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ORIGINAL PAPER

Clinical efficacy of *Saccharomyces boulardii* or metronidazole in symptomatic children with *Blastocystis hominis* infection

Ener Cagri Dinleyici · Makbule Eren · Nihal Dogan · Serap Reyhanioglu · Zeynel Abidin Yargic · Yvan Vandenplas

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Abstract Although many *Blastocystis* infections remain asymptomatic, recent data suggest it also causes frequent symptoms. Therapy should be limited to patients with persistent symptoms and a complete workup for alternative etiologies. The goal of this study was to compare the natural evolution (no treatment) to the efficacy of *Saccharomyces boulardii* (*S. boulardii*) or metronidazole for the duration of diarrhea and the duration of colonization in children with gastrointestinal symptoms and positive stool examination for *Blastocystis hominis*. This randomized single-blinded clinical trial included children presenting with gastrointestinal symptoms (abdominal pain, diarrhea, nausea–vomiting, flatulence) more than 2 weeks and confirmed *B. hominis* by stool examination (*B. hominis* cysts in the stool with microscopic examination of the fresh stool). The primary end points were clinical evaluation and result of microscopic stool examination at day 15. Secondary end points were the same end points at day 30. Randomization was performed by alternating inclusion: group A, *S. boulardii* (250 mg twice a day, Reflor®) during 10 days; group B, metronidazole (30 mg/kg twice daily) for 10 days; group C, no treatment. At day 15 and 30 after inclusion, the patients were re-evaluated, and stool samples were examined microscopically. On day 15, children that were still symptomatic and/or were still *B. hominis*-infected in group C were treated with metronidazole for 10 days. There was no statistically significant difference between the three study groups for age, gender, and the presence of diarrhea and abdominal pain. On day 15, clinical cure was observed in 77.7% in group A (n, 18); in 66.6% in group B (n, 15); and 40% in group C (n:15) ($p<0.031$, between groups A and C). Disappearance of the cysts from the stools on day 15 was 80% in group B, 72.2% in group A, and 26.6% in group C ($p=0.011$, between group B and group C; $p=0.013$, between group A and group C). At the end of the first month after inclusion, clinical cure rate was 94.4% in group A and 73.3% in group B ($p=0.11$). Parasitological cure rate for *B. hominis* was very comparable between both groups (94.4% vs. 93.3%, $p=0.43$). Metronidazole or *S. boulardii* has potential beneficial effects in *B. hominis* infection (symptoms, presence of parasites). These findings challenge the actual guidelines.

E. C. Dinleyici (✉) · S. Reyhanioglu · Z. A. Yargic
Department of Pediatrics,
Eskisehir Osmangazi University Faculty of Medicine,
Eskisehir, Turkey
e-mail: timboothtr@yahoo.com

M. Eren
Department of Pediatrics, Division of Pediatric Gastroenterology and Hepatology,
Eskisehir Osmangazi University Faculty of Medicine,
Eskisehir, Turkey

N. Dogan
Department of Parasitology,
Eskisehir Osmangazi University, Faculty of Medicine,
Eskisehir, Turkey

Y. Vandenplas
Universitair Ziekenhuis Brussel Kinderen,
Vrije Universiteit Brussel,
Brussels, Belgium

Introduction

Blastocystis hominis (*B. hominis*) is a common human intestinal parasite with high prevalence in developing countries (Tan et al. 2002; Yakoob et al. 2010a) and has increased impact in public health (Yakoob et al. 2010a). *B. hominis* is the leading intestinal parasite in Turkey (Dagci et al. 2008). Although many *Blastocystis* infections remain

asymptomatic, several recent data suggest it is a frequent cause of gastrointestinal symptoms in children and adults (Tan et al. 2002). Jones et al. (2009) suggest that there is an association between *Blastocystis* infection and chronic gastrointestinal illness. Today, there is a consensus that isolation of *B. hominis* does not necessitate treatment, even in symptomatic or immunocompromised patients (Tan et al. 2002). Therapy should be limited to patients with persistent symptoms and a complete negative workup for alternative etiologies. Several studies have shown the efficacy of metronidazole, emetine, furazolidone, trimetroprim-SMX, iodochlorhydroxyquin, pentamidine, and nitazoxanide (Moghaddam et al. 2005; Rossignol et al. 2005). The goal of this study was to compare the natural evolution (no treatment) to the efficacy of *S. boulardii* or metronidazole on the duration of diarrhea and the duration of colonization in immune competent patients with gastrointestinal symptoms and positive stool examination for *B. hominis*.

Material and methods

This randomized single-blinded clinical trial was performed in the Eskisehir Osmangazi University Faculty of Medicine Hospital, Turkey. Children presenting with gastrointestinal symptoms (abdominal pain, diarrhea, nausea–vomiting, and flatulence) more than 2 weeks and confirmed *B. hominis* by stool examination (*B. hominis* cysts in the stool with microscopic examination of the fresh stool) were eligible for inclusion (1). A traditional fecal examination (microscopic examination, rotavirus antigen test, bacterial culture) was performed in all study patients.

The primary end points were clinical evaluation and microscopic stool examination at day 15. The secondary end points were the same end points at day 30.

Exclusion criteria were hospitalization (for any reason), the use of medication for any underlying disease and antibiotic use during the previous month. A positive stool result for rotavirus, bacteria, fungi, or protozoa other than *B. hominis* was an exclusion criterion.

Randomization was performed by alternating the inclusion of each patient to one of the three treatment arms. Group A was treated with lyophilized *S. boulardii* (250 mg twice a day, Reflor®, Biocodex) during 10 days; group B was treated with metronidazole (30 mg/kg twice daily) alone for 10 days. No treatment was given to group C. At day 15 and 30 after inclusion, patients were clinically re-evaluated and stool samples were examined microscopically for the presence of *B. hominis*. The parasitological examinations of all stool specimens were performed by the same parasitologist (N.D.) who was unaware about the patient information and treatment. In group C, children that were still symptomatic and/or were still *B. hominis*-infected on day 15, were treated with metronidazole for 10 days.

Clinical evaluation and duration of diarrhea according to the Bristol criteria were performed by a pediatrician unaware about the treatment group of the patient.

Statistical analysis was performed with SPPS for Windows 13.0. Independent *t* test, Chi-square test and McNemar's tests were used for comparisons. $P<0.05$ was considered as statistically significant. This study was approved by the local ethical committee; an informed consent was obtained from at least one parent.

Results

During the study period (January 2006–June 2008), 68 symptomatic children with positive stool examinations for *B. hominis* were enrolled. Twenty-five children were excluded because of underlying chronic conditions, immunosuppressive conditions, co-existence with other microorganisms, and a history of medication use.

Group A was composed of 18 children treated with *S. boulardii* during 10 days. Group B contained 15 children and was treated with metronidazole. Group C consisted of 15 children and was not treated. Age, gender distributions, and clinical findings of each patient at inclusion are summarized in Table 1. There was no statistically significant difference between the three study groups for age, gender, and the presence of diarrhea and abdominal pain ($p>0.05$) (Table 1).

On day 15, clinical cure was observed in 77.7% in group A, in 66.6% in group B, and 40% in group C (resulting in a statistically significant difference between group A and group C ($p<0.05$)). The cure rate is slightly higher in group A than in group B without a statistical difference ($p>0.05$).

Disappearance of the cysts from the stools on day 15 was 80% in group B, 72.2% in group A, and only 26.6% in group C (26.6%) ($p<0.05$ between group B and group C; $p<0.05$ between group A and group C). Parasitological cure rate was not statistically different between group A and group B ($p>0.05$) (Table 2; Fig. 1).

In group C, children that were still symptomatic ($n=9$) and/or were still *B. hominis*-infected ($n=11$) on day 15 were treated with metronidazole for 10 days. Nine out of these 11 children were successfully treated with metronidazole resulting in two children who were asymptomatic but had still positive parasitological findings for *B. hominis.*

At the end of the first month, clinical cure rate was 94.4% in group A and 73.3% in group B ($p=0.11$). Parasitological cure rate for *B. hominis* was very comparable between both groups (94.4% vs. 93.3%, $p>0.05$) (Table 2; Fig. 1).

Table 1 Demographic and clinical findings of study groups

	S. boulardii group *n*=18	Metronidazole group *n*=15	Control group (no treatment) *n*=15
Age (months)	99.1±43.8	94.6±37.4	90.2±46.7
Gender (girls/boys)	7/11	7/8	8/7
Symptoms			
Diarrhea	9	7	6
Abdominal pain	10	11	10
Loss of appetite	3	1	2
Nausea/vomiting	3	2	3
Flatulence	1	–	1

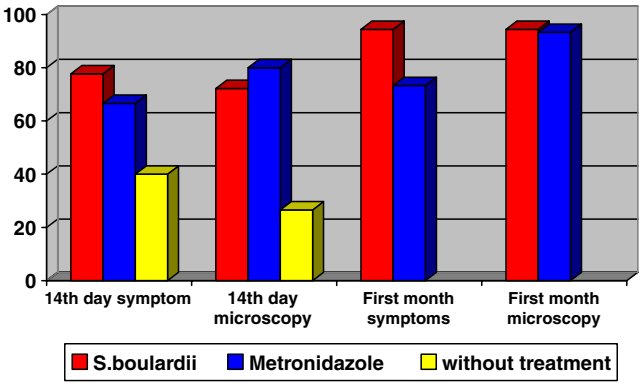

Fig. 1 Cure rate for clinical findings and parasitological examinations between study groups on the 14th day and first month

Discussion

Many infections with *B. hominis* remain asymptomatic, but symptomatic cases have also been recorded. Although the pathogenic potential of *B. hominis* remains controversial, many parasitologists now insist that when *B. hominis* organisms are present in large numbers in stool examinations, even in the absence of other known bacterial, viral, or parasitic agents, treatment should be proposed (Tan et al. 2002). In our study, 68 symptomatic children with positive stool examinations for *B. hominis* were enrolled. Twenty-five children were excluded because of underlying chronic conditions, immunosuppressive conditions, co-existence with other microorganisms, and history of medication. In clinical practice, metronidazole, TMP/SMX, iodoquinol, tinidazole, furazolidone, and currently nitazoxanide have been used as treatment of individuals harboring *B. hominis* in their intestinal tract (Moghaddam et al. 2005; Rossignol et al. 2005). Metronidazole is the most recommended agent in the treatment for *B. hominis* infection and placebo-controlled trial showed that 88% of clinical resolution in patients with *B. hominis* infection treated with metronidazole (Moghaddam et al. 2005). In contrast, some studies showed no beneficial effects for blastocystosis (Nigro et al. 2003). Up to now, there is a consensus that therapy should be limited to patients with persistent unexplained symptoms after a thorough evaluation and a complete (negative) screening for alternative etiologies. In the study by Moghaddam et al. (2005), 28 of the 104 *B. hominis*-infected individuals were discharging large numbers of parasites before treatment. Of the 28 individuals with a high number of parasites in the stool, 12 were treated with metronidazole and four out of 12 was eradicated (Moghaddam et al. 2005). The drug may directly affect *B. hominis* or it may act by destroying the bacterial flora necessary for its growth or both. There are several randomized placebo-controlled studies showing the efficacy of *S. boulardii* in the management and prevention of acute childhood diarrhea (Dinleyici et al. 2009; Htwe et al. 2008; Villarruel et al. 2007; Szajewska et al. 2007; Vandenplas and Benninga 2009; Kurugöl and Koturoğlu 2005; Eren et al. 2010). Little is known about the efficacy of *S. boulardii* against

Table 2 Cure rate for clinical findings and parasitological examinations between study groups on the 14th day and first month

	S. boulardii group *n*=18	Metronidazole group *n*=15	without treatment *n*=15	*P*
Cure rate for symptoms on the 14th day, *n* (%)	14/18	10/15	6/15	*P1*> 0.05
	77.7%	66.6%	40%	*P2*< 0.05
				P3> 0.05
Cure rate for parasitological findings on the 14th day, *n* (%)	13/18	12/15	4/15	*P1*> 0.05
	72.2%	80.0%	26.6%	*P2*< 0.05
				P3< 0.05
Cure rate for symptoms on the first month, *n* (%)	17/18	11/15		*P1*> 0.05
	94.4%	73.3%		
Cure rate for parasitological findings on the first month, *n* (%)	17/18	14/15		*P1*> 0.05
	94.4%	93.3%		

P1 S. boulardii vs. metronidazole group, *P2 S. boulardii* vs. without treatment group, *P3* metronidazole vs. without treatment group

protozoal infections. Currently we showed that the addition of *S. boulardii* to metronidazole for the treatment of acute bloody diarrhea due to intestinal amebiasis significantly decreases the duration of (bloody) diarrhea and enhances the gastrointestinal clearance of the amebic cysts as compared to metronidazole alone (Dinleyici et al. 2009). In adults like our study, co-administration of lyophilized *S. boulardii* with conventional treatment in acute amebic colitis significantly decreased the duration of symptoms and cyst carriage after 4 weeks (Mansour-Ghanaei et al. 2003). Besirbellioglu et al. (2006) compared the efficacy of *S. boulardii* in addition to metronidazole in patients with giardiasis. The combination therapy resulted in a disappearance of the giardia cyst 2 weeks after the start of the treatment; however, 17.1% of the patients treated with 10 days of metronidazole as monotherapy still had *Giardia lamblia* cysts in the stool (Besirbellioglu et al. 2006). To the best of our knowledge, there are no published data on the efficacy of *S. boulardii* in children with *B. hominis* infection. According to our study results, clinical cure was observed in 77.7% in children that received *S. boulardii* and in 66.6% in the metronidazole group. Both treatment options result in a better cure rate than in the group without treatment (40%). Disappearance of the cysts from the stools on day 15 was 80% in the metronidazole group, 72.2% in the *S. boulardii* group, and only 26.6% in the no-treatment group. Parasitological cure rate was similar between children that received *S. boulardii* or metronidazole.

At the end of the first month, clinical cure rate was 94.4% in the *S. boulardii* group and 73.3% in the metronidazole group. Parasitological cure rate for *B. hominis* was very comparable between both groups.

The data reported in this study are in line with the results of the previously published data in amebiasis; cysts and clinical findings disappeared more rapidly. Although the mechanisms by which *S. boulardii* might exert its activity remain unclear, several have been proposed. Clinical resolution and clearance of the organism may be due to the efficacy of the treatment on *B. hominis* and/or because of elimination of other undetected organisms and/or because of an improved balance of the gut microflora.

There were two reports on the possible association of *B. hominis* infection with irritable bowel syndrome, a non-inflammatory bowel disease; however, it is unclear from these studies if *B. hominis* is a primary etiological agent in irritable bowel syndrome as it is just as possible that a disruption of the microbial flora had provided conditions for *B. hominis* to thrive (Yakoob et al. 2004; Hussain et al. 1997). Infections with *B. hominis* are associated with abdominal pain, bloating, and alteration of bowel habits resembling irritable bowel syndrome (Yakoob et al. 2004). *B. hominis* was positive 49% with stool microscopy, 53% with stool culture, and 44% with polymerase chain reaction in adult patients with irritable bowel syndrome with diarrhea and significantly higher than healthy adults (Yakoob et al. 2010b). Subtype I determined all of symptomatic *B. hominis* patients (Eroglu et al. 2009; Yakoob et al. 2010a). In our study protocol, we did not evaluate symptoms of children for irritable bowel syndrome; however, we would perform a clinical study for clinical efficacy of *S. boulardii* in children with irritable bowel syndrome associated with infectious origin.

In a symptomatic patient with a positive stool smear for *B. hominis*, a thorough search should be performed to look for other unrecognized enteric pathogens and noninfectious causes of GI symptoms should be carefully excluded. A presumptive treatment with *S. boulardii* or metronidazole may be proposed keeping in mind that the resolution of symptoms may be secondary to elimination of unidentified pathogens as well as to the eradication of *B. hominis*. Metronidazole or *S. boulardii* has potential beneficial effects in *B. hominis* infection (symptoms, presence of parasites). The findings of this study challenge the actual guidelines to not treat *B. hominis* infection.

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