Original Article

Compare the Effect of Zinc–Probiotic versus Zinc Therapy in Acute Watery Diarrhea in Children

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Abstract

Background: *Acute watery diarrhea still remains a major health problem among under 5 children worldwide. Apart from oral rehydration solution, continued feeding and oral zinc therapy the administration of adequate amounts of probiotics seems beneficial for acute diarrheal episodes in children in the developing world.*

Objective: *To compare the efficacy of zinc-probiotic combination therapy versus zinc-only therapy in children with acute watery diarrhea.*

Materials and Methods: *This was a hospital based randomized controlled clinical trial (RCT) conducted from July 2019 to June 2021 in the Department of Pediatrics, Khwaja Yunus Ali Medical College & Hospital. Total 70 children aged 6 months to 5 years admitted in hospital with acute watery diarrhea (AWD) with severe dehydration or some dehydration with intractable vomiting were included in this study. Patients were equally divided into 2 groups. Group A received oral zinc sulfate 20 mg/day for 10 days combined with oral Bacillus clausii probiotic 4million spores/day for 5 days. Group B received only oral zinc sulfate at the same dosage as group A. We also studied the relationship between mother`s education, knowledge of ORS preparation and child's feeding practices and nutritional status with the occurrence of diarrhea in children.*

Results: *Frequency of diarrhoea was significantly higher in group B (Zinc only) in comparison to group A (Zinc and probiotic). Mean frequency of diarrhea, Mean duration of diarrhea and Mean length of hospital stay was significantly higher in group B (Zinc) than group A (Zinc+Probiotic).*

Conclusion: *In comparison to oral Zinc therapy only; the combination of oral zinc and probiotic therapy is clinically more effective in reducing the frequency of acute watery diarrhea in under 5 year children.*

Key words: *Acute watery diarrhea, Zinc, Probiotic.*

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Introduction

Diarrhea is a common problem among children in Bangladesh.[1] Diarrhea is defined as a condition that involves unusually frequent and liquid bowel movements, three or more times in a 24-hour period. Diarrhea can be characterized as `acute watery diarrhea' if it lasts less than 14 days.[2] Undernutrition is a crucial risk factor for morbidity and mortality associated with diarrhea.[3] Despite a global decline acute watery diarrhea is still the second cause of mortality among children under the age of five years.[4] As a result an effective and comprehensive diarrhea management is critical.[5] Zinc plays an important role in modulating the host resistance to infectious agents and reduces the risk, severity and duration of diarrheal diseases.[6] In recent years, probiotics have been widely studied in preventing and treating diarrhea, particularly in the pediatric population.[7] Apart from oral rehydration solution, continued feeding and oral zinc therapy which have proven to improve the case management, the administration of probiotics in adequate amounts seemed to be beneficial, with modest efficacy, for the outcome of acute diarrheal episodes in children in the developing world.[8] Probiotics are living microorganisms that survive in the gastrointestinal tract and when ingested in a sufficiently large amount, provides a health benefit on the host.[9] Various studies were done on the role of zinc therapy and probiotic therapy in reducing the duration and severity of acute watery diarrhea.[10] But not many studies have compared the use of a combined zinc-probiotic therapy to zinc therapy alone. So our study is designed to compare the efficacy of zinc probiotic combination therapy versus zinc therapy alone among children with acute watery diarrhea.

Materials and Methods

This study was a hospital based randomized controlled clinical trial (RCT) conducted from July 2019 to June 2021 in the Department of Pediatrics, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Chauhali, Sirajganj-6751, Bangladesh. Total 70 children aged 6 month to 5 year admitted in Hospital with acute watery diarrhea (AWD) were included in this study.

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The inclusion criteria were the severity of diarrhea on admission to hospital which was based on: (a) The status of dehydration on clinical assessment; it was either acute watery diarrhea with severe dehydration or acute watery diarrhea with some dehydration with intractable vomiting, and (b) the frequency of diarrhea (no. of times stools passed/day), and the duration of diarrhea (hours) after initial drug intake and the length of hospital stay (hours).

The exclusion criteria were children who had diarrhea that has been treated for more than 3 days at home, dysentery, severe malnutrition, who has received any type of medication (antibiotics, antiprotozoal etc.) except fluid and zinc, septicemia or any other inflammatory diseases, any cardiac anomaly and immunodeficiency condition. Children with AWD meeting the inclusion criteria were selected for the study immediately after getting admitted into hospital. A consent form was signed by the parents before initiating any treatment.

The study cases were divided equally into two groups. The case was randomized & purposively selected as group A (zinc plus probiotic) and group B (Zinc alone). Group A (zinc plus probiotic) received oral zinc sulfate monohydrate 5ml twice daily for 10 days. Each 5ml syrup containing 10mg of zinc sulfate (total 20mg /day). Zinc was combined with oral Bacillus clausii probiotic suspension 5ml mini bottles (vials) twice daily for 5 days, each vial containing 2 million spores of Bacillus clausii (total 4 million spores per day). Group B (zinc alone) patients received only zinc sulfate at the same dosage as group A.

On daily follow up presence of fever, vomiting, frequency (number of times stool passed/day) with consistency (loose or watery stool) was recorded and sign of dehydration was assessed. ORS and IV cholera saline were given to the patient according to the need. During follow up the intake of ORS and IV cholera saline was measured carefully and the output of vomitus was recorded. Fresh stool was collected at admission for a routine microscopic test, but stool culture and presence of Rotavirus by ELISA was not done because of the high cost required.

Acute watery diarrhea caused by rotavirus and cholera was distinguished clinically by (i) stool consistency: loose or watery stools in Rota viral diarrhea and"rice watery" consistency laced with bile and mucus in cholera, (ii) age: the proportion of rotavirus is significantly higher than that of cholera in children aged less than 18 months, (iii) severe dehydration: frequent, voluminous, loose stools quickly led to severe dehydration with hypovolemic shock in cholera compared to rotavirus diarrhea, (iv) symptoms occurred during known diarrheal outbreaks involving children and adults in cholera. Monitoring of the duration and frequency of diarrhea was done during hospitalization and after the patient was discharged. Toxicity and side effects relating to the administration of zinc and probiotics were also observed (nausea, vomiting, abdominal pain, and sepsis). We defined recovery from diarrhea as stool passed < 3 times with normal consistency. At home the child received zinc sulfate at a the same dose of 20 mg/day for a total of 10 days and Zinc sulfate tablets were dissolved in 5 ml of boiled water. Both doctors and parents were aware of the therapies given. Home monitoring was done by contacting the parents or caregivers. All data were compiled and edited meticulously by thorough checking and rechecking. All omissions and inconsistencies were corrected and removed methodically. The results were collected, tabulated and statistically analyzed by using window based computer software device with statistical package for social science (SPSS-23).

Results

Mean age was found 13.12±9.25 months in group A and 11.91±7.25 months in group B. Male was found 22(62.9%) in group A and 24(68.6%) in group B. Female was 13(37.1%) and 11(31.4%) in group A and group B respectively. Mean weight was 8.2±2.9 kg in group A and 7.5±2.8 kg in group B. Majority mother were SSC education level in both groups, 15(42.9%) in group A and 9(25.7%) in group B. Age-appropriate feeding was 23(65.7%) in group A and 21(60.0%) in group B. In group A, 5 (14%) and 30 (86%) children had severe dehydration and some dehydration with intractable vomiting respectively. In group B, it was 3 (8.5%) and 32 (91.5%) respectively. Good nutritional status was found 26(74.3%) in group A and 21(60.0%) in group B. Knows ORS preparation was 27(77.1%) in group A and 29(82.9%) in group B. Age, sex, weight, mother education, feeding history, nutritional status and knows ORS preparation was not statistically significant (p>0.05) between two groups (Table-I). Before treatment, mean frequency of diarrhea was 7.9±3.4 times/day in group A and 8.9±2.6 times/day in group B. Before treatment, mean duration of diarrhea was 60.6±16.7 hours in group A and 54.5±19.8 hours in group B. The difference was not statistically significant (p>0.05) between two groups (Table-II).

Figure 1 shows the frequency and duration of diarrhea before treatment. Regarding frequency of diarrhea after treatment, mean frequency (no. of times/day) of diarrhea was significantly higher in group B than group A.

At 1st day (8.7±2.51 vs 7.5±2.55),at 2nd day (7.1±2.63 vs 4.8±2.42),at 3th day (3.3±2.39 vs 1.9±1.37) and at 4th day (1.7±2.02 vs 0.9±1.23) (Table-III).

Figure 2 shows the gradual reduction of Frequency of diarrhea in different day of follow-up after treatment. After treatment Mean frequency of diarrhea was significantly higher in group B than group A (3.3±1.32 vs 2.3±1.01 times/day).After treatment Mean duration of diarrhea was significantly higher in group B than group A (74.7±21.53 vs 53.8±20.51 times/day). After treatment Mean length of hospital stay was significantly higher in group B than group A (99.7±21.42 vs 58.7±20.35 times/day) (Table-IV).

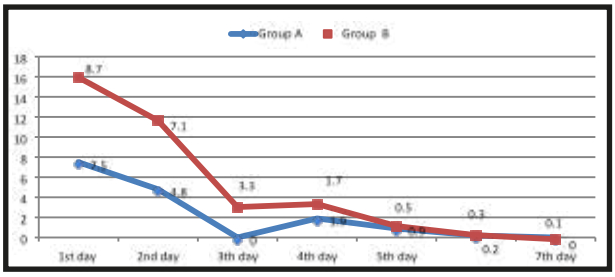

Figure 2: Gradual reduction of Frequency of diarrhea in different day of follow-up after treatment.

Table I: Baseline characteristics of the study population (N=70).

Characteristics	Group A (Zinc+probiotic) (n=35)		Group B (Zinc only) (n=35)		P value
Mean age±SD (months)	13.12±9.25		11.91±7.25		0. 544 ns
Sex					
Male	22	62.9 %	24	68.6 %	
Female	13	37.1 %	11	31.4 %	
Mean weight±SD (kg)	8.2±2.9		7.5±2.8		
Mother's education					
No education	3	8.6 %	4	11.4 %	
Primary	6	17.1 %	7	20.0 %	
HSC	8	22.9 %	8	22.9 %	
SSC	15	42.9 %	9	25.7 %	0.505 ns
Graduate	3	8.6 %	7	20.0 %	
Feeding history					
Age -appropriate	23	65.7 %	21	60.0 %	0.620 ns
Mismanaged	12	34.3 %	14	40.0 %	
Degree of Dehydration					
Severe Dehydration	5	14%	03	8.5%	
Some Dehydration with intractable vomiting	30	86%	32	91.5%	
Nutritional status					
Good	26	74.3	21	60.0	
Mild malnutrition	5	14.3	9	25.7	0.409 ns
Moderate malnutrition	4	11.4	5	14.3	
Knows ORS preparation					
Yes	27	77.1	29	82.9	0.550 ns
No	8	22.9	6	17.1	

Table II: Frequency of diarrhea and duration of diarrhea before treatment.

Before treatment	Group A (n=35)	Group B (n=35)	P value
	Mean±SD	Mean±SD	
Frequency of diarrhea before treatment (No. of times/day)	7.9±3.4	8.9±2.6	0.171 ns
Duration of diarrhea before treatment (hours)	60.6±16.7	54.5±19.8	0.168 ns

s=significant; ns=not significant
P value reached from unpaired t-test

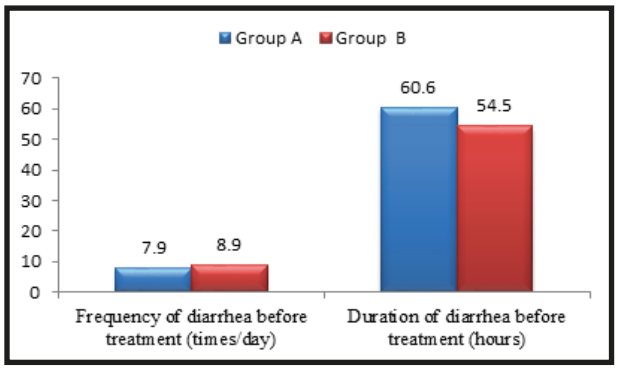

Figure-1: Frequency of diarrhea and duration of diarrheabe-fore treatment.

Table III: Gradual reduction of frequency (No. of times/day) of diarrhea in differentday of follow-up after treatment.

Day of intervention	Group A (n=35)	Group B (n=35)	P value
	Mean±SD	Mean±SD	
1st day	7.5±2.55	8.7±2.51	0.007 s
2nd day	4.8±2.42	7.1±2.63	0.001 s
3rd day	1.9±1.37	3.3±2.39	0.003 s
4th day	0.9±1.23	1.7±2.02	0.049 s
5th day	0.2±0.42	0.5±1.39	0.225 ns
6th day	0.0±0.0	0.3±1.0	-
7th day	0.0±0.0	0.1±0.01	-

s=significant; ns=not significant
P value reached from unpaired t-test

Table IV: Frequencyof diarrhea,duration of diarrhea and length of hospital stayafter treatment.

After Treatment	Group A (n=35)	Group B (n=35)	P value
	Mean±SD	Mean±SD	
Frequency of diarrhea (no. of times/day)	2.3 ±1.01	3.3 ±1.32	0.001 s
Duration of diarrhea (hours)	53.8 ±20.51	74.7 ±21.53	0.001 s
Length of hospital stay (hours)	58.7 ±20.35	99.7 ±21.42	0.001 s

s=significant
P value reached from unpaired t-test

Discussion

In the present study the clinical efect of zinc-probiotic combination therapy has been compared with zinc monotherapy in children with acute watery diarrhea. In this study the mean age of children with AWD was 13.12±9.25 months in the combination group and 11.91±7.25 months in the zinc group. Most of the patients (60% and 54%) are below 12 months in both groups. A study done by Nikhurpa and Agnihotri reported the mean age of patients in combination group is 14.02 ± 13.2 months and 12.9 ± 11.4 months in zinc group.(10) This is similar to previous a study by Azim which suggested that acute diarrhea due to rotavirus is also prevalent in 0-12 month old.[5] Hatta reported the mean age of children with acute diarrhea was 27.4 months in the combination group and 21.5 months in the zinc group. In this study male was found 22 (62.9%) in combination group and 24 (68.6%) in zinc group and female was 13 (37.1%) and 11 (31.4%) in combination group and zinc group respectively. A greater number of the patients were male in both groups.[11] Previous epidemiological studies by Nguyen found that children with acute diarrhea were aged 0 to 12 months.[12] This is similar to the studies of Sultana who found more male patients in each group.[1] Same reports of more males in both groups are given by Azim but did not discuss possible theories for this occurrence.[5] Hatta reported male was 23 in Zinc-probiotic group and 21 in zinc group. Female was 17 and 13 in zinc-probiotic and zinc group respectively.[11] This male gender predisposition for acute watery diarrhea is still unclear. Current study observed that the mean weight as 8.2±2.9 kg in combination group and 7.5±2.8 kg in zinc group. Nikhurpa and Agnihotri reported the mean weight of patients in combination group is 8.5 ± 2.7 kg and 7.8 ± 2.4 kg in zinc group.[10] Similar reports in studies by Azim (8.21 ± 2.6 versus 8.09 ± 2.7), and Sultana (8.6 ± 1.57 versus 8.5 ± 2.16). [1,5]

Majority of mothers were SSC education level in both groups, 15 (42.9%) in combination group and 9 (25.7%) in zinc group. Age-appropriate feeding was 23 (65.7%) in versus 21 (60.0%). Good nutritional status was found in 26 (74.3%) in combination group and 21 (60.0%) in zinc group. Nikhurpa and Agnihotri reported considering nutritional assessment (using the WHO classification of weight for age), 80% (42) of subjects belongs to good nutrition in combination group as compared to 61% (32) in Zinc-only group.(10) Mother knows ORS preparation was 27(77.1%) in combination group and 29(82.9%) in zinc group.

Similar observation was found in Nikhurpa and Agnihotri study who observed mother knows ORS preparation was 38(73.0%) in combination group and 42(80.7%) in zinc group which is a similar observation.[10]

Present study observed that before treatment, mean frequency of diarrhea was 7.9±3.4 times/day in combination group and 8.9±2.6 times/day in zinc group. Before treatment, mean duration of diarrhea was 60.6±16.7 hours in versus 54.5±19.8. The difference was not statistically significant (p>0.05) between two groups.

Nikhurpa and Agnihotri study showed that the mean frequency of diarrhea before treatment in combination group was 7.46±4.1 times/day as compared to 6.69±3.6 times/day in zinc group. Mean duration of diarrhea in combination group was 53.5±30.5 hours as compared to 57.6±34.3 hours in zinc group.(10) Hatta also observed the mean frequency of diarrhea before treatment in zinc-probiotic was 8.2±3.19 times/day as compared to 9.2±2.41 times/day in zinc group. Mean duration of diarrhea in zinc-probiotic was 62.4±16.87 hours as compared to 56.0±23.05 hours in zinc group. Hatta reported during treatment, there were significant differences in diarrheal frequency in the two groups from the first to fourth days.[11] Our study showed gradual reduction of frequency of diarrhea in different day of follow-up after treatment in the two groups. It was seen in our study that by the end of 3rd day most patients who were given combination therapy showed decrease in frequency to less than 3 stools/day as well as improvement in consistency of stools. Among patients who received oral zinc monotherapy some still continued passing watery stools even after 72 hours of starting treatment. In addition the duration of the diarrhea (hours) and length of hospital stay (hours) was significantly shorter in children receiving combination therapy in comparison to those receiving monotherapy.

Hatta also reported that the duration of diarrhea, as well as length of hospital stay were lower in the combination group than in the zinc group (p=0.001)11. They found no obvious reasons why the frequency of diarrhea in the fifth to seventh days of therapy did not differ in both groups.

Anggarwal used zinc supplementation and found that the duration of diarrhea after therapy was 3 days 14 .[13] They had similar results to our study. Length of hospital stay cannot be used as an indicator of therapeutic success due to many other factors that affect the length of patient hospitalization, such as time delays in hospital discharge caused by the parents' requests or payment issues.

In our study, we monitored the results only up to 7 days because no diarrhea was present by the 8th day of therapy. However, therapy was given for 10 days. It appears that intestinal recovery in acute diarrhea occurs within 7 to 10 days.[14]

Conclusion

World Health organization (WHO) does not recommended the use of probiotic in diarrhea, but in our country the use of probiotic is increasing day by day in acute watery diarrhea. From this study we concluded that although oral zinc therapy is effective in decreasing the frequency and duration of diarrhea but the combination of oral zinc and probiotic therapy is clinically more effective than oral zinc alone in decreasing the frequency of stools in under 5 year children with acute watery diarrhea.

Limitation

This study was conducted on a small group of subjects so further studies on larger scale should be conducted so that results can be extrapolated to larger populations.

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