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Effect of *Saccharomyces boulardii* in the Treatment of Acute Watery Diarrhea in Myanmar Children: A Randomized Controlled Study

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Abstract. This study was conducted to evaluate the efficacy of *Saccharomyces boulardii* in acute diarrhea. One hundred hospitalized children in Myanmar (age range = 3 months to 10 years) were included. Fifty were treated with *S. boulardii* for five days in addition to oral rehydration solution (ORS) and 50 were given ORS alone (control group) in an alternating order. The mean duration of diarrhea was 3.08 days in the *S. boulardii* group and 4.68 days ($P < 0.05$) in the control group. Stools had a normal consistency on day 3 in 38 (76%) of 50 patients in the *S. boulardii* group compared with only 12 (24%) of 50 in the control group ($P = 0.019$). On day 2, 27 (54%) of 50 had less than three stools per day in the *S. boulardii* group compared with only 15 (30%) of 50 in the control group ($P = 0.019$). *Saccharomyces boulardii* shortens the duration of diarrhea and normalizes stool consistency and frequency. The shortening of the duration of diarrhea results in a social and economic benefits.

INTRODUCTION

Rapid rehydration and realimentation remain the cornerstone of treatment of acute gastroenteritis. Probiotics administered as add-on medications are likely to decrease the duration of acute infectious gastroenteritis with approximately 24 hours. Studies show a statistically significant benefit, mainly in infants and young children, in the treatment of persons with acute watery diarrhea. Because of strain specificity, only those organisms that have been clinically tested can be recommended.¹

Saccharomyces boulardii is a probiotic yeast that has a direct antagonistic effect on many pathogens. The efficacy of *S. boulardii* is attributed to a direct inhibitory effect on the growth of pathogenic strains, an anti-secretory effect by specifically binding toxins to intestinal receptors, and a trophic effect on enterocytes with stimulation of enzymatic activity and non-specific anti-infectious mechanisms, such as anti-inflammatory activity.² The polyamine increase induced by *S. boulardii* in humans results in an increased secretion of brush border disaccharidases and enzymes (lactase, sucrase, maltase, and aminopeptidase).² The increased secretion of polyamines enhances maturation of enterocytes. Polyamines increase the glucose carrier activity on the membrane of enterocytes, which is essential to achieve maximal glucose absorption.²

Few studies with *S. boulardii* have been performed in Asia. The aim of this prospective study was to determine the effect of *S. boulardii* on the clinical course of acute watery diarrhea in hospitalized children. This aim was assessed by measurement of the duration of diarrhea and the frequency and consistency of stools. Acute diarrhea in Myanmar is caused mainly by enteropathogenic and enterotoxigenic *Escherichia coli*.^{3–5} Patients were tested selectively for the presence of these pathogens.

MATERIALS AND METHODS

One hundred children 3 months to 10 years of age (89 were 3 months to 2 years of age and 11 were more than 2 years of

age) with acute watery diarrhea with a duration of less than seven days before inclusion were recruited in the pediatric ward of the North Okkalapa General Hospital in Yangon, Myanmar. Exclusion criteria were a fever $> 38.5^{\circ}\text{C}$, clinically severe dehydration, macroscopic blood in the stools, intake of anti-fungal drugs, or existing severe malnutrition (weight-to-height ratio $< 70\%$).

Patients were alternately assigned to receive the active product (*S. boulardii*) in addition to oral rehydration solution (ORS) or ORS alone. One hundred patients were divided into two groups; 50 patients were treated with *S. boulardii*, 250 mg twice a day for 5 days in combination with ORS (*S. boulardii* group) and 50 patients were given ORS alone (control group). The ORS was administered according to World Health Organization guidelines for management of diarrhea.⁶ Informed consent was obtained verbally from the parents before starting the study.

The duration of diarrhea and consistency and frequency of stools were recorded according to the information provided by the mother or attendant every morning starting from day 1. On admission, stool samples were taken from all patients for *E. coli* culture (Because this study was performed without any involvement of the company commercializing *S. boulardii*, the budget was limited). Diarrhea was defined as passing three or more loose stools per day (loose stool is a stool that takes the shape of the container). Diarrhea was considered to have stopped when the child passed less than three stools per day or stools with a solid consistency only. Data analysis was performed using the SPSS software version 11 (SPSS Inc., Chicago, IL). The chi-square test was used and a P value < 0.05 was considered significant.

RESULTS

Patient characteristics at baseline did not differ between the two groups. The mean duration of diarrhea was 3.08 days in *S. boulardii* group and 4.68 days in the control group ($P < 0.05$). On day 2, the defecation frequency was less than three times a day in 27 (54%) of 50 in the *S. boulardii* group and 15 (30%) of 50 in the control group ($P = 0.019$) (Table 1). On day 3, *S. boulardii* and ORS was two times more likely to reduce the frequency of stools to less than three per day than ORS alone. On day 4, 48 (96%) of 50 in the *S. boulardii* group

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TABLE 1
Stool frequency in the study population*

Day	Controls		<i>Saccharomyces boulardii</i>		P
	< 3 times	≥ 3 times	< 3 times	≥ 3 times	
1	0	50	0	50	NS
2	15	35	27	23	0.019
3	28	22	39	11	0.019
4	39	11	48	2	NS
5	48	2	50	0	NS
6	50	0	50	0	NS
7	50	0	50	0	NS

* NS = not significant.

had less than three stools per day compared with 39 (78%) of 50 in the control group.

On day two, *S. boulardii* had no significant effect on the consistency of stools. However, after day 3, stool consistency was significantly more solid in the *S. boulardii* group (Table 2). On day 3, 38 (76%) of 50 patients in the *S. boulardii* group passed solid stools compared with only 12 (24%) of 50 in the control group ($P < 0.005$). On day 4, patients were 13 times more likely to pass solid stools after receiving *S. boulardii* plus ORS than patients who received only ORS. After day 5, no patients in the *S. boulardii* group had liquid stools.

In the subgroup with *E. coli* gastroenteritis, stool consistency also normalized more rapidly in the *S. boulardii* group. This finding resulted in a significant difference in stool consistency on day 3 and 4 ($P = 0.004$ and $P = 0.025$, respectively).

DISCUSSION

The efficacy of *S. boulardii* has been documented in various types of diarrhea such as the prevention of antibiotic-associated diarrhea,⁷ *Clostridium difficile*-associated enteropathies,⁸ chronic diarrhea caused by giardiasis^{9,10} and amebiasis,¹¹ prevention of traveler's diarrhea,¹² prevention of diarrhea in critically ill tube-fed patients,¹³ and treatment of human immunodeficiency virus-associated diarrhea.¹⁴ However, the major indication is acute diarrhea in children and adults.¹⁵⁻¹⁹

The results presented in this trial in children in Myanmar hospitalized because of acute watery diarrhea confirm previous studies on *S. boulardii* for this indication.^{20,21} Acute diarrhea in Myanmar is caused mostly by enteropathogenic and enterotoxigenic *E. coli*, *Salmonella*, *Shigella*, *Vibrio cholerae*, and to a lesser extent by other microorganisms.³⁻⁵ In this study, pathogenic *E. coli* was isolated from 21 of 100 patients.

TABLE 2
Stool consistency in the study population*

Day	Controls		<i>Saccharomyces boulardii</i>		P	Odds ratio (95% CI)
	Solid	Liquid	Solid	Liquid		
1	0	50	0	50		
2	1	49	3	47	0.307	
3	12	38	38	12	< 0.005	3.167 (1.888-5.312)
4	30	20	49	1	< 0.005	13.17 (1.909-88.889)
5	40	10	50	0	0.001	13.025 (1.909-88.889)
6	48	2	50	0		
7	50	0	50	0		

* CI = confidence interval.

The cause of diarrhea in the remaining patients was not known. The present study showed some beneficial effects of *S. boulardii* in treatment of diarrhea caused by *E. coli*.

The overall assessment of the clinical response showed a significant difference in favor of the active treatment group compared with the group treated with ORS alone, which confirmed the beneficial effects of *S. boulardii* for acute diarrhea. *Saccharomyces boulardii* has been shown to reduce the duration of diarrhea and the duration of hospitalization by approximately 24 hours.^{16,18,20,21} Greater efficacy has been shown if the treatment is started early.¹⁸ No severe side effects were observed during the trial.

In conclusion, the result of this prospective randomized study confirms that *S. boulardii* in combination with ORS reduces the duration of acute non-specific watery diarrhea in children in Myanmar. This biotherapeutic agent showed an obvious therapeutic effect in acute watery diarrhea with regard to consistency of stools, frequency of stools, and duration of diarrhea. Shortening the duration of diarrhea and reducing hospital stay result in a social and economic benefits.

Received July 6, 2007. Accepted for publication October 23, 2007.

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