

Original Article



Treating Viral Diarrhea in Children by Probiotic and Zinc Supplements

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Conflict of Interest

The authors deny any source or type of conflict
of interest during the study. All honoraria were
provided out of the research center fund and
disbursed accordingly.

ABSTRACT

Purpose: The aim of this study was to analyze the effects of probiotics and zinc supplements on the mean duration and frequency of acute diarrhea in children aged 6 months to 2 years.

Methods: In this clinical trial of infants aged between 6 months and 2 years, eligible patients were divided into 3 groups: Zinc Receiving Group (ZRG), Probiotic Receiving Group (PRG), and a control group receiving supportive care alone. The frequency of diarrhea was evaluated in the test groups during the first 24 hours and 48–72 hours, along with the duration of hospitalization and diarrhea persistence for 3–7 days.

Results: Diarrhea persisted for until the third day of admission in 100% of the infants in PRG compared with only 76.1% in ZRG. The relative risk of diarrhea persistence in the PRG was 1.31 times more than in ZRG until the third day. Also, 80% of diarrhea cases in the PRG persisted until the fourth day of admission, compared with 47.8% in the ZRG group, and this value was significant. The relative incidence of diarrhea persistence in the PRG was 36.4 times greater than in the ZRG until the day 4. Also, the percentage of post-treatment complications was 35.5% in the PRG and 2.6% in the ZRG, which was significant.

Conclusion: In our study, the effectiveness of zinc at a dose of 20 mg was higher than that of probiotics. The complications associated with zinc supplementation were lower than those of probiotics.

Keywords: Diarrhea; Pediatrics; Probiotics; Viral diarrhea; Zinc

INTRODUCTION

Diarrhea is one of the main causes of childhood disability and death worldwide, resulting in 5–10 million deaths annually [1]. Diarrhea causes millions of deaths in Asia, Africa, and Latin America in the age group of 0–4 years. In Iran, diarrhea is the second leading cause of death in children after respiratory infections [2]. The risk factors include contaminated water, poor health, or conditions such as malnutrition and factors like high-level contact with pathogens and reduced breast milk safety [3]. Diarrhea is one of the most common clinical signs of infection associated with the lower parts of the digestive tract, and is defined as a watery stool occurring at least 3 times in a 24-hour period. Diarrhea can be divided into acute and

chronic categories: acute diarrhea is the most severe type caused by viral, bacterial, fungal, and parasitic infections. Rotaviruses and *Escherichia coli* are the main causes of diarrhea [4].

The role of zinc in human nutrition has increased significantly. It is one of the micronutrients that is very effective in human health, especially in children [5,6]. Several reports correlate diarrhea with abnormal zinc levels. The duration of diarrhea depends on several factors, among which age-related weight loss and reduced cellular immunity are established [7]. Zinc deficiency is associated with both factors [8]. Therefore, zinc deficiency is thought to play a key role in children's diarrhea, and zinc supplements are effective in ameliorating and preventing the symptoms [9]. Zinc therapy improves the absorption of water and electrolytes from the intestine, stimulates epithelialization, increases the level of intestinal enzymes, and enhances the immune response, resulting in rapid clearance of diarrhea [10].

The use of probiotics in the prevention and control of gastrointestinal diseases, in particular, diarrhea resulting from prolonged use of antibiotics, has been considered over the past two decades [11]. Probiotics are vital microorganisms, which support the intestinal flora, and reduce bacterial invasion of the intestinal wall. Thus, they prevent the growth of pathogens, enhance the production of antimicrobial substances and changes in the acidity of the intestinal environment, thereby minimizing the chances of infection by producing short-chain fatty acids [12]. Probiotics, such as *Lactobacillus acidophilus* and *Enterococcus faecium* SF68, are used to prevent or treat diarrhea. Probiotics have also been evaluated for the control of rotaviral diarrhea in children and travelers' diarrhea. Probiotics are important in controlling and reducing the symptoms of acute gastroenteritis, poisoning, irritable bowel syndrome and food allergies [13].

Therefore, the aim of this study was to determine and compare the effects of probiotics and zinc supplements on the mean duration and frequency of acute diarrhea in children aged 6 months to 2 years.

MATERIALS AND METHODS

In this clinical study, all infants aged 6 months to 2 years who were admitted to Shahid Madani Hospital of Khorramabad with moderate to severe diarrhea, were surveyed using a questionnaire after obtaining consent from their parents. In this study, a total of 146 infants were studied (50 infants taking probiotics, 46 treated with zinc, and 50 in the control group, receiving supportive care only). The variables studied were weight, number of fecal episodes per day, vomiting after drug administration (zinc and probiotics), and duration of hospitalization. Improvement in diarrhea was defined by reduced frequency of bowel movements and increased stool consistency.

The inclusion criteria were patients admitted to the hospital at the age of 6 months to 2 years, with moderate to severe diarrhea. Sample exclusion criteria were a history of antibiotic administration during the last week before admission, antibiotic therapy during hospitalization, the presence of white blood cells or red blood cells in stool, bacterial diarrhea, immunocompromised patients, and patients with malabsorption diseases.

After selection of patients according to the entry criteria, the patients were divided into 2 groups: Zinc Receiving Group (ZRG) and Probiotic Receiving Group (PRG), using

randomized block allocation. In the PRG, infants between 6 months and 1 year of age received 1 capsule of probiotic daily with yogurt, and those between 1 and 2 years received 1.5 capsules daily (type of drug: PROKID capsule; Gostaresh Milad Pharmed Co., Tehran, Iran). Probiotics indicated for children and infants contain more than $10^9 \times 6$ probiotic units per capsule. The probiotic products contained *Bifidobacterium lactis*, *Lactobacillus* and *Bifidobacterium bifidum*, and *Lactobacillus rhamnosus*. ZRG participants received 20 mg of elemental zinc as zinc gluconate syrup (5 mg/5 mL) each day (Al-Hawi pharmaceutical Co., Tehran, Iran). However, zinc may trigger gastrointestinal complications, such as vomiting and stomach ache, and therefore, it was administered with meals or milk.

The frequency of diarrhea in the 2 groups was monitored during the first 24 and 48–72 hours. The duration of hospitalization and diarrhea persistence for 3 to 7 days was evaluated. The persistence of diarrhea in children discharged from the hospital was evaluated by calling the parents. Patients in both groups were followed up using the outcomes indicated by someone other than the researchers (trained nurses).

This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences (LUMS.REC.1396).

Statistical analysis

Data analysis of the 96 infants was conducted using Statistical Procedures for Social Sciences (SPSS version 19.0; Chicago, IL, USA). An independent-sample-*t*-test was carried out for comparison by repeated measurement ANOVA. The *p*-values <0.05 were considered statistically significant.

RESULTS

In this study, a total of 96 children (50 treated with probiotics and 46 with zinc) were studied. The mean age of the children in PRG group was 11.8 ± 5.95 months and that of the ZRG was 11.15 ± 5.51 months, which was not statistically significant ($p=0.586$) based on the independent *t*-test. Also, no significant differences existed between the ground based on sex distribution, place of residence, mother's educational level, and type of nutrition. Based on the independent *t*-test, the difference in mean weight ($p=0.794$) and frequency of bowel habits ($p=0.334$) in the 2 groups was not statistically significant before the administration of probiotics and zinc supplements (**Table 1**).

According to the results, we compared the weight of children in the 2 groups at different times. The difference in the weight of children during the time (time effect) in each group

Table 1. Comparison of the mean variables of weight and bowel habits during different days of admission

Variables	Groups	Day 0	Day 1	Day 2	Day 3	Day 4	Time effect	Group effect	Interactive effect/ time group
Weight ($\mu \pm SD$)	PRG	9.66 \pm 2.42	9.4 \pm 2.3	9.38 \pm 2.38	9.54 \pm 2.34	-	F=11.3	F=0.386	F=0.323
	ZRG	9.52 \pm 2.69	9.72 \pm 2.61	9.74 \pm 2.55	9.85 \pm 2.53	-	$p < 0.001$	$p = 0.536$	$p = 0.669$
	Control	9.57 \pm 2.19	9.77 \pm 2.51	9.54 \pm 2.95	9.75 \pm 2.73	-			
Bowel habits ($\mu \pm SD$)	PRG	8.18 \pm 5.55	7.07 \pm 3.52	6.11 \pm 3.15	4.69 \pm 2.65	3.69 \pm 2.24	F=37.37	F=0.05	F=0.248
	ZRG	7.2 \pm 4.08	7.00 \pm 3.07	5.68 \pm 2.35	4.47 \pm 2.52	3.68 \pm 1.73	$p < 0.001$	$p = 0.824$	$p = 0.753$
	Control	10.18 \pm 5.55	10.07 \pm 3.52	9.11 \pm 3.15	7.69 \pm 2.65	6.69 \pm 2.24			

Data are shown as mean \pm SD or number (%).

SD: standard deviation, PRG: Probiotic Receiving Group, ZRG: Zinc Receiving Group.

was statistically significant ($p < 0.001$); however, the difference in the weight of children between the 2 groups (group effect) was not statistically significant ($p = 0.336$). Furthermore, the weight of children between the 2 groups at each time interval was determined separately on each of the first ($p < 0.835$), second ($p < 0.714$) and third ($p < 0.449$) admission days, which was not statistically significant.

Based on the results, the frequency of daily bowel habits in children under each group over time was statistically significant ($p < 0.001$). However, the difference in frequency of bowel habits between the 2 groups was not statistically significant ($p = 0.824$). Significant differences existed between the 2 groups in terms of age (time effect) ($p < 0.001$). Also, the mean frequency of bowel habits in the 2 groups of children at each corresponding time interval was determined, based on the independent *t*-test on each of the first ($p = 0.657$), second ($p = 0.530$), third ($p = 0.406$), and fourth ($p = 0.700$) admission days.

Based on the results shown in **Table 2**, the difference in the improvement of diarrhea in the PRG was not statistically significant in terms of gender, maternal education, and type of nutrition. However, according to χ^2 test results, the difference in the frequency of diarrhea improvement in the PRG based on the location of the child was statistically significant. In this group, the percentage of improvement in children living in rural area was significantly more than in the children residing in urban areas ($p = 0.029$).

According to the analyses, the ZRG showed no significant difference in the percentage of diarrhea improvement in terms of gender, place of residence, maternal education, or type of nutrition.

In the PRG group, diarrhea persisted in 100% of cases until the third day of admission, while in the ZRG group, it was only observed in 76.1% of children until day 3 of admission, and this difference was statistically significant ($p < 0.001$). The relative risk of persistent diarrhea until day 3 in the PRG was 1.31 times that of the ZRG.

Also, in the PRG group, diarrhea persisted in 80% of cases until day 4 of admission, whereas in the ZRG group, it was only in 47.8% of children until day 4 of hospitalization, and this difference was significant ($p < 0.001$). The relative persistence of diarrhea until day 4 in the PRG was 36.4 times higher than in the ZRG.

The incidence of post-treatment complications was 35.5% in the PRG and 2.6% in the ZRG, which was statistically significant (**Table 3**). The treatment satisfaction rate in the PRG was 91.4% and that of the ZRG was 97.3%, which was not statistically significant.

DISCUSSION

In this clinical study, we compared the effects of probiotics and zinc supplements on the treatment of acute viral diarrhea in children aged 6 months to 2 years.

In a study by Abraham et al. [14] the combination of zinc supplements and probiotic therapy was superior to probiotics alone in terms of alleviation of vomiting and diarrhea symptoms in children.

Table 2. Frequency distribution of variables in children showing improvement in diarrhea

Groups	Yes	No	Total	p-value
PRG				
Sex				0.302
Male	27 (84.4)	5 (15.6)	32 (100)	
Female	13 (72.2)	5 (27.8)	18 (100)	
Living place				0.029
Urban area	32 (88.9)	4 (11.1)	36 (100)	
Rural area	8 (61.5)	5 (38.5)	13 (100)	
Mother's education				0.232
Elementary	11 (68.8)	5 (31.3)	16 (100)	
Intermediate	24 (88.9)	3 (11.1)	27 (100)	
Upper intermediate	5 (71.4)	2 (28.6)	7 (100)	
Nutrition type				0.116
Breast milk	29 (87.9)	4 (12.1)	33 (100)	
Powder milk	7 (63.6)	4 (36.4)	11 (100)	
Both above	1 (50)	1 (50)	2 (100)	
ZRG				
Sex				0.238
Male	13 (56.6)	10 (43.5)	23 (100)	
Female	9 (39.1)	14 (60.9)	23 (100)	
Living place				0.072
Urban area	16 (55.2)	13 (44.8)	29 (100)	
Rural area	4 (26.7)	11 (73.3)	15 (100)	
Mother's education				0.484
Elementary	3 (33.3)	6 (66.7)	9 (100)	
Intermediate	15 (53.6)	13 (46.4)	28 (100)	
Upper intermediate	3 (37.5)	5 (62.5)	8 (100)	
Nutrition type				0.647
Breast milk	14 (46.7)	16 (53.3)	30 (100)	
Powder milk	2 (28.6)	5 (71.4)	7 (100)	
Both above	1 (33.3)	2 (66.7)	3 (100)	
Control				
Sex				0.302
Male	13 (56.6)	10 (43.5)	23 (100)	
Female	9 (39.1)	14 (60.9)	23 (100)	
Living place				0.029
Urban area	16 (55.2)	13 (44.8)	29 (100)	
Rural area	4 (26.7)	11 (73.3)	15 (100)	
Mother's education				0.232
Elementary	3 (33.3)	6 (66.7)	9 (100)	
Intermediate	15 (53.6)	13 (46.4)	28 (100)	
Upper intermediate	3 (37.5)	5 (62.5)	8 (100)	
Nutrition type				0.116
Breast milk	14 (46.7)	16 (53.3)	30 (100)	
Powder milk	2 (28.6)	5 (71.4)	7 (100)	
Both above	1 (33.3)	2 (66.7)	3 (100)	

Values are presented as number (%).

PRG: Probiotic Receiving Group, ZRG: Zinc Receiving Group.

Table 3. Frequency distribution of variables

Variables	Groups	Yes	No	Total	p-value
Diarrhea persistence until the third day	PRG	50 (100)	0 (0)	50 (100)	<0.001
	ZRG	35 (76.1)	11 (23.9)	46 (100)	
Diarrhea persistence until the fourth day	PRG	40 (80)	10 (20)	50 (100)	<0.001
	ZRG	22 (47.8)	24 (52.2)	46 (100)	
Complications of treatment	PRG	16 (35.6)	29 (64.4)	45 (100)	<0.001
	ZRG	1 (2.6)	38 (97.4)	39 (100)	
Satisfaction with the treatment	PRG	41 (91.4)	4 (8.8)	45 (100)	<0.05
	ZRG	39 (97.3)	1 (2.7)	37 (100)	

Values are presented as number (%).

PRG: Probiotic Receiving Group, ZRG: Zinc Receiving Group.

In a randomized controlled trial by Brooks et al., [15] 275 infants aged 1 to 6 months with acute watery diarrhea were randomly treated with 20 mg elemental zinc administered as zinc acetate daily and placebo. No significant differences were found between the duration of diarrhea and infant weight gain in the intervention and control groups, which was consistent with our recent conclusions regarding infant weight gain. However, there was a significant difference between the duration of diarrhea, the length of hospitalization and the reduction of complications after treatment with Zn [13]. In our study, the relative risk of persistent diarrhea until day 3 in the probiotic group was 1.31 times that of the ZRG, and the relative risk of persistent diarrhea until day 4 in the PRG was 36.4 times greater than in the ZRG. This result indicated a better effect of zinc supplementation compared with probiotics.

In a randomized controlled trial conducted in India by Sachdev et al., [16] involving infants with watery diarrhea, it was found that the duration of diarrhea and the frequency of bowel habits after zinc therapy was significantly reduced only in patients with severe zinc deficiency, and the results of diarrheal duration were consistent with our study findings [13].

In a randomized trial conducted in Bangladesh by Qadir et al., [17] involving 190 children aged between 3 and 24 months, and diagnosed with diarrhea, the duration of the disease in low-weight children following zinc supplementation was reduced to 33%. Additionally, the recovery time of boys who received zinc supplements was significantly shorter compared with boys in the control group [17]. This recent study was not consistent with our findings of the mean weight of children under study. In our study, the difference in mean weight ($p=0.794$) in the 2 groups was not statistically significant before the administration of probiotic and zinc.

In a randomized double-blind study conducted in India, 287 boys (3 to 36 months) with a maximum of 72h lapse since the onset of diarrhea, showed significant changes in bowel habits following zinc therapy., which was consistent with our findings [18]. In our study, based on the results of the PRG group, involving 100% of cases, diarrhea persisted until the third day of admission (72 hours), compared with only 76.1% of diarrhea in ZRG. This difference was statistically significant ($p\leq 0.001$).

According to the 2005 study of Bhandari et al., [19] zinc supplements can be used to treat malnourished children with acute diarrhea or even more generalized malnourished children living in areas at increased risk.

In a study conducted by Boran et al. [20] in 280 children aged 6 to 60 months, the intervention group received zinc supplements for 14 days. The subsequent plasma levels of zinc were higher than in the control group, and the duration and frequency of diarrhea was lower in the treatment group compared with the control group, without any significant differences. This study was consistent with our study in terms of the duration of diarrhea [20].

In a study by Torabi et al., [21] treatment of diarrhea with zinc sulfate resulted in favorable patient outcomes. The results were consistent with our study showing the positive effects of zinc in patients with diarrhea. However, a recent study by Mazumder et al. [22] did not show reduced frequency and duration of diarrhea in children treated with zinc therapy, which was consistent with our findings.

The varying results can be attributed to the varying status of serum zinc status in patients in different region with the number of samples studied. Studies based on serum zinc levels are specific to the geographic area.

Clinical studies have shown that the intake of bacteria producing lactic acid at 10^9 – 10^{11} can reduce the incidence, duration, and severity of some of the digestive diseases [23]. In the present study, it was observed that probiotics alleviated diarrhea on days 3 and 4, although not as strongly as the group that received zinc supplements, despite significant differences compared with the control group ($p < 0.001$) (Table 3). It has been observed that probiotics maintain intestinal flora and prevent digestive complications such as diarrhea associated with antibiotic therapy, inflammatory bowel disease, childhood diarrhea, traveler's diarrhea, lactose intolerance, *Helicobacter pylori* infection, irritable bowel syndrome, and bowel disease caused by *Clostridium difficile* [24]. In addition, clinical and laboratory studies have shown that probiotics strongly prevent or ameliorate genital and urinary tract infections, high blood lipids, allergies, and septicemia. Of course, to demonstrate these effects, robust and well-controlled scientific studies are needed including double-blind multicenter clinical trials with a control group, along with pharmacokinetic studies [25].

Research has shown that 20% of patients lose microbial flora following antibiotic treatment. Probiotics are effective for the treatment and prevention of these types of diarrhea. Probiotics are effective for the treatment of diarrhea in travelers and the disease with an infectious origin, such as rotavirus in children [26]. Probiotics including certain strains of *Lactobacillus* (e.g., *rhamnosus*) reduce the risk of diarrhea in children. Inflammation of the intestinal mucous membrane or gastroenteritis is one of the main causes of acute diarrhea, which usually lasts for several days [27]. Viruses, bacteria and parasites trigger gastroenteritis. In children, rotavirus is the main cause of the gastroenteritis. Although administration of water and oral electrolytes is the most common treatment, it does not reduce the duration of the disease. Evidence suggests that intake of probiotics reduces the duration of diarrhea, especially, when started promptly at the first signs of symptom onset. However, probiotic treatment may not be effective in advanced cases warranting intravenous interventions [27].

Multiple studies provide clear evidence of the efficacy of probiotics in intestinal disease. Szajewska et al. [28] reported a meta-analysis of studies showing the effects of probiotics for the treatment and prevention of acute infectious diarrhea involving infants and children. This study examined the role of *Lactobacillus rhamnosus* GG (LGG) in infectious and acute diarrhea involving newborns and children. No adverse effects were observed with LGG [28].

Various probiotic species such as *Lactobacillus reuteri* 55730 ATCC, LGG (*L. rhamnosus*), *Lactobacillus 114001-DNcasei* and *Saccharomyces boulardii* are effective in reducing the severity and duration of acute infectious diarrhea in children. The duration of acute diarrhea in children treated with probiotics is reduced by about 1 day [29,30]. Live organisms including LGG and yeast such as *S. boulardii* show beneficial therapeutic effects for the prevention of antibiotic-associated diarrhea, with proven efficacy in adults and children treated with antibiotics demonstrated experimentally [31,32].

The mechanism underlying the effect of different probiotics should be elucidated in greater detail in order to select the most appropriate probiotic species for use against a specific pathogen. Further, the dosage and the length of the treatment period should be addressed [33]. In this study, the effectiveness of zinc at a dose of 20 mg was higher than that of probiotics. However, the complications of zinc supplementation were lower than those associated with probiotics.

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