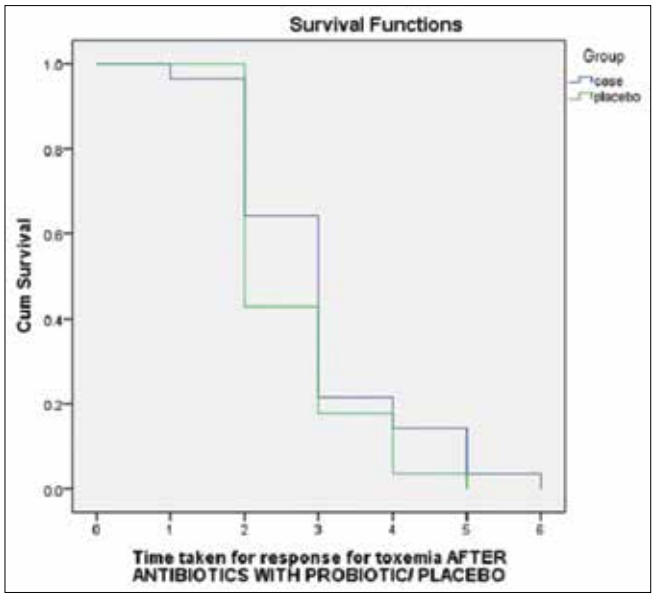

Figure 3: Comparison of duration for resolution of toxemia after treatment initiation between intervention and control groups

condition for at least two reasons. First reason is the compelling scientific plausibility and second, the high safety profile of these probiotic drugs. Salmonella is an organism that is enteric and hence probiotics may have a direct local effect as they do have in other diseases involving the Gastrointestinal tract (GIT).

Conclusions

The present study results shows that addition of the probiotic LGG per oral at a dose of 3×10^9 CFU for 7 days to standard intravenous antibiotic therapy for enteric fever did not show a significant reduction in the fever duration and resolution of toxemia. However, further studies with different probiotic strains or a higher dose of the same strain, LGG may be considered in further studies before concluding their lack of benefit in the therapy of enteric fever.

Limitations

The limitations of this study were the sample size, a larger sample size may be needed, to prove the significance of LGG. Resolution of toxemia mentioned as secondary outcome in this study, is highly subjective since many other factors such as age, nutritional status, and hydration status could also have influenced the resolution of toxemia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Typhoid; 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/typhoid. [Last accessed on 2022 Sep 15].
2. Stanaway JD, Reiner RC, Blacker BF, Goldberg EM, Khalil IA, Troeger CE, *et al*. The global burden of typhoid and paratyphoid fevers: A systematic analysis for the global burden of disease study 2017. Lancet Infect Dis 2019;19:369-81.
3. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F, *et al.* The use of probiotics in pediatric gastroenterology: A review of the literature and recommendations by Latin-American experts. Paediatr Drugs 2015;17:199-216.
4. FAO/WHO. Joint FAO/WHO Working group report on drafting guidelines for the evaluation of probiotics in food. London, Ontario, Canada. 2002:39-46. Available from:https://www.fao.org/3/a0512e/a0512e.pdf [Last accessed on 2023 May 31].
5. Indriyani A, Juffrie M, Setyati A. Effects of live versus heat-killed probiotics on acute diarrhea in young children. Paediatr Indones 2012;52:249-54.
6. Weichert S, Schroten H, Adam R. The role of prebiotics and probiotics in prevention and treatment of childhood infectious diseases. Pediatr Infect Dis J 2012;31:859-62.
7. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human *Lactobacillus* strain (*Lactobacillus casei* sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 1991;88:90-7.
8. Shornikova AV, Isolauri E, Burkanova L, Lukovnikova S, Vesikari T. A trial in the Karelian republic of oral rehydration and *Lactobacillus* GG for treatment of acute diarrhoea. Acta Paediatr 1997;86:460-5.
9. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 2010;2010:CD003048.
10. Pant AR, Graham SM, Allen SJ, Harikul S, Sabchareon A, Cuevas L, *et al. Lactobacillus* GG and acute diarrhoea in young children in the tropics. J Trop Pediatr 1996;42:162-5.
11. Raza S, Graham SM, Allen SJ, Sultana S, Cuevas L, Hart CA. *Lactobacillus* GG promotes recovery from acute non bloody diarrhea in Pakistan. Pediatr Infect Dis J 1995;14:107-11.
12. Bousvaros A, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, *et al.* A randomized, double-blind trial of *Lactobacillus* GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. Inflamm Bowel Dis 2005;11:833-9.
13. Abdel-Daim A, Hassouna N, Hafez M, Ashor MS, Aboulwafa MM. Antagonistic activity of *Lactobacillus* isolates against *Salmonella* typhi *in vitro*. Biomed Res Int 2013;2013:680605.
14. Lu R, Fasano S, Madayiputhiya N, Morin NP, Nataro J, Fasano A. Isolation, identification, and characterization of small bioactive peptides from *Lactobacillus* GG conditional media that exert both anti-gram-negative and gram-positive bactericidal activity. J Pediatr Gastroenterol Nutr 2009;49:23-30.
15. Kothari A, Pruthi A, Chugh TD. The burden of enteric fever. J Infect Dev Ctries 2008;2:253-9.
16. Reller M, Long S, Pickering L, Prober C. *Salmonella* species. In: Principles and Practice of Pediatric Infectious Diseases. 3rd ed. Edinburgh, W.B: Saunders; 2008. p. 812-6.
17. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains – A randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;23:247-53.
18. Szajewska H, Setty M, Mrukowicz J, Guandalini S. Probiotics in gastrointestinal diseases in children: Hard and not-so-hard evidence of efficacy. J Pediatr Gastroenterol Nutr 2006;42:454-75.
19. Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, *et al*. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 2020;12:CD003048.
20. Truusalu K, Mikelsaar RH, Naaber P, Karki T, Kullisaar T, Zilmer M, *et al.* Eradication of *Salmonella typhimurium* infection in a murine model of typhoid fever with the combination of probiotic *Lactobacillus fermentum* ME-3 and ofloxacin. BMC Microbiol 2008;8:132.
21. Fadare OS, Singh V, Enabulele OI, Shittu OH, Pradhan D. *In vitro* evaluation of the symbiotic effect of probiotic *Lactobacillus* strains and garlic extract against *Salmonella* species. LWT 2022;153:112439.