Original Article

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Safety and Efficacy of *Lactobacillus rhamnosus* GG (ATCC 53103) in Children with Functional Abdominal Pain: A Randomised, Double-blinded, Placebo-controlled Trial

Paediatrics Section

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ABSTRACT

Introduction: Functional Abdominal Pain (FAP) is a major concern in developing countries, especially in school-going children. Recently, some probiotics have shown clinical evidence in managing abdominal diseases. The role of *Lactobacillus rhamnosus* GG (LGG) (ATCC 53103) for FAP in children has not been studied in India.

Aim: To evaluate the safety and efficacy of LGG (ATCC 53103) in children with FAP in terms of frequency, severity, and adverse effects.

Materials and Methods: This double-blinded, placebo-controlled study was conducted at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India, from February 2021 to July 2022, after obtaining permission from the Institutional Ethical Committee (IEC). Children aged 5-18 years with FAP were included in the study. A total of 82 children were included in the study and were randomised into the LGG group and placebo group. The LGG group received LGG (ATCC 53103), and the placebo group received sugar powder for a period of four weeks. These patients were followed-up after 2, 4, and 8 weeks for evaluation. Student's t-test (unpaired) was used for quantitative data, and Chi-square test was used for qualitative data. Statistical Package for the Social Sciences (SPSS) PC-20.0 version was used to evaluate the data.

Results: Out of 82 children, a total of 77 children were enrolled during the study period, with 38 in the LGG group and 39 in the placebo group. The severity of abdominal pain at four weeks and eight weeks was significantly less compared to placebo (p-value=0.009 and p-value=0.01, respectively). The frequency of abdominal pain at four weeks and eight weeks was also significantly less compared to placebo (p-value ≤0.001 and p-value ≤0.001, respectively). There was no statistically significant difference in adverse effects between the two groups (p-value=0.115).

Conclusion: This study concluded that LGG decreases both the severity and frequency of abdominal pain in children aged 5-18 years without any significant side-effects. Thus, it can be safely used in the management of childhood FAP.

Keywords: Bowel syndrome, Probiotics, Wong-Baker pain FACES scale

INTRODUCTION

FAP, not otherwise specified, occurs atleast four times per month with either intermittent or continuous abdominal pain not associated with a particular activity or coincident to another physiological event, such as menses or eating. It cannot be explained by any other underlying medical condition and lasts for atleast two months [1]. FAP is described as continuous, nearly continuous, or frequent recurrent pain localised in the abdomen but poorly related to gut function [2]. Because of this change in bowel function, this type of abdominal pain is often referred to as 'FAP'.

Estimates of the incidence and prevalence vary depending on the diagnostic criteria and setting, but about 10-20% of the school-aged population may be affected. However, it is rarely observed in children below five years and adults above 18 years. The prevalence rate of FAP ranges from 0.3-19% in school-going children in the United States and Europe [3].

In recent years, both research and consumers interest in probiotics have grown. Increasing clinical evidence supports some of the proposed health benefits related to the use of probiotics, particularly in managing certain abdominal diseases. Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. Although the exact mechanisms by which probiotics may exert their actions in patients with FAP are not fully understood, several mechanisms have been suggested [4]. The available pharmacological interventions are limited in children, and therefore, management has focused on combined approaches, including mind-targeted interventions and diet (probiotics) [5]. In the past few years, probiotics have shown some effectiveness in the treatment of FAP. Multiple studies in adults [6-8] have shown that certain probiotic strains are clinically more effective than placebo in treating some categories of FAP, mainly irritable bowel syndrome. However, limited paediatric data are available [9].

Very few studies are available in the literature on LGG (ATCC 53103) for FAP, and no study was found in India among children [9,10]. The present study was undertaken to evaluate the efficacy of LGG (ATCC 53103) in children with FAP in terms of frequency and severity, as the primary objective, and to evaluate safety in terms of adverse effects, as the secondary objective.

MATERIALS AND METHODS

This double-blinded randomised controlled trial was conducted at the Department of Paediatrics, Geetanjali Medical College and Hospital in Udaipur, Rajasthan, India from February 2021 to July 2022, after obtaining approval from the Institutional Research Review Board and IEC (Ref: GU/HREC/EC/2021/1894). This study was also registered with the Clinical Trial Registry of India (CTRI registration No: 2022/01/039373). Consecutive sampling was used to enroll the patients, and informed patient consent/assent was obtained from all the parents.

Inclusion criteria: Children aged between 5 to 18 years of either gender, who met the FAP criteria according to Rome IV [11], were included in the study.

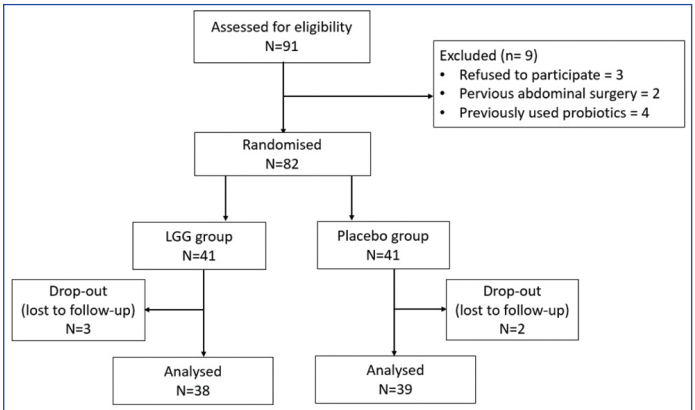
Exclusion criteria: Children with any chronic disease, those who had used probiotics in the last two months, or had a history of previous abdominal surgery were excluded from this study.

Sample size: The following formula was used to calculate the sample size:

$$N=(Z\alpha+Z1-\beta)^2P(1-P)/E^2$$ [12]

where N is the sample size, Zα is 1.96 at a 95% confidence level, Z1-β is 0.8413 at 80% power of the study, 'P' is the expected prevalence, and 'E' is the margin of absolute error. The prevalence was estimated to be 2.7% [13], and the margin of error was set at 7.5%. The final sample size calculated was 37. Considering a 10% dropout rate in each group, a minimum of 41 children were enrolled in each group during the study period.

After the initial assessment for eligibility in 91 children, 9 children were excluded due to refusal to participate, previous use of probiotics, and previous abdominal surgery. Therefore, a total of 82 children were enrolled in the study during the study period. Three children from the LGG group and two children from the placebo group were lost to follow-up. Hence, the results of 77 children were studied [Table/Fig-1].



[Table/Fig-1]: Consort diagram of the study.

Procedure

Children who were clinically diagnosed according to the Rome IV criteria were enrolled in the study. After obtaining a detailed medical history, conducting a clinical examination, and relevant investigations, the patients were randomly assigned to either the LGG or placebo groups. Randomisation was performed using computer-generated random numbers. The LGG group received one sachet of LGG (ATCC 53103), which contained 10 billion (10^{10}) Colony Forming Units (CFU), while the placebo group received one sachet of sugar powder. Both sachets weighed 1 gram and had the same shape, taste, dimensions, and appearance. Both preparations were administered orally, one sachet per day, for four weeks. Neither the participants nor the researchers knew which sachet was given to each participant until the study was complete. The sachets were administered by a third person who was not involved in the research. The children returned for follow-up visits after 2, 4, and 8 weeks to monitor the progress of the study.

The primary outcome assessed was the severity and frequency of abdominal pain, and the secondary outcome was the occurrence of adverse effects in both groups. The Wong-Baker Pain Scale, which consists of six types of pain faces with corresponding scores, was used to measure the severity of abdominal pain in children [14]. Additionally, demographic parameters such as age, gender, residence, and socio-economic status were compared in both groups. The Modified Kuppuswamy socio-economic scale was used to classify the children based on socio-economic data [15].

STATISTICAL ANALYSIS

The collected data were transformed into variables, coded, and entered into Microsoft Excel. The data were then analysed and statistically evaluated using SPSS-PC-20.0 version. Quantitative data were expressed as mean and standard deviation, and the difference between the two comparable groups was assessed using Student's t-test (unpaired). On the other hand, qualitative data were expressed as percentages. Statistical differences between proportions were tested using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

No statistically significant difference was found in the demographic data between both the groups [Table/Fig-2].

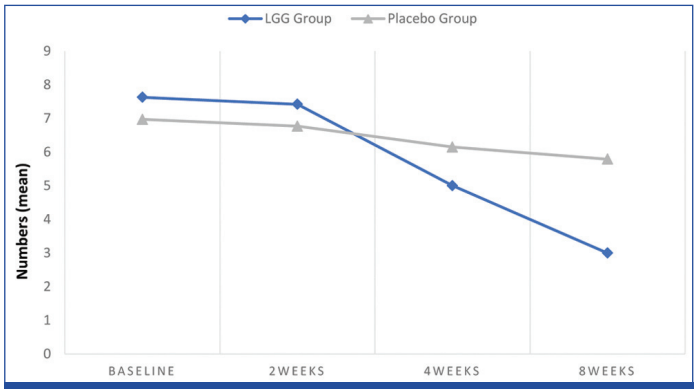
Variables		LGG group (n=38) n (%)	Placebo group (n=39) n (%)	p-value*
Gender	Female	22 (57.9)	23 (59.0)	0.923
	Male	16 (42.1)	16 (41.0)	
Age group (years)	<10	17 (44.7)	19 (48.7)	0.938
	>10	21 (55.3)	20 (51.3)	
Residence	Rural	18 (47.4)	20 (51.3)	0.731
	Urban	20 (52.6)	19 (48.7)	
Socio-economic status [13]	Lower	6 (15.8)	8 (20.5)	0.961
	Lower middle	11 (28.9)	11 (28.2)	
	Upper	3 (7.9)	4 (10.3)	
	Upper lower	7 (18.4)	7 (17.9)	
	Upper middle	11 (29)	9 (23.1)	

[Table/Fig-2]: Demographic data distribution between both Groups.
*Chi-square test was applied

The pain severity, as rated on the Wong-Baker Faces Pain Scale [14], is shown in [Table/Fig-3,4]. There was no statistically significant difference at baseline (p-value=0.149) and two weeks (p-value=0.152) between both groups. However, there was a statistically significant difference at four weeks (p-value=0.009) and eight weeks (p-value=0.01) between both groups [Table/Fig-3,4].

Severity	LGG group Mean±SD	Placebo group Mean±SD	p-value
Baseline	7.63±1.91	6.97±2.05	0.149
2 weeks	7.42±1.85	6.77±2.08	0.152
4 weeks	5±1.59	6.15±2.12	0.009*
8 weeks	3±1.66	5.79±2.24	0.01*

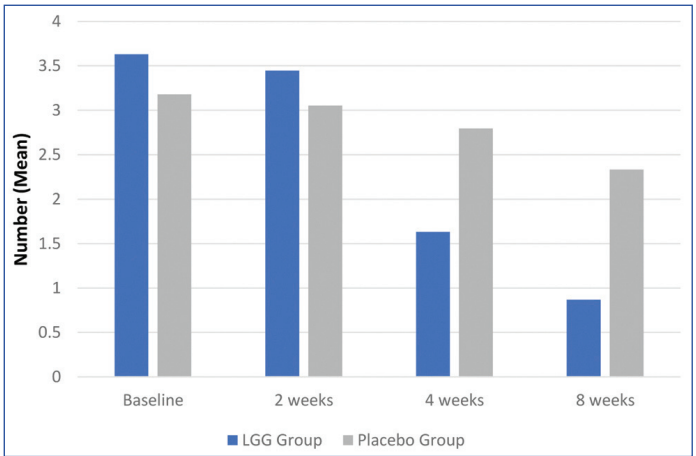
[Table/Fig-3]: Comparison of severity of abdominal pain between both the groups.
*Significant using unpaired t-test



[Table/Fig-4]: Comparison of severity of abdominal pain between both the groups.

The pain frequency, measured in terms of episodes per week, in the LGG group was 3.63±1.42 at baseline, 3.44±1.37 at two weeks, 1.63±1.06 at four weeks, and 0.86±0.83 at eight weeks. In the placebo group, these values were 3.17±1.41, 3.05±1.39, 2.79±1.09, and 2.33±0.91, respectively. There was no statistically significant difference at baseline (p-value=0.171) and two weeks (p-value=0.219) between both groups. However, there was a

statistically significant difference at four weeks (p-value ≤0.001) and eight weeks (p-value ≤0.001) between both groups [Table/Fig-5].



[Table/Fig-5]: Comparison of frequency of abdominal pain between both the groups.

In the LGG group, a total of two children (5.3%) experienced vomiting at two weeks, and three children (7.9%) experienced vomiting at four weeks. No side-effects were reported in the placebo group. There was no statistically significant difference in adverse effects between both groups (p-value=0.115).

DISCUSSION

The FAP can be episodic or continuous. Although the exact cause is not known, nerve signals or chemicals secreted by the gut or brain may make the gut more sensitive to triggers that normally do not cause significant pain. Probiotics are commonly targeted for illnesses associated with the gastrointestinal tract, mainly due to their ability to restore gut flora. Due to their safety profile, probiotics seem to be an attractive therapeutic option for gastrointestinal tract diseases. These are used for the prevention and treatment of various medical conditions and to support general wellness [10,16,17].

In this present study, probiotics were compared with a placebo to assess their safety and efficacy. The authors attempted to reduce possible confounding factors by using a sugar powder as a placebo. In the present study, both groups were demographically similar. The severity of abdominal pain, based on the Wong-Baker Faces scale [14], significantly reduced in the LGG group after eight weeks of intervention. There was no significant change in the severity of abdominal pain in the placebo group. A significant change occurred at the 4th (p-value=0.009) and 8th week (p-value=0.001) when these two groups were compared.

Similar results were found in a study conducted by Francavilla R et al., in which 141 children treated with LGG showed a significant reduction in the severity of abdominal pain (p-value <0.01) [10]. Gawron´ska A et al., also found that the LGG group was more likely to have treatment success (no pain) compared to those in the placebo group (25% versus 9.6%) [9]. Additionally, Kianifar H et al., observed in their study that LGG administration resulted in a significant difference in abdominal pain severity after four weeks (p-value=0.001) [18].

These positive results may be due to the fact that LGG, upon reaching the intestine, inhibits the growth or reduces the activity of pathogens by colonising the gut. It involves the production of various substances, such as hydrogen peroxide, organic acids, bacteriocins, and biosurfactants that are toxic to pathogenic microorganisms. LGG also has the ability to produce a low-molecular-weight compound that inhibits broad-spectrum bacteria [19-21].

In contrast to previous studies by Bausserman M and Michail S, who observed that LGG had no significant effect on abdominal pain severity compared to placebo in FAP [22], this discrepancy may be attributed to the use of inulin as a placebo, which acted as a prebiotic [22]. Prebiotics are substances that help in the growth of protective bacteria in the gut [23].

In the study conducted by Francavilla R et al., where 141 children were treated with LGG, the number of pain episodes per week at baseline was 3.7 in the probiotic group and 3.5 in the placebo group. After 12 weeks, it decreased to 1.1 and 2.2, respectively (p-value <0.01), and at the end of the follow-up period, episodes of pain decreased to 0.9 (0.5) in the probiotic group and 1.5 (1.0) in the placebo group (p-value <0.02) [10]. Similarly, Gawrońska A et al., (p-value=0.02) and Weizman Z et al., (p-value <0.02) found in their studies that LGG reduced the frequency of pain compared to children who were given a placebo [9,24]. The decrease in the frequency of pain in the LGG group could also be explained based on the probiotic mechanism [19-21].

Only the LGG group reported vomiting as a side-effect in the present study, but it was statistically non significant. Kajander K et al., found gastrointestinal symptoms as an adverse effect in the participants taking probiotics in their study [25]. Other studies have also reported similar results, but they were non significant [9,10].

Limitation(s)

The present study was a single-centre study. Other multicentre studies conducted in different parts of India can be performed on a larger population. The study may be underpowered for specific diagnoses. In one group, a placebo was used, and the effect of the placebo may be responsible for the lack of an obvious effect of the LGG treatment. The study was conducted in a tertiary care hospital, so there is a possibility that more severely affected children were included. There were also chances of recall bias during follow-ups.

CONCLUSION(S)

LGG can be safely used in the management of children with FAP as it decreases both the severity and frequency of abdominal pain in children aged 5-18 years without any significant side-effects.

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