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Saccharomyces boulardii plus azithromycin is superior to azithromycin alone in reducing the duration of diarrhea in children with acute colitis: a double-blind randomized placebo-controlled trial

Mitra Ahmadi[1], Neda Mohtasham[2], Ahmad Shamsizadeh[3], Hazhir Javaherizadeh[4*], Bahman Cheraghian[5], Masumeh Alizadeh[2]

[1]Department of Pediatric Gastroenterology, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Department of Pediatrics, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Pediatric Infectious Disease, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Alimentary Tract Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Department of Biostatistics, Faculty of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

***Correspondence to**
Hazhir Javaherizadeh, Email: Hazhirja@yahoo.com, Hazhirja@ajums.ac.ir

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Abstract

Introduction: Diarrheal disorders remain a major disease burden throughout the world in pediatrics that remains a health problem. Several treatment methods have been proposed to treat diarrhea, however each of them has some problems.
Objectives: The aim of this study was the evaluation the effect of oral *Saccharomyces boulardii* on the duration and severity of colitis.
Patients and Methods: This randomized clinical trial study included ninety-four patients with acute colitis were enrolled. The children were divided randomly into case and control groups. The control group received supportive treatment including intravenous or oral fluid therapy (ORS solution), antibiotic treatment with azithromycin suspension, and zinc sulfate syrup daily for five days. In addition to the mentioned treatments, the intervention group received *S. boulardii* as a probiotic capsule. Then, the duration and severity of diarrhea based on the Vesikari score were evaluated for all the patients for five first days.
Results: The mean of Vesikari score after the first day in both groups was similar, while after the third and fifth day in the probiotic group this score was lower than the control group (5.11 ± 1.73 versus 6.13 ± 2.25, P=0.031 and 2.36 ± 1.16 versus 4.28 ±1.19, P<0.001, respectively). Furthermore, the number of diarrhea per day in the probiotic group was significantly lower after the first day in contrast to the control group, which remains significant at the end of the fifth day (2.32 ± 0.51 versus 2.83 ± 1.23, P=0.047). Moreover, we found that the diarrhea duration (P<0.001), fever duration (P=0.029), and duration of hospitalization (P=0.006) were statistically lower in the case group as compared to the control.
Conclusion: *Saccharomyces boulardii* had a beneficial effect as a probiotic agent in reducing the severity and duration of diarrhea, which could be beneficial for the treatment of colitis.
Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20161026030525N2); https://www.irct.ir/trial/24229; ethical code: IR.AJUMS.REC.1395.54.

Introduction

Diarrhea remains a major disease burden throughout the world among children, which is the second cause of mortality in children. Diarrhea is defined as three or more loose or watery stools in 24 hours and acute diarrhea is less than 14 days, and persistent is defined as 14 days or more (1). Therefore, definitions of diarrheal episodes are usually based on the duration of symptoms rather than etiology. In a systematic review by Johnston et al, multiple definitions of diarrhea and resolution were introduced (2). Acute diarrhea caused by pathogens may induce colitis with features of gastroenteritis, bloody stool, or severe intra-abdominal infections (3). Another suggested method for the treatment of diarrhea is probiotics. A probiotic is a living microorganism that is beneficial for the host.

Key point

Oral *Saccharomyces* can be added to azithromycin in the treatment of infectious colitis. Duration of diarrhea, duration of fever, and duration of hospitalization were lower in the group who were treated with azithromycin and *Saccharomyces boulardii* compared to azithromycin alone.

Different mechanisms such as antibacterial action (4), degradation of toxin (5), and bacterial adherence to the probiotics are the suggested mechanisms (6). Few clinical trials were conducted about the effects of probiotics in acute infectious diarrhea, therefore, we decided to evaluate and compare the duration of diarrhea after oral probiotic treatment in children with acute colitis.

Objectives

The aim of this study was to compare *Saccharomyces boulardii* plus azithromycin versus azithromycin alone in the treatment of acute colitis.

Patients and Methods

Target group

This double-blind randomized placebo-controlled clinical trial was carried out in the pediatrics department of Ahvaz Abuzar children's hospital, southwest of Iran from November 2019 to May 2020. The duration of diarrhea and other healing parameters of patients receiving oral probiotics (intervention group) were compared to patients receiving traditional treatment (control group). Inclusion criteria consisted of children referred to emergency and pediatrics department with acute colitis with diarrhea manifestation, parents who signed a consent form to participate in the study, patients with fever and watery stools more than three times a day and less than 72 hours after the onset of the disease (7) with dysentery or more than five white blood cells and any number of red blood cells in the stool test (consider as colitis), and aged 3 months to 14 years. Exclusion criteria consisted of patients with immunodeficiency, severe abdominal distension, coexisting acute systemic illnesses (eg, sepsis and pneumonia), an underlying disorder with inflammatory bowel disease or clinical evidence of chronic disease (eg, chronic liver disease), a history of surgical operation of the gastrointestinal tract, antibiotics or probiotics use in the two weeks preceding starting therapy, oral intolerance or lack of response to treatment that needs for antibiotics other than azithromycin. Azithromycin was selected according to the result of the local studies for antibiotic resistance. We also excluded patients with uncompleted data.

Study design

One hundred patients with acute colitis, who had been diagnosed by pediatric specialists and based on clinical and para-clinical findings and inclusion and exclusion criteria were included. The study flowchart is shown in Figure 1.

The participants were randomly allocated into two groups using a block randomization procedure with matched subjects in each block based on gender and age. Ninety-four patients completed the study; 47 from

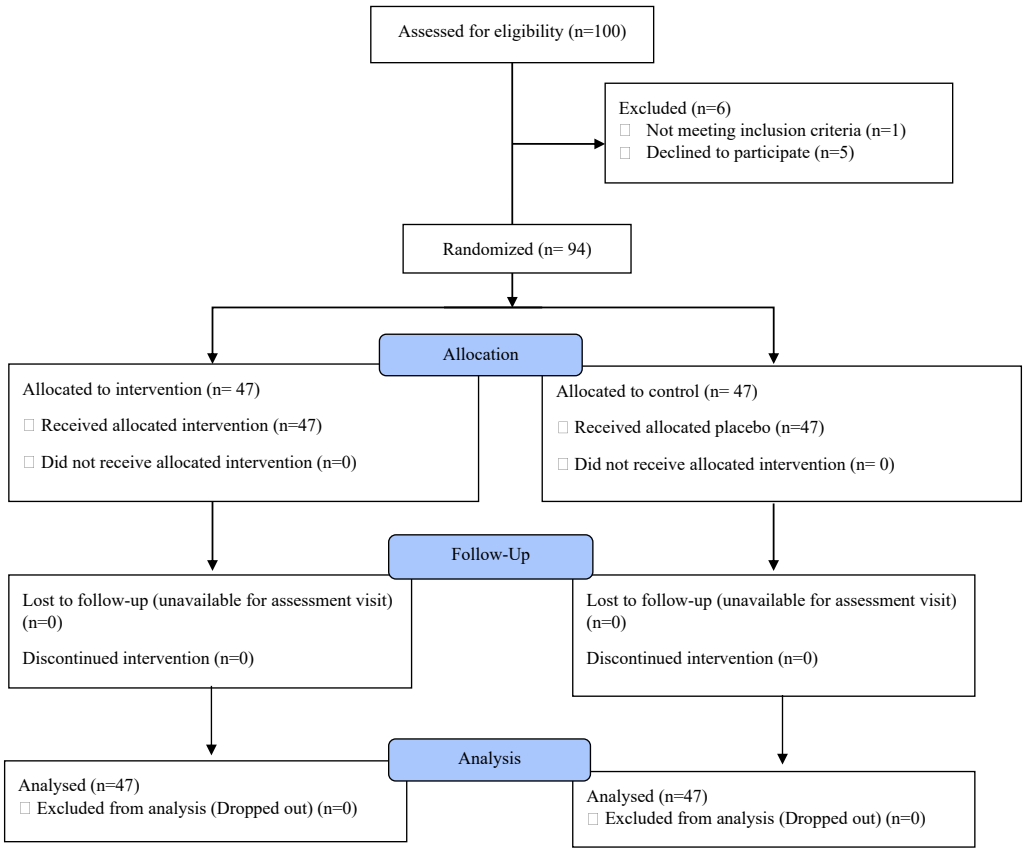

Figure 1. CONSORT flowchartof the study.

the intervention group and 47 from the control group. After obtaining informed consent, eligible patients were enrolled. The control group received supportive treatment including intravenous or oral fluid therapy (oral rehydration solution), antibiotic treatment with azithromycin suspension (Azirosin, Tehran Shimi Pharmaceutical Company) with a dosage of 12 mg/kg on the first day and then 6 mg/kg daily and the duration of treatment was five days and received 20 mg of zinc sulfate syrup daily (Alborz Daru Pharmaceutical Company). In addition to the mentioned treatments, the intervention group received *S. boulardii* as a probiotic capsule under the brand name Yomogi (250 mg) (Ardeypharm GmbH, German). Children over three months receive a 250 mg capsule every 12 hours for up to five days (8).

The control group received the placebo in the form of capsules similar to Yomogi capsules in shape and color (containing starch from the German company Merck with code number 11886) but without *S. boulardii*. Probiotic powders and placebo were similar in appearance, taste, and smell. Stool samples were taken for stool exam and stool culture and also blood sample for leukocytosis or leukopenia or eosinophilia was taken from all patients. From randomization to the end of the 5-day treatment period, parents were asked to record the following clinical parameters in a subject diary: the total number of stools daily and diarrhea or fecal consistency, constipation, vomiting, the total volume of oral rehydration solution taken during the day, the date and time of the first semisolid stool. Some other clinical parameters were evaluated by the physician according to the following: appetite and daily intake, body-weight change, bloating or abdominal distension, abdominal pain, colic pain, and fever which were also assessed. Moreover, the severity of clinical symptoms was recorded based on Vesikari score (9, 10) (Table 1).

Data analysis

Data were analyzed and reported only for patients with completed information. Statistical analysis of data was done using SPSS version 22 software (SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare qualitative variables between groups. Kolmogorov-Smirnov test, student *t* test, Mann-Whitney U test, Wilcoxon, ANOVA were used for data analysis. The two-tailed *P* value of less than 0.05 was considered significant.

Results

Demographic features in terms of age ($P=0.628$) and gender ($P=0.836$) in both probiotic and control groups were similar (Table 2). Six patients were dropped out and finally, 94 patients completed the research (Figure 1). Before the intervention, studied variables including the number of diarrhea per day and Vesikari score did not show a significant difference between the groups ($P>0.05$).

Mean Vesikari score after the first day in both groups was similar, while after the third and fifth day in the probiotic group were lower than the control group (5.11 ± 1.73 versus 6.13 ± 2.25, $P=0.031$ and 2.36 ± 1.16 versus 4.28 ±1.19, $P<0.001$, respectively). The number of diarrhea per day in the probiotic group was significantly lower after the first day in contrast to the control group, which remains significant at the end of the fifth day (2.32 ± 0.51 versus 2.83 ±1.23, $P=0.047$). As shown in Table 1, a significant interaction effect between time and group on all outcome measures was observed in the terms of the number of diarrhea ($F(1, 92) = 15.39$, $P<0.001$) and Vesikari score ($F(1, 92) = 4.05$, $P=0.007$). Diarrhea duration ($P<0.001$), fever duration ($P=0.029$), and duration of hospitalization ($P=0.006$) were significantly lower in the probiotic group as compared to the control ($P<0.05$; Table 1).

Discussion

Acute diarrhea is an important cause of childhood health problem especially in third world countries (11). Several types of drugs were recommended to reduce the duration of acute diarrhea (12). Our study evaluated the clinical effectiveness of probiotic products on acute diarrhea. According to our results, *S. boulardii* can reduce the severity of diarrhea with statistical significance as compared to individuals in the control group.

Our results were similar to the results of previous studies (13-16). Moreover, Vesikari score improved under probiotic colonization, which contains different parameters

Table 1. Vesikari clinical severity scoring system parameters and scores

Parameter	1	2	3
Diarrhea			
Maximum number of stools per day	1-3	4-5	≥6
Diarrhea duration (day)	1-4	5	≥6
Vomiting			
Maximum number per day	1	2-4	≥5
Vomiting duration (day)	1	2	≥3
Maximum body temperature (℃)	37.1–38.4	38.5–38.9	≥39.0
Severity of dehydration (%)	N/A	1–5	≥6
Treatment	Rehydration	Hospitalization	N/A
Severity rating scales	<7 (mild)	7–10 (moderate)	≥11(severe)

Table 2. Patient demographics and clinical characteristics

Variables	Groups		*P* value[a]	*df*, Error	F	Sig.[b]
	Probiotic (n=47)	Control (n=47)				
Age (year)	6.06 ± 2.78	5.91 ±2.99	0.628	-	-	-
Gender (male)	23 (48.9 %)	22 (46.8 %)	0.836	-	-	-
Number of diarrhea (per day)						
At admission	8.17 ± 2.75	8.55 ±2.16	0.217			
Day 1	6.53 ± 2.34	7.57 ±1.7	0.038	(1, 92)	15.39	<0.001
Day 3	2.72 ± 1.41	4.51 ±2.5	0.001			
Day 5	2.32 ± 0.51	2.83 ±1.23	0.047			
Vesikari score						
At admission	10.53 ± 2.52	10.06 ±2.28	0.408			
Day 1	6.77 ± 2.36	7.15 ±2.65	0.404	(1, 92)	4.05	0.047
Day 3	5.11 ± 1.73	6.13 ±2.25	0.031			
Day 5	2.36 ± 1.16	4.28 ±1.19	<0.001			
Diarrhea duration (day)	2.19 ± 1.22	3.83 ±2.2	<0.001	-	-	-
Fever duration (day)	2.34 ± 0.98	2.77 ±0.89	0.029	-	-	-
Duration of hospitalization (day)	2.21 ± 0.69	2.51 ±0.505	0.006	-	-	-

[a] Comparison between two group of study for each day separately.
[b] Total comparison for day 1, day 3, and day 5 for both group.

including diarrhea parameters, vomiting parameters, body temperature, the severity of dehydration, and treatment. Probiotics also reduced the duration of fever after the start of the treatment, as well as the reduction in duration of hospitalization.

The study conducted by Souza and Jorge (17) showed no beneficial effect of probiotics on the course of diarrhea. The species of probiotics, the dosage, or antibiotics therapy may reduce the anaerobic bacteria of the intestinal flora.

The study by Allen et al showed that probiotics reduced the duration and severity of diarrhea(1). Furthermore, Huang et al (18) have shown that bacterial probiotic therapy shortens the duration of acute diarrheal illness in children. Mourey et al (19) have shown that probiotics in children with acute diarrhea were shown effective in decreasing the severity and duration of diarrhea in children.

Promotion of gut mucosal barrier integrity, anti-pathogenic effect as well as modulation of host immunity may be the effect of *S. boulardii* (12, 20). Furthermore, some studies showed an approximately one day faster recovery from diarrhea with *S. boulardii* (21-25). *S. boulardii* may be beneficial for the treatment of acute colitis in children.

Conclusion

This study showed the beneficial effects of *S. boulardii* as a probiotic agent in reducing the severity and duration of diarrhea. However, more studies are recommended for better results.

Limitations of the study

This study was a single-center and limited sample size. Further multi-centric studies on this subject recommend.

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Authors' contribution

MiA, NM, HJ and AS were the principal investigators. MA, HJ and BC wrote the draft of the manuscript. MA, NM, HJ and MiA were included in data collection. HJ and BC analyzed data. MA, HJ and AS supervised research and reviewed the manuscript. All authors read and approved the content of the manuscript and confirmed the content and integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the ethical committee of the Ahvaz Jundishapur University of Medical Sciences (No. IR.AJUMS.REC.1395.54). Written informed consent was signed by parents or legal guardians.

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