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Role of a probiotic (*Saccharomyces boulardii*) in management and prevention of diarrhoea

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of the side effects during treatment period.

CONCLUSION: *S. boulardii* significantly reduces the frequency and duration of acute diarrhoea. The consistency of stool also improves. The drug is well-tolerated.

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Key words: Acute watery diarrhoea; Probiotic; *Saccharomyces boulardii*; Frequency of episodes of diarrhoea; Weight gain

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Abstract

AIM: To assess the efficacy and safety of *Saccharomyces boulardii* (*S. boulardii*) in acute watery diarrhoea and its role in reducing the frequency of episodes of diarrhoea in subsequent two months.

METHODS: Children from 2 mo to 12 years of age, with acute diarrhoea were selected according to inclusion criteria and randomised in *S. boulardii* group (treated with ORS, nutritional support and *S. boulardii*, 250 mg bid) and in control group (treated with ORS and nutritional support only). Active treatment phase was 5 d and each child was followed for two months afterwards. Frequency and consistency of stools as well as safety of drug was assessed on every visit. A comparison of two groups was done in terms of number of diarrhoeal episode in subsequent two months.

RESULTS: There were fifty patients in each group. Baseline characteristics such as mean age and the average frequency of stools were comparable in *S. boulardii* and control group at the time of inclusion in the trial. By d 3 it reduced to 2.7 and 4.2 stools per d respectively and by d 6 it reduced to 1.6 (*S. boulardii* Group) and 3.3 (control group). The duration of diarrhoea was 3.6 d in *S. boulardii* group whereas it was 4.8 d in control group ($P = 0.001$). In the following two months, *S. boulardii* group had a significantly lower frequency of 0.54 episodes as compared to 1.08 episodes in control group. The drug was well accepted and tolerated. There were no reports

INTRODUCTION

Acute infectious diarrhoeal disease is a worldwide problem with over two million deaths each year. Diarrhoeal diseases are a leading cause of childhood morbidity and mortality and over 200 000 children die every year (600 deaths per day) in Pakistan. Repeated episodes of diarrhoea lead to under-nutrition. In Pakistan, every child gets, on average, 5-6 episodes of diarrhoea per year.

Last couple of decades has seen greater understanding of pathogenesis and simple methods of management of diarrhoea. Various modalities of interventions have been used in different parts of the world to improve the diarrhoeal mortality and morbidity which include oral rehydration salt (ORS), cereal based ORS, antibiotics, anti-diarrhoeals, antispasmodics and anti-emetics. Some of these modalities later proved to have variable harmful effects. These harmful effects include worsening of diarrhoea, increased duration of diarrhoea, adverse effects on gut motility leading to paralytic ileus. In addition, there are other systemic untoward effects^[1,2].

Gastrointestinal disease is often a consequence of a myriad of factors, which disturb the bowel's complex ecosystem. The concept of modulating bacterial activities, directed towards improving gut microbial function, has a long history. The use of yoghurt (as probiotic) in the treatment of diarrhoea has been known for a long time. It is now recognised that the most frequently used method of influencing the gut flora composition is that of probiot-

ics. A probiotic is a living micro organism administered to promote the health of the host by treating or preventing infections owing to strains of pathogens^[3]. Bio-therapeutic agents are defined as probiotics registered as drugs.

The modern view of probiotic therapy derives from the concept of a well functioning gut barrier and a normal balanced microbiota.

Numerous probiotic agents have been studied for the management of diarrhoeal disease. In particular, the prevention and management of acute viral diarrhoea, the treatment of recurrent *Clostridium difficile* diarrhoea, as well as the control of antibiotic-associated diarrhoea seem to be areas of significant potential benefit. A few agents, including *Lactobacillus GG*, *Lactobacillus reuteri*, and *Saccharomyces boulardii* (*S. boulardii*), seem to be promising agents for the amelioration of the course of acute diarrhoea in children when used therapeutically^[4]. Amongst these, all are bacteria except *S. boulardii*, which is yeast.

S. boulardii is a non-pathogenic yeast first isolated from lychee fruits in Indonesia and used first in France to treat diarrhoea, in the beginning of the 1950s. A lyophilised form is in clinical use in Europe, Asia, Africa, and Central and South America.

Preclinical and experimental studies of *S. boulardii* have demonstrated an anti-inflammatory, antimicrobial, enzymatic, metabolic and antitoxic activity. *S. boulardii* secretes a 54-KDa protease which has been shown to neutralize certain bacterial toxins; *S. boulardii* is also able to stimulate an immune response in the intestinal mucosa. It has a trophic effect by enhancing the metabolic function of the mucosa. *S. boulardii* releases polyamines, which are implicated in stimulating the enzymatic activity of the colonic mucosa^[3,5].

Based on our previous experience of use of *S. boulardii* in the treatment of diarrhoea, this study was undertaken to assess the efficacy of *S. boulardii* in the treatment of diarrhoea and reoccurrence of diarrhoea in subsequent two months.

MATERIALS AND METHODS

Patients

This randomised controlled clinical trial was carried out at Kharadar General Hospital, Karachi, catering to the needs of approximately one million population and situated in the middle and low-income community. An informed consent was obtained from parent/guardian of every child included in the trial. The children from 2 mo to 12 years of age presenting with acute watery diarrhoea of mild to moderate severity, fulfilling the inclusion criteria were included in this trial.

Children with severe inter-current illnesses, severe diarrhoea and dehydration requiring hospitalisation and intravenous therapy, presenting with temperature above 38.5°C, who were treated by any other anti-diarrhoeal/antibiotics in last 24 h as well as severely malnourished children were excluded from the trial. At inclusion, stool specimen was sent for bacterial culture and sensitivity as well as for Rota virus detection.

The study population of 100 children was randomised into two groups. In *S. boulardii* group, patients were

Table 1 Baseline characteristics

Patient characteristics	<i>S. Boulardii</i> (n = 50)	Control (n = 50)	P value
Age (mo)			
Mean	18.3	26.01	0.08
SD	20.33	23.37	
Weight (kg)			
Mean	8.2	9.15	0.224
SD	3.58	4.13	
Sex			
Female	50%	50%	1
Male	50%	50%	
Stool culture/Sensitivity	26%		
Bacteria isolated	74%	12%	0.125
Not isolated		88%	
Rota virus			
Positive	16%	20%	0.795
Negative	84%	80%	

managed by WHO-CDD protocol^[6] plus *S. boulardii* (250 mg bid) administered orally diluted in water or other semi-solid food. The product was manufactured by Hilton Pharma (Pvt) Ltd. under the license of Biocodex, France. In the control group patients were managed by WHO-CDD protocol only. The active treatment period was 5 d. Treatment of the subsequent episodes of diarrhoea was at the discretion of the treating physician.

All study participants were examined on d 0 (inclusion day), and followed up on d 3 and d 6 during active treatment phase and every month for two months thereafter for observation.

The first visit data collection included date of onset of diarrhoea, previous treatment (where applicable), weight of child, number and consistency of stools, vomiting, body temperature, sign of dehydration and any other data by clinical examination. The second visit information variables included date of stoppage of diarrhoea in case of inter-current recovery, weight of child, daily record of frequency and consistency of stools, tolerance and acceptability of treatment. Similarly on third visit, date of stoppage of diarrhoea in case of inter-current recovery, weight of child, daily record of frequency and consistency of stools, tolerance and acceptability of treatment were recorded in the study record forms.

A monthly observational follow-up data for two months included weight of child at monthly interval and any new episodes of diarrhoea in both the groups.

Statistical analysis

For statistical analysis, *t*-test was applied to measure the variation in means. $P < 0.05$ was taken as significant.

RESULTS

One hundred patients were analysed in the study, fifty patients in each group. Patient baseline characteristics in control and study groups were comparable (Table 1). Bacteria were isolated in 26% and 12% of the *S. boulardii* and control groups respectively while Rota virus detection

Table 2 Mean numbers of stools and duration of diarrhoea

	<i>S. boulardii</i>	Control	<i>P</i> value
Mean number of stools reported on d 0	9.5	8.8	0.37
Mean number of stools reported on d 3	2.8	4.4	0.01
Mean number of stools reported on d 6	1.6	3.3	0.001
Duration of diarrhoea (d)	3.6	4.8	0.001

Table 3 Number of episodes of diarrhoea

	<i>S. boulardii</i>	Control	<i>P</i> value
No. of episodes at 1 mo	0.2	0.64	0.001
No. of episodes at 2 mo	0.32	0.56	0.04

Table 4 Weight gain

	Group	% of mean weight gain	<i>P</i> value
% increase in wt. at 1 mo	<i>S. boulardii</i>	4.4	0.902
	Control	4.2	
% increase in wt. at 2 mo	<i>S. boulardii</i>	9.9	0.067
	Control	6.2	

revealed 16% and 20% positive for test and control group respectively.

On d 3 and d 6, there was a significant reduction in reported number of stools in *S. boulardii* group as compared to the control group. The mean duration of diarrhoea was 3.5 d in *S. boulardii* group and 4.8 d in the control group ($P = 0.001$) (Table 2).

Follow-up for the next two months also revealed interesting results. Mean numbers of episodes of diarrhoea by the end of two months, were 0.56 in control group as compared to 0.32 in *S. boulardii* group, which is almost half of that of control group (Table 3).

S. boulardii was well accepted and tolerated by the children and there were no reports of any side effects during the study period.

Table 4 also shows mean weight gain in both groups at mo 1 and 2. Although the difference of gain between the two groups has not reached statistical significance, the percentage of average increase in the experimental group was 9.9% as compared to 6.2% in the control group.

DISCUSSION

There are over 10^{9-12} bacteria per gram of faeces and about 400 different species, more than 10 times the human cells^[7]. The intestinal flora is intimately associated with the organ which contains it and with which it forms an ecosystem. Equilibrium within this ecosystem is essential to good health of the individual. It influences the structure, motility, physical and chemical conditions of intestinal tract, metabolic and enzyme activity of

mucosa and establishment and maturation of immune system. Finally and above all, the intestinal microbial flora forms a true resistance to colonisation of digestive tract by pathogenic microorganisms. Disruption of intestinal ecosystem occurs in many pathological situations such as infectious diarrhoea or diarrhoea and colitis linked to antibiotic treatment.

Despite awareness about preventive aspects of diarrhoea it remains one of the leading causes of morbidity and mortality in children, because of lack of clean water supply and sanitation.

Search for newer, less harmful agent is continued. Biological agents ("biotherapeutic agents" or "probiotics") have been used to treat a variety of infections, most notably infections of mucosal surfaces such as the gut and vagina. These biotherapeutic agents include certain bacteria and the yeast *S. boulardii*. Given orally, *S. boulardii* seem to be promising agents for the amelioration of the course of acute diarrhoea in children^[8].

The current study was based on our previous clinical observation, which revealed that children treated with *S. boulardii* had a decreased number of episodes of diarrhoea in following months.

This study verified our previous observation, as there was a 50% reduction in the number of episodes of diarrhoea in the treatment group as compared to control group (Table 2).

This study also showed a significant improvement in frequency and consistency of stool and reduction in duration of illness in patients who were given *S. boulardii* along with WHO-CDD protocol.

Several studies of *S. boulardii* have been done in children and adults in the treatment of acute diarrhoea^[9]. The results of our studies are consistent with some of these studies. However, the current study is the first one to observe the reduction in number of episodes of diarrhoea in the post-treatment follow-up period of two months. Stimulation of local immunity, as demonstrated by the increase of IgA, together with the enhancement of the trophic activity of the mucosa (through the release of polyamines) by *S. boulardii* may, at least in part, explain the long term effect of the yeast.

A meticulous follow-up of the patient resulted in very good compliance. No side effects were observed during the active treatment period with the use of *S. boulardii*. McFarland *et al* also highlight the safety profile in their review on *S. boulardii*^[10].

CONCLUSION

Based on our experience of this trial we conclude that *S. boulardii* is a useful and welcome addition to the treatment of acute diarrhoea in children. *S. boulardii* reduces the frequency of stool, and duration of illness. It also reduces the number of episodes of diarrhoea by 50% in the subsequent period of two months.

Though this is the first study of its kind in Pakistan, we are of the opinion that multicenter double blind placebo controlled trials need to be conducted to confirm our observations. Investigators have been using probiotics as

prophylaxis in childhood infection whereby it has been shown to reduce the rate of infection^[7,11].

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