Efficacy and safety of *Saccharomyces boulardii* in amebiasis-associated diarrhea in children

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SUMMARY: Savaş-Erdeve Ş, Gökay S, Dallar Y. Efficacy and safety of *Saccharomyces boulardii* in amebiasis-associated diarrhea in children. Turk J Pediatr 2009; 51: 220-224.

The efficacy and safety of adding *Saccharomyces boulardii* to antibiotic treatment for amebiasis-associated acute diarrhea in children were assessed in this study.

Forty-five children in Group I received only metronidazole per oral for 10 days while 40 patients in Group II received *S. boulardii* in addition to the same medication. The major outcomes investigated were duration of acute and bloody diarrhea, frequency and consistency of stools, resolution time of the symptoms, and the tolerance and side effects of the treatment regimens.

The median duration of acute diarrhea was 5 (1-10) days in Group I and 4.5 (1-10) days in Group II (p=0.965). The median number of stools on follow-up and duration of bloody diarrhea, fever, abdominal pain and vomiting were similar in the two groups. *S. boulardii* was well tolerated by the children and no side effects were recorded.

Addition of *S. boulardii* to antibiotic treatment of amebiasis-associated acute diarrhea in children does not seem to be more effective than metronidazole treatment alone.

Key words: amebiasis, children, diarrhea, Entamoeba histolytica, probiotics, Saccharomyces boulardii.

Human infection with *Entamoeba histolytica* (*E. histolytica*), known as amebiasis, is prevalent worldwide and is common in children in the developing world; endemic foci are particularly common in the tropics, especially in areas with low socioeconomic status and sanitary standards[1]. Approximately 10% of the world population is infected with *E. histolytica*, yet 90% of patients are asymptomatic. Of the roughly 50 million symptomatic cases occurring each year, up to 100,000 are fatal[2]. After malaria, it is likely that *E. histolytica* is the world's second leading protozoan cause of death[3].

Diarrhea is a major contributor to childhood mortality and morbidity in the developing world, causing an estimated 2.5 million deaths each year and long-term effects on growth and cognitive functions. One etiology of diarrheal disease is amebiasis, which is endemic in the developing world[4]. Both infection and diarrhea associated with *E. histolytica* are predominantly self-limited, but 19% of episodes of *E. histolytica*-associated diarrhea require metronidazole therapy[5].

Probiotics may present a viable new approach in the management of diarrhea. Numerous probiotic agents have been studied for the management of diarrheal diseases[6]. Probiotics, mostly lactic acid bacteria such as *Lactobacilli* and *Bifidobacteria*, but also the yeast *Saccharomyces boulardii* (*S. boulardii*), have been tried in a few double-blinded, randomized, placebo-controlled studies in children. The first pioneering study about the efficacy of *S. boulardii* in antibiotic-associated diarrhea in children was conducted in our institute by Erdeve et al.[7], and some other later studies confirmed the efficacy of the drug in prevention of diarrhea. Although there are several well-conducted meta-analyses available now, more researches are needed for a better understanding of probiotics in children, addressing issues such as the role of probiotics

in special diseases with acute diarrhea in children and the appropriate dose for these diseases. Most of the research on probiotics has been done in adults, and no consensus has been reached as to whether probiotics may be active in pediatric diarrhea[8].

Mansour-Ghanaei et al.[9] investigated the efficacy of *S. boulardii* in addition to antibiotics in acute amebiasis in adults. As far we know, this is the only study published in the literature, and there has not been any trial concerning probiotics in amebiasis-associated diarrhea in children. Amebiasis is more common and both the efficacy and safety of probiotics may differ in children; therefore, we aimed to investigate the efficacy and safety of *S. boulardii* for amebiasis-associated diarrhea in the childhood age group.

Material and Methods

Patients

The children aged from 1 to 15 years who presented with *E. histolytica*-associated diarrhea between January 2006 and April 2007 were enrolled in the study. In this open-prospective study, children with severe intercurrent illnesses who were treated by any other anti-diarrheal/antibiotics within two months, who were treated by probiotics within one week, were severely malnourished, or had chronic disease/immune deficiency were excluded. An informed consent was obtained from the parents of every child who was enrolled in the study. The study was approved by the Ethical Committee of our institution.

E. histolytica infection was diagnosed by compatible clinical presentations (acute diarrhea, fever and abdominal pain) and presence of *E. histolytica* trophozoite engulfing red blood cells in diarrheal stool by light microscopy (fresh and trichrome staining)[3,10]. All microscopic examinations were done by an experienced microscopist during the daytime. Stool cultures were also obtained from all patients as routine evaluation of dysenteria. Diarrhea was defined as unformed stools of more than two per a 24-hour period[8]. Dysenteric diarrhea was defined by gross blood in the stools and/or microscopic stool examination showing red blood cells $\geq$1/high-power field[10].

Treatment

A total of 90 children were randomized into two groups. The 45 patients in Group I received metronidazole 30-50 mg/kg/day orally for 10 days (maximum: 500-750 mg), while the 45 patients in Group II received the same medication plus lyophilized *S. boulardii* (Reflor®, Sanofi-Synthelabo, France) 250 mg (includes 5,000,000 living microorganisms) orally once a day.

Analysis

The patients were evaluated for date of onset of diarrhea, number and consistency of stools and bloody diarrhea, and presence of vomiting, abdominal pain or fever. The major outcomes of the study were defined as the duration of acute diarrhea; daily record of frequency and consistency of stools and presence of bloody diarrhea; resolution time of vomiting, abdominal pain and fever during the treatment; and the side effects of the treatment. All data were recorded on a study record sheet during the 10 days of treatment by parents, and patients were reevaluated after 10 days. Two weeks after the cessation of treatment, all patients were invited back for *E. histolytica* cyst investigation in the stool.

Statistical analysis was performed by Student's t-test, chi-square test and Mann-Whitney U test, and a p value <0.05 was defined as significant.

Results

Ninety-six patients with diarrhea in whom *E. histolytica* was examined in their stool were included in the study. Six patients were excluded before the randomization due to: malnutrition[1], intercurrent disease[3], probiotic use in the previous week[1], and chronic disease[1]. Although both groups consisted of the same number of patients, 5 patients from Group II were excluded because of non-compliance to the study, and the completion rate for the study was recorded as 94.4%.

The demographic data including age, sex and clinical manifestations were similar in both groups and groups were comparable for baseline characteristics (Table I). There were no reported positive stool cultures for the patients. The median duration of acute diarrhea, bloody diarrhea and resolution time

Table I. Initial Clinical Manifestations in Both Groups

Patient characteristics	Group I (metronidazole)	Group II (metronidazole + *S. boulardii*)	p value
Age (years)	4.2±3.8	5.1±3.6	0.098
Sex (female/male)	20/25	19/21	0.778
Median duration (range) of diarrhea (day)	2 (1-15)	2 (1-7)	0.232
Median number (range) of stools/day	6 (3-30)	6 (2-20)	0.141
Median number (range) of vomiting/day	2.5 (1-15)	2 (1-15)	0.926
Rate of fever (n, %)	25/45 (55.6%)	21/40 (52.5%)	0.778
Rate of abdominal pain (n, %)	42/45 (93.3%)	39/40 (97.5%)	0.619

for symptoms including vomiting, fever and abdominal pain were not significantly different between groups (p>0.05) (Table II). There was also no significant difference in the frequency of diarrhea records on daily sheets between groups (p>0.05) (Fig 1). *S. boulardii* was well tolerated by all children and no side effect was recorded during the active treatment period. Differences in the efficacy of the drug on bloody diarrhea and cyst carrier rate were also not significant.

A probiotic is a living microorganism administered to promote the health of the host by treating or preventing infections owing to strains of pathogens. *S. boulardii* is a saprophytic yeast that is recommended for the prevention

Table II. Comparison of Groups for Median (Range) Resolution Time of Symptoms and Signs

	Group I (metronidazole)	Group II (metronidazole + *S. boulardii*)	p value
Duration of diarrhea (day)	5 (1-10)	4.5 (1-10)	0.965
Duration of bloody diarrhea (day)	2 (1-3)	2 (1-5)	0.486
Duration of vomiting (day)	1 (1-8)	1 (1-4)	0.322
Duration of fever (day)	1 (1-3)	1 (1-5)	0.250
Duration of abdominal pain (day)	2 (1-10)	3 (1-10)	0.054

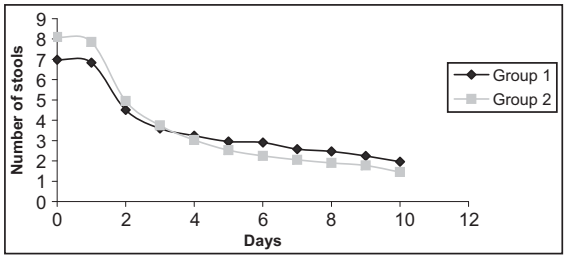

Fig. 1. Number of stools per day during the 10-day treatment period in both groups.

The rate of patients who were amebic cyst carriers in the two weeks after the cessation of the treatment was 8.8% (4/45) in Group I and 7.5% (3/40) in Group II (p=1.000).

Discussion

Our study, which was conducted in children, showed that *S. boulardii* addition to conventional treatment with metronidazole has no effect on the frequency and duration of diarrhea on follow-up during the active treatment period. and treatment of septic enteritis, especially diarrhea caused by *Clostridium difficile*[11]. There are some studies that have shown its efficacy in reducing the incidence of traveler's diarrhea[12], preventing the occurrence of diarrhea in acutely ill patients fed by nasogastric tube[13], and treatment of Crohn's disease[14]. The main field in which *S. boulardii* has been used is in the prevention of antibiotic-associated diarrhea, and some well-conducted meta-analyses have reported its proven efficacy and safety even in children[7,8,15]. The exact mechanism by which this yeast prevents or improves diarrhea is still unclear. Preclinical and experimental studies of *S. boulardii* have demonstrated an anti-inflammatory, antimicrobial, enzymatic, metabolic and antitoxinic activity of the agent. It has a trophic effect by enhancing the metabolic function of the mucosa. *S. boulardii* releases polyamines, which are implicated in stimulating the enzymatic activity of the colonic mucosa[16,17].

Although there are some meta-analyses about *S. boulardii* in the treatment of acute diarrhea in adults, the data about its efficacy in children

with acute diarrhea caused by different agents are not well analyzed and are insufficient. The pooled risk estimates in meta-analysis found probiotics to reduce the mean duration of diarrhea by only 13 hours in children[18].

Mansour-Ghanaei et al.[9] showed that co-administration of lyophilized *S. boulardii* in addition to conventional treatment for acute amebic colitis significantly decreased the duration of symptoms, including the stool frequency and duration of illness in adults. They proposed that lyophilized *S. boulardii* would be a useful addition to the treatment of acute amebic dysentery, and this effect may be due to its potential to restore the beneficial normal flora of the gut. The results in our study did not show significant decrease in duration of symptoms including diarrhea, vomiting, abdominal pain and fever, or in the rate of cyst carriers in patients who were given *S. boulardii* along with conventional treatment for acute amebic colitis.

The safety of probiotics should be considered for children. *S. boulardii* seems to be safe in children in this study and these data match with the other trials in the literature[6,8,18]. Although case reports of fungemia have been reported in the literature, no side effect occurred in patients enrolled in this study. It is reported that caution should be exercised for patients who are severely ill and receiving nutrition or antibiotics through a potentially open portal (catheter or nasogastric tube)[19,20]. As many of the trials did not report safety data or evaluate cost-effectiveness, these issues should also be considered in *S. boulardii* usage[18].

There are a few limitations of our trial. This was a pioneering study without a placebo-controlled group. We did attempt to obtain a placebo from the manufacturer of the drug but it was not possible. In a recent review by McFarland[18], it was reported that the type of controls did not significantly affect the efficacy in a meta-analysis concerning probiotics for the prevention and treatment of acute pediatric diarrhea. A second limitation concerns the diagnosis of amebiasis. Although observation of erythrophagocytic amoebae in dysentery in a symptomatic patient was reported to have a high predictive value for amebiasis, the common idea is that it is essential to perform stool-antigen enzyme linked immunosorbent assay (ELISA) or polymerase chain reaction for a more accurate diagnosis[10,21,22]. It is hard to say whether these more specific and sensitive tests are commonly and widely used for *E. histolytica*-suspected dysenteric patients in our country.

In summary, based on our experience related to this trial, we conclude that *S. boulardii* is not useful for the treatment of amebiasis-associated diarrhea in children. Addition of *S. boulardii* to the usual treatment of acute amebiasis does not efficiently improve clinical signs or symptoms of the disease. However, this trial is a pioneer study and placebo-controlled randomized trials are required to confirm these data.

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