Turk J Gastroenterol *2016; 27: 537-40*

Effects of zinc or synbiotic on the duration of diarrhea in children with acute infectious diarrhea

BOWEL

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ABSTRACT

Background/Aims: Probiotic effects on acute infectious diarrhea are strain(s) specific, and all formulations should be evaluated by clinical trials. We aimed to evaluate the effect of a synbiotic preparation on the duration of diarrhea in children compared to a zinc suspension.

Materials and Methods: We conducted a single-center, randomized, and controlled clinical trial in children with acute infectious diarrhea. The first group received a synbiotic preparation containing *Lactobacillus casei*, *L. plantarum, L. rhamnosus, Bifidobacterium lactis* and prebiotics; the second group received a zinc suspension (15 mg/day) for 5 days in addition to oral rehydration solution (ORS) and/or intravenous therapy. The third group received ORS and/or intravenous therapy (control group). The primary endpoint was the duration of diarrhea (in hours). The secondary endpoint was the percentage of children with diarrhea during each day of intervention.

Results: The duration of diarrhea was significantly reduced in the *synbiotic* and the zinc groups compared to the control group (91.0±28.9 hours vs. 114.3±30.9 hours, $p<0.001$; 86.4±30.8 hours vs. 114.3±30.9 hours, $p<0.001$, respectively). There was no significant difference in the duration of diarrhea between the synbiotic and zinc groups ($p>0.05$). At 72nd and 96th hours, the percentage of children with diarrhea was lower in the zinc group than in the synbiotic group ($p<0.05$ for both).

Conclusion: Our study showed that zinc or synbiotic supplementation reduced the duration of diarrhea, with better clinical outcomes at 72nd and 96th hours, and both can be used in children with acute diarrhea. To the best of our knowledge, this was the first study to make a comparison between zinc and synbiotics.

Keywords: Synbiotics, zinc, acute diarrhea, children

INTRODUCTION

Acute infectious diarrhea still remains a leading cause of morbidity and hospitalization in developed countries, and also a cause of mortality in low resource countries (1,2). Recent clinical studies and guidelines proposed some complementary therapies for acute infectious diarrhea, such as zinc and probiotics, in addition to the mainstay treatment with oral rehydration solution (ORS) (3). There are contradictory results about the zinc supplementation for acute infectious diarrhea during childhood. The beneficial effects of zinc supplementation have been shown in children aged >6 months in developing countries; however, current European guidelines suggest that zinc supplementation has no effect on acute diarrhea when zinc deficiency is rare (4). Many randomized, controlled studies and well-conducted meta-analyses are now available about the use of probiotics for treatment of acute diarrhea; however, the effects of probiotics on acute infectious diarrhea are strain-specific (4-8). There are several studies about the use of synbiotic preparations with different strains, and all of these combinations should be evaluated for their effectiveness (3,9-11). We aimed to evaluate the effect of synbiotic preparations (containing *Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus plantarum, Bifidobacterium lactis,* and prebiotics) and zinc on the duration of diarrhea in children.

MATERIALS AND METHODS

We conducted a single-center, randomized, parallel group, controlled, clinical trial in outpatient children (6–120 months) with acute infectious diarrhea in Turkey.

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Received: August 9, 2016 **Accepted:** October 3, 2016
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2016.16396

Original Article

The study protocol was approved by the local ethical committee. Informed consent was obtained from all parents. Children with severe dehydration and/or requiring intensive care unit stay were excluded. Other exclusion criteria were the use of antibiotics or probiotics up to 8 weeks before admission, malnutrition, and chronic underlying diseases. All children were randomly assigned to 3 interventions (synbiotic, zinc or control group) according to a computer-generated randomization list.

The first group received synbiotic preparations (NBL Probiotic ATP® sachet, Nobel İlaç, Turkey; one sachet per day) containing *L. casei, L. rhamnosus, L. plantarum, B. lactis* (4.5×10^9 CFU in total), prebiotics such as fructose and galactooligosaccharides and polydextrose (1996.57 mg), Vitamin C, Vitamin E, riboflavin, pyridoxine, and thiamine for 5 days in addition to ORS with or without intravenous therapy. The second group received a zinc suspension (15 mg per day for 5 days, Berko İlaç; Turkey) in addition to ORS and/or intravenous therapy. The third group (controls) received ORS and/or intravenous therapy only.

Upon admission, demographic and clinical findings (fever, body weight, and degree of dehydration) of the patients were recorded. A fluid/electrolyte replacement was performed using hypo-osmolar ORS based on the status of each patient. The primary endpoint was the duration of diarrhea. The secondary endpoint was the number of children with diarrhea at the third day of intervention and each day of the five-day intervention. Consistency and frequency of each stool were recorded. The duration of diarrhea was defined as the time in hours from admission until cessation of diarrhea, which was defined as the first normal stool. Stool evaluation was made according to the Bristol score, where a score <5 was described as normal. The forms were filled out by the parents.

Statistical Analysis

Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc.; Chicago, IL, USA). Variables were evaluated for normal distribution, and comparisons were tested using a t-test and χ^2 or Fisher's exact tests as appropriate. Risk ratio and a 95% confidence interval were used for comparisons between synbiotic group and controls, and zinc group and controls. Risk difference and a 95% confidence interval were used for comparisons between the synbiotic group and the zinc group. Statistical significance was set at p<0.05.

RESULTS

The study included 165 children (55 in synbiotic group, 55 in zinc group, and 55 in the control group). The mean age and sex of the children in the synbiotic, zinc, and control groups were similar (p>0.05) (Table 1). Presence of dehydration was similar in all three groups. The duration of diarrhea was significantly reduced (~24 hours) in the synbiotic group compared to the control group (91.0±28.9 hours *vs.* 114.3±30.9 hours, p<0.001, respectively). The duration of diarrhea was significantly reduced (~28 hours) in the zinc group compared to the control group (86.4±30.8 hours *vs.* 114.3±30.9 hours, p<0.001, respectively). No statistical significance was observed between the synbiotic and zinc groups (91.0±28.9 hours vs. 86.4±30.8 hours, p>0.05, respectively) (Table 1).

No effect on diarrhea was observed at 24th hours of synbiotic intervention. The effects of synbiotics (diarrhea-free percentage of children) started to be observed by 48 hours (Table 2). At Day 3, 61.8% of the children receiving synbiotics still had watery diarrhea while 83.6% of the controls had watery diarrhea (p=0.01). At 96 and 120 hours of intervention, the diarrhea-free percentage of children was still lower in the synbiotic group than in the control group (p<0.01 for both) (Table 2).

The effects (diarrhea-free percentage of children) of the zinc started to be observed at 48 hours of intervention (Table 3). After 48 hours, 81.8% of the children receiving zinc still had watery diarrhea while it 98% of the children in the control group still had watery diarrhea (p=0.01). After 72, 96, and 120 hours, the number of children receiving zinc who still had watery diarrhea was significantly lower compared to the control group (p<0.01 for all groups).

The effect of synbiotics and zinc was similar at 24 and 48 hours of intervention (p>0.05) (Table 4). At 72 hours, 45.4% of children receiving zinc still had watery diarrhea, which was significantly lower than in the synbiotic group with 61.8%, (p<0.05). At 96 hours of intervention, the percentage of children with diarrhea was lower in the zinc group compared to the synbiotic group (p<0.05). There was no difference in the percentage of diarrhea-free children between the zinc and probiotic groups (p>0.05).

Table 1. Demographic findings and duration of diarrhea in the study groups

	Synbiotic group (n=55)	Zinc group (n=55)	Controls (n=55)
Age (months)	36.4±32.7	54.9±44.3[b]	49.5±37.6
Sex (Girls/Boys)	24/31	28/27	28/27
Duration of diarrhea (hours)	91.0±28.9[a]	86.4±30.8b	114.3±30.9

*Values of age, duration of diarrhea, and length of hospital/ER stay are expressed as mean±SD. [a]p<0.001; synbiotic vs. control group. [b]p<0.001; zinc vs. control group

Table 2. Percentage of children with diarrhea at Day 3 and Day 5 in the synbiotic and control groups

	Synbiotic group (n=55)	Control group (n=55)	RR (95% CI)	p
24th hour	54/55 (98.1%)	55/55 (100%)	0.98 (0.93–1.03)	p>0.05
48th hour	45/55 (81.8%)	54/55 (98.1%)	0.83 (0.73–0.95)	p<0.01
72nd hour	34/55 (61.8%)	46/55 (83.6%)	0.74 (0.58–0.94)	p=0.01
96th hour	15/55 (27.2%)	30/55 (54.5%)	0.50 (0.30–0.82)	p<0.01
120th hour	4/55 (7.2%)	16/55 (29%)	0.25 (0.09–0.70)	p<0.01

RR: relative risk; CI: confidence interval

Table 3. Percentage of children with diarrhea at Day 3 and Day 5 in the zinc and control groups

	Zinc group (n=55)	Control group (n=55)	RR (95% CI)	p
24th hour	55/55 (100%)	55/55 (100%)	1.00 (0.97–1.04)	p>0.05
48th hour	46/55 (83.6%)	54/55 (98.1%)	0.85 (0.75–0.96)	p=0.01
72nd hour	25/55 (45.4%)	46/55 (83.6%)	0.54 (0.40–0.74)	p<0.001
96th hour	8/55 (14.5%)	30/55 (54.5%)	0.27 (0.13–0.53)	p<0.001
120th hour	6/55 (10.9%)	16/55 (29%)	0.38 (0.16–0.89)	p<0.05

RR: relative risk; CI: confidence interval

Table 4. Percentage of children with diarrhea at Day 3 and Day 5 in the synbiotic and zinc groups

	Synbiotic group (n=55)	Zinc group (n=55)	Risk difference (95% CI)	p
24th hour	54/55 (98.1%)	55/55 (100%)	-0.02 (-0.07–0.03)	p>0.05
48th hour	45/55 (81.8%)	46/55 (83.6%)	-0.02 (-0.16–0.12)	p>0.05
72nd hour	34/55 (61.8%)	25/55 (45.4%)	0.16 (-0.02–0.35)	p<0.05
96th hour	15/55 (27.2%)	8/55 (14.5%)	0.13 (-0.02–0.28)	p<0.05
120th hour	4/55 (7.2%)	6/55 (10.9%)	-0.04 (-0.14–0.07)	p>0.05

CI: confidence interval

DISCUSSION

The initial therapy recommended for acute diarrhea is treatment with oral fluids and use of ORS (4). However, ORS neither reduces the frequency of fluid loss or bowel movements nor shortens the duration of diarrhea; therefore, further adjunctive therapy options have been extensively studied (3). In the present study, the synbiotic formulation reduced the duration of diarrhea for approximately 24 hours, with a similar efficacy to other clinical studies and guidelines related to other probiotic strains (3,4,8,12). Our study was the first to evaluate the effect of synbiotic preparations containing *L. casei, L. plantarum L. rhamnosus,* and *B. lactis*. These are well-known and commonly studied bacterial strains as probiotics for different clinical conditions; however, probiotic effects on acute infectious diarrhea are strain(s) specific, and all formulations should be evaluated by clinical trials (4). In the present study, the effects of synbiotic preparations started to be observed at 48 hours; and at 96 hours of intervention, the percentage of diarrhea-free children was 73% while it was 45% in the control group. Our previous study with another synbiotic preparation containing *L. rhamnosus L. acidophilus, B. bifidum, B. longum, Enterococcus faecium* (2.5×10^9 CFU in total of live bacteria daily) and 625 mg fructooligosaccharide for 5 days had also shown significant reduction in the duration of diarrhea. The duration was reduced approximately 36 hours in children with acute infectious diarrhea, and the effects were visible after 24th hours, with a better outcome at 48 and 72 hours of intervention (9). Two studies conducted in Belgium (11) (*Streptococcus thermophilus, L. rhamnosus, L acidophilus, B. lactis, B. infantis,* and fructooligosaccharide) and Italy (10) (*Lactobacillus paracasei B21060* with arabinogalactan and xylooligosaccharides) (4) also showed promising results related to the effects of synbiotics on acute infectious diarrhea. Current ESPID/ESPGHAN guidelines does not recommend any of the studied synbiotics (each combination with only one clinical study) until further confirmatory studies are available (4). For strong recommendation, further studies are needed for the same synbiotic preparations in different clinical settings.

Many studies have reported on the efficacy of zinc for treatment of acute diarrhea during childhood, and contradictory results have been published concerning the geographical region and age (3, 4). Zinc deficiency is a major determinant factor of immunity and low weight in developing countries, and both are related with the duration of diarrhea (13-15). The administration of zinc was shown to reduce the duration of the diarrhea as well as frequency and amount of the stool in randomized controlled trials and reviews (16-18). The World Health Organization recommends routine use of zinc supplementation, at a dosage of 20 mg per day for children older than six months. In our study, we preferred to use a standard dose of 15 mg per day with a liquid formulation. The duration of diarrhea was significantly reduced in the zinc group compared to the control group (approximately 28 hours). The effect of the zinc preparation started to be observed at 48 hours of intervention. At 72 and 96 hours, the zinc group had less diarrhea compared to the control group (45% vs. 86%, respectively). A meta-analysis (including 18 clinical trials with 6165 participants) showed that zinc supplementation resulted in a shorter diarrhea duration in acute diarrhea, and less diarrhea at Day 3 and Day 5, similar to our results (17). In contrast to other studies, a recently made double-blind randomized study about zinc supplementation for acute diarrhea in Switzerland showed that zinc treatment decreases the frequency and severity of diarrhea in children aged 2 months to 5 years old, but not the duration of diarrhea (20). In developing countries, zinc supplementation might be useful in the treatment of acute diarrhea for children older than 6 months. However, no benefit from the use of zinc was documented in regions where zinc deficiency is rare (4).

We found no significant difference between the synbiotic and zinc groups (91.0±28.9 hours vs. 86.4±30.8 hours); however, it seems that zinc supplementation had a faster effect than the synbiotic supplementation, and the percentage of diarrhea-free children was significantly higher in the zinc group than in the synbiotic group at 72 and 96 hours of intervention. By the fifth day, the significance between the two groups disappeared. There was also no significant difference between the synbiotic and zinc groups in the duration of diarrhea (91.0±28.9 hours vs. 86.4±30.8 hours, respectively). To our knowledge, this was the first study to make a comparison between zinc and synbiotics. Further studies with larger cohorts are required to clarify the effect of zinc and/or synbiotics on fecal microbiota composition in children with acute diarrhea.

Our study had some limitations. We did not perform a stool analysis for etiological causes of acute infectious diarrhea, and had no chance to evaluate the effects of zinc or synbiotics on different etiological causes of diarrhea. This study was not a placebo-controlled study. Despite randomization of three interventions, the children in the zinc group were found to be older than the other groups, and we had no chance to evaluate the age-specific effects of zinc on the duration of diarrhea.

In children with acute diarrhea, our study showed that zinc or synbiotic supplementation reduced the duration of diarrhea. Children receiving zinc or synbiotics were more likely to be diarrhea-free after the first 48 hours of intervention, with better outcomes at 72 and 96 hours. Zinc or synbiotic preparations containing *Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus plantarum, Bifidobacterium lactis,* and prebiotics may be used in children with acute diarrhea.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Clinical Trials Ethical Commitee of Ümraniye Training and Research Hospital (24 March 2016).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S.Y., S.G., E.C.D.; Design - A.S.Y., S.G., E.C.D.; Supervision - E.C.D.; Funding - A.S.Y., S.G.; Materials - A.S.Y., S.G.; Data Collection and/or Processing - A.S.Y., S.G.; Analysis and/or Interpretation - E.C.D.; Literature Review - A.S.Y., S.G., E.C.D.; Writer - A.S.Y., S.G., E.C.D.; Critical Review - E.C.D.

Conflict of Interest: Ener Çağrı Dinleyici is a consultant and speaker for Biocodex.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. Lancet 2013; 381: 1405-16. **[CrossRef]**
2. Leung DT, Chisti MJ, Pavia AT. Prevention and Control of Childhood Pneumonia and Diarrhea. Pediatr Clin North Am 2016; 63: 67-79. **[CrossRef]**
3. Pieścik-Lech M, Shamir R, Guarino A, Szajewska H. Review article: the management of acute gastroenteritis in children. Aliment Pharmacol Ther 2013; 37: 289-303. **[CrossRef]**
4. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; European Society for Pediatric Infectious Diseases. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr 2014; 59: 132-52. **[CrossRef]**
5. Floch MH, Walker WA, Sanders ME, et al. Recommendations for Probiotic Use--2015 Update: Proceedings and Consensus Opinion. J Clin Gastroenterol 2015; 49(Suppl 1): S69-73. **[CrossRef]**
6. Cruchet S, Furnes R, Maruy A, et al. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Paediatr Drugs 2015; 17: 199-216. **[CrossRef]**
7. Dinleyici EC; PROBAGE Study Group, Vandenplas Y. Lactobacillus reuteri DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. Acta Paediatr 2014; 103: e300-5.
8. Dinleyici EC, Eren M, Ozen M, Yargic ZA, Vandenplas Y. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. Expert Opin Biol Ther 2012; 12: 395-410. **[CrossRef]**
9. Dinleyici EC, Dalgic N, Guven S, et al. The effect of a multispecies synbiotic mixture on the duration of diarrhea and of hospital stay in children with acute diarrhea in Turkey. Eur J Ped 2013; 172: 459-64. **[CrossRef]**
10. Passariello A, Terrin G, Cecere G, et al. Randomised clinical trial: efficacy of a new synbiotic formulation containing Lactobacillus paracasei B21060 plus arabinogalactan and xilooligosaccharides in children with acute diarrhoea. Aliment Pharm Ther 2012; 35: 782-8. **[CrossRef]**
11. Vandenplas Y, De Hert SG; PROBIOTICAL-study group. Randomised clinical trial: the synbiotic food supplement Probiotical vs. placebo for acute gastroenteritis in children. Aliment Pharmacol Ther 2011; 34: 862-7. **[CrossRef]**
12. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. Pediatrics 2010; 126: 1217-31. **[CrossRef]**
13. Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. Am J Clin Nutr 1984; 39: 87-94.
14. Baqui AH, Sack RB, Black RE, Chowdhury HR, Yunus M, Siddique AK. Cell-mediated immune deficiency and malnutrition are independent risk factors for persistent diarrhea in Bangladeshi children. Am J Clin Nutr 1993; 58: 543-8.
15. Sandstead HH. Is zinc deficiency a public health problem? Nutrition 1995; 11: 87-92.
16. Trivedia SS, Chudasamab RK, Patel N. Effect of zinc supplementation in children with acute diarrhea: Randomized double blind controlled trial. Gastroenterol Res 2009; 2: 168-74. **[CrossRef]**
17. Lazzerini M, Ronfani L. Oral zinc for treating diarrhea in children. Cochrane Database Syst Rev 2008: CD005436.
18. Patel A, Mamtani M, Dibley MJ, Badhoniya N, Kulkarni H. Therapeutic value of zinc supplementation in acute and persistent diarrhea: a systematic review. Plos One 2010; 5: e10386. **[CrossRef]**
19. http://www.who.int/elena/titles/bbc/zinc_diarrhoea/en/
20. Crisinel PA, Verga ME, Kouame KS, et al. Demonstration of the effectiveness of zinc in diarrhea of children living in Switzerland. Eur J Pediatr 2015; 174: 1061-7. **[CrossRef]**