

ORIGINAL ARTICLE

Comparison of Zinc-Probiotic Combination Therapy to Probiotic Therapy Alone in Treating Acute Diarrhea in ChildrenZAKAULLAH KAKAR¹, ABDUL BAQI ESSAZAI², SYED MOEED AHMED³, NASEEB ULLAH⁴, PIR JAN⁵, NAJEEBULLAH⁶¹Medical Officer, Bolan Medical Complex Hospital, Quetta, Pakistan.²Senior Medical Officer, Shaikh Khalifa Bin Zaid Hospital, Quetta, Pakistan.³Medical Officer, Department of Pediatrics, Civil Hospital, Quetta, Pakistan.⁴Senior Medical Officer, Shaheed Benazir Bhutto General Hospital, Quetta, Pakistan.⁵Department of Pediatrics, Makran Medical College, Turbat.⁶Medical Officer, Bolan Medical Complex Hospital, Quetta, Pakistan.Correspondence to: Syed Moeed Ahmed, Email: drsyedmoeedahmed@gmail.com, Cell: +92 336 3552701**ABSTRACT****Objective:** To compare the efficacy of zinc-probiotic combination therapy and probiotic therapy alone in the treatment of acute pediatric watery diarrhea.**Study Design:** Randomized Clinical Controlled trial.**Setting:** The study was completed at The Department of Pediatrics, Unit I, Bolan Medical Complex Hospital, Quetta, Pakistan from July 2021 to January 2022.**Methodology:** A total number of 144 children of either gender aged 3 months to 5 years presented with acute watery diarrhea were included. Patients were randomly allocated into either Group-A (zinc supplementation with probiotics) or Group-B (only probiotics) for the treatment of acute diarrhea. Relief from diarrhea and duration of diarrhea were the main study end-points.**Results:** In a total of 144 children, the mean age was 27.04±14.43 months while the mean duration of diarrhea was 8.05±5.18 hours. On comparison of recovery from diarrhea, all the 72 children who received combination of probiotics and zinc were recovered from diarrhea, while 4 children (5.6%) children did not recovered from diarrhea within 5 days after starting the treatment in probiotics alone group (p=0.04). Duration of diarrhea was 27.63±14.22 hours in probiotics plus zinc group and 38.86±20.70 hours in probiotics only group (p<0.001).**Practical Implications:** Combination of probiotics with zinc resulted in early recovery among children with acute diarrhea but further randomized controlled trial enrolling large sample size from local population are necessary to verify the findings of this study.**Conclusion:** Combination of probiotics and zinc was superior as compared to the probiotics alone in the treatment of acute diarrhea in children.**Keywords:** Diarrhea, probiotics, recovery, stool, treatment, zinc.**INTRODUCTION**

Diarrhea is defined as loose or watery stool passing more than three times in a day, with or without blood or mucus in stool.¹ Diarrheal episodes are usually acute but sometimes these may last even for weeks.² Diarrhea is a leading cause of death of children not only in Pakistan but also in many other countries of the world. Among 10 commonest causes of mortality in children, one of these is diarrhea.²

Antibacterial, anti-amoebic and antidiarrheal drugs have a very little role to play in diarrheal management, as expressed by "World Health Organization (WHO)" in their guidelines.³ The frequency of diarrhea in zinc deficient children is higher, and in most of these cases, zinc supplements are effective.^{3,4} Over the last few years, probiotics (lactobacillus rhamnosus and lactobacillus reuteri species) have been studied extensively in order to prevent and treat acute watery diarrhea, specifically in children.^{5,6} Probiotics (lactobacillus rhamnosus and lactobacillus reuteri species) are basically live microorganisms, that boost the health of the host when consumed adequately. Although, numerous studies have been performed on the treatment of diarrhea all over the world, but as far as zinc-probiotic combinations are concerned, very few studies were conducted in the recent past. In 2015, Crisinel et al⁷ conducted a study and concluded that combination of zinc and probiotics is superior to probiotic administration alone in children with severe diarrhea. In their study, the frequency of children who recovered from diarrhea within five days after starting treatment was 95.0% versus 80.0% in children who took probiotics alone. They also found shorter duration of diarrhea in children with zinc plus probiotic administration, 47.5±18.3 hours versus 76.3±32.99 hours in probiotics alone group. Lezzerini et al⁸ in their meta-analysis reported that the duration and episodes of diarrhea per day are not effected by zinc supplementation or alone administration, so there is no need to add zinc in routine practice for treatment of diarrhea. They also concluded that Zinc administration may be partly useful in children in developing countries.

Pakistan, being a third world country, has many children deficient in zinc. Therefore, zinc is routinely advised for the treatment of diarrhea but probiotic is used by some pediatricians and not used by most for the treatment of acute watery diarrhea. The purpose of our study was to compare the treatment effects of probiotics plus zinc administration versus probiotic administration alone, to treat children of less than 5 years of age with acute watery diarrhea. The results of this study were thought to help us in determining whether zinc and probiotic combination is more effective or only probiotics to be used. If the efficacy of probiotics plus zinc is found to be better, then the advocacy could be done to promote zinc and probiotic combination in treating acute watery diarrhea in children. The study outcome were also thought to encourage the researchers and provide a base to conduct further studies in this subject. Our hypothesis was that efficacy of Zinc-Probiotic combination therapy is better than probiotic therapy alone in treating acute diarrhea in children.

METHODOLOGY

This randomized controlled trial was conducted at The Department of Pediatrics, Unit-I, Bolan Medical Complex Hospital, Quetta, Pakistan from July 2021 to January 2022. A sample size of 144 (72 in each group) was calculated taking frequency of recovery from diarrhea in probiotic plus zinc group as 95.0%,⁷ and frequency of recovery from diarrhea in probiotic alone group as 80.0%,⁷ considering level of significance at 5.0% and power of test as 80.0%. Simple random sampling technique was adopted. Inclusion criteria were children aged 3 months to 5 years (because acute watery diarrhea is more common in this age group) having >3 times stools/day for > one day, irrespective to degree of dehydration. Exclusion criteria were children who had received antibiotics, probiotics or any other anti-diarrheal agents in the last 15 days or those who had diarrhea secondary to other medical problem like celiac disease, food poisoning, tuberculosis or other intestinal pathology etc. children having diarrhea with a disease of duration of 5 days were also not included. Patient with severe

malnutrition were not enrolled (as per clinical assessment and medical history).

After getting approval for this study from the "Ethical Committee of Bolan Medical Complex Hospital, Quetta", the patients who presented in Pediatrics unit I of Bolan Medical Complex Hospital and fulfilling the inclusion criteria were included. Children were examined in the presence of their parents properly for signs of dehydration and other issues like diaper rash in an environment friendly and polite conditions for the child so that to alleviate the anxiety of child if any. For diaper rash, mother was guided to apply zinc oxide on rashes and keep the diaper dry. An informed consent was taken from the parents/legal guardians of all babies before including them in this study.

Patients were randomly allocated into two equal groups (Group-A or Group-B). In Group-A, zinc supplementation was given along with probiotics for the treatment of diarrhea. In Group-B, only probiotics were given. Treatment of diarrhea in both groups of these children was given under the supervision of a consultant pediatrician and efficacy of both of these treatments was determined by a consultant pediatrician having at least five years of post-fellowship experience. Outcomes of the study were noted on a predesigned proforma. The efficacy was measured in terms of recovery from diarrhea and duration of diarrhea. Recovery from diarrhea was defined in term of reduction in frequency and volume of stool. Reduction in the frequency of diarrhea meant passing of stools less than three times a day. Reduction in consistency of diarrhea meant changing consistency of stool from watery (liquid) to semi-solid (or solid). Reduction in volume of stool meant reduction in volume of stool each time the child is passing which may be as high as as 100-150 grams each stool during diarrhea to its normal volume ranging as low as 5 grams (grape size) to 40 grams (large sausage). Weight of stool was detected by weighting the weight of diaper dry from wet (normal weight of diaper is 20-35 grams depending on the age and weight of child). Recovery from diarrhea was noted within five days after starting the treatment. Total duration of diarrhea was noted in terms of hours to days from the start of treatment to the time of recovery from the diarrhea.

Data analysis was carried out using "Statistical Package for Social Sciences (SPSS)", version 26.0. Mean and standard deviation were calculated for age of children, duration of presentation, and total duration of diarrhea. Frequency and percentage were calculated for gender and frequency of recovery from diarrhea within five days after starting the treatment. Chi-square test was used to compare frequency of recovery within Group-A and Group-B while independent sample t-test was used to compare duration of diarrhea between the groups. Confounder variables such as age of children, gender and duration of presentation were controlled by stratification. Post-stratification, chi-square test and independent sample t-test were applied to

determine the effect of these confounder variables on frequency of recovery from diarrhea and duration of diarrhea respectively. P-value ≤ 0.05 was considered as significant.

RESULTS

In a total of 144 children, 94 (65.3%) were boys and 50 (34.7%) girls representing a boys to girls ratio of 1.88:1. The mean age was 27.04±14.43 months (ranging from 5 months to 59 months). The mean duration of diarrhea was 8.05±5.16 hours while most of the children reached within 10 hours in hospital after start of the diarrhea.

On comparison of recovery from diarrhea, all the 72 children who received combination of probiotics and zinc were recovered from diarrhea, while 4 children (5.6%) children did not recovered from diarrhea within 5 days after starting the treatment in probiotics alone group, p=0.04 (Table-2).

The total duration of diarrhea was 33.25±18.64 hours in study patients after starting the treatment. The minimum duration was 6 hours and maximum duration was 5 days. On comparison of duration of diarrhea after starting the treatment, duration of diarrhea was significantly less in patients who received combination therapy of probiotics and zinc as compared to the children who received probiotics only. Duration of diarrhea was 27.63 (14.22) hours in probiotics plus zinc group and 38.86 (20.70) hours in probiotics only group. This difference was statistically significant with a p-value of <0.001 (Table-3).

We did stratification on the basis of age, gender and duration of presentation in hospital after diarrhea to determine the effect of these confounder variables on frequency of recovery from diarrhea and total duration of diarrhea as shown in table-4 and 5.

Table-1: Demographic and Clinical Characteristics (n=144)

Characteristics	Frequency (%)
Gender	
Boys	94 (65.3%)
Girls	50 (34.7%)
Age	
5 months to 2 years	86 (59.7%)
Above 2 years up to 5 years	58 (40.3%)
Duration of presentation	
DOP < 6 hours	80 (55.6%)
DOP 6-12 hours	38 (26.4%)
DOP >12 hours	26 (18.1%)

Table-2: Comparison of Recovery from Diarrhea (n=144)

Recovery from Diarrhea	Probiotics plus Zinc (Group-A=72)	Probiotics alone (Group-B=72)	P-value
Yes	72 (100.0%)	68 (94.4%)	0.04
No	0 (0.0%)	4 (5.6%)	

Table-3: Comparison of Total Duration (hours) of Diarrhea (n=144)

Duration of Diarrhea (hours)	Probiotics plus Zinc (Group-A=72)	Probiotics Alone (Group-B=72)	P-value
Mean	27.63	38.86	<0.001
S.D.	14.22	20.70	

Table-4: Stratification of Study Variables With respect to Recovery from Diarrhea in both Study Group (n=144)

Study Variables	Recovery from Diarrhea	Probiotics plus Zinc (Group-A)	Probiotics Alone (Group-B)	P-value	
Age	Age Group (5 months to 2 years)	Yes	45 (100%)	39 (95.1%)	0.13
		No	-	2 (4.9%)	
	Age Group (2 years to 5 years)	Yes	27 (100%)	99 (98.0%)	0.17
		No	-	2 (2.0%)	
Gender	Boys	Yes	50 (100%)	42 (95.5%)	0.12
		No	-	2 (4.5%)	
	Girls	Yes	22 (100%)	26 (92.9%)	0.20
		No	-	2 (7.1%)	
Duration of Diarrhea	<6 hours	Yes	42 (100%)	36 (94.7%)	0.13
		No	-	2 (5.3%)	
	6-12 hours	Yes	20 (100%)	18 (100%)	-
		No	-	-	
	>12 hours	Yes	10 (100%)	14 (87.5%)	0.24
		No	-	2 (12.5%)	

Table-5: Stratification of Study Variables with respect to Duration of Diarrhea in both Study Groups (n=144)

Study Variables	Duration of Diarrhea	Probiotics plus Zinc (Group A)	Probiotics Alone (Group B)	P-value	
Age	Age Group (5 months to 2 years)	Mean±SD	28.00±15.21	35.21±13.62	0.04
	Age group (2 years to 5 years)	Mean±SD	27.03±12.66	43.67±20.14	<0.001
Gender	Boys	Mean±SD	27.28±39.90	13.17±18.84	<0.001
	Girls	Mean±SD	28.45±17.06	37.21±20.06	0.04
Duration of Diarrhea	<6 hour	Mean±Sd	24.90±13.00	41.42±22.03	<0.001
	6-12 hours	Mean±SD	27.80±14.83	39.44±21.49	0.05
	>12 hours	Mean±SD	22.12±13.70	38.80±15.61	0.02

DISCUSSION

The children of developing countries, most frequently come across morbidity and mortality due to diarrhea.^{9,10} Diarrhea leads towards certain conditions like dehydration, acidosis, renal dysfunction and secondary infections which are significantly associated to the mortality among pediatric age groups.¹¹⁻¹³ It is estimated that 17.3% population of the whole world is at risk of zinc deficiency.¹⁴ In economically strong regions, 7.5% is the estimated frequency of inadequate zinc intake which rises up to 30% for South Asian region.¹⁵ The foods like meat and fish are rich in zinc, but relatively expensive.¹⁶ Nuts, legumes, seeds, and whole grain cereals, also contain zinc but its absorption is altered due to the phytate content which is present in these foods. Human body cannot store zinc and almost 50% of zinc is excreted out through gastrointestinal tract while during diarrheal episodes, excretion of zinc is further increased.¹⁷⁻¹⁹

In present study, we evaluated that either combination of probiotics and zinc results in early recovery from diarrhea or not. In our study, duration of diarrhea resolution was significantly less in combination therapy group 27.63±2.39 hours versus 38.86±3.47 hours in probiotics only group. We also found significant difference in recovery from diarrhea in both groups, with a recovery rate of 100% versus 94.5% in probiotics plus zinc groups and probiotics alone group respectively. Szajewska and Mrukowicz reviewed ten randomized, double-blind, placebo-controlled studies and established that the duration of symptoms of acute diarrhea were substantially reduced to an average of 20 h, by consuming probiotics.²⁰ In addition, D'Souza et al revealed through a meta-analysis that probiotics were effective in the prevention of antibiotic induced diarrhea.²¹ In children presenting acute infectious diarrhea, the effectiveness of lactobacilli was reported in nine randomized controlled studies. van Niel et al reviewed the studies and described that not only there was significant reduction in the duration of diarrhea averaging 0.7 days, but daily stool frequency was also reduced.²² McFarland et al examined the efficacy of probiotics in pediatric diarrhea by analyzing 39 randomized, controlled and blinded clinical trials comprising a total of 41 probiotic treatment arms.²³ Of these, 32 (78%) reported efficacy. Another meta-analysis of 39 trials by Sazawal et al showed that probiotics prevented acute diarrhea, with a risk reduction among children of 57% (range: 35–71%).²⁴ Abraham et al. conducted a study on combination of probiotics and zinc co-administration in children with acute diarrhea and found that combination of zinc and probiotics is superior to probiotics alone for the treatment of watery diarrhea. These authors found a significant faster recovery from diarrhea in children who were treated with combination therapy but these authors did not mentioned the duration of treatment and duration of diarrhea after starting the treatment in their study.²⁵ Another study by Maladkar et al concluded that combination of probiotics and zinc is superior in the treatment of diarrhea and these authors found recovery from diarrhea in 95% children with 5 days after starting the treatment. However, these authors did not compared these patients with other group e.g. probiotics alone group. These authors also found that combination of probiotics and zinc is well tolerated by the patients without any severe adverse effects.²⁶

CONCLUSION

Combination of probiotics and zinc was superior as compared to the probiotics alone in the treatment of acute diarrhea in children.

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