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A randomized, double-blind, placebo controlled trial to evaluate the efficacy and safety of probiotic preparation in children with acute Diarrhea

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Abstract: To investigate the efficacy of probiotic preparation in the management of acute diarrhea in children, 100 children (aged 3 months to 5 years) were randomized into 2 groups – probiotic and control group. The probiotic group received Bacillus Clausii - 2 billion, Streptococcus Thermophilus St-21 – 100 million, Bacillus coagulans - 50 million, and Bacillus mesentericus TO-A - 1 million twice a day for 7 days. The control group received a placebo twice a day for 7 days. Both groups received ORS and Zinc. The mean duration of diarrhea was shorter in the probiotic group (2.90 ± 0.86 days) compared to the control group (4.0 ± 1.16 days), $p<0.001$. Patients in the probiotic group exhibited rapid improvement in terms of a decrease in the frequency of episodes of diarrhea within 48-72 hours. Most patients in the probiotic group recovered from diarrhea on the 2nd and 3rd day, compared to the 4th and 5th day in the control group. The probiotic preparation was found to be effective in the management of acute diarrhea in children and was well tolerated without any adverse effects. Thus, probiotics should be considered an integral part of the management of diarrhea.

Keywords: *Bacillus Clausii, Bacillus coagulans, Bacillus mesentericus TO-A Diarrhoea, Probiotic, Streptococcus Thermophilus St-21.*

1. Introduction

Diarrhoea is the second leading cause of death in children under five years of age across the globe. When three or more loose or watery stools occur every day for 14 days or less, it is referred to as acute diarrhoea. The most common age group affected due to diarrhoea are children aged 6 to 24 months [1]. The most frequent causative agents include *rotavirus*, *cryptosporidium parvum*, *giardia intestinalis*, *entamoeba histolytica*, *cyclospora cayetanensis*, *escherichia coli*, *campylobacter*, *shigella species*, and *vibrio cholera*.

Diarrhoea is a significant health concern in Indian children, contributing to morbidity, mortality, and malnutrition [2]. According to World Health Organization (WHO), diarrhea is responsible for 13% of all deaths in children under 5 years in India [3]. The cornerstone of treatment for diarrhoea is fluid replenishment. Oral rehydration salts (ORS) is used to treat mild dehydration, whereas intravenous fluids are used to treat severe dehydration [4]. Probiotics have shown beneficial roles in the management of acute diarrhoea in children and the effects are strain specific [5]. The WHO defines probiotics as "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [6]. Probiotics can affect the host in a variety of ways, such as reducing the pH of the intestinal tract, preserving the integrity of the mucosal barrier by producing short-chain fatty acids, displacing pathogens from the adhesion sites and production of bacteriocins, to mention a few [7]. By replenishing the gut with beneficial microbes and boosting the immune system, probiotics can help alleviate diarrhoea and promote overall gut health [8].

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Diarrhoeal disease among children has become crucial health concerns in India. In spite of having different interventions and schemes to control, diarrhoeal death in children under five years of age in India is still alarming [9]. There are lots of studies done in the western world which has shown the beneficial effect of probiotics in acute diarrhea, but Indian studies are very limited. Therefore, the present study was designed to examine the effect of probiotic preparation in reducing the incidence and severity of acute diarrhoea in children when taken along with standard therapy.

2. Materials and Methods

This randomized, double-blind, placebo-controlled trial was carried out between September 2023 to January 2024 at the Department of Paediatrics in Chettinad Hospital and Research Institute, Kelambakkam, T.N, India. Before the study initiation, approval was obtained from The Chettinad Institutional Human Ethics Committee and the same was registered in Clinical Trial Registry India (CTRI Number: CTRI/2023/08/056064). 100 children with diarrhoea, aged 3 months to 5 years, both male and female, were recruited in the study after obtaining informed consent from their parents or guardians. The inclusion and exclusion criteria are given as under.

2.1. Inclusion Criteria

After obtaining written informed consent from a parent or guardian, eligible children were included to the study. The criteria for inclusion are listed as under (1) Children suffering from acute diarrhoea, (2) Both sexes, (3) Age group between 3 months to 5 years and (4) Duration less than 3 days

2.2. Exclusion Criteria

Following were the exclusion criteria (1) Severe malnourishment, (2) Severe dehydration, (3) Children with chronic/ severe respiratory, cardiovascular, central nervous disorder, gastrointestinal and endocrinal disorders, (4) Children with malabsorption syndromes, (5) Children with known hypersensitivity for probiotics and (6) Children with previous intake of probiotics in the last 1 month.

At the first visit, after obtaining consent, patient details and medical history were recorded. All patients were subjected to a detailed clinical examination and the degree of dehydration was assessed.

All children were randomized into two groups, Group A and B, based on randomization by an independent statistician. Group A received probiotic preparation (Biosun Kids sachet) and standard treatment. The probiotic preparation was given twice a day after mixing in 10 ml of water for 1 week. Each probiotic sachet contained the following: *Bacillus Clausii* 2 billion, *Streptococcus Thermophilus St-21* 100 million, *Bacillus coagulans* 50 million and *Bacillus mesentericus TO-A* 1 million. Group B received placebo and standard treatment. Placebo had same colour, texture, taste and smell and was same excipients as intervention except the active ingredients (probiotics).

Standard treatment was given for a period of 7 days which includes ORS and oral zinc supplementation (elemental zinc 10 mg/day for children aged < 6 months and 20 mg/day for children aged > 6 months). Patients were assessed for a period of 1 week and were followed up on daily basis assessing for decrease in frequency and duration of diarrhoea.

2.3. Outcome Measures

The efficacy variables used to determine the outcome of the study are as follows: (a) Mean duration of diarrhea in days, (b) Number of episodes of diarrhea in a day, (c) Day wise recovery from diarrhoea, (d) Degree of dehydration & (e) Stool consistency.

2.4. Statistical Analysis:

Statistical analysis was done using IBM SPSS software 27 Version. After confirming the normality test using Kolmogorov-Smirnov test, parametric tests were done. For continuous variables mean and standard deviation were done. For comparison between probiotic group and placebo group, independent

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sample t test was used. For comparing the no. of stool, repeated measures ANOVA was used. p value < 0.05 was considered as a significant at 95% confidence interval.

2.5. Demographics

Out of 100 children, 50 children were assigned to Group A and 50 children to the Group B. Age and gender of both groups are shown in Table 1.

Table 1.
Demographic characteristics of the study population.

Characteristic	Group A (Probiotic Group)	Group B (Control Group)
Number of Patient	50	50
Age in years (mean ±SD)	3.28 ± 1.30	3.01 ± 1.07
Male: Female	1.23: 1	1.17: 1

3. Results

3.1. Mean Duration of Diarrhea in Days

The mean duration of diarrhea was significantly reduced in Group A (probiotic group) 2.90 ± 0.86 days compared to Group B (control group) 4.06 ± 1.16 days ($p<0.001$), which clearly demonstrates that probiotic group had faster recovery from diarrhea in comparison to control group (Table 2).

Table 2.
Mean duration (days) of diarrhoea between probiotic group and control group.

Group	N	Mean (days)	SD	P-value
Group A (Probiotic group)	50	2.90	0.863	< 0.001
Group B (Control group)	50	4.06	1.168	

3.2. Frequency of Diarrhea in a Day

The number of episodes of stools per day was significantly less in the probiotic group as compared to the control group, starting from 24 h of therapy (Table 3).

Table 3.
Frequency of diarrhea in probiotic and control group.

Parameter	Group A (Probiotic group)		Group B (Control group)		p-value
	Mean	SD	Mean	SD	
Number of stool episodes per day after 24 hrs	4.26	1.882	5.02	1.801	<0.042
Number of stool episodes per day after 48 hrs	2.94	1.743	3.84	1.608	<0.009
Number of stool episodes per day after 72 hrs	1.44	0.993	2.66	1.319	<0.0001
Number of stool episodes per day after 96 hrs	1.14	0.606	1.92	1.027	<0.0001

3.3. Day Wise Recovery from Diarrhea

As per-protocol analysis, maximum recovery from diarrhoea in probiotic group was noticed in on 2nd and 3rd day i.e., 38 (76%) out of 50 patients were recovered, while in control group most of the patients recovered on day 4th and 5th i.e., 31 (62%) out of 50 patients Table 4. Thus faster recovery from diarrhea was achieved in probiotic group.

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Table 4.
Number of patients recovering from diarrhea in probiotic and control group, each day.

	Group A (Probiotic Group)	Group B (Control Group)
No. of patients recovered from diarrhea on Day 1	3	1
No. of patients recovered from diarrhea on Day 2	10	4
No. of patients recovered from diarrhea on Day 3	28	11
No. of patients recovered from diarrhea on Day 4	7	12
No. of patients recovered from diarrhea on Day 5	2	19
No. of patients recovered from diarrhea on Day 6	0	3

3.4. Degree of Dehydration

On day 2, it was noted 26 out of 50 patients experienced no dehydration in probiotic group, while in control group, 13 patients experienced no dehydration, which was statistically significant (P= 0.001) Table: 5.

Table 5.
Degrees of Dehydration between probiotic and control group (HS = Highly Significant).

Day	Degree of Dehydration	Group A (Probiotic Group)	Group B (Control Group)	P value
Day 0	Mild	11	12	
	Moderate	39	38	
Day 1	Mild	35	22	P=0.031
	Moderate	12	22	
	No dehydration	3	2	
Day 2	Mild	20	19	P=0.001
	Moderate	4	18	
	No dehydration	26	13	
Day 3	Mild	4	21	P=0.000 (HS)
	Moderate	0	3	
	No dehydration	46	26	
Day 4	Mild	0	10	P=0.02
	Moderate	0	1	
	No dehydration	50	39	
Day 5	Mild	0	2	P=0.153
	No dehydration	50	48	
Day 6	No dehydration	50	50	

3.5. Stool Consistency

According to Bristol stool chart, in the beginning of the study (day 0) 41 patients in group A and 42 patients in group B had a type 7 stool consistency. By the end of the study (day 6), all participants had type 4 stool consistency.

3.6. Side Effects & Adverse Effects

Children in both the groups did not experience any notable adverse effects, such as bloating, stomach discomfort, vomiting, constipation, or an allergic reaction.

4. Discussion

Acute diarrhoea is a leading cause of childhood mortality and morbidity which burdens the society and the families of afflicted children financially. Probiotics have shown promising results in the treatment of acute diarrhea. According to a Cochrane meta-analysis of 23 RCT, probiotics were helpful adjuncts to rehydration therapy in the treatment of acute infectious diarrhea. Our study reconfirms the clinical effectiveness of probiotics in the management of acute diarrhoea in children [5].

Our study assessed the safety and efficacy of a probiotic preparation containing four beneficial bacteria namely *Bacillus Clausii*, *Streptococcus Thermophilus* St-21, *Bacillus coagulans* and *Bacillus*

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mesentericus TO-A in children suffering from acute diarrhoea. The mean duration of the diarrhea was shorter in the probiotic group (2.90 ± 0.86 days) as compared to the control group (4.0 ± 1.16 days), with a statistical significance of $p<0.001$. Children in the probiotic group exhibited rapid improvement in terms of decrease in the frequency of episodes of diarrhea per day i.e., within 48-72 hours. Maximum recovery from diarrhea in the probiotic group was seen on the 2nd and 3rd day, while in the control group, most of the patients recovered on the 4th and 5th day. Thus, in this study, children who received probiotics experienced a statistically significant decrease in the frequency and duration of diarrhoea.

Previous studies have reported the beneficial effects of using combination of probiotics in children. Kumar, et al. [10] demonstrated that probiotics reduced the duration of diarrhea in children [10]. A study by Bhat and Shivam [11] found that early probiotic use effectively reduces the episodes of acute diarrhea in children when given along with ORS and zinc [11]. A study conducted by Narayanappa [12] showed that probiotics significantly reduced the frequency of diarrhoea, duration of diarrhoea and degree of dehydration [12]. Our findings in this study are consistent with previous studies showing that probiotics are effective in reducing the duration and frequency of diarrhea in children.

5. Conclusion

When given along with standard treatment, probiotic preparation showed clinical as well as statistically significant reduction in number of episodes (frequency) of diarrhea in a day, mean duration of diarrhea and degree of dehydration as compared to placebo. Moreover, more number of children recovered from diarrhea faster upon administration of probiotic preparation. It can be concluded from the study, that the addition of probiotic preparation to standard therapy for the management of acute diarrhea in children is safe and effective. Thus, probiotics should be considered as an integral part in the management of diarrhoea.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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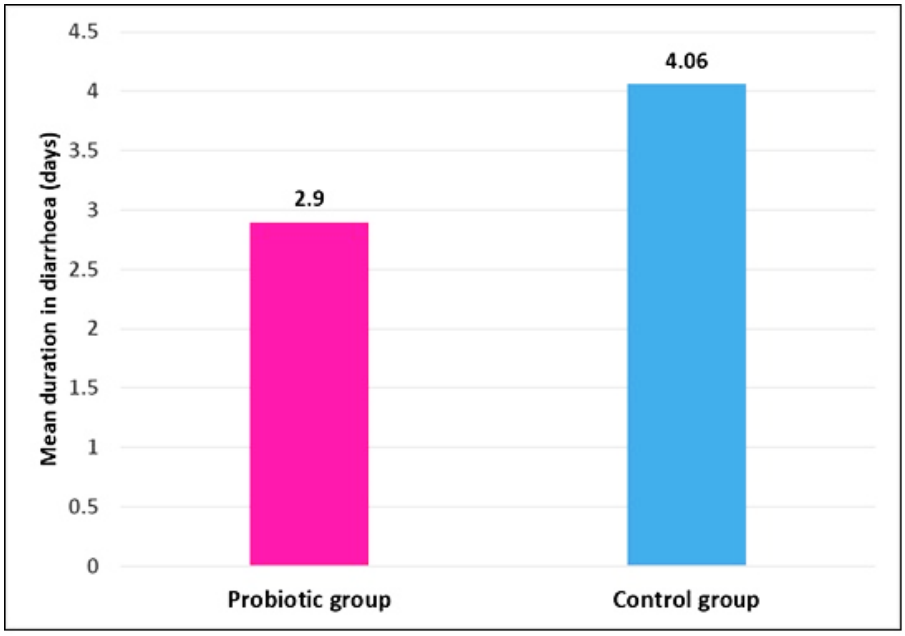

Figure 1.
Mean duration (days) of diarrhea between probiotic group and control group.

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