RESEARCH ARTICLE

Evaluation of treatment in acute gastroenteritis: A comparative study

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Abstract

Objective: To compare the efficacy of only dietary recommendations, zinc, probiotics and combination therapies in children admitted with acute gastroenteritis.

Method: The comparative, prospective, double-blind, placebo-controlled study was conducted from October 2020 to April 2021 at the Paediatric Emergency Service after approval from the ethics review committee of Diyarbakir Gazi Yasargil Training and Research Hospital, Turkey, and comprised infants with a diagnosis of acute gastroenteritis who were divided into four groups. Only appropriate dietary recommendations were given to the control group 1, while group 2 was given a single probiotic containing bifidobacterium breve, bifidobacterium bifidum, bifidobacterium infantis and bifidobacterium longum strains. Group 3 was given zinc and group 4 was given probiotics and zinc. Demographic data of the patients, admission complaints, physical examination findings, dehydration degrees, and laboratory findings were recorded and analysed.

Results: Of the 132 subjects, 79 (59.8%) were males. The overall mean age was 27.5±3.6 months. There were 22 (16.7%) patients in group 1, 34 (25.8%) in group 2, 28 (21.2%) in group 3, and 48 (36.4%) in group 4. The mean duration time to diarrhoea termination was 84.5±10.7 hours (range: 79-89 hours) in group 1, 73.05±6.8 hours (range: 70.5-75.4 hours) in group 2, 80.1±10.3 hours (range: 76-84 hours) in group 3, and 43.5±9.6 hours (range: 46-48 hours) in group 4. Group 4 outcome was statistically significant ($p<0.001$).

Conclusions: The efficiency of combined treatment with probiotics and zinc was found to be significantly better in the treatment of childhood acute gastroenteritis.

Keywords: Child, Gastroenteritis, Probiotic, Zinc. (JPMA 72: 2019; 2022)

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Introduction

Acute gastroenteritis (AGE) is a clinical syndrome characterised by three or more watery stools within 24 hours or a few loose/watery bowel movements that exceed two or more than the child's normal daily number of bowel movements. It may also be accompanied by vomiting, fever or abdominal pain.[1] It usually lasts less than a week and not more than two weeks. Most children have more than one episode of AGE before the age of 2 years. Rate of diarrhoea in children aged 0-6 years in Turkey ranks second at 32.3%.[2] Deaths due to diarrhoea in children aged 1-months is ranked second.[3] While death is generally seen in low- and middle-income countries (LMICs), it is the leading cause of hospitalisations in developed countries although deaths rarely occur. The World Health Organisation (WHO) reported in 2003 that approximately 1.87 million deaths due to diarrhoea in children under the age of 5 years and 80% of these deaths occurred in the first two years of life.[4] Most deaths from diarrhoea are due to dehydration. Oral rehydration solution (ORS) treatment is accepted as the first-line treatment of AGE. ORS is absorbed in the small intestine even during severe diarrhoea, thus replacing lost water and electrolytes in the stool. ORS and other fluids can also be used as a home treatment to prevent dehydration.[4] The main elements in the treatment of children with diarrhoea are the treatment of ORS, the provision of continuous nutrition, and the use of antimicrobials for those with bloody diarrhoea, severe cases of cholera, or severe extraintestinal infections.[4] Zinc and probiotics are used as other treatment agents in gastrointestinal tract (GIT) infections. The use of probiotics in the treatment of gastroenteritis is increasing. Probiotics are microorganisms that have beneficial properties for the host. It has profitable effects, such as suppression of the growth of pathogenic bacteria or of epithelial attachment/invasion, improvement of intestinal barrier function, modulation of the immune system, and modulation of pain perception. According to the World Gastroenterology Organisation Global Guidelines, some probiotic strains have been reported to be useful in reducing the severity and duration of acute infectious diarrhoea in children.[5] In 2014, the European Association of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) concluded that the use of probiotics for the treatment of AGE in children may be considered and lactobacillus (L.) rhamnosus, named after Gorbach and

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Goldin (GG), (LGG) (moderate level of evidence) and Saccharomyces boulardii strains (moderate evidence level) or strain combinations were recommended.[1]

Zinc has an important role in cellular growth and the function of the immune system, so the WHO recommends for all children with diarrhoea zinc supplementation of 10mg/day for children under 6 months, and 20 mg/day for older children for 10-14 days.[4]

The current study was planned to compare the efficacy of probiotics, zinc, and combined therapies in addition to ORS in children admitted with AGE.

Patients and Methods

The comparative, prospective, double-blind, placebo-controlled study was conducted from October 2020 to April 2021 at the Paediatric Emergency Service after approval from the ethics review committee of Diyarbakir Gazi Yasargil Training and Research Hospital, Turkey. The sample was raised using random sampling technique. The patients and the observing physicians were kept blinded to the treatment. The patients were followed up for 10 days. Three or more watery or loose stools in 24 hours for a minimum of one day and a maximum of 14 days were considered diarrhoea.

The patients included were aged between 6 months and 6 years, had acute diarrhoea, defined as $\geq$ 3 loose, watery stools/day within the preceding 24 hours, had diarrhoea <2 weeks, had stool samples available and whose parents furnished informed consent.

Those excluded were outside the age range, had blood in the stool, had hospital-acquired or infectious diarrhoea requiring antibiotic treatment, those with chronic diarrhoea, or with severe dehydration and/or needing intensive care unit (ICU) care, patients in need of hospitalisation due to acute diarrhoea, patients with persistent vomiting, abdominal swelling, seizures, having malnutrition, any chronic illness, central nervous system infection or respiratory tract infection, diarrhoea for >14 days, those using vitamins, zinc, antibiotics or probiotics for the preceding three months, and those having received treatment in other medical facility before admission.

AGE severity was evaluated by using the Vesikari score, which includes diarrhoea, vomiting, fever, dehydration and treatment parameters.[6] Those who scored 1-10 were considered mild cases, and those who scored 11 and above were considered severe cases.

Dehydration was evaluated using the WHO guidelines.[4] Patients with mild to moderate dehydration were administered ORS in a volume of 50-100ml/kg depending on the patient's condition for 4-8 hours in the observation room. The patient was followed up by the doctor in charge of the emergency department (ED). After the follow-up, the patient was discharged if her/his vital signs were stable with good oral intake and had no vomiting. When patients' hydration and oral intake improved, they were divided into four groups before going home. Only appropriate dietary recommendations were given to the control group 1. The recommended foods included an age-appropriate, readily available, high-energy, adequate amount of essential micronutrients, and were given a lactose-restricted diet. Breastfeeding continued. Foods such as yoghurt, cereal, meat, fish, eggs, bananas and fresh fruit juice were offered to those who took the supplement. Frequent, small feedings were recommended to the child every three or four hours. Group 2 was given a single probiotic containing bifidobacterium breve (BR3), bifidobacterium bifidum (BF3), bifidobacterium infantis (BT1) and bifidobacterium longum (BG7) strains 5x108 cfu for 10 days. Group 3 was given zinc suspension 20 mg/day for 10 days, and group 4 was given probiotics and zinc. The patients were called for check-up on the 5th day, and they were questioned about the treatment methods they had used, the number of daily diarrhoea and vomiting, and possible side effects. Children were evaluated in the ED observation room and were not hospitalised. The percentiles and z-score of weight, height and body mass index (BMI) were calculated using the WHO Anthroplus v 1.0.4 software.[7]

Demographic data of the patients, admission complaints, physical examination findings, dehydration degrees, and laboratory examinations were recorded.

Fresh stool was examined in terms of erythrocytes, leukocytes, parasite cysts, trophozoites and eggs. Adenovirus, rotavirus, amoeba antigen and stool culture were evaluated in the stool samples taken. The presence of rotavirus, human adenoviruse (HAdV), giardia (G.) lamblia and entamoeba (E.) histolytica/dispar agents in stool samples was investigated by the enzyme immunoassay (EIA) method using the stool micro enzyme-linked immunosirbent assay (ELISA). The antigenic structures of the agents were studied on the Triturus (Biomerioux, France) device in accordance with the manufacturer's instructions, using RIDASCREEN® (R-biopharm AG, Germany) commercial kits. The samples were kept in the refrigerator at 2-8°C until they were studied on the same day. Quality controls of EIA tests were performed using positive and negative controls in each run. Whole blood and biochemistry examinations of the patient were performed and recorded on the

registration form. Statistical analyses were performed using SPSS v. 22.0 software (Statistical Package for Social Sciences, Inc.). Before starting the research, priori power analysis was performed using Students t-test/Mann Whitney U test in independent groups and paired t-test/Wilcoxon signed rank test in dependent groups for our primary hypotheses, and in order to reach a minimum power of 80% with an error of α=0.05 (double test). As a result of the power analysis obtained by using the Cohen Effect size calculated according to the literature information, it was decided to take a minimum of 20 samples in the independent and dependent groups.

Data with normal distribution was reported as mean ± standard deviation, and data not showing normal distribution was reported as median (range). Comparisons of independent binary groups with normal distribution were made using t test, and analysis of variance (ANOVA) was applied to hypervariable groups. Mann-Whitney U test was used to compare two groups of data not showing normal distribution, whereas Kruskal-Wallis test was used to compare the median values of hypervariable and non-normally distributed groups. Mean values were used for continuous variables. For the comparison of frequencies and percentages of qualitative data, chi-square test and z-test were applied. Univariate regression odds ratio (OR) was presented with 95% confidence intervals (CI). p<0.05 was considered statistically significant.

Results

Of the 132 subjects, 79 (59.8%) were males. The overall mean age at admission was 27.5±3.6 months (range: 6-66 months). The mean number of stools per day at the time of admission was 7.1±2.0 (range: 4-14), mean number of vomiting was 1.6±0.94 (range: 0-5), mean Vesikari score was 7.9±1.8 (range: 4-12) and mean observation time in hospital was 5.2±1.0 hours (range: 3-7 hours). At the time of admission, 84 (63.6%) patients had moderate and 48 (36.4%) had mild dehydration, while 41 (31%) patients had fever ≤38 degrees. Of all the patients, only 35 (26.5%) were receiving breast milk.

At the time of discharge, there were 22 (16.7%) patients in group 1, 34 (25.8%) in group 2, 28 (21.2%) in group 3, and 48 (36.4%) in group 4. When the admission symptoms, such as diarrhoea (Figure-1), vomiting, Vesikari score, dehydration >5%, hospital observation times were

Table: Evaluation of demographic characteristics among the groups.

	Group 1 (n=22)	Group 2 (n=34)	Group 3 (n=28)	Group 4 (n=48)	p value
Demographic variables					
Age (months)	31.0(7-36) **	22.1(6-24)**	30.4(6-33) **	28.0(8-30,6)**	0.125
Gender (female/male)	15/7	12/22	10/18	16/32	0.340
Height z- score	-0.39±0.01*	-0.35±0.01*	-0.46±0.01*	-0.37±0.01*	0.960
Weight z- score	-0.18±0.07*	-0.21±0.01*	-0.31±0.01*	-0.08±0.16*	0.742
BMI z- score	-0.06±0.01*	-0.02±0.01*	-0.03±0.01*	-0.04±0.01*	0.962
Clinical/Research Outcomes					
Admission diarrhoea number	6.8±0.3*	7.8±0.21*	8.07±0.29*	9.1±0.33*	<0.001
Admission vomiting	1.36±0.15*	1.64±0.16*	1.35±0.38*	2.04±0.15*	0.005
Vesikari score	6.5±0.22*	7.5±0.31*	7.4±0.31*	9.1±0.22*	<0.001
Dehydration (>5%)	10 (45.4%)	21 (61.7%)	16 (57.1%)	37 (77%)	0.059
Fever (>38º)	2 (9%)	12 (35%)	9 (32.1%)	18 (62.5%)	<0.001
Observation time (hours)	4.5±0.9	5.4±0.8	5.0±0.9	5.4±1.07	0.001
Duration of the termination of diarrhoea	84.5±10.7*	73.05±6.8*	80.1±10.3*	43.5±9.6*	<0.001
Sodium, mmol/L	136.3(129-145) **	136.4(130-140)**	136.7(130-139)**	136.4(133-141) **	0.933
Potassium, mmol/L	4.3±0.47*	4.4±0.63*	4.1±0.48*	4.3±0.50*	0.154
Urea, mg/dL	20.5±1.9*	18.7±1.4*	19.0±1.54*	22.6±1.1*	0.141
Creatinine, mg/dL	0.45±0.01*	0.44±0.01*	0.45±0.009*	0.45±0.01*	0.884
Glucose, mg/dL	90.8(73-112)**	89.2(67-110)**	89.7(63-117)**	91.1(56-114) **	0.958
pH	7.36±0.036	7.36±0.045	7.34±0.06	7.35±0.051	0.295
HCO3, mmol/L	21.7±1.23*	21.1±1.3*	21.07±1.26*	21.2±1.4*	0.429
Lactate, mmol/L	1.60±0.54*	1.50±0.34*	1.66±0.50*	1.57±0.41*	0.670
White blood cell, 103/µL	11.9±3.2*	10.3±3.4*	9.05±3.3*	10.9±3.46*	0.210
Platelets, 103/µL	351.1(220-410) **	384.5(196-420) **	340.6(167-426)**	359.8(210-432)**	0.249
Haemoglobin, g/dL	11.6±1.07*	11.4±1.02*	11.4±1.2*	11.7±1.2*	0.727

Group 1: control, Group 2: probiotic, Group 3: zinc, Group 4: zinc+probiotic, p<0.05.

* Normally distributed ** Not normally distributed.

BMI: Body mass index, pH: Potential hydrogen, HCO3: Bicarbonate.

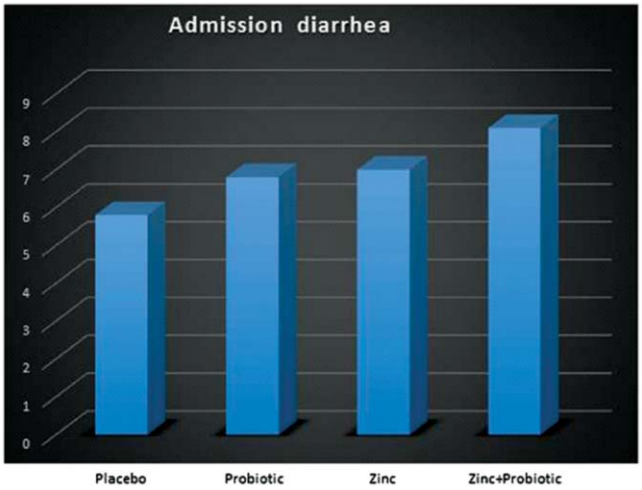

Figure-1: Evaluation of the number of diarrhoea among the groups at the time of admission.

compared, significant difference was found in group 4 patients (Table). The mean duration time to diarrhoea termination was 84.5±10.7 hours (range: 79-89 hours) in group 1, 73.05±6.8 hours (range: 70.5-75.4 hours) in group 2, 80.1±10.3 hours (range: 76-84 hours) in group 3, and 43.5±9.6 hours (range: 46-48 hours) in group 4. Group 4 outcome was statistically significant (p<0.001) (Figure-2).

When the duration of the termination of diarrhoea of group 1 and other groups was compared, no significant difference was found with group 3 (p=-.138), while a significant difference was found with group 2 (p=0.001) and group 4 (p<0.001). When groups 2 and 3 were compared, the duration of the termination of diarrhoea was significantly shorter in group 2 (p=0.006). No side effect in respect of the administered treatment regimen was observed.

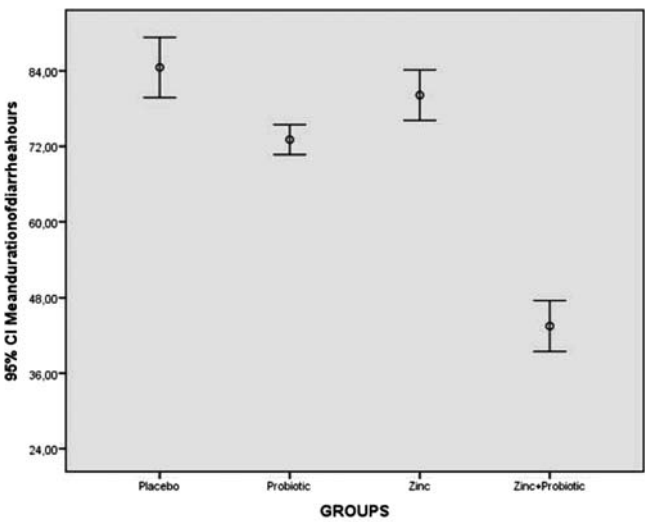

Figure-2: Comparison of the duration till diarrhoea termination among the groups.

Rotavirus antigen was found positive in 40 (30.3%) patients, adenovirus antigen in 3 (2.3%), and amoeba antigen in 3 (2.3%). No growth of giardia was detected in stool culture of any patient.

When the groups were compared in terms of gender, mean age, height z-score, weight z-score, BMI z-score, haemoglobin (Hb), white blood cell (WBC), neutrophil, thrombocyte, urea, creatinine, glucose, sodium, potassium, chlorine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood potential hydrogen (pH), bicarbonate (HCO3) and lactate levels, no statistically significant difference was found (p>0.05).

Rotavirus positivity in stool tests was detected in 13.6% patients of group 1, 35.2% group 2, 21.4% group 3, and 39.5% group 4. Patients with adenovirus 3 (6.25%) and amoeba antigen positivity 3 (6.25%) were found in group 4.

Discussion

To the best of our knowledge, the current study is the first to evaluate control, zinc, probiotic, and combined (zinc+probiotic) therapy in children.

According to the WHO, ORS, oral nutrition and zinc supplements are recommended in the treatment of diarrhoea.[4] With regards to the health of the children, it has been recognised by the WHO as an effective and cost-effective treatment in addition to ORS. Some guidelines in high-income countries (HICs) recommended additional interventions, such as probiotics, racecadotril and smectite, and/or did not recommend the use of zinc.[1] In developing countries, zinc supplementation has shown a significant reduction in the duration, severity and persistence of diarrhoea. Furthermore, zinc may improve immune status, intestinal permeability, epithelial and enzymatic functions, and transport of electrolytes.[8] In randomised controlled trials (RCTs) conducted in developing countries, the efficacy of zinc in the treatment of acute diarrhoea in children has been shown.[9] In a study involving 2002 children (2-59 months) in developing countries, Brazil, Ethiopia, Egypt, India and the Philippines, a decrease in diarrhoea has been reported since the third day of treatment with zinc use (20 mg/day for 2 weeks).[10] There is poor evidence for zinc use in children who are not undernourished. Its use has no proven benefit in European children or children with AGE generally living in developed countries.[11] However, in areas where zinc deficiency is rare, no benefit of zinc use has been documented.[12]

In a study in Turkey, the mean duration of diarrhoea in children with acute diarrhoea was 3.02±2 days in the zinc

group and 3.67±3.2 days in the control group (p>0.05).[13] The current study also had similar findings as there was no statistical significance in terms of the duration of the termination of diarrhoea. This period was approximately 0.18 days. According to a Cochrane meta-analysis, zinc supplementation could shorten the mean duration of diarrhoea by about half a day in children older than six months.[12] In the current study, the absence of a statistical difference in the patients who received zinc in the treatment of AGE compared to the control group was evaluated as the absence of malnutrition in the children receiving the treatment.

There may be difference when a few strains (single or in combination) are evaluated for the efficacy of probiotics for the management of AGE in children. Although it was reported in studies that Bacillus clausii strains decreased the duration of diarrhoea by 9.12 hours,[14] no significant difference was found between the probiotic group and the placebo group in terms of the mean duration of diarrhoea with L. helveticus R0052 and L. rhamnosus R0011 strains.[15] It was reported that the diarrhoea phase decreased by very low certainty of evidence in patients receiving probiotics in treatment with L. rhamnosus 19070-2 and L. Reuteri DSM (Deutsche Sammlung von Mikroorganismen) 12246 strains.[16] The total duration of diarrhoea was found to be significantly shorter in patients who received bacillus mesentericus TO-A (kindly provided by Dr. G. Seo, Toa Pharmaceutical Co., Ltd.), enterococcus faecalis T-110, and clostridium butyricum TO-A strains.[17] In a meta-analysis, a 0.85 day decrease in the duration of diarrhoea was reported with the use of LGG as a probiotic compared to placebo.[18] A systematic study showed that saccharomyces boulardii reduced the duration of diarrhoea by 1.1 days compared to the control group.[19] In some clinical treatment guidelines, the use of selected probiotic strains is encouraged.[1] The use of LGG as an effective treatment in addition to ORS is officially recommended in Australian guidelines.[20] Guidelines from India state that probiotics are effective in developed regions, but are not used in India due to the lack of supporting evidence in developing environments.[20] An analysis[21] found that in studies performed with probiotic (L. casei, L.plantarum, L. rhamnosus, B. lactis, and prebiotics) zinc and the control group, probiotic and zinc significantly decreased the duration of diarrhoea.

In the current study, when compared with the control group, probiotic treatment was found to reduce the duration of diarrhoea by 0.5 days and this was statistically significant. When examined together with studies cited above, it is thought that each probiotic should be evaluated separately.

It has been reported that rotavirus diarrhoea responds better to the treatment of probiotics, and LGG is an effective probiotic.[22]

In the current study, the viral agent was determined as the cause of diarrhoea in 43(32.5%) patients. Rotavirus antigen was detected in 40(30.3%) patients. The rotavirus antigen was found positive in 35.2% patients in group 2 and 39.5% in group 4. This was similar to other studies.[23]

In the current study, the best response was obtained with probiotic and zinc combination therapy, which is similar to literature.[11] Maragkoudaki et al. showed that in paediatric patients, the use of both L. reuteri DSM 17938 and zinc-supplemented ORS was able to significantly reduce the severity of diarrhoea on the second day.[24] A prospective study of 50 paediatric patients reported that probiotics and zinc supplementation showed benefit in paediatric patients with acute diarrhoea secondary to pneumonia.[25] Studies have shown that oral zinc supplementation in addition to probiotics can reduce the duration and severity of acute diarrhoea in children.[21]

There are some limitations to the current study, like a small sample size raised from a single centre. Besides, plasma zinc concentrations were not measured, and there was no long-term follow-up.

Prospective comparative studies with a combination of zinc and probiotic organisms are required to better define treatment duration to be recommended and dose for each child with AGE.

Conclusion

The efficiency of combined treatment with probiotics and zinc was found to be significantly better in the treatment of childhood acute gastroenteritis.

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