Probiotics in acute diarrhea: A randomized control trial

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ABSTRACT

Background: Probiotics have been used for long in the treatment of acute diarrhea although their efficacy has always remains the subject of discussion. **Objective:** To determine the effect of probiotics in acute diarrhea among the children in rural population. **Method:** Double-blinded randomized control trial. We included children of age group 6 months - 5 years suffering from acute diarrhea of <48 h and fulfilling the inclusion criteria. All children were given oral rehydration salts (ORS) ad-lib till the resolution of diarrhea and zinc 20 mg/day for 14 days while intervention arm (n=101) were given probiotic sachet twice a day for 7 days containing *Streptococcus faecalis* 30 million, *Clostridium butyricum* 2 million, *Bacillus mesentericus* 1 million, *Lactobacillus sporogenes* 50 million, control group were given identical placebo apart from ORS and zinc. Duration of diarrhea in both the groups was measured as primary outcome while secondary outcome was to know the days of maximum recovery from diarrhea in both groups. **Results:** Totally, 207 patients were randomized to control and study group, out of which, 195 completed the study. Out of total 195 patients, 94 (48.2%) patients were treated with standard treatment of diarrhea without probiotics while 101 (51.8%) patients were given probiotics apart from standard treatment of diarrhea. The mean duration of diarrhea was found to be reduced in the study group (4.6 days [2.84-4.776 days]) as compared to control group (5.31 days [5.108-5.512 days]), p<0.001. **Conclusion:** Probiotics significantly reduced the duration of acute diarrhea in children.

Key words: *Acute diarrhea, Oral rehydration salts, Probiotics, Zinc*

The root of word probiotic comes from the Greek word and means "pro-life". "Pro" meaning promoting and "biotic" means life [1]. The World Health Organization's (WHO) 2001 definition of probiotics is "live microorganisms which, when administered in adequate amounts, confer a health benefits on the host" [2]. The beneficial effects of probiotics are seen in various diseases such as acute infectious diarrhea, antibiotic-associated diarrhea, necrotizing enterocolitis, irritable bowel syndrome, celiac disease, *Helicobacter pylori* etc., [3]. Probiotics act in so many ways such as, favorably affect the host by local and/or immune modulation pathway, compete the pathogens for nutrients in gut, produce bacteriocin which act as local antibiotics against pathogens, are able to decrease enteroaggregative *Escherichia coli* virulence factor, inhibit pathogen growth by producing lactic and acetic acid resulting in lowering the luminal pH, stimulate mucin production and maintain integrity of mucosal barrier etc., [3].

Diarrhea is one of the major causes of morbidity and mortality in developing world. Acute diarrhea is defined as the abrupt onset of 3 or more loose stools per day and lasts no longer than 14 days; chronic or persistent diarrhea is defined as an episode that lasts longer than 14 days [4]. Oral rehydration salts (ORS) and zinc have a definite role in the treatment of diarrhea, but the role of probiotics still needs more studies. There are lots of studies done in the Western world which shows the beneficial effect of probiotics in acute diarrhea, antibiotic-associated diarrhea, *clostridium* difficile infection other diseases also, but Indian studies are very limited. According to the American Academy of Pediatrics several randomized clinical trials in developed countries indicate that probiotics reduce the number of diarrheal stools and the duration of diarrhea by approximately 1 day [5]. As far as, Indian setting is concerned, there is no sufficient evidence to recommend the probiotics in treatment of acute diarrhea [6]. Objective of our study was to determine the effect of probiotics in acute diarrhea among the Indian children of rural area as diarrhea accounts for over 20% of all deaths in under-5-children [7].

MATERIAL AND METHODS

A randomized control trial was done in the Department of Pediatrics, Uttar Pradesh University of Medical Sciences, Saifai, and Etawah from January 2015 to April 2016. Children

admitted to pediatrics ward with complaint of acute diarrhea, age group 6 months-5 years were enrolled in the study. Acute diarrhea is defined as more than 3 loose or watery stools in the last 24 h and duration of diarrhea is < 48 h. Children who had severe dehydration [8], severe malnutrition (weight for age 51-60% of 50th percentile as per Indian academy of pediatrics classification of malnutrition) [9], dyselectrolytemia, diarrhea not improving in 14 days, history of allergy to probiotics, acute abdomen or colitis, probiotic or symbiotic intake in the last 1 month, probiotic or prebiotic containing foods intake in form of curd, dark chocolate yoghurt, fermented barley, pickles, etc., in the previous 48 h, chronic and persistent diarrhea, patients who need antibiotics and other drugs during the treatment period, patient suffering from any chronic or severe respiratory, cardiovascular, central nervous system, gastrointestinal or other systemic diseases, already taken antibiotic or anti-diarrheal drug for existing episode of diarrhea, patients whose parents or attendant did not give informed consent were excluded from the study.

Sample size has been calculated from the data shown in the previous study from south India. In that study, mean duration of diarrhea was found to be 7.67±4.76 days in the control group and the mean difference in duration of diarrhea between study and control group was 2.15 days [10]. As in our study, outcome is quantitative data; accordingly, we need to study 77 experimental and 77 controls to be able to reject the null hypothesis with the predictive power of 80%, with an alpha error of 5% [11]. We took total 195 patients, of which 94 are in the control group and 101 in the study group.

After taking approval from the Institutional Ethics Committee, children fulfilling the inclusion criteria were enrolled in the study. Written and informed consent of parents were taken. Baseline data included name, age, sex, address, duration, and frequency of diarrhea was taken. Proper history, anthropometric examination, general and systemic examination were done, and investigation such as complete blood count (to rule out infection) and serum electrolytes were done in every patient. Stool culture was done if required.

Subjects were randomized to intervention following simple randomization procedure with the computer-generated random numbers. Children were randomized to Group A, those received study drug in white paper packing and Group B which received identical placebo for 1 week. Placebo was also provided in identical white paper packing of same size and quantity as the study drug. It was ensured that when study drug or placebo was mixed with 10 ml of water, they look identical. Proper coding was done and treatment given accordingly. As per the allocation, drugs were prescribed to the patients by a pediatrician. Treating pediatricians were aware of allocation arm, but attendants of patients, staff nurses who provided the drug at bed side, outcome assessor who was one of the senior residents of our department and data analysts were kept blinded to the allocation.

All patients were treated with WHO ORS required as per the WHO criteria for no and some dehydration or intravenous fluid if needed, till the resolution of diarrhea and zinc 20 mg/day for

14 days. Apart from this standard treatment, study group was given probiotic sachet constituting *Streptococcus faecalis* 30 million, *Clostridium butyricum* 2 million, *Bacillus mesentericus* 1 million, *Lactobacillus sporogenes* 50 million twice a day after mixing in 10 ml of water while the control group was given only standard treatment of diarrhea and placebo mixed in 10 ml of water.

Records were kept for frequency and consistency of diarrhea and vomiting for every 24 h till diarrhea subsided. Each study day was defined as 24 h counted for the administration of the 1st dose of the study drug. Daily weight charting and assessment of dehydration were done and any adverse effects such as vomiting, constipation, bloating, pain abdomen, and anaphylactic reaction were noted. Patients were assessed daily for frequency and consistency of stool. Duration of diarrhea was counted from the day of admission to the resolution of diarrhea. Passage of 2 consecutive formed stools and/or having no stool passing till 12 h was considered as a resolution of diarrhea patients were discharged one day after the resolution of diarrhea.

Statistical analysis was done using SPSS software 21 Version test and Independent sample test or Mann-Whitney U-test were used for statistical analysis.

RESULTS

Total 220 patients were screened for eligibility criteria. 13 patients were excluded as they were not fulfilling the inclusion criteria. 207 patients were randomized to control and study group, in which 101 patients were assigned to the control group and 106 patients to the study group. From control group, 7 patients and from study group, 5 patients were excluded due to various regions. Total 195 patients completed the study. Out of these, 94 (48.2%) were treated with standard treatment without probiotics (control group), while 101 (51.8%) patients were given probiotics apart from the standard treatment of diarrhea (study group) (Fig. 1)

Both the groups were comparable with reference to age, weight, gender, height and severity of disease (p>0.05) as shown in Table 1.

The mean duration of diarrhea was found to be significantly reduced in the study group (4.60±0.88 days) as compared to the control group (5.31±0.98 days) (p<0.001). So study group had earlier recovery in comparison to control group (Table 2). No significant side effects like bloating, stomach ache, vomiting; constipation and anaphylactic reaction were seen in any group. The number of stools per day was significant less in the treatment

Table 1: Demographic characteristics of the study population

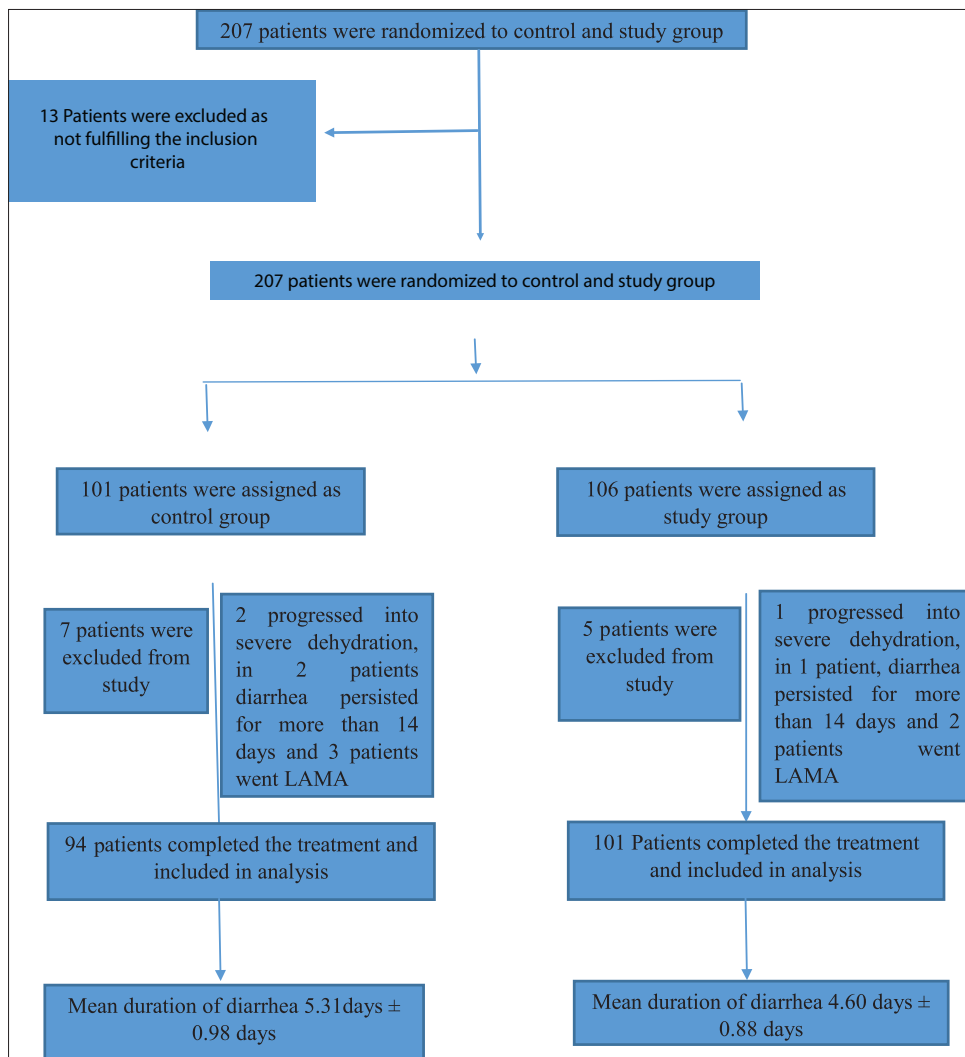| Characteristic	Study group	Control group
Number of patients	101	94
Male:Female	1.19:1	0.91:1
Age in months (mean±SD)	18.22±15.03	18.31±15.18
Weight in kg (mean±SD)	8.84±3.76	8.89±3.63
Height in cm (mean±SD)	73.4±14.76	72.7±15.04

SD: Standard deviation

Figure 1: Flowchart showing the outcome in study population

Table 2: Duration of diarrhea in study and control group

Intervention groups	Number of patients	Mean duration of diarrhea (days)	SD	Standard error of mean	p value
Control group	94	5.31	0.98	0.101	<0.001
Study group	101	4.60	0.88	0.088	

SD: Standard deviation

group as compared to the control group, starting from 24 h of therapy (Table 3).

As per-protocol analysis, maximum recovery from diarrhea in the study group was seen on 4th and 5th day, 80 (79.20%) out of 101 patients were recovered, while in control group most of the patients recovered on day 5th and 6th i.e., 70 (74.46%) out of 94 patients (Fig. 2).

DISCUSSION

Probiotics reported to significantly reduce the duration of acute diarrhea in children. Our study aimed to know the effects of probiotics on acute diarrhea in children living in rural area. We found that the duration of diarrhea was significantly reduced in the study group. The beneficial effects of probiotics in acute diarrhea

have been always controversial despite few Western studies have shown their beneficial effect. Possible mechanisms that have played a role in reducing the duration of acute diarrhea are immune modulation pathway, compete the pathogen for nutrients in gut, bacteriocin production, a decrease in enteroaggregative *E. coli* virulence factor, lowering the luminal pH, etc., [3].

In Indian setting where the breastfeeding rates are high, and the microbial colonization of the gut is different [6], our study can strengthen the role of probiotic in diarrhea. In a study, Applegate et al. also reported that probiotics may be efficacious in reducing diarrhea duration and stool frequency during a diarrhea episode [12]. Burande and Burande compared the efficacy of *Saccharomyces boulardii* strain in the treatment of acute diarrhea in Indian children and found that the mean duration of diarrhea for the study group was 3.4±1.4 days and for control group was 5.5±2.1 days (Z value
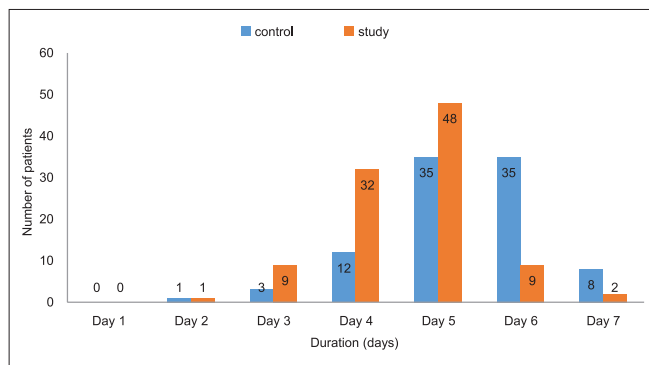
Figure 2: Number of patients recovering from diarrhea in both groups each day

Table 3: Number of stools after 24 h, 48 h and 72 h of diarrhea

Parameter	Group n	mean±SD	p-value
Number of stools per day After 24 h	Study 101	9.66±2.71	<0.005
	Control 94	10.97±3.69	
Number of stools per day After 48 h	Study 101	7.17±2.28	<0.0001
	Control 94	8.90±2.88	
Number of stools per day After 72 h	Study 101	5.04±2.00	<0.0001
	Control 94	7.19±2.49	

4.9). In our study also, mean duration of diarrhea in the study group is 4.60±0.88 days and control group 5.31±0.98 days (p<0.001). The difference in duration of diarrhea in both the studies may be because of the different strains of probiotics were used [13].

Bhat and Adhisivam evaluated the safety, efficacy, and tolerability of symbiotic on reducing and frequency and duration of acute diarrhea children of age group 6 months-10 years. In their study, mean duration of diarrhea was 5.52±1.98 days in the study group in comparison to 7.67±4.77 days in control group which is comparable to our study. The difference in duration of diarrhea may be due to the difference in sample size and age of the children [10].

According to the article by Ciorba, the American Academy of Pediatrics states that the probiotics for preventing acute infectious diarrhea are not universally endorsed, but it acknowledges that they may have a role in special circumstances [14]. Meta-analysis done by Salari et al. concluded that probiotics may reduce the duration of diarrhea and fever in children, but their exact efficacy in the treatment of diarrhea is not obvious yet [15].

The strength of our study was its pinpointed approach to see the effect of probiotics in Indian rural children with defined strain, dose and also with zinc as per the world health organization recommendations. Confounding factors such as severe dehydration, severe malnutrition, probiotic or prebiotic containing food intake, any chronic illness, etc., were removed to increase the strength of our study. The limitation of our study was no follow-up after discharge. The effect of probiotics in dysentery

and in severe dehydration was also not investigated. Further, studies are needed to resolve these limiting issues.

CONCLUSION

The probiotics significantly reduce the duration of acute diarrhea in children. Reduction of the duration of diarrhea of about 1 day by probiotics use is helpful to satisfy the anxiety of parents but as far as physicians are concern the decision of use of probiotics in diarrhea should be individualized.

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