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The Clinical Efficacy of Multi-strain Probiotics in the Management of Acute Watery Diarrhoea of Children aged 2 Months to 5 Years-a Randomized Controlled Trial

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Abstract

Background: *Acute gastroenteritis is considered as one of the most common causes of under-five morbidity and mortality worldwide. Standard treatment is the use of oral rehydration solution (ORS), intravenous fluid if indicated, and zinc supplement. Recently, the use of probiotics has been introduced as an adjunct to the treatment of acute gastroenteritis. The aim of this study is to determine the clinical efficacy of multi-strain probiotics as adjunct treatment of acute gastroenteritis.*

Methodology: *A randomized controlled trial was done in 250 bed district Sadar Hospital, Brahmanbaria, Bangladesh from January 2016 to June 2017. After fulfilling the inclusion criteria, 507 children aged 2 months to 5 years were enrolled in this study. Those with dysentery, chronic diarrhea, diarrhea due to known genetic disorder, chronic illness, malnutrition, systemic infection, CNS disorder and congenital malformation were excluded. Children were divided into two groups randomly. One group was With Probiotic, zinc and standard WHO (ORS) as case and other group was Without Probiotic, zinc and standard WHO ORS as control.*

Results: *Among 507 children, 257 were without probiotic while 250 were with probiotic. The mean difference in stool frequency between the two groups were 3.3 after 24 hours, 3.5 after 48 hours and 1.6 after 72 hours after hospitalization which was statistically significant (p=0.000). Reduction of stool frequency was highest after 48 hours of admission. Mean duration of hospital stay was 4.40±1.22 days in control and 4.03±.89 days in case group. Probiotic group children with exclusive breastfeeding had mean recovery time of 3.95±0.85 days and those who were not exclusively breastfeed had recovery time of 4.2±0.95 days (p=0.025).*

Conclusion: *Probiotic is efficacious in reducing purging duration and frequency of acute watery diarrhea in children.*

Key words*: Diarrhoea, Acute gastroenteritis, Probiotics, Management of diarrhea.*

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Introduction

Acute diarrhea is a disease of great concern worldwide with a high morbidity and mortality in under-five children. Acute diarrhea is responsible for over 1.8 million deaths per year. The world health organization suspects that there are >700 million episodes of diarrhea annually in under-five children in developing countries. The incidence of diarrhea is about 3.2 episodes per child per year[1, 2]. According to WHO/UNICEF report (2009) more than 2 billion cases of diarrhea occur among under 5 children each year and more than 50% of these cases are in South East Asia and sub Saharan Africa[3]. Acute diarrhea is a leading preventable cause of death and morbidity

particularly in developing countries[4]. So, there is utmost interest in the research field to study the factors useful in declining incidence and mortality from diarrheal diseases[5]. WHO and other health related organizations have given utmost importance in research for the innovation of the prevention strategies and treatment option for diarrhea. Access to safe and clean drinking water, improved sanitation and proper nutrition are some preventive strategies[6]. Researcher has also reported that early rehydration therapy, proper nutrition and zinc have been shown to be the main intervention measure in management of diarrhea[7, 8]. It is estimated that using ORS alone is responsible for the prevention of about three million dehydration related deaths worldwide per year[9]. However, rehydration therapy is not effective in reducing severity and duration of acute diarrhea[10]. Antibiotic has very limited role in management of acute diarrhea[11]. As there is risk of serious complication from diarrheal fluid loses, there is need for invention of further intervention measures to reduce duration and severity of diarrhea[12]. Probiotics can be another option for the management of diarrhea[13]. In several studies it was shown that probiotics reduce duration, hospital stay and severity of diarrhea[14]. Bangladeshi studies are limited in number regarding this. So this study was designed to see the efficacy probiotics in the management of acute diarrhea in a secondary level hospital setting.

Materials and methods

This was a randomized controlled trial (RCT) study done in 250 bed district sadar hospital, Brahmanbaria, Bangladesh from January 2016 to June 2017. After taking approval from the Institutional Ethical Committee, 507 children fulfilling the inclusion criteria were enrolled in the study. Children between the ages of two months to five years with diarrhea were included. Those with dysentery, chronic diarrhea, diarrhea due to known genetic disorder, chronic illness, malnutrition, systemic infection, sign symptom of CNS disorder and congenital malformation were excluded. Children with prior use of antibiotic or probiotics were also excluded. Written and informed consent of parents were taken. Baseline data included name, age, sex, address, duration, and frequency of diarrhea, hydration status was recorded. 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. Children were divided into two groups randomly. Subjects were randomized to intervention following simple randomization procedure with the computer-generated random numbers. One group was given the probiotics, zinc 20 mg/day and standard WHO oral rehydration solution considered 'With Probiotic group' and the other group was given only zinc 20 mg/day and standard WHO oral rehydration solution considered 'Without Probiotic group'. We used a multi-strain probiotic with 4 Lactobacillus sp. and 2 Bifidobacterium species. The investigator and patients both were blinded to the intervention group. The packet was given for three consecutive days. The primary outcome measure was the duration of diarrhoea. Passage of three consecutive semisolid stool or no stool for last 12 hours were recorded as cure. Duration of hospital stay, improvement in the frequency of stool, were the secondary outcome measure. The data were analyzed by SPSS software version 23. t test was performed on all continuous variables and chi-square test, Man Whitney U test and Fisher extract test was done to compare proportions between two individual groups. P value of less than 0.05 was considered significant.

Results

A total 507 children were included in the study among which 257 were not given any probiotic (Without Probiotic group) while 250 were given probiotic (With Probiotic group) . The demographic characteristics, breastfeeding status, weight, height and weight for height Z-scores were identical in two groups ('with probiotic' and 'without probiotic') ($p > 0.05$). It was noted that incidence of diarrhoea was more in the lower age groups (< 1 year). Disease course of the study population before starting treatment was similar in two groups ($p>0.05$). Majority of patients (45.63%) were admitted on 2nd day of illness. Forty-five point three six percent (45.36%) of children came to hospital on 2nd day of illness, followed by 28.60% on 3rd day (Table I).

There was no significant purging rate difference between two groups. The mean difference in stool frequency between the two groups were 3.3 after 24 hours, 3.5 after 48 hours and 1.6 after 72 hours which was statistically significant ($p=0.000$). Reduction of stool frequency was highest after 48 hours of admission followed by 24 hours after admission. Mean duration of hospital stay was 4.40±1.22 days in control group and 4.03±.89 days in probiotic group (Table II).

Table I

Demographic variables of children according to use of probiotic

Demographic variable	Use of probiotic			p-value
	Without Probiotic (n=257)	With Probiotic (n=250)		
Age (in months)				
Up to 11	124(50.0)	124(50.0)	248(48.91)	0.855
12 – 23	103(50.5)	101(49.5)	204(40.24)	(Fisher's Exact Test)
24 – 35	22(57.9)	16(42.1)	38(7.50)	
36 – 47	4(40.0)	6(60.0)	10(1.97)	
48 – 59	4(57.1)	3(42.9)	7(1.38)	
Mean±SD	13.94±8.09	13.28±7.98	13.62±8.04	
Gender Female	81(49.1)	84(50.9)	165(32.54)	0.36
Male	176(51.5)	166(48.5)	342(67.46)	(Fisher's Exact Test)
Breastfeeding status				
No/Partial breastfeeding	82(49.7)	83(50.3)	165(32.54)	0.756
Exclusive breastfeeding	175(51.2)	167(48.8)	342(67.46)	(Chi-square Test)
Weight for height Z-score				
Mean±SD	-.89±.78	-.81±.86	-.85±.82	0.304
Episode of diarrhea				(Mann-Whitney U Test)
1st	138(49.6)	140(50.4)	278(54.83)	0.211
2nd	104(54.5)	87(45.5)	191(37.67)	(Chi-square Test)
3rd	15(39.5)	23(60.5)	38(7.50)	

Table II

Comparison of frequency of purging and recovery time according to use of probiotic

Frequency of purging	Use of probiotic			p-value
	Without Probiotic	With Probiotic	Mean difference	
24 hours before hospitalization				
Mean±SD, N	12.46±3.12, 257	12.56±2.58, 250	0.10	0.566
				(Mann-Whitney U Test)
24 hours after hospitalization (Day 1)				
Mean±SD, N	11.5±3.2, 257	8.2±3.1, 250	3.3	0.000
				(Mann-Whitney U Test)
48 hours after hospitalization (Day 2)				
Mean±SD, N	8.5±3.2, 256	5.0±2.1, 247	3.5	0.000
				(Mann-Whitney U Test)
72 hours after hospitalization (Day 3)				
Mean±SD, N	4.6±2.6, 252	3.0±1.9, 222	1.6	0.000
				(Mann-Whitney U Test)
5 days or more days after hospitalization (Day 5 or beyond)				
Mean±SD, N	2.6±1.0, 56	2.0±1.1, 20	0.6	0.002
				(Mann-Whitney U Test)
Recovery time				
Up to 3 days	58(47.5)	64(52.5)	NA	0.000
4 days	96(42.7)	129(57.3)	NA	(Chi-square Test)
5 days	65(61.9)	40(38.1)	NA	
6 or more days	38(69.1)	17(30.9)	NA	
Mean±SD(days)	4.40±1.22	4.03±.89	0.37	0.001
				(Mann-Whitney U Test)

Table III

Comparison of recovery time for 'with probiotic group' according to breast feeding status

Breastfeeding status	Complete recovery time from diarrhoea (days)				
	N	Mean	Std. Deviation	Mean difference	p-value
No/Partial breastfeeding	83	4.20	0.947	0.25	0.025
Exclusive breastfeeding	167	3.95	0.845		(Mann-Whitney U Test)
Total	250	4.03	0.887	NA	

The probiotic group, the children with exclusive breastfeeding had mean recovery time of 3.95±0.85 days and those who were not exclusively breastfeeding had recovery time of 4.2±0.95 days which was statistically significant (p=0.025) (Table III).

Discussion

Despite improvement in prevention and treatment of acute diarrhea, this condition still causes a large proportion of the morbidity and mortality in children particularly in developing countries. Moreover, it is an important factor in the genesis of stunting and malnutrition. Diarrheal disease, if it evolves into more prolonged and chronic forms, it may cause disruption of the absorptive process, which may be more difficult to manage. Antibiotic has limited role in the management of acute diarrhea. Probiotics can be another alternative in the management of Acute Diarrhea as revealed in several western studies, though some controversies also present. In the present study probiotic was found effective in the management of acute diarrhea.

In the present study it was revealed that use of probiotic along with standard treatment regimen of acute watery diarrhea reduces duration, frequency and hospital stay in under five children. In a study by kumar et al.[7], in India, probiotic was found effective in reducing duration of diarrhea and frequency of stool. It is assumed that Indian people has high breast-feeding rates like ours and has similar type of bacterial colonization of gut. Similar result was found in the study by Appleget et al[15]. The mean recovery time in our study in control group was 4.40±1.22 days and in probiotic group was 4.03±0.89 days (p=0.001.) In the study by Kumar et al.[7] recovery time was 4.60±0.88 days in intervention group and 5.31±0.98 days in control group which is close to our study. In some studies recovery time was much shortened by using probiotic. In a finish study duration of diarrhea was reduced by 1.7 days[16]. A review study by Guandalini and colleagues[17] showed that probiotic can reduce duration of diarrhea by more than a day. This difference may be due to the fact that we had to rely on the statement of the mother of the children and most of them are rural woman. In our experience rural woman frequently exaggerate their children's symptom.

The mean difference in stool frequency between the two groups were 3.3 after 24 hours, 3.5 after 48 hours and 1.6 after 72 hours which was statistically significant (p=0.000). It was found that probiotic was more efficacious during first 48 hours. It was also found in the study by Kiran azim[5] that probiotic was more efficacious in reducing stool frequency during first 48 hours. This fact is important because whenever a child starts suffering from loose motion, reduction in the stool frequency on first day assures the mother.

Another important finding in our study was that in the probiotic group, the children with exclusive breastfeeding had mean recovery time of 3.95±0.85 days and those who were not exclusively breastfed had recovery time of 4.2±0.95 days (p=0.025). This finding will encourage our campaign for exclusive breastfeeding.

A 2010 Cochrane[14] systematic review of the use of probiotic for the treatment of acute diarrhea found a significant reduction in the mean duration of diarrhea (24.76 hours; 95% CI 15.91-33.61) and stool frequency on the second day of treatment (mean difference 0.80; 95% 0.45-1.14). The shortening of duration of diarrhea and reduction of stool frequency is important when we consider the prevalence of this ailment in our country particularly in a rural situation. Moreover, the overall improvement is also important in reducing the sufferings of the parents and caregivers to a great extent.

Conclusion

From the above study we may conclude that probiotic is efficacious in reducing duration of diarrhea and stool frequency in children. Further well-designed large-scale study is required to generalize its use in the treatment of acute watery diarrhea.

Limitation

The data was a one-point source and so could not evaluate the outcome trends over time.

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