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Prophylactic *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea: A prospective study

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Background:

Interest to probiotics for the prevention and treatment of antibiotic-associated diarrhea is increasing gradually. The most promising seems to be *Saccharomyces boulardii*. Using a double-blind controlled study, we investigated the preventive effect of *S. boulardii* on the development of antibiotic-associated diarrhea in patients under antibiotherapy but not requiring intensive care therapy.

Material/Methods:

All the patients were hospitalized at the Gulhane Military Medical Academy, Department of Infectious Diseases and Clinical Microbiology. *S. boulardii* was given twice daily during the course of antibiotic therapy and application was initiated in all patients as late as after 48 hours of antibiotic therapy. A total of 151 patients completed the study.

Results:

The antibiotic-associated diarrhea development ratio in placebo group was 9% (7/78) and in the study group 1.4% (1/73) ($p < 0.05$). Stool samples from the patients with antibiotic-associated diarrhea were stored at -70°C and *Clostridium difficile* toxin A assay was performed using Enzyme Immune Assay as late as in seven days. *C. difficile* toxin A assay yielded positive results in two (2/7) stool samples from the patients with antibiotic-associated diarrhea in the placebo group and a negative result in the only patient who developed antibiotic-associated diarrhea in the study group.

Conclusions:

The results implied that prophylactic use of *Saccharomyces boulardii* resulted in reduced, with no serious side effects, antibiotic-associated diarrhea in hospitalized patients.

Key words:

antibiotic-associated diarrhea • probiotics • prevention • *S. boulardii*

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BACKGROUND

The use of antibiotics is commonly accompanied by diarrhea: idiopathic diarrhea with benign progress and pseudomembranous colitis caused by *Clostridium difficile*. *C. difficile* colonizes the gastrointestinal tract and produces a toxin in cases when the normal flora is suppressed by antibiotics. Pseudomembranous colitis most frequently appears after application of clindamycin, lincomycin, ampicillin, cephalosporins, and other antibiotics. The diagnosis is confirmed if there is evidence of *C. difficile* toxin in feces [1]. Probiotics are living organisms which, when ingested, have a beneficial therapeutic effect. Examples are bacteria, especially *Lactobacillus rhamnosus* GG, and the yeast *Saccharomyces boulardii* [2]. *S. boulardii* is non-pathogenic yeast first isolated from lychee fruit and was first used for the treatment of the diarrhea in the 1950s in France [3]. This kind of yeast has the unusual optimal growth temperature of 37°C. In France, its lyophilized form was marketed in 1962 and this form is still widely used and sold in Europe, Asia, Africa, and Central and South America. Each dosage, consisting of 250 mg active ingredient, includes 5×10^9 *S. boulardii* cells [4]. *S. boulardii* is resistant to gastric acidity and proteolysis. In the gastrointestinal tract it reaches high concentration level in a very short time and persists in viable forms. It does not permanently colonize colonic mucosa and does not live except in the intestinal channel [5–7]. The aim of this study was to investigate the preventive effect of *S. boulardii* on antibiotic-associated diarrhea development in the patients under antibiotherapy but not requiring intensive care therapy.

MATERIAL AND METHODS

This study was performed between November 2000 and September 2002. One hundred and fifty-one inpatients of the Gulhane Military Medical Academy School of Military Medicine, Department of Infectious Diseases and Clinical Microbiology, were enrolled in the study. The patients had to receive chemotherapy but did not require an intensive care unit. All the subjects had to have the following features: (a) 25–50 years of age and not pregnant or lactating, (b) no chronic illness (such as heart failure, chronic renal failure, chronic obstructive lung disease, hypertension, diabetes mellitus, chronic hepatitis B or C virus infection, Crohn's Diseases, colitis ulcerous, etc.), (c) not receiving antacids, H₂ receptor blockers, or proton pump inhibitors, (d) not immunodeficient and with no oncological or hematological disease, (e) no history of past intestinal parasitic disease, (f) not receiving vancomycin, teicoplanin, or metronidazole antibiotherapy, (g) not under immunosuppressive therapy, (h) no history of gastrointestinal surgery, (i) no history of lactose intolerance and having no diarrhea, (j) this his/her first hospitalization for therapeutic purposes, and (k) no known allergy to antibiotic drugs. Signed consent with detailed information was obtained from the volunteer patients suitable for the study.

The subjects enrolled in our study were randomly divided into two groups before the initiation of the antibiotherapy. Seventy-eight patients (74 male and 4 female) were given "antibiotics + placebo" and 73 (65 male and 4 female) patients were given "antibiotics + *S. boulardii*". The patients were also divided into groups in terms of antibiotics used. If the therapy included β lactam antibiotic, the patient was enrolled in the β lactam group. Placebo or *S. boulardii* were

Table 1. Distribution of patients with and without diarrhea into groups.

	Patients with diarrhea	Patients without diarrhea
Placebo group	7 (9.0%)	71 (91.0%)
<i>S. boulardii</i> group	1 (1.4%), $p < 0.05$	72 (98.6%)
Mean age	30.9 ± 10.7	23.5 ± 6.7
Total	8 (5.3%)	143 (94.7%)

Table 2. Comparison of patients receiving and not receiving β lactam antibiotics in terms of diarrhea (If the combination included β lactam antibiotic, the patient was enrolled in β lactam group).

	Patients with diarrhea	Patients without diarrhea	Total
Receiving β lactam antibiotic	8 (6.4%), $p > 0.05$	117 (93.6%)	125 (100.0%)
Not receiving β lactam antibiotic	0 (0.0%)	26 (100.0%)	26 (100.0%)
Total	8 (5.3%)	143 (94.7%)	151 (100.0%)

Table 3. Distribution of CdTA (+) cases into groups.

	CdTA (+) cases	CdTA (–) cases	Total
Placebo group	2 (2.6%), $p > 0.05$	76 (97.4%)	78 (100.0%)
<i>S. boulardii</i> group	0 (0.0%)	73 (100.0%)	73 (100.0%)
Total	2 (1.3%)	149 (98.7%)	151 (100.0%)

applied to the patients 48 hours after antibiotherapy was initiated. They were administered 2 × 1 per day and half an hour before or two hours after meals. Each day the patients were questioned if they had diarrhea. Microscopic and macroscopic stool examinations were performed for the patients who developed diarrhea. The stool samples were stored at –70°C. The patients were also questioned about antibiotic-associated diarrhea (AAD) for 4 weeks after the cessation of antibiotherapy. *Clostridium difficile* toxin A (CdTA) was assayed by enzyme-linked immuno sorbent assay (ELISA) (Bartels, Trinity, Biotec Company; Bray, Ireland).

Data obtained were analyzed with the Statistical Package for the Social Sciences (SPSS) 9.05 for Windows. The chi-square test was used for comparisons of grouped variables (such as sex). Fisher's exact chi-square was used instead of chi-square when the ratio of the expected values was over 25%. Student's *t*-test was used for the comparison of measurement-dependent permanent variables.

Table 4. Studies on effectiveness of *S. boulardii* in the prevention of AAD.

Authors, year	Study type	Number of cases	<i>S. boulardii</i> duration of therapy	AAD seen		<i>p</i>
				<i>S. boulardii</i> group	Placebo group	
Adam et al. 1977	DBPC	388	7 days	4.5%	17.5%	<0.001
Surawicz et al. 1989	DBPC	180	28 days	9.5%	22.0%	<0.05
Mc Farland et al. 1995	DBPC	193	28 days	7.2%	14.6%	<0.05

AAD – antibiotic-associated diarrhea; DBPC – double-blind placebo-controlled.

RESULTS

Seven (9.0%) of the patients in the placebo group developed diarrhea and only one (1.4%) patient in the *S. boulardii* group had diarrhea ($p<0.05$). The mean age of the patients with diarrhea was significantly higher than the patients without diarrhea ($p<0.05$). The distribution of patients with and without diarrhea into groups and their mean ages are given in Table 1. There was no significant difference between patients receiving β lactam and those not in terms of diarrhea ($p>0.05$). Comparison of patients receiving and not receiving β lactam antibiotics in terms of diarrhea is shown in Table 2. Stool samples were positive for CdTA assay in only two of the placebo group, and there was no significant difference between the groups in terms of stool CdTA positivity ($p>0.05$). The distribution of patients with AAD into groups in terms of CdTA detection in stool is given in Table 3.

DISCUSSION

Antibiotic-associated diarrhea is a serious issue, and interest in probiotics used for the prevention and treatment of AAD is increasing gradually. The most promising one among the probiotics used seems to be *S. boulardii*. As seen in Table 1, the AAD ratio in the *S. boulardii* group was significantly less than in the placebo group ($p<0.05$). This finding shows that *S. boulardii* is an effective agent in the prevention of AAD. The contribution of *S. boulardii* to intestinal epithelium integrity, its inhibitory effect on pathogenic microbes, and protective effect on intestinal floral equilibrium may have caused the reduced AAD ratio in the *S. boulardii* group.

In a study by Adam et al, AAD development was 17.5% in a placebo group and 4.5% in a *S. boulardii* group ($p<0.001$) [8]. In another study by Surawicz et al. AAD was seen in 21.8% of placebo group as 9.5 in *S. boulardii* group ($p<0.05$) [9]. Mc Farland et al. has detected AAD in 7.2% of an *S. boulardii* group and in 14.6% of a placebo group ($p<0.05$) [10]. Brief information about previous studies on the effectiveness of *S. boulardii* in the prevention of AAD is given in Table 4. AAD in all our cases was less than in the previous studies summarized in Table 4. The reason for this finding may be the exclusion of cases with features such as old age, surgical invention, and underlying serious disease.

It is claimed that AAD arises 8 to 10 weeks after antibiotherapy ends, but it usually begins 4 to 9 days after antibiotherapy is stopped [11]. In the placebo group of our study only two of seven AAD patient developed AAD just after antibiotherapy stopped: two in five days and three in 5 to 10 days.

AAD in the *S. boulardii* group developed just in the second day of antibiotherapy.

β lactam antibiotics are known to be among the group of AAD-predisposing antibiotics [10,12–17]. In our cases there was no significant difference between patients receiving β lactam antibiotics in terms of diarrhea, but the frequency of AAD in the β lactam group was insignificantly higher than in the non- β lactam group ($p<0.05$).

Age is a significant risk factor for AAD [13,14,18,19]. In our study the mean age of the AAD group was significantly higher than the non-AAD group. This result corroborates age being a risk factor.

In various studies, *C. difficile* was found to be the causative agent in 26% to 50% of AAD cases [9,10,20–22]. Eleftherios et al. [23] found *C. difficile* responsible for 25% of AAD cases, Modi et al. [24] 20%, and Mc Farland 10% to 33% [25], but Pituch et al. [26] stated that *C. perfringens* is not a major primary cause of antibiotic-associated diarrhea. In our study, CdTA was positive in only two of eight AAD cases and the rate was 25%. All the CdTA (+ve) cases were in the placebo group. The number of CdTA (+ve) cases was too small to compare statistically.

CONCLUSIONS

Our study corroborates previous studies on the effectiveness of *S. boulardii* preparation in the prevention of AAD. The conclusion of the results of both previous studies and of ours is that *S. boulardii* preparation seems to be an appropriate choice and should be used in the prevention of AAD.

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