Clinical Efficacy Comparison of *Saccharomyces boulardii* and Yogurt Fluid in Acute Non-Bloody Diarrhea in Children: A Randomized, Controlled, Open Label Study

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Abstract. The purpose of this trial is to evaluate the clinical efficacy and cost/effectiveness of *Saccharomyces boulardii* compared with yogurt fluid (YF) in acute non-bloody diarrhea in children. This randomized, prospective open-label clinical trial includes 55 children (36 boys, 19 girls; mean age 21.2 ± 28.2 months). Group A ($N = 28$) received lyophilized *S. boulardii* and group B ($N = 27$) received YF. The duration of diarrhea was shorter with *S. boulardii* but the hospital stay was reduced with YF, although these differences were not significant. However, diarrhea had resolved in significantly more children on day 3 in the *S. boulardii* group (48.5% versus 25.5%; $P < 0.05$). In outpatient cases, yogurt treatment was cheaper than *S. boulardii* whereas in hospitalized patients, treatment cost was similar. In conclusion, the effect of daily freshly prepared YF was comparable to *S. boulardii* in the treatment of acute non-bloody diarrhea in children. The duration of diarrhea was shorter in the *S. boulardii* group, expressed as a significantly higher number of patients with normal stools on day 3.

INTRODUCTION

Gastroenteritis of infectious origin remains a worldwide problem of healthcare with about four billion diarrheal episodes each year.¹ Diarrhea is defined as an increase in the frequency (more than 3 times a day), water content, and volume of stools. Treatment with oral rehydration solutions (ORS) has reduced significantly the incidence of mortality and morbidity caused by diarrhea but ORS does not shorten the duration of diarrhea, does not change the consistency of the stools, and it does not normalize gastrointestinal flora.²

Probiotics are living microorganisms that survive in the gastrointestinal tract and, when ingested in sufficient large amount, confer a health benefit on the host. There is evidence that selected strains of probiotics decrease the duration of acute diarrhea.^{2–5} The best studied probiotics include some *Lactobacilli* species (*Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*) and *Saccharomyces boulardii*.^{4,5} Yogurt is a coagulated milk product that is the result of fermentation with *Lactobacillus bulgaricus* and *Streptococcus thermophilus* and its fluid shelters these probiotic microorganisms.⁶ In Turkey, yogurt is easily available and part of regular eating habits. This prospective study was designed to compare the clinical efficacy and cost/effectiveness of *S. boulardii* compared with yogurt fluid (YF) in acute non-bloody diarrhea in children.

PATIENTS AND METHODS

This randomized, prospective but open clinical trial was conducted in children (age 5 months–16 years) who were admitted with acute diarrhea to the Pediatric Department of Eskisehir Osmangazi University Hospital, Turkey. Acute diarrhea was defined as the presence of 3 or more liquid or loose stools per day lasting for less than 14 days.⁷ The exclusion criteria were: severely malnourished children (2nd and 3rd degree malnutrition defined according to the criteria described

by Waterlow⁸), antibiotic treatment during the preceding 7 days, known chronic uncontrolled intestinal disease such as celiac disease, pancreatic insufficiency, parasitic infestations, and bacterial diarrhea suspected by the presence of leukocyte and erythrocyte in stool examination in 2–3 hours of admission. All patients that were mild and moderately dehydrated⁹ were treated according to the World Health Organization recommendations with ORS and zinc supplements (10 mg/day in infants ≤ 6 months and 20 mg/day in patients > 6 months¹⁰).

Patients were randomized according to their patient ID number and enrolled in 2 groups. Patient with an odd ID-number composed group A and those with an even ID-number composed group B. Treatment was continued until diarrhea resolved. Group A received lyophilized *S. boulardii* (Reflor[®], Sanofi-Aventis, Turkey) (250 mg twice a day in children ≥ 2 years and 125 mg twice a day in children < 2 years of age) and group B received YF (a fluid extracted from Pinar[®] yogurt made by a ferment containing *Lactobacillus bulgaricus* and *S. thermophilus*, 10⁷ microorganism/100 mL, provided by manufacturer) (15 mL twice a day for children < 2 years and 30 mL twice a day for children ≥ 2 years of age). For the purpose of this study, the yogurt was freshly prepared daily and YF was prepared immediately. Yogurt fluid was prepared by filtering 200 grams of the commercialized yogurt through a special filter bag made from cambric, which resulted in approximately 60 mL of YF. Intake of any other fermented milk product, including yogurt itself, or any probiotics was forbidden in both groups. All patients were examined by 1 pediatric gastroenterologist on admission and re-evaluated every morning by the same doctor until resolution of diarrhea and discharge. Demographic data, nutritional status, dehydration stage, duration of diarrhea, number and consistency of the stools, duration and number of episodes of vomiting, and duration of hospitalization were recorded. Day 1 was defined as “24 hours of treatment.” Stool samples were examined for rotavirus (evaluated with rotavirus antigen test), bacteria, fungi, or protozoa. Traditional fecal cultures were performed for all study patients including *Salmonella*, *Shigella*, and *E. coli*. Protozoal or parasitological infections were evaluated with microscopic examinations.

The primary end point was the comparison of clinical efficacy (duration of diarrhea, hospitalization, and duration of

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vomiting) of *S. boulardii* and YF. Duration of diarrhea was defined according to Bristol Criteria; a score lower than 5 is described as normalization of stool.¹¹ The secondary end-point was the evaluation of the cost-effectiveness analysis of both interventions.

The study was approved by the institutional ethics committees and parents gave a written consent. Statistical analysis was performed with SPSS for Windows 13.0. Independent *t* test, χ^2 test, Mann-Whitney *U* tests, and Wilcoxon sign test were used for comparisons. Duration of diarrhea and diarrhea resolution at days 3 and 5 were studied in a per protocol (PP) analysis (including the data on the children that completed the study) and in an intention to treat (ITT) analysis (including the data of all the children who were eligible at the beginning of the study). *P* values of < 0.05 were considered statistically significant.

RESULTS

Sixty-seven consecutive children presenting with acute diarrhea (1–7 days, duration of diarrhea before admission; 2.38 ± 1.46 days) were prospectively evaluated between April 2007 and January 2009. Twelve children were excluded: 7 patients needed antibiotics due to complicating extraintestinal infection like urinary tract infection and pneumonia; 3 patients violated the fermented milk restriction; 1 patient was diagnosed with secondary hemophagocytic syndrome and died on the 15th day after admission; and 1 patient was diagnosed posteriorly with celiac disease. The data of 55 children (36 boys and 19 girls) ages 5–168 months (mean age 21.2 ± 28.2 months, 1–7 days duration of diarrhea before admission, 2.32 ± 1.41 days) were available for evaluation (per protocol), of whom 48 children were hospitalized and 7 were followed daily in the outpatient clinic by the same doctor (M.E.). Twenty-eight patients were allocated to group A (*S. boulardii* group) and 27 patients to group B (YF group). Demographic characteristics and nutritional status were comparable (Table 1). However, more patients were dehydrated in group B (Table 1). Rotavirus antigen was identified in 32 patients (16 in both groups). The remaining 23 patients had also a negative stool examination for *Shigella*, *Salmonella*, or any parasitic cyst or ova.

Although the duration of the diarrhea was shorter in group A, the statistical analysis showed no significant difference between group A and B, both with the PP and ITT analyses (4.54 ± 2.36 versus 4.81 ± 1.79 days; $P > 0.05$ (PP); 4.45 ± 2.46 versus 5.38 ± 3.14 days; $P > 0.05$ (ITT)). Normalization of stool consistency occurred in both groups nearly at the same moment (3.07 ± 2.01 days versus 3.07 ± 1.73 days;

$P > 0.05$ (PP)). At day 3, the per protocol analysis showed a resolution of diarrhea in 13 patients (46.4%) in group A and in 6 patients (22.2%) in group B ($P = 0.059$). However the intention to treat analysis showed a statistically significant result favoring *S. boulardii* over YF (16 patients (48.5%) versus 8 patients (25.5%); $P = 0.033$). At day 5, in the PP analysis, diarrhea had resolved in 20 (71.4%) in group A and 18 (66.7%) in group B ($P = 0.70$). But according to the ITT analysis, on day 5, diarrhea had resolved in 23 (69.6%) patients in group A and in 21 (61.7%) patients in group B ($P = 0.49$).

Regarding daily stool frequency change, a significant reduction in stool frequency was observed at day 1 with *S. boulardii*, whereas a significant reduction with YF was achieved at day 2. Stool frequency reduced from a mean of 8.18 ± 3.64 to 6.43 ± 3.97 at day 1 in the *S. boulardii* group ($P = 0.016$). On the other hand, in the YF group, stool frequency decreased from 7.93 ± 3.97 to 7.14 ± 3.90 at day 1 ($P = 0.139$) and to 6.22 ± 3.77 at day 2 ($P = 0.045$) (Figure 1). There was no difference among both groups in the duration of hospitalization (4.68 ± 2.37 versus 4.23 ± 1.72 days; $P = 0.45$) (PP).

Regarding the duration of emesis, it was shorter in the YF group but again statistically insignificant (1.42 ± 1.64 versus 1.33 ± 1.88 days, 95% confidence interval (CI): 1.04–0.85, $P = 0.84$, PP) daily. On day 1, a reduction of episodes of vomiting was observed in 14 patients (50.0%) in group A and in 17 patients (62.9%) in group B, which was a significant decrease in both groups (0.96 ± 2.40 ; 95% CI: 0.05–1.88; $P = 0.039$ versus 2.15 ± 2.54 ; 95% CI: 1.14–3.15; $P = 0.0001$).

A subgroup analysis was performed in the patients with rotavirus diarrhea. Thirty-two patients (16 in group A and 16 in group B) were infected with rotavirus. The duration of diarrhea was 5.37 ± 2.4 days in group A compared with 3.25 ± 1.7 days in group B (PP) ($P = 0.33$) or 5.47 ± 2.37 days in group A and 4.61 ± 1.68 in group B (ITT) ($P = 0.74$). There was no statistically significant difference in duration of hospitalization (5.13 ± 2.53 days versus 4.12 ± 1.62 ; 95% CI: –0.58–2.56) and normalization of stool consistency in rotavirus-infected patients (3.75 ± 1.94 versus 3.25 ± 1.69 ; 95% CI: –0.82–1.82) ($P > 0.05$ for both). A significant reduction of daily stool frequency was observed on day 3 in rotavirus infected patients in Group B (4.13 ± 4.63 ; 95% CI: 0.35–1.66, $P = 0.003$), whereas a significant reduction occurred only on day 5 in group A rotavirus infected patients (4.88 ± 5.11 ; 95% CI: 2.15–7.60; $P = 0.002$) (Figure 2). On day 3, the per protocol analysis, showed a resolution of diarrhea in 5 (31.3%) children with rotavirus in group A and in 3 (18.8%) in group B (18.8%) ($P = 0.41$). Intention

TABLE 1
Clinical and demographical findings of the study groups

	<i>S. boulardii</i> group (N = 28)	Yogurt group (N = 27)	<i>P</i>
Gender (M/F)	18/10	18/9	NS
Age (months)	24.4 ± 37.7	17.9 ± 12.5	NS
Malnutrition (%)	7 (25)	6 (22.2)	NS
Dehydration (%)	17 (60.7)	22 (81.4)	0.07
Positivity of rotavirus antigen test	16	16	NS
Cost of therapy (\$)	2.21 ± 1.18	0.35 ± 0.22	$P < 0.0001$
Total cost of hospitalization (\$)	443 ± 248	360 ± 249	NS

FIGURE 1. Daily change of stool frequency of study groups. *Y axis: mean of daily stool number.

FIGURE 2. Daily changes of stool frequency in rotavirus positive patients. *Y axis: Mean of daily stool number.

to treat analysis showed a resolution of diarrhea in 5 (29.4%) rotavirus infected children from group A (29.4%) and in 4 (22.2%) in group B ($P = 0.62$). At day 5, per protocol analysis showed resolution was observed in 9 (56.3%) patients in group A and in 12 (75.0%) in group B ($P = 0.26$). At day 5, the ITT analysis showed recovery in 9 (53%) children in group A and in 13 (72.2%) children in group B ($P = 0.23$) (Figure 3).

The cost of 30 mL yogurt is \$0.059, whereas the cost of 1 sachet of *S. boulardii* is \$0.388. In outpatient cases, yogurt treatment was cheaper than *S. boulardii* whereas in hospitalized patients, treatment cost was similar between 2 study groups because of the cost of hospitalization (Table 1).

DISCUSSION

In Europe, besides appropriate rehydration and patient education, probiotics are also advised in the management of acute diarrhea in childhood.³ Probiotics are live microorganisms that survive in the gastrointestinal tract and have a health benefit on the host. *S. boulardii* is a non-pathogenic probiotic yeast, which is naturally resistant to gastric acidity and antibiotics. Extensive research has shown a significant reduction of the duration of acute watery diarrhea of infectious origin.⁵ Also bloody diarrhea due to amebiasis in children is short-

FIGURE 3. Percentage of patients with resolution of diarrhea in both groups. ** Percentage of patients with resolution of diarrhea; *S. boulardii* versus YF (48.5% versus 25.5%; $P = 0.033$) with ITT analysis.

ened in comparison to placebo when *S. boulardii* is added to metronidazole.¹² Yogurt is a coagulated fermented milk product that is the result of fermentation with *L. bulgaricus* and *S. thermophilus* and its fluid shelters these probiotic microorganisms.⁵ The therapeutic dose of yogurt has been reported to be around 10^6 – 10^9 CFU of *Lactobacilli* and *Bifidobacteria*.^{13,14} The yogurt fluid used in this study was extracted from a commercially available yogurt (Pinar®, Pinar JSC, Eskisehir, Turkey) containing 10^7 colony forming unit (CFU) per 100 gram. *L. bulgaricus* and *S. thermophilus* that are used to ferment milk to yogurt, are considered to be probiotics and yogurt fluid shelters these probiotics (information provided by the manufacturer). Mixtures of *L. bulgaricus* and *S. thermophilus* and formulas supplemented with *S. thermophilus* have been shown to be beneficial in the treatment by decreasing the duration and frequency of non-bloody diarrhea in children and in the prevention of diarrheal episodes.^{15–17} Boudraa et al.¹⁸ compared the same formula, not-fermented and fermented with *L. bulgaricus* and *S. thermophilus*, in children with acute watery diarrhea. The yogurt feeding was associated with a 31% decrease in the median duration of diarrhea and a decrease in stool frequency in favor of the yogurt group.¹⁸ In a randomized controlled trial performed in 80 children, the authors reported an average mean duration of hospitalization of 2.7 days in the yogurt group, which was significantly (0.4 day) shorter than the control group, in whom only routine hospital treatment of diarrhea was applied.¹⁷ A meta-analysis performed by Van Niel et al.¹⁹ demonstrated a reduction in diarrhea duration of about 0.7 days with yogurt compared with placebo, with different protocols, and also showed reduction of stool frequency on second day of yogurt.

According to a meta-analysis, *S. boulardii* reduces the duration of diarrhea by approximately 1 day and leads to complete healing at day 3.^{5,20–23} In another Turkish study, Kurugol and Koturoğlu²² compared the effect of *S. boulardii* in 200 children and showed that duration of diarrhea shortened from 5.5 to 4.7 days, while the mean duration of hospitalization was shortened from 3.9 days to 2.9 days in *S. boulardii* treated patients. We also observed that diarrhea lasted approximately 4.5 day with *S. boulardii* treatment. In our study, compared with YF, *S. boulardii* did not shorten the duration of hospitalization.

This clinical trial is unique in terms of comparing YF with *S. boulardii*. We preferred YF because most of the ill children prefer to drink rather than to eat during an episode of acute diarrhea. It is easier for children to drink 30–60 mL fluid instead of eating 100–200 gr yogurt.

Previously, Gaon et al.²⁴ evaluated the efficacy of cow milk with *S. boulardii*. They randomized 89 children with persistent diarrhea to receive pasteurized cow milk alone, or supplemented with *Lactobacillus casei* and *L. acidophilus* or *S. boulardii* (10^{10} – 10^{12}) CFU. Both mix probiotic groups and *S. boulardii* reduced the duration of diarrhea compared with cow milk alone in patients infected with Shigella, *E. coli*, and Salmonella. There was no difference in the subgroup infected by rotavirus. We also could not find a difference in rotavirus infected patients. Although the duration of diarrhea shortened by approximately 2 days and the hospital stay duration was reduced about 1 day in the YF group compared with the *S. boulardii* group, these findings were not significant. In terms of vomiting, this study demonstrated an equal effect between *S. boulardii* and YF.

In regard to the duration of diarrhea (4.5 versus 4.8 days) and hospitalization days (4.7 versus 4.7 days), the 2 were

comparable. However, regarding the number of children with resolution of diarrhea on day 3, efficacy tended to be greater in the *S. boulardii* group for the per protocol analysis. However, the intention to treat analysis showed a statistically significant difference favoring *S. boulardii* over YF for the number of patients with normal stools in day 3 (16 patients (48.5%) versus 8 patients (25.5%); $P = 0.033$).

Compared with *S. boulardii*, YF can be easily made at home and needs no prescription. But YF is much more difficult to administer in hospitalized patients. In our hospital settings, yogurt was freshly prepared and directly delivered from the manufacturer to the hospital and YF was prepared daily. But one must realize that an ideal probiotic culture should contain 10^6 – 10^8 CFU viable cells per milliliter and that most of this fermentative bacteria's have a poor viability.²⁵ We could not perform a daily bacterial count from YF. But the manufacturer provided that 100 mL YF fluid contains 10^7 microorganism at the end of their shelf life. But still because of the lack of data on viability of the bacteria in YF in different environmental conditions, the results of this trial cannot be extrapolated to the normal daily situation, because it cannot be excluded that the YF of not day-fresh yogurt may contain fewer viable probiotic microorganisms.

In conclusion, the effect of daily freshly prepared YF was comparable to *S. boulardii* in the treatment of acute non-bloody diarrhea in children. Although the overall duration of diarrhea in both groups was not different, normalization of stool composition and frequency was more rapid in the *S. boulardii* group. On day 3, significantly more patients were cured in the *S. boulardii* group than in the YF group. These results should be confirmed with a large scale placebo controlled clinical trial evaluating the efficacy of commercialized yogurt.

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