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A randomized controlled open labelled study to evaluate clinical efficacy of Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) in the management of acute diarrhoea in children

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ABSTRACT

Background: Acute Diarrhoea in children is the most frequent gastroenterological disorder and is a common cause of dehydration in children. The management of acute diarrhoea consists of the replacement of lost fluid with glucose-electrolyte oral rehydration solution. Probiotics have been used as adjunctive therapy in the treatment of acute diarrhoea.

Materials and Methods: In this study we evaluated the efficacy of Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) in management of Acute diarrhoea in children. 48 children aged between 6 months and 15 years with acute bacterial gastroenteritis or acute viral gastroenteritis were included in the study. The study group received poly antibiotic resistant B. clausii strains (TIL 19T, TIL 21C, TIL 28S, TIL 30R) as a probiotic along with standard treatment for diarrhoea and the control group received standard treatment for diarrhoea without B. clausii.

Results: The results at the end of 48 hours showed a significant improvement in very severe and high grade diarrhoea category in the children belonging to the study group. That is, all patients had recovered to low grade or normal grade ($P < 0.01$). Analysis of diarrhoeal stool group showed 64% of children in the control group continued to have loose stools as compared to just 24% in the study group ($P < 0.01$). No serious adverse events were recorded in both the groups.

Conclusion: The use of B. clausii strains (TIL 19T, TIL 21C, TIL 28S, TIL 30R) in Acute Diarrhoea in children has shown to improve the recovery time from the illness and improvement in stool consistency due to its probiotic effect.

1. Introduction

Acute gastroenteritis is an infectious syndrome that represents the first cause of hospitalization in children.[1] Diarrhoea is usually a symptom of an infection in the intestinal tract, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking water, or from person-to-person as a result of poor hygiene.[2] Diarrhoea due to infection is widespread throughout developing countries. In developing countries, children under 5 years of age experience on average three episodes of diarrhoea every year.[3] One out of every five children who die of diarrhoea worldwide is an Indian. Repeated episodes of diarrhoea in children can result in long-term deleterious effects on nutritional status, possibly due to intestinal damage. Each episode deprives the child from the basic nutrition necessary for growth. As a result, diarrhoea is a major cause of

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malnutrition, and malnourished children are more likely to fall ill from diarrhoea.[2] The management of acute diarrhoea consists of the replacement of lost fluid with glucose-electrolyte oral rehydration solution. However, ORS reduces neither the severity nor the duration of diarrhoea[4] but has substantial benefit in preventing major morbidities due to dehydration and even mortality. The need of the hour is a probiotic strain which reduces both severity and duration of diarrhoea without any major impact on the intestinal motility retardation.

Probiotics are live microbial feed supplements that beneficially affect the host by improving its microbial balance. They are commonly used in the treatment and prevention of acute diarrhoea. The rationale for using probiotics in acute infectious diarrhoea is based on the assumption that they act against intestinal pathogens through a variety of physiological and mechanical hostility to pathogens.[5]

Out of many probiotics available, Bacillus clausii is found to be beneficial in reducing duration and severity of diarrhoea.[6] This study is aimed to evaluate efficacy of poly antibiotic resistant Bacillus clausii strains (TIL 19T, TIL 21C, TIL 28S, TIL 30R) in treatment of acute diarrhoea in children.

2. Materials and Methods

This was a prospective, randomized, controlled, open labelled interventional study conducted at the Department of Paediatrics, Panimalar Medical College Hospital & Research Institute, Chennai, India. The study was conducted from November 2021 to January 2022. Approval from the Institutional Ethics Committee was obtained prior to the commencement of the study (IEC No. PMCHRI-IHEC-041). The study was conducted according to the International Council for Harmonisation – Good Clinical Practice guidelines.[7] Informed consent was obtained from the guardians of participants agreeing to follow the study protocol.

Children aged between 6 months and 15 years with acute bacterial gastroenteritis or acute viral gastroenteritis were included in the study. Confounding factors taken into account were socioeconomic status and level of education of caretakers /guardians in both groups which were matched. To avoid bias, patient families earning below Rs.15000/year and level of education below primary school were excluded from the study, this is due to the fact that questionnaires such as measure of frequency and consistency of stool require a reasonable level to understand and to record in patient diary.

Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically 3 in 24 hours), with or without fever or vomiting. Children with severe dehydration and electrolyte imbalance, presence of systemic infections, known immunocompromising morbidities, chronic or severe respiratory, cardiovascular, central nervous system, endocrine and other gastrointestinal disorders on clinical examination were excluded from the study. Children were recruited on OPD basis for the study and did not include cases of diarrhoea with severe dehydration which required hospitalization.

The method of randomization and enrolment is illustrated in the consort diagram (Figure 1). At the time of enrolment, each child who satisfied the inclusion criteria was alternatively allotted into treatment and control groups. The children were sequentially randomized and included in the study over a period of 3 months. This was followed by a 3-day treatment regimen and improvement of duration, frequency and consistency of stools which assessed the effect of the treatment given was noted.

The symptoms were graded according to the frequency of loose stools as:

1. Very Severe: stools > 10 times/ day
2. High Grade: 6-10 times/ day
3. Low grade: 3-5 times/ day
4. Normal: include grades based on stools - <3 times/day

The frequency and consistency of the stool was assessed by caretakers of the children as they were trained to note normal or loose stools through pictorial illustrations.

2.1. Procedure

Forty-Eight children between ages 6 months and 15 years, diagnosed with Acute diarrhoea were included for the study after taking written informed consent from the guardians. Sample size for the study (n=48) was calculated with Alpha error as 5% and power of the study at 80%. The children were divided into two groups -Study group or the Probiotic group and the Control group. Children in Study group (n=24) received standard treatment for Acute diarrhoea for 3 days along with Poly Antibiotic Resistant Bacillus clausii strains (TIL 19T, TIL 21C, TIL 28S, TIL 30R) which was manufactured by Allianz Biosciences Private limited (ABPL). Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) was administered at a dose of 2 Billion CFU twice daily. Children in control group (n=24) received standard treatment alone for Acute diarrhoea for 3 days. Standard treatment for Acute diarrhoea included ORS (Oral rehydration salt) and Zinc therapy for 14 days.

In the due course the children in both groups were assessed for improvement of symptoms, changes in the frequency of stools and evaluated for changes in stool consistency as noted by the caretakers. In addition, occurrence of adverse effects such as allergic reactions, bloating and flatulence was also monitored in all the follow-up visits. All participants of the trial were insured as per the guidelines of ethics committee. The guardians were informed of compensation that would be provided by Institute Department of Paediatrics, Panimalar Medical

College Hospital & Research Institute, Chennai, India if any adverse effects were noted.

3. Results

The baseline characteristics in both study and control groups were similar (Table 1). The mean age in Study and Control group was 4 years and 4.8 years respectively. The mean weight in Study and Control group was 15.3 Kgs and 15.9 Kgs respectively. Children with very severe diarrhoea and high grade diarrhoea at baseline were included in both groups. Children in both groups showed good compliance to medications administered.

Grades of diarrhoea in study and control group after 48 hrs of treatment were as follows (Table 2): 41.7% had low grade diarrhoea in study group as compared to 79.2% patients in control group ($P < 0.01$). 58.3% patients had normal stools in the study group compared to 20.8% patients in control group ($P = 0.008$). The odds ratio of patients reporting reduction in stool frequency in study group was 1.71. This meant that the children in the study group had 1.7 times better chance of improvement as compared to the control group. The results at the end of 48 hours showed a dramatic improvement in very severe and high-grade diarrhoea category wherein all patients had recovered to low grade or normal grade which was statistically significant ($P < 0.01$).

Evaluation of changes in stool consistency within 48 hrs of treatment in study and control group (Table 3): 54.2% of patients had normal stools after 2 days of therapy in the study group compared to 33.3% in the control group. We analysed the diarrhoeal stool group further to understand the effect on children with loose stools. 64% of children in the control group continued to have loose stools at 48 hours of follow up as compared to just 24% in the study group (Table 4) which is statistically significant ($P = 0.004$).

Table 1: Baseline characteristics

S.No	Demographic variable	Number (percentage)	
		Control group	Study group
	Age		
	< 1 year	5	7
1	1 – 5 years	12	12
	5- 10 years	4	3
	> 10 years	3	2
	Sex		
2	Male	15	12
	Female	9	12

4. Discussion

We conducted an open label randomized control trial comprising of 48 children with acute diarrhoea to study the effects of Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) on the improvement of symptoms. By 48 hours of follow up, significant number of children had normal stools after Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) administration as compared to the control group. These findings were consistent with the study done by Sudha MR et al.[8]

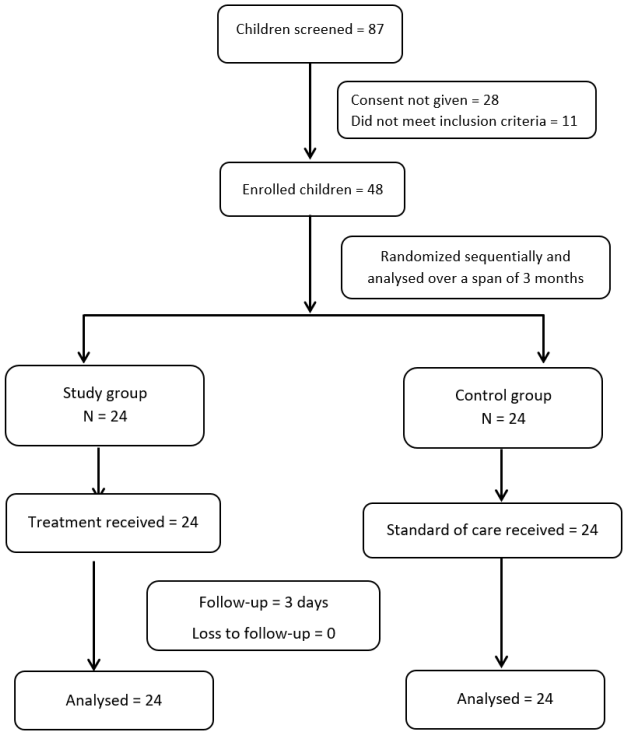

Fig. 1: Consort diagram

The duration of loose stools was also reduced in the study group as compared to the control group which was statistically significant ($P < 0.01$). This was similar to the studies by Laniro et al.[9]

There were no significant adverse effects noted and Bacillus clausii administration in children was considered safe. These findings were consistent with the study done by Lahiri et al.[10]

Hence, in our study we noted a significant reduction in both frequency as well as duration of loose stools following administration of Bacillus clausii in children with acute diarrhoea which is consistent with the study conducted by Castro et al.[11]

This was the first study conducted with the Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) strains. The study group included children of different ages and efficacy of Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) strains in treating Acute Diarrhoea was demonstrated in all age groups.

The limitation of the study was that it could have included a larger sample size. Based on the results of the current study it is possible to initiate a trial with larger

Table 2: Grades based on no. of stools per day after 48 hrs of treatment

Crosstab			Group		Total
			Study group	Control group	
Grades of Diarrhea at 48 hours	Low grade	Count	10	19	29
		% within group	41.7%	79.2%	60.4%
	Normal	Count	14	5	19
		% within group	58.3%	20.8%	39.6%
Total		Count	24	24	48
		% within group	100.0%	100.0%	100.0%

Table 3: Changes in Stool consistency within 48 hrs

Crosstab		Study Group	Control Group	Total
Normal Stools	Count	13	8	21
	% within group	54.2%	33.2%	43.75%

Table 4: Changes in Stool consistency within 48 hrs in loose stool subgroup

Crosstab		Study Group	Control Group	Total
Loose Stools	Count	6	16	22
	% within group	24%	64%	44%

sample size in the future.

5. Conclusion

This study showed a significant improvement in the duration and severity of diarrhoea following intake of Bacillus clausii strains (TIL 19T, TIL 21C, TIL 28S, TIL 30R) 2 billion CFU, twice a day. The improvement was apparent within 48 hours of follow-up and majority had normal stools within 48 hours. In summary, our results indicate that Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) might represent an effective therapeutic option in acute childhood diarrhoea, with a good safety profile. The authors recommend to conduct a similar study with a larger sample size, based on the results the probiotic Bacillus clausii (TIL 19T, TIL 21C, TIL 28S, TIL 30R) can be considered as a part of guideline in management of Acute diarrhoea in children.

6. Source of Funding

None.

7. Conflict of Interest

None.

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