Efficacy of *Saccharomyces boulardii* strain in acute diarrhoea in children: An Indian Perspective

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Research Article

Abstract: **Context**: There are different probiotic preparations are available in Indian market, but the efficacy & superiority over each other or ORS & zinc only is not established with certainty. At the same time whatever information is available none is conducted over Indian children so far. Hence, there is a need to study the efficacy of *Saccharomyces boulardii* in diarrhoea in Indian children. **Aims:** To compare the efficacy of ORS + Zn verses ORS + Zn + Probiotics *Saccharomyces boulardii* strain in treatment of acute diarrhoea in Indian children. **Settings and Design**: prospective, parallel, single blind randomized controlled clinical trial in Hospital attached with Medical College. **Methods and Material**: 75 children up to 5 years of age suffering from acute diarrhoea (three or more unformed stools within last 24 hrs) of less than 48 hours with CBC and stool microscopy negative for infection. All children were given ORS ad lib till resolution of diarrhoea and Zinc 10 mg per day in child of less than 6 month and 20 mg per day for child above 6 month a day for 14 days. While intervention arm (n=35) were also given *Saccharomyces Boulardii* 250 mg orally two times a day for 5 days. Main Outcomes Measured were duration of diarrhoea and duration of vomiting in days. **Statistical analysis used**: Z test and student t test **Results:** Mean duration of diarrhoea for study group was 3.4 days $\pm$ 1.4 days and for control group was 5.5 days $\pm$ 2.1 days (Z value 4.9). Average time of recovery from vomiting was 2.5 $\pm$1.2 days for study group & for control were 3.3 $\pm$ 1.2 days (t17 = 3.3, P< 0.01). **Conclusions:** *Saccharomyces boulardii* in the treatment of acute diarrhoea significantly reduces the duration of diarrhoea as well as vomiting.

Key-words: Probiotic; *Saccharomyces boulardii*; Acute diarrhoea; Indian children.

1. Introduction:

Acute diarrhoea is still major cause of childhood morbidity. It represents a heavy economic burden for family, society as well as nation [1, 2]. Treatment of acute diarrhoea consists of maintenance of rehydration by giving oral rehydrating solution or intravenous fluids as well as zinc supplementation as per the WHO guidelines.

Probiotics are defined as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" s per WHO and proposed as adjunctive treatment in management of diarrhoea [3]. They are considered to be food additives rather than drug, so only safety measures & no proof of efficacy is required for marketing [4]. On the other hand these drugs are gaining popularizing in treatment of diarrhoea without established efficacy [5, 6].

Cochrane meta-analysis of 23 randomized control manners found mild benefit from Probiotics that was regardless of organism [7]. A study from BMJ has conducted randomized clinical trial of five different probiotics preparation & concluded that all probiotics are not same regarding efficacy and depend on the strain of probiotic used [8].

There are different probiotic preparations are available in Indian market, but the efficacy & superiority over each other or ORS & zinc only is not established with certainty. At the same time whatever information is available none is conducted over Indian children so far. Hence, there is a need to study the efficacy of *Saccharomyces boulardii* in diarrhoea in Indian children.

2. Subjects and Methods:

The study was designed as prospective, parallel, single blind, randomized controlled clinical trial with allocation ratio 1:1. After getting the approval from institutional ethical committee study was conducted the study was conducted from July 2009 to December 2011 as per Helsinki declaration in tertiary care hospital attached with Medical College, including the children who were attended the outpatient department of paediatrics and were diagnosed as acute [child having 3 or more unformed stool in last 24 hours and duration of diarrhoea is less than 48 hrs] diarrhoea with no dehydration or some dehydration and without severe dehydration as per the WHO criteria by the expert in paediatrics. While non infective cases were defined as acute diarrhoea negative for *Vibrio cholarae* by hanging drop method, *Entamoeba histolytica* and *Giarrdea lamblia* by stool microscopy examination. The study protocol was explained in detail to the parent and informed written consent was obtained. \\

2.1 Sample size Sample size was calculated for equivalence study of a continuous response variable from independent control and experimental subjects. With the data shown in previous studies [9] duration of diarrhoea was 3.8 days in control group as compare to 2.8 in treatment arm and the response within each subject group was normally distributed with standard deviation 1.26. Accordingly we needed to study 34 experimental

subjects and 34 control subjects to be able to reject the null hypothesis with predictive power of 90%, with an alpha error of 5%. Hence 35 patients in each group were decided to be included.

2.2 Enrolment – children under 5 years of age with acute diarrhoea [three or more unformed stools] in last 24 hours with duration of less than 48 hours having no dehydration or some dehydration as per WHO criteria were included. Children with any concurrent chronic illness, severe and very severe under nutrition [weight for age less than 60% of 50th percentile of CDC 2000 standards as this is the classification used by Indian academy of Paediatrics and part of ICDS programme too], severe dehydration [as per WHO criteria] allergy or history of use of probiotic, antibiotic or antidiarrhoeal in last 24 hours were excluded. Of these who demonstrated stool microscopy negative for infective pathology [presence of Vibrio cholerae by hanging drop method, Entamoeba histolytica and Giardia lamblia by simple microscopy] were finally analyzed for intention to treat analysis. While children found positive for above organisms were excluded from the study. Reports were made available on the same day.

2.3 Data collection – Baseline data was collected including name, age, address, contact numbers, duration of illness, frequency of diarrhoea and vomiting, presence of associated symptoms i.e. abdominal pain, fever and headache. History of use of any probiotic, antibiotic or antidiarrhoeal was elicited. Evaluation was done for the sign of dehydration as per WHO criteria for no dehydration or some dehydration. Weight was recorded to nearest 0.1 kg and height was recorded to nearest 0.1 cm by the same observer with standard scale.

2.4 Randomization and Allocation – Patients were assigned a study number corresponding to their entry in trial. They were randomized to intervention following simple randomization procedure with the help of computer generated random numbers. Randomization Sequence was assessed by the third person and was declared only after the patient was decided to be included in trial. As per the allocation, drugs were prescribed to the patients by the pediatrician. Data was collected by and analyzed by investigators. Patients and treating Pediatricians were aware of the allocation arm but outcome assessor and data analysts were kept blinded to the allocation.

2.5 Intervention - All children included in the study were received received Oral Rehydrating Solution as much as required after passing of each stool or vomiting or both and whenever child demand for it, as per WHO criteria for no dehydration as well as with some dehydration till resolution of diarrhoea and zinc 10 mg per day in child of less than 6 month and 20 mg per day for child above 6 month a day for 14 days. Children in study arm also received *Saccharomyces boulardii* 250 mg orally two times a day for 5 days. *Saccharomyces boulardii* was available as lyophilized powder in sachet weighing 282.5 mg equivalent to 250 mg of yeast available as "ECONORM" by Dr. Reddy's lab. Preparation was given directly, or with water or other beverages at room temperature. Each study day was defined as 24 hours counted from the administration of study drug. Patient was monitored daily on OPD basis till recovery from diarrhoea and vomiting and up to 14 days which ever occurred later. Record was kept for frequency of diarrhoea and vomiting, consistency of stool for every 24 hours. We also noted for any possible adverse events like hypersensitivity reactions.

2.6 Outcome measures –

2.6.1 Time of recovery from diarrhoea – patients were assessed daily on OPD basis for frequency and duration of diarrhoea in days in which consistency of stool has come to Normal i.e. hard and formed stools as per the Kings scoring system [9] from the time of admission. Passage of two consecutive formed stools or having no stool passing till 12 hours was considered as resolution of diarrhoea.

2.6.2 Time of recovery from vomiting – duration in days in till last episode of vomiting from the time of admission.

3 Results:

The Demographic statistics and associated symptoms of both the group were described in Table 1.

Table No – 1 Demographic characteristics and associated symptoms of both groups

Characteristic	Study Group N=35	Control Group N=35
Mean age ± SD (months)	11.46 ± 8.64	13.55 ± 12.84
Mean weight ±SD (Kg)	7.98 ± 3.21	8.51± 3.81
Male	17 (48.6%)	14 (40%)
Female	18 (51.4%)	21 (60%)
Cold	2 (5.7%)	1 (2.9%)
Sneezing	0 (0%)	1 (2.9%)
Fever	16 (45.7%)	13 (37.1%)
Cough	2 (5.7%)	2 (5.7%)
Irritability	1 (2.9%)	1 (2.9%)
Pain in abdomen	5 (14.3%)	7 (20%)
Weakness	3 (8.6%)	2 (5.7%)
Some dehydration	3 (8.6%)	4 (11.4%)
No dehydration	32 (91.4%)	31 (88.6%)

Foot note – value in parenthesis are percentage

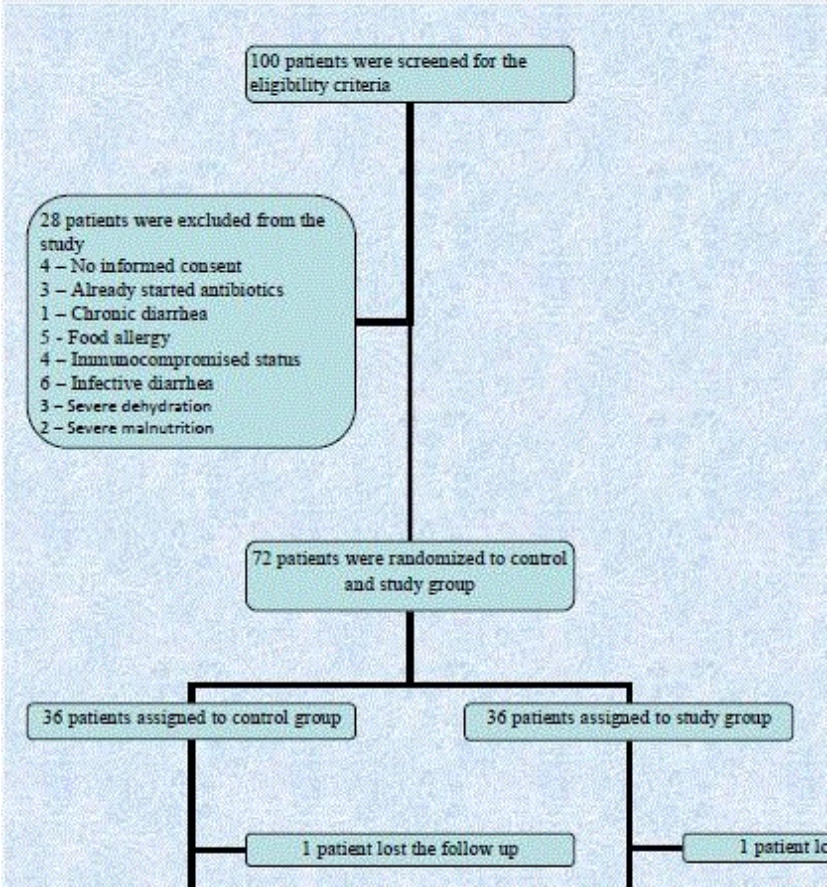
Difference between these parameters was non significant between study and control group and equally distributed. Associated symptoms like cold, sneezing, cough and irritability was treated by steam inhalation in both group at home while fever was treated by paracetamol 5mg/kg three times a day till temperature

come to normal. For weakness, pain in abdomen and dehydration, ORS was given as per protocol. Gripe water was not given to any of child. All these symptoms were reduced to nil by the end of 3 days in both groups

Total of 100 patients were screened and 28 were excluded due to various reason [refer Fig 1: Profile of randomized trial], 36 each were included in study and Control group respectively and 1 patient from each group had lost the follow up. Hence 35 patients from each group were included in the analysis.

Eligible participants were recruited and follow up till 14 days after enrollment of the patient was done.

The patients included in analysis were 35 in each group. 3 patients in study group and 4 patients in control group had some dehydration while 32 patients in study group and 31 patients in control group have no dehydration at the time of presentation.



3.1 Time of recovery from Loose Motions –

Average time for recovery for study group was 3.4 days ± 1.4 days and for control group was 5.5 days ±2.1 days [Z value 4.9]. Hence, the patient who was receiving *Saccharomyces boulardii* has early recovery from loose motions as compared to patient who are not receiving Refer Table no 2.

3.2 Time of recovery from Vomiting –

There were 11 patients in study group & 8 patients in control group also having the vomiting. Average time of recovery for study group was 2.5 ±1.2 days & for control were 3.3 ± 1.2 days. [Value of two tailed unpaired student t test at the degree of freedom of 7 was 3.3, P< 0.01] Refer table no 2

Table No 2 - Mean duration of recovery

Time for recovery	Study group(mean ±SD)	Control group (mean ±SD)	P value
Diarrhoea	3.4 ± 1.4 days	5.5 ±2.1 days	Z value 4.9
Vomiting	2.5 ± 1.2 days	3.3 ±1.2 days	t17 value =3.3, P< 0.01

4 Discussion:

Reduction in duration of diarrhoea by *Saccharomyces boulardii* was found significant by some authors [9, 10, 11] while non-significant by others [12].

Our study shows the reduction in the duration of diarrhoea in *Saccharomyces boulardii* group as compare to control group not received the probiotic.

We had tried to remove the confounding factors like severe dehydration, malnutrition, history of any

concurrent chronic illness, allergy or use of probiotic/ antibiotic/ antidiarrhoeal in the excluding criteria. The decreased duration of diarrhoea by 2 to 3 days has welcomed by parents as well as it probably may have indirect effects like decrease absenteeism, less risk of post diarrhoeal consequences like malnutrition and decreased absenteeism for parents and kids alike.

In our study the group receiving the *Saccharomyces boulardii* is having the significantly early recovery by from vomiting as compare to control group. Earlier studies by Raza et al [13] also shows the significant earlier recovery from vomiting by Lactobacillus probiotic while Grandy G et al [14] shows the significant reduction in duration of vomiting by *Saccharomyces boulardii* in his study of rotaviral diarrhoea.

The beneficial effects of *Saccharomyces boulardii* may be due to antitoxin effect against the bacteria, antibacterial activity by preservation of tight junction and preventing the bacterial invasion, modulation of intestinal flora or by increasing the short chain fatty acids in lumen. Trophic action involves increased enzymes against viral infection and increased IgA activity while anti-inflammatory effects may be due to decreased synthesis of inflammatory cytokines. They have been documented by many authors in various studies including the review and meta-analysis by McFarland LV [15].

The strength of our study is the first study to see the effect of probiotic in Indian perspective with standardized strain, dose and also with Zn as per the WHO criteria, and has been conducted in the tertiary hospital attached with the medical college. As we may not extrapolate the results of western population in Indian children due to higher breast feeding rate and different microbiological colonization [16], our study may provide the data base for further research.

5 Conclusion:

Findings from the present study conclude that addition of *Saccharomyces boulardii* in the treatment of acute diarrhoea significantly reduce the duration of diarrhoea as well as vomiting.

Key Messages:

Saccharomyces boulardii is effective in reducing the duration of diarrhoea as well as vomiting in Indian paediatric acute diarrhoea with acceptable tolerability.

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