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ORIGINAL ARTICLE

Effects of *Saccharomyces boulardii* in children with acute diarrhoea

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Abstract

Aim: Certain probiotic agents, e.g. *Lactobacillus* GG, have shown efficacy in clinical trials for the treatment of acute childhood diarrhoea, but few studies have examined the effect of *Saccharomyces boulardii*. We evaluated the effect of *S. boulardii* in children with acute diarrhoea. *Methods:* Two hundred children were randomized to receive *S. boulardii* in a granulated form in a daily dose of 250 mg (*S. boulardii* group) or placebo (placebo group) for 5 d. Clinical and demographic characteristics on admission were similar between the study groups. *Results:* The medians of the average stool frequency after the second day of the treatment were significantly lower in the *S. boulardii* group than in the placebo group ($p = 0.003$). The duration of diarrhoea significantly reduced in the *S. boulardii* group compared with the placebo group (4.7 vs 5.5 d, $p = 0.03$). The effect of *S. boulardii* on watery diarrhoea became apparent after the second day of the treatment. The duration of hospital stay was shorter in the *S. boulardii* group than in the placebo group (2.9 vs 3.9 d, $p < 0.001$). Four children from the placebo group versus only one child from the *S. boulardii* group had persisting diarrhoea.

Conclusion: The placebo-controlled study suggested that *S. boulardii* significantly reduced the duration of acute diarrhoea and the duration of hospital stay. *S. boulardii* seems to be a promising agent for the amelioration of the course of acute diarrhoea in children when used therapeutically.

Key Words: *Childhood diarrhoea, probiotics, Saccharomyces boulardii*

In recent years, education and the widespread use of oral rehydration therapy have reduced the number of diarrhoeal deaths in Turkey. However, the morbidity rate for diarrhoea still remains high, placing an enormous burden on the healthcare system. Morbidity and hospitalization rates might substantially be reduced with improved case management and an increased emphasis on patient education. Probiotics may present a viable new approach in the management of diarrhoea. Certain probiotic agents, such as *Lactobacillus* GG, have been shown in several studies to have a beneficial effect in children with acute diarrhoea [1–5]. A recent study demonstrated that other probiotic strains, e.g. *L. reuteri* and *L. rhamnosus*, provided a significant reduction in the duration of diarrhoea and in the duration of hospital stay in children with acute gastroenteritis [6].

Several studies have demonstrated that *Saccharomyces boulardii* has proved to be effective in the prevention of antibiotic-associated diarrhoea [7, 8]. *S. boulardii* may also be useful in preventing relapse of Clostridium difficile infection [9]. However, there is little evidence from studies that examined the effect of *S. boulardii* on acute childhood diarrhoea [10–13]. Therefore, we designed a double-blind, placebo-controlled study to evaluate the efficacy and safety of *S. boulardii* in children with acute diarrhoea.

Patients and methods

This study was performed at the Paediatric Department of Ege University in Izmir, Turkey. Children 3 mo to 7 y old, who presented with acute diarrhoea, were eligible for inclusion. Acute diarrhoea was defined as liquid, mucous or bloody stools passed at least twice as frequently than usual for a minimum of 24 h before admission but not for longer than 7 d. Children who had chronic disease or malnutrition, who had

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Table I. Clinical characteristics on admission.

	S. boulardii group ($n=100$)	Placebo group ($n=100$)	p
Age (mo)[a]	43.9 ± 27.4	41.3 ± 27.5	0.55[b]
Gender (M : F)	64 : 36	61 : 39	0.63§
Duration of diarrhoea before admission (d)	1.6 ± 0.9	1.5 ± 0.9	0.64[b]
Rotavirus-positive	39 (39)[c]	44 (44)	0.21 S
Faecal frequency (stools/d)[a]	7.9 ± 5.4	7.2 ± 4.8	0.31[b]
Vomiting	69 (69)	64 (64)	0.42[d]
Fever (>38°C)	56 (56)	50 (50)	0.27[d]
Dehydration			
None	80 (80)	71 (71)	0.37[d]
Mild	17 (17)	24 (24)	
Moderate/severe	3 (3)	5 (5)	

[a] Values are mean ± SD.
[b] Student's *t*-test.
[c] Numbers in parentheses, percent.
[d] χ^2 test.

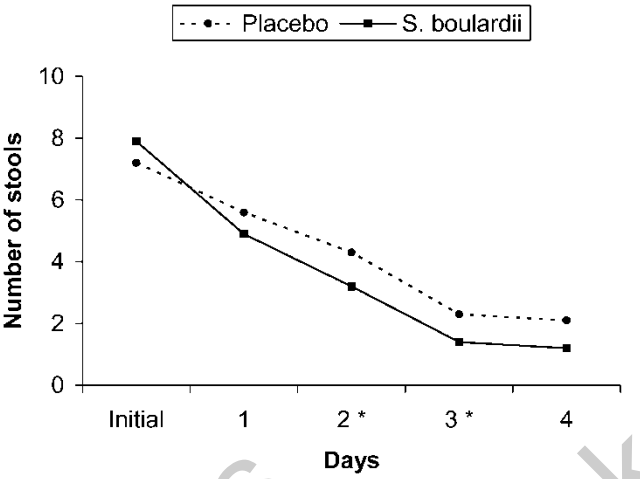

Figure 1. Number of stools during the 5-d intervention period. *Statistically significant difference between the *S. boulardii* and placebo groups.

previously received antibiotics, antidiarrhoeals or other drugs that influence intestinal motility, were excluded.

On admission, a paediatrician examined all children clinically and recorded the symptoms and hydration status on a follow-up chart. The patients were randomly allocated in a double-blind, placebo-controlled fashion to two groups. The patients in group I (*Saccharomyces boulardii* group) received 250 mg/d *S. boulardii*, diluted with water or juice in accordance with the manufacturer's instructions (Sanofi, Turkey). Those in group II (placebo group) received identical-looking placebo. The duration of the treatment was 5 d in each case. The patients were given oral rehydration therapy and normal food for their age. Parenteral rehydration was established in necessity.

The paediatrician called the parents (the children's parents or guardians) each day during the study period, and completed a registration scheme. For each child, the number of stools, the number of vomiting episodes and the body temperature were recorded. The duration of diarrhoea, i.e. the time from the start of the treatment until the appearance of the first normal stool, was chosen as the main outcome criterion. In addition, the occurrences of side effects were monitored until recovery or for 14 d.

Stool specimens were cultured by standard methods for bacterial pathogens, i.e. *Salmonellae, Shigella, Campylobacter jejuni, Vibrio cholerae* and *Escherichia coli*. Fresh faecal specimens were examined by light microscopy for parasitic ova and cysts. Rotavirus antigen was identified using an ELISA kit (IDEIA^{TM} rotavirus test, Dako, UK).

Statistical analysis was performed with SPSS for Windows version 10.0. Student's *t*-test and the χ^2 test were used when appropriate. *P*-values of <0.05 were considered statistically significant.

The study was approved by the Research Ethics Committee of the Medical Faculty, Ege University.

Results

A total of 232 children were enrolled in the study. Thirty-two children were excluded. Twenty-three children, 10 from the *S. boulardii* group and 13 from the placebo group, were prescribed antibiotics during the study period. Four children from the placebo group and five from the *S. boulardii* group were non-compliant to the protocol. Two hundred children completed the study. Rotavirus antigen was identified in 83 children (41.5%). In five cases *Shigella flexneri* and in four *Salmonella typhimurium* were cultured from stool samples. Parasites (*Entamoeba histolytica, Giardia lamblia*, Cryptosporidium) were detected in six, three and two cases, respectively. Ninety-seven cases (48.5%) remained aetiologically unresolved.

Table I gives the admission clinical and demographic characteristics of the 100 children enrolled in the *S. boulardii* group and of the 100 children enrolled in the placebo group. No significant differences regarding age, gender, aetiology or duration of diarrhoea before admission were found between the study groups. Severity of diarrhoea, as determined by the number of stools per day, frequency of vomiting or degree of dehydration, did not differ between the two groups. Fourteen children from the placebo group and 15 from the *S. boulardii* group received parenteral reyhdration ($p>0.05$).

Figure 1 shows the number of stools during the 5-d intervention period. There were no significant differences in the number of stools between the two groups in the first 24 h of the treatment. However, the number of stools showed a significant reduction in the *S. boulardii* group than in the placebo group after

Table II. Effect of *Saccharomyces boulardii*.

	S. boulardii group ($n=100$)	Placebo group ($n=100$)	p[b]
Duration of diarrhoea (d)	4.7 ± 2.5[a]	5.5 ± 3.2	0.03
Duration of watery diarrhoea (d)	2.8 ± 1.1	3.8 ± 1.4	<0.001
Duration of vomiting (d)	1.2 ± 1.0	1.3 ± 1.0	0.61
Duration of temperature $>37.5^{\circ}$C (d)	1.0 ± 0.8	1.1 ± 0.9	0.28
Length of hospital stay (d)	2.9 ± 1.2	3.9 ± 1.5	<0.001

[a] Values are mean $\pm$ SD.
[b] Student's t-test.

the second day of treatment ($p=0.003$ for day 2, $p=0.002$ for day 3).

The duration of diarrhoea significantly reduced in children receiving *S. boulardii* compared with children receiving placebo (4.7 ± 2.5 vs 5.5 ± 3.2 d, $p=0.03$) (Table II). No significant difference in duration of vomiting between the *S. boulardii* and placebo group was observed. *Saccharomyces boulardii* was also not effective on the length of the febrile period. However, the duration of hospital stay was shorter in the *S. boulardii* group than the placebo group (2.9 vs 3.9 d; $p<0.001$). Diarrhoea persisted over 14 d in four children in the placebo group, whereas only one child who was treated with *S. boulardii* had persisting diarrhoea.

Ninety-five percent had watery diarrhoea on admission; the frequency of watery diarrhoea in the *S. boulardii* group did not differ significantly from the frequency found in the placebo group. The frequency of watery diarrhoea after the second day of treatment was found significantly lower in the *S. boulardii* group than in the placebo group (Figure 2).

No serious adverse reactions in the *S. boulardii* group were registered during the clinical study. One child had a complaint of meteorism.

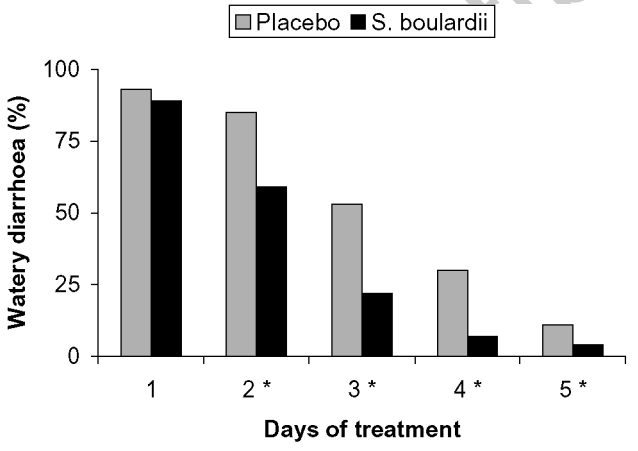

Figure 2. Percent distribution of patients with watery diarrhoea during the 5-d intervention period. All patients have been followed-up for 5 d, even if diarrhoea stopped earlier. *Statistically significant difference between the two groups.

Discussion

The results of studies on the effect of *S. boulardii* in acute diarrhoea have been controversial. In a study on infants with acute diarrhoea, Cetina-Souri et al. [10] reported that more clinical cure was obtained in the group treated with *S. boulardii* than in the placebo group. Similarly, a study of French children reported that *S. boulardii* improved outcomes in acute diarrhoeal disease as a part of oral rehydration therapy [11]. In a study of HIV-associated acute diarrhoea, it was reported that 56% of patients treated with *S. boulardii* had their symptoms resolved, compared with only 6% of placebo-treated patients [12]. However, in a recent comparative study, where a preparation containing the yeast *S. boulardii* was used to treat acute diarrhoea, no clinical difference was observed between the *S. boulardii* and placebo groups [13]. In the present study, we have shown that *S. boulardii* has significantly reduced the duration of acute diarrhoea and the duration of hospital stay as well. The effect of *S. boulardii* seems to be comparable to other well-described probiotics such as *Lactobacillus* GG and *Lactobacillus reuteri* [5, 6]. Although no effect on the frequency of vomiting and the duration of the febrile period was found, *S. boulardii* might provide non-specific benefits and promote general well-being.

In a previous study [10], a reduction in the number of stools after the 24th h of treatment was seen in patients receiving *S. boulardii*. In our study, the number of stools in the first 24 h of the treatment was not different between the *S. boulardii* and placebo groups. The number of stools after the second day of treatment was found to be significantly lower in the *S. boulardii* group than the placebo group. Moreover, the percentage of children with watery diarrhoea after the second day of treatment was lower in the *S. boulardii* group than in the placebo group (Figure 2). Thus, our data support previous findings. The effect of *S. boulardii* on diarrhoea became apparent after the second day of treatment.

In the study, we registered stool consistency not only during the hospital stay but for 14 d or until diarrhoea had stopped. Thus, we assessed the risk for persisting diarrhoea and found that the number of patients with persisting diarrhoea significantly decreased after treatment with *S. boulardii*.

In the last 10 years, some cases of fungaemia with *S. boulardii* have been published in the international literature [14–16]. However, a review of the literature demonstrates that fungaemia is a rare complication of the administration of *S. boulardii*, and it is reported only in severely ill patients in intensive care units, mechanically ventilated, treated by broad-spectrum antibiotics with central venous catheter, or in immunocompromised adult patients. No fungaemia has been reported in otherwise healthy adults and children

receiving lyophilized preparations of this probiotic yeast for supportive therapy of diarrhoea. Our study confirms that *S. boulardii* is a safe probiotic agent in otherwise healthy children with acute diarrhoea.

In conclusion, the placebo-controlled study suggests that *S. boulardii* has significantly reduced the duration of acute diarrhoea and the duration of hospital stay. *S. boulardii* seems to be a promising agent for the amelioration of the course of acute diarrhoea in children when used therapeutically.

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