Original Article

Use of Probiotics in the Management of Acute Watery Diarrhoea in Nigerian Children: How Effective are S. Boulardii only Preparations?

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Abstract

Background: Diarrhoeal diseases are a major cause of death worldwide particularly among under-fives and probiotics is used in the management of diarrheal diseases. While some probiotics are of unproven usefulness, others are. Despite the burden of diarrhoea diseases in Africa; there is paucity of studies to support the efficacy or otherwise of S. boulardii among children with diarrheal disease. This study examined the impact of S. boulardii on the clinical course of acute watery diarrhea in children in a tertiary hospital in Nigeria.

Methodology: Two hundred and fifty under-five children with acute watery diarrhoea were recruited and treated in the hospital. One hundred and twenty-five were given probiotics (S. boulardii) in addition to Oral Rehydration solution (ORS), zincand antibiotics while the other one hundred and twenty-five were noton probiotics (Controls). Their stool frequency on the 3rd and 5th day and the duration of the diarrhea, were used to assess outcome. Information was obtained using a questionnaire and then analysed.

Result: Majority of the children (58.8%) were at their second half of infancy (7-12 months).The average number of diarrheal episodes was significantly lower among the subjects by the 3rd day of intervention ($t = 2.496$, $p = 0.013$) but not by the 5th day ($t = 0.212$; $p = 0.832$). Duration of diarrhea however, was not significantly different between the subjects and controls ($p = 0.246$).

Conclusion:S. Boulardiionly probiotic preparations reduce the number of diarrhoeal episodes but not the duration of diarrhea among under- 5s.

Key words: S. Boulardii; Probiotics; Diarrhoea; Children; Nigeria.

Introduction

According to the World Health Organization, acute watery diarrhoea is defined as the abrupt onset of three or more loose stools per day and lasts not longer than 14 days. Diarrhoeal diseases are a major cause of death among children worldwide. Worldwide among under-fives, 2.5 billion episodes of diarhoea occur per year[1] and diarrhea accounts for 15% of childhood deaths.[2]Probiotics are live microorganisms that confer a health benefit on the host, [3] and have been used to treat multiple gastrointestinal (GI) diseases including diarrheal diseases.[4]While some probiotics are of unproven usefulness, others have been widely studied and found to be useful more so in some particular type of gastrointestinal diseases. An increasing number of potential health benefits are being attributed to probiotic treatments.[7,8,9,10] However, only a limited number have been confirmed in well-designed and conducted randomized controlled trials (RCTs).[5] This is even more evident in the paediatric population where only a few studies exist on the efficacy of probiotics particularly *S. boulardii* in children.[5]

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Ahmadi et al[10] in 2015 did a systematic review of randomized controlled trials about the administration of probiotics in the treatment of acute rotavirus diarrhea in children. Thepooled estimate of efficacy of probiotics in prevention or treatment of disease yielded in all studies a mean difference of 0.41 (CI 95%: -0.56 to –0.25; $p<0.001$). Furthermore, the pooled estimate of efficacy of *lactobacillus rhamnosus* GG and other probiotics significantly reduced the duration of diarrhea. Among trials, the overall reduction of Lactobacillus rhamnosus GG (LGG) was 0.47 (CI 95%: -0.80 to -0.14; $p= 0.020$). They concluded that probiotics exert positive effect in reducing the duration of watery/loose stools related to rotavirus diarrhea.

The nonpathogenic yeast *Saccharomyces boulardii* has been prescribed in the past 30 years for prophylaxis and treatment of diarrheal diseases caused by bacteria.[5]However, although *S. boulardii* has been reported to demonstrate clinical and experimental effectiveness in gastrointestinal diseases, its efficacy particularly in the treatment of childhood diarrhoea is poorly studied and remains unclear.[6]*S. boulardii* is a live yeast used extensively as a probiotic and often marketed as a dietary supplement.[11] Several mechanisms of action have been identified directed against the host as well as pathogenic microorganisms.[12, 13,14] Randomized Controlled Trials [15,16] using *S. boulardii* showed that this probiotic may be effective in treating acute adult diarrhea due to a variety of causes and can significantly lower diarrhea severity score compared with controls.

While studies abound on the usefulness of *S.boulardii*, only a few [5, 7] exist on its role when given as a lone probiotic (*S boulardii* only preparation), and not in a mix with other probiotics, in the management of acute diarrhoeal disease in children. Canani et al[17] in 2007 examined the use of probiotics for treatment of acute diarrhoea in children and concluded that not all commercially available probiotic preparations are effective in children with acute diarrhea and recommended that paediatricians should choose bacterial preparations based on effectiveness data.

Most of the studies on probiotics were done outside the African continent and largely on adults. Despite the fact that more children die from diarrheal disease in sub-Saharan Africa, there is paucity of studies to support the efficacy or otherwise of *S. boulardii*only probiotic preparations among children with diarrheal disease in Africa. The goal of this study is to review the impact of *S. boulardii* on the clinical course of acute watery diarrhea in children in Enugu State University Teaching Hospital (ESUTH), Parklane, a tertiary hospital in Enugu, South East Nigeria.

Materials and methods

Ethical Considerations

Ethical approval was obtained from the Health Research Ethics Committee of the ESUTH Parklane, Enugu with approval number ESUTH/C-MAC/RA /034/078. Written informed consent was obtained from the caregivers of all participants. This work was done in keeping with the Helsinki declaration of 1975 as revised in 2000.

Inclusion criteria

All children less than 5 years with acute watery diarrhea were included in the study.

Exclusion Criteria

Children who have diarrhoea lasting more than 14 days; have existing severe malnutrition (below -3 Z scores) or require intensive care management were excluded from the study. Additionally, children on Anti-fungal medications and those whose parents did not consent to the study were excluded from the study.

Background/Setting

This study was conducted at the Children Emergency Room (CHER) of the Department of Paediatrics, ESUTH Parklane in Enugu State, South East Nigeria between October 2017 and March 2019.

Study design

All children who presented at the Children emergency room with diarrhea were informed about the study and written consent obtained before they were screened for eligibility for inclusion in the study. Subsequently their vital signs and anthropometry (weight, height/ length and mid upper arm circumference) ascertained. The anthropometry was used to ascertain their nutritional status. The weight for age was plotted on the WHO weight for age chart appropriate for gender and was expressed in Z scores. Children whose weight fell below 3- Z scores were considered to be severely malnourished and were excluded from participating in the study.

There after two hundred and fifty under-five children (One hundred and twenty- five each of Subjects and Controls) with acute watery diarrhoea(less than fourteen days duration),who met the inclusion criteria

and whose parents gave consent for participation in the study, were consecutively recruited.

Patients were consecutively assigned to receive the active product, *S. boulardii* (*Sacrovisk*®) in addition to fluid therapy (ORS and or Intra-venous fluid) and zinc gluconate (for subjects) or fluid therapy (ORS and or intra-venous fluid) and zinc gluconate alone (for controls) till the sample size was reached. The subjects received *S. boulardii* 250mg twice daily for 5 days. The ORS was administered according to the World Health Organisation guidelines for management of diarrhea. Zinc gluconate was also given at 10mg once daily for 10 days for children whose body weight is 10kg and below and 20mg daily for children above 10 kg body weight.

The frequency and duration of diarrhea was recorded daily in the proforma designed for the study until the patients recorded less than three episodes of loose stool in a day. Patients that were transferred to the paediatric wards were followed up to update the proforma while those that were discharged from hospital before the 3rd day of intervention were followed via phone calls and follow up visits. The frequency (number of diarrhoeal stools/episodes) on the 3rd and 5th day and the duration of the diarrhea from the onset of interventions, were used to assess outcome.

In this study, diarrhea is defined as passing three or more loose stools per day (loose stool is a stool that takes the shape of the container) based on the WHO definition.[18] Cessation of diarrhea was therefore regarded as passage of less than three stools per day or stools only. Criteria for discharge were cessation of diarrhea and resolution of fever.

Statistics

Information obtained from the participants was recorded in the questionnaire and subsequently transferred to the data editor of SPSS for analysis. Descriptive statistics (mean) was obtained for variables such as age and anthropometric measurements that were normally distributed whereas categorical variables were summarized using frequencies and percentages. The comparison of means which were normally distributed was done using Student's *t*-test. The significance of the associations between categorical variables was determined using Chi-square statistical test. All the tests were taken as statistical significance at $P< 0.05$. Results were presented in tables and prose.

Results

The participants were children less than 5 years of age with majority (58.8%) belonging to the second half of infancy (7-12 months) while the least were in the age group of 13-59 months (10.4%). There were more male amongst the Subjects compared to the controls but the difference was not statistically significant ($p = 0.445$).

Table 1: Demographic characteristics

	Subject n (%)	Control n (%)	*T*	*p* value
Age group(months)				
< 7	41 (32.8)	36 (28.8)	0.495	0.781
	71 (56.8)	76 (60.8)		
13– 59	13 (10.4)	13 (10.4)		
Sex				
Male	72 (57.6)	66 (52.8)	0.582	0.445
Female	53 (42.4)	59 (47.2)		

Although the mean ± SD age and weight of the subjects was higher than those of the controls; they were not statistically significant. Similarly the height and mid upper arm circumference of the controls were higher than those of the subjects however the differences were not statistically significant. (Table II)

Table 2: Comparison of mean age and anthropometry of the participants

	Subject Mean ± SD	Control Mean ± SD	*T*	*p* value
Age	11.79 ± 1.20	9.92 ± 1.49	1.022	0.308
Weight	9.32 ± 8.38	8.35 ± 2.63	1.229	0.220
Height/length (cm)	70.47 ± 13.60	70.71 ± 12.58	0.142	0.887
Mid upper arm circumference	14.71 ± 2.16	14.98 ± 1.74	1.080	0.281

Table 3 shows that 37 (14.8%) of the children had microscopic blood in stool and that a significantly higher percentage of the subjects had blood in the stool compared to the controls ($X^2 = 5.361, p = 0.021$). From the table, more of the controls had passage of loose stool of less than 4 days duration before presentation but was not statistically significant. Additionally, more Subjects than controls had stool frequency of 1-4 episodes per day but the difference was not statistically significant.

Table 3: Comparison of history of diarrhea between subjects and controls

	Subject n (%)	Control n (%)	χ^2	*p* value
How many days has your child been passing watery stools?				
1-3 days	76 (60.8)	79 (63.2)	0.153	0.696
>3 days	49 (39.2)	46 (36.8)		
Frequency of diarrhea (No. Of episodes per day)				
1 – 4	71 (56.8)	57 (45.6)	3.138	0.076
>4	54 (43.2)	68 (54.4)		
Is there blood in stool?				
Yes	25 (20.0)	12 (9.6)	5.361	0.021
No	100 (80.0)	113 (90.4)		

Table 4 shows that the average number of diarrheal episodes was significantly lower among the children on probiotics when compared to those not on probiotics by the 3rd day of intervention (t = 2.496, *p* = 0.013) but not by the 5th day of intervention (t = 0.212; *p* = 0.832). Duration of diarrhea however, was not significantly different between the subjects and controls (p = 0.246)

Table 4: Comparison of frequency and duration of diarrhea between subjects and controls

	Children on Probiotics Mean ± SD	Children not on Probiotics Mean ± SD	T	*p* value
No. of diarrheal episodes on the 3rd day of intervention	3.06 ± 1.49	3.58 ± 1.74	2.496	0.013
No. of diarrheal episodes on the 5th day of intervention	1.18 ± 1.51	1.22 ± 1.46	0.212	0.832
Duration of diarrhea (days)	4.42 ± 1.64	4.21 ± 1.28	1.163	0.246

Discussion

Diarrhoea remains a major cause of mortality among under-5s around the world, especially in developing world.[19,20] The higher incidence rates in the developing world is reportedly due to inadequate water, poor sanitation and suboptimal breastfeeding, zinc and vitamin A deficiency[20–23] Furthermore some studies opine that amongst the under5s; it is more common on children less than 2 years.[24,25] This is supported by the finding in this study that majority of the under 5s with diarrhea were in their second half of infancy. The reasons for this is not very clear however it could be due to suboptimal breastfeeding, as well as zinc and Vit A deficiency as earlier documented.[20-23] However this finding may also be connected with the fact that by the second half of infancy the maternally derived anti-bodies are beginning to wane and the child is beginning to get more active making the child more prone to infections including diarrhoeal diseases.

The finding of significantly less episodes of diarrhea in subjects on day three in this study agrees with other studies using *S. boulardi.*[6, 26,27] The finding of no significant difference in episodes on 5th day can be explained since most acute watery diarrhea last less than 7 days without probiotic treatment. So by the 5th day the diarrhea illness in control group would be expected to be resolving.

There was no significant difference in the duration of diarrhea between the subjects and control in this study. This is at variance with other studies.[6,26-28] A position paper published by European Society for Paediatric Gastroentorology Hepatology and Nutrition (ESPGHAN) Working Group for Probiotics and Prebiotics based on a systematic reviews and randomized controlled trials suggested that *S boulardii* (low quality of evidence) may be considered in the management of children with acute gastroenteritis in addition to rehydration therapy.[28]

A meta-analysis of data from Randomized Control Trials (RCT) reported that the use of *boulardii S.* day in healthy children is associated with clinical benefits in the treatment of AGE, specifically a reduction in the duration of diarrhoea by approximately 1 day.[29] The authors however stated that the finding should be interpreted with caution because of the methodological limitations and heterogeneity of studies recruited in the study. [29]Some authors have considered viability of the probiotics and the dose given as possible factors influencing the outcome of its use apart from the type of diarrhea the child has.[30-32] Some other factors such as not being breastfed, blood in stool have been identified as risk factors for prolong duration of diarrheal illness and may affect outcomes even when probiotics is used.[33,34]

This study however did not separately analysestools samples of children who have blood in stool. The higher number of subjects having blood in stool compared to controls in this study may have contributed to the finding of no significant difference in the duration of illness. Additionally, since zinc is known to reduce the duration of diarrhea; the inclusion of zinc to the medications in both groups of subjects may have dwarfed into insignificance the impact of *S.boulardii* on stool duration in these children.

Conclusion

Although probiotics preparations containing *S. Boulardii* alone reduce diarrhoea episodes, it does not significantly reduce the overall duration of diarrhea in these children.

Recommendation

Studies involving larger population sizes and with *S. Boulardii* alone may be needed to further elucidate this finding.

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Conflicts of interest

There are no conflicts of interest

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