COMPARISON OF WORLD HEALTH ORGANIZATION TREATMENT FOR ACUTE WATERY DIARRHEA IN CHILDREN WITH AND WITHOUT SACCHROMYCES BOULARDII IN TERMS OF MEAN DURATION OF DIARRHEA

Ali Raza, Muhammad Zahid*, Ehsan Qadir, Nazir Ahmed Malik***, Sohail Aslam****, Kashif Siddique*****

Combined Military Hospital Tarbela/National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Sargodha/ National University of Medical Sciences (NUMS) Pakistan, **Combined Military Hospital Mangla/National University of Medical Sciences (NUMS) Pakistan, ***HITEC Institute of Medical Sciences, Taxilla/National University of Medical Sciences (NUMS) Pakistan, ****Combined Military Hospital Kharian/National University of Medical Sciences (NUMS) Pakistan, *****University of Lahore, Lahore Pakistan

ABSTRACT

Objective: To compare World Health Organization treatment for acute watery diarrhea in children with and without probiotic Saccharomyces boulardii in terms of mean duration of diarrhea.

Study Design: Comparative cross sectional study.

Place and Duration of Study: Combined Military Hospital Tarbela, Pakistan, from Jan 2019 to Jul 2019.

Methodology: Eighty four children were enrolled in this study using inclusion and exclusion criteria. Two groups were made. Group A was treated with oral Zinc (10mg for <6 months old, 20mg for >6 months old for 14 days); low osmolarity Oral rehydration salt by 5 ml/kg per hour and continuation of nutritious feeding. Group B was treated with 250mg twice daily Sacchromyces boulardii along with oral Zinc (10mg for <6months old, 20mg for >6 months old for 14 days); low osmolarity Oral rehydration salt by 5 ml/kg per hour and continuation of nutritious feeding. Assessment included anthropometric measurements, hydration status, daily frequency and consistency of stools. Baseline investigations were sent to Combined Military Hospital, Tarbela Laboratory. Data was recorded on a specially designed proforma.

Results: Duration of diarrhea was significantly lower in children who were given Saccharomyces boulardii with Zinc as compared to children who were given Zinc alone. i.e., group-A (Zinc): 53.31 hrs vs. group-B (Zinc+ Saccharomyces boulardii): 36.37 hrs, $p<0.001$

Conclusion: Saccharomyces boulardii can be effectively used with Zinc to treat acute watery diarrhea in children less than five years of age as it significantly reduces mean duration of diarrhea.

Keywords: Children, Diarrhea, Probiotic, Saccharomyces boulardii, World Health Organization.

INTRODUCTION

Diarrhea as defined by the World Health Organization (WHO) is passing three or more loose or watery stools and an increase in stool frequency over 24-hour period[1]. Annually greater than 750,000 deaths occur in children under five year of age, especially in developing countries; making it second leading cause of death in this age group[1]. Oral rehydration salt (ORS), continued nutritious feeding and zinc are mainstay of World Health Organization recommended treatment for acute watery diarrhea[2].

One of the natural approaches for acute watery diarrhea is use of probiotics[3]. Probiotics are living microorganisms that, when used in adequate amount, are beneficial for the health of the host[4]. They provide protective barriers; enhance immune responses, and clear pathogens from the gastrointestinal tract[3].

Saccharomyces boulardii (SB) is one of the most commonly used probiotics[5]. It is a yeast that was first isolated from lychee in 1923[6]. It has been safely prescribed over past 50 years as probiotic[5].

With diarrhea being second leading cause of death among children under five year of age there is need to look for alternative treatment modalities to reduce the burden of this illness. Saccharomyces boulardii is a time-tested probiotic. Evidence from different centers around the globe can lead to inclusion of this probiotic to World Health Organization standard treatment

Correspondence: Dr Ali Raza, Consultant Pediatrician, Combined Military Hospital, Tarbela, Pakistan

Received: 20 Oct 2019; revised received: 22 Jan 2020; accepted: 27 Jan 2020

protocol along with low osmolarity ORS, continued feeding and Zinc.

METHODOLOGY

Our study, was carried out at Combined Military Hospital Tarbela, from Jan 2019 to Jul 2019 after the approval of Ethics Review Board (Ref no. 2018-14, dated Dec 12, 2018). Sample size was calculated using WHO calculator (1.1) with level of significance = 5%, power of test = 80%, pool standard deviation=27.5 (7), population mean=52.08 (7), test value= 64.04 (7) and sample size in each group (n) = 42 (7).

Non-probability consecutive sampling was used. Inclusion criteria were children between 3 months to 60 months of age; children with acute watery diarrhea for last 24 hours and admitted cases of both genders. Exclusion criteria were children having blood in stool or evidence of bacterial infection; children with severe dehydration; children having history of allergy to probiotics/yeast; children on anti-fungal medication and immuno-compromised children. Patients fulfilling the inclusion criteria were selected. The parents of the patients were explained accordingly and informed written consent was taken after assuring them, benefits and risks of the study. Hospital registration number, name, age and gender were noted. Two groups were made by lottery method. Group A was treated with oral Zinc (Zincat OD by ATCO pharma; 10mg for <6months old, 20mg for >6 months old for 14 days); low osmolarity ORS by 5 ml/kg per hour and continuation of nutritious feeding. Group B was treated with 250mg twice daily Sacchromyces boulardii (Enflor sachet by Hilton pharma; spores of similar pharmaceutical company) along with oral Zinc (Zincat OD by ATCO pharma; 10mg for <6 months old, 20mg for >6 months old for 14 days); low osmolarity ORS by 5 ml/kg per hour and continuation of nutritious feeding. Assessment included anthropometric measurements, hydration status, daily frequency and consistency of stools. Baseline investigations including blood complete picture; C-reactive protein; serum urea, creatinine & electrolytes and stool routine examination were sent to Combined Military Hospital, Tarbela Laboratory. Date & time for intervention and improvement in stool consistency/frequency were recorded on a specially designed proforma.

Data analysis was computer based with the use of SPSS-16. Mean and standard Deviation (SD) were calculated for quantitative variables like age and duration of diarrhea. Frequency and percentage were used for qualitative variables like gender. Independent sample t-test was applied to compare mean duration between two groups. A *p*-value <0.05 was taken as significant.

RESULTS

It was observed that duration of diarrhea was significantly lower in children who were given Saccharomyces boulardii (SB) with Zinc as compared to children who were given Zinc alone. i.e. group-A (Zinc): 53.31 ± 12.18 hrs vs. group-B (Zinc + SB): 36.37 ± 9.79 hrs, *p*-value <0.01.

Mean ± SD age of children in group-A and in group-B was shown in table-I. In both treatment groups minimum and maximum age of children was 3 and 60 months respectively.

Table-I: Demographic characteristic of patients in study groups: Age in months.

	Group-A	Group-B
n	42	42
Mean ± SD	18.26 ± 17.76	20.26 ± 17.42
Min	3.00	3.00
Max	60.00	60.00

Group-A= Zinc, Group-B= Zinc + Saccharomyces boulardii

Table-II: Demographic characteristic of patients in study groups: gender distribution.

	Group-A	Group-B
Male	27 (64.3%)	27 (64.3%)
Female	15 (35.7%)	15 (35.7%)

Group-A= Zinc, Group-B= Zinc+ Saccharomyces boulardii

Gender distribution in both groups was shown in table-II.

Mean duration of duration of diarrhea was significantly shorter for children in group-B as compared to children in group-A. i.e. *p*-value <0.01, shown in table-III.

Among children in the age group 3-15 months and 16-30 months; mean duration of diarrhea was significantly shorter in group-B. However among children who were 31-45 months and 46-60 months old; duration of diarrhea was shorter in group-B but it was not statistically significant as shown in table-IV.

Among male and female children mean duration of diarrhea was significantly shorter in group-B as compared to group-A (table-V).

Table-III: Clinical characteristic of patients in study group: mean duration of diarrhea (Hrs).

	Group-A	Group-B
n	42	42
Mean ± SD	53.31 ± 12.18	36.37 ± 9.79
Min	27.60	17.30
Max	80.70	50.60

Group-A= Zinc, Group-B= Zinc+ Saccharomyces boulardii

Table-IV: Clinical characteristic of patients in study groups: mean duration of diarrhea stratified for Age (Months).

	Group-A	Group-B	*p*-value
n	42	42	
3-15	59.68 ± 8.73	40.57 ± 7.82	<0.01
16-30	44.23 ± 9.74	29.20 ± 9.33	<0.01
31-45	45.23 ± 10.47	33.33 ± 8.73	>0.01
46-60	42.70 ± 13.80	32.38 ± 11.65	>0.01

Group-A= Zinc, Group-B= Zinc+ Saccharomyces boulardii

Table-V: Clinical characteristic of patients in study groups: mean duration of diarrhea stratified for gender.

	Group-A	Group-B	*p*-value
n	42	42	
Male	52.05 ± 13.11	37.78 ± 8.57	<0.01
Female	55.59 ± 10.33	33.82 ± 11.55	<0.01

DISCUSSION

Worldwide diarrhea is responsible for 1 in 9 child deaths making it second largest cause of death in children under 5 years of age[9]. Diarrhea is responsible for 17% of all deaths among under five children; a percentage higher than combined percentage of measles, malaria and AIDS[9]. Causes of diarrhea can be viral, bacterial, and parasitic[10]. Most common cause of acute water diarrhea in children is rotavirus and its treatment includes oral rehydration therapy and Zinc[11]. Misuse of antibiotics by some general practitioners in acute watery diarrhea leads to antibiotic-resistance, adverse effects and unnecessary costs. It is therefore very important to look for alternate therapies in effectively treating this global burden in pediatric population.

One of the alternative therapies is use of Probiotics[8]. Probiotic is a Latin word meaning "for life"[13]. They are defined as live microorganisms that, when given in adequate amount, are beneficial for the health of the host[14]. Concept of probiotics dates back to many centuries when fermented milk was used to confer benefits related to health[13]. Mechanisms of action of probiotics include resistance to colonization of organisms; production of acids and short-chain fatty acid; intestinal transit regulation; normalisation of disturbed microbiota; increased enterocytes turnover and competitive resistance to pathogens[15].

Probiotics are generally safe and well tolerated in human beings but life threatening bacteremia and fungemia can occur after their use[16].

Effects of probiotics in Pediatric population include decreased duration of diarrhea; prevention of antibiotic associated diarrhea; prevention of hospital acquired diarrhea; prevention of day care infections; reduced risk of allergies; reduced risk of necrotizing enterocoloitis;reduced crying time in infantile colic; induction of remission in inflammatory bowel diseases; decreased severity of pain in irritable bowel syndrome and increased eradication rate of *H.pylori*[15].

Most commonly used probiotic yeast is Saccharomyces boulardii[15]. It was discovered in 1923 by a French scientist Henri Boulard in tropical fruit (lychee & mangosteen)[17]. It is a eukaryotic, single cell yeast with cell diameter of 2-3 µm and length of 2.5-10.5 µm. It reproduces asexually by budding and sexually by conjugation. Optimal temperature for growth is 37°C[18]. Its extract had inhibitiory effects against more than 25 food borne bacteria[18]. Its use in diarrhea has been studied for more than 30 years and it is safe in children[17,8].

In our study it was observed that duration of diarrhea was significantly lower in children who were given Saccharomyces boulardii (SB) with Zinc as compared to children who were given Zinc alone. i.e. group-A (Zinc): 53.31 ± 12.18 hrs vs. group-B (Zinc + SB): 36.37 ± 9.79 hrs, *p*-value <0.01.

Efficacy of Saccharomyces boulardii is shown by several studies across the globe for treating acute diarrhea in children. In 2012, Riaz *et al* conducted a double blind randomized control trial in which mean duration of diarrhea (after introduction of Saccharomyces boulardii) was significantly (95% CI = -28.13 to -5.43) shorter in WHO treatment with probiotic saccharomyces boulardii group (52.08 ± 24.57 hrs) as compared to other group containing World Health Organization treatment with puffed rice powder (64.04 ± 30.43 hrs). The time of appearance of first semi formed stool in Saccharomyces boulardii group (39.48 ± 23.09 hrs) was significantly (95% CI -25.4 to -3.87) shorter than other group containing World Health Organization treatment with puffed rice powder (54.13 ± 28.21 hrs)[7].

In 2010, Eren *et al* compared effect of saccharomyces boulardii and yogurt fluid on childhood diarrhea. Stool consistency normalized in both groups almost at the similar time 3.07 ± 2.01 days versus 3.07 ± 1.73 days; *p*>0.05 (PP). But much decrease in frequency of stools was observed on first day with Saccharomyces boulardii, and on second day with yogurt fluid. Frequency of stools decreased from a mean of 8.18 ± 3.64 to 6.43 ± 3.97 on first day in the Saccharomyces boulardii group (*p*=0.016). While in the yogurt fluid group, frequency of stoolsdecreased from 7.93 ± 3.97 to 7.14 ± 3.90 on first day (*p*=0.139) and to 6.22 ± 3.77 on second day (*p*=0.045). There was no difference in the total duration of hospital stay (4.68 ± 2.37 versus 4.23 ± 1.72 days; *p*=0.45) (PP)[19].

In 2017 Farhat *et al* compared clinical efficacy of combined versus monotherapy of oral Zinc and Saccharomyces boulardii in pediatric acute diarrhea at a tertiary care facility. Group A was given Zinc; group B was given probiotic and group C was given zinc and probiotic combination. On 3rd day 96% patients of group C had improved stool consistency and decreased frequency of diarrhea as compared to group A (78%) and group B (32%)[20].

In 2016, Yazar *et al* conducted a study at Istanbul (Turkey) comparing the effect of a synbiotic and Zinc on the duration of diarrhea in children. The duration of diarrhea was decreased significantly (~24 hours) in the synbiotic group compared to the control group (91.0 ± 28.9 hours vs. 114.3 ± 30.9 hours, *p*<0.001 respectively). The duration of diarrhea was decreased significantly (~28 hours) in the zinc group compared to the control group (86.4 ± 30.8 hours vs. 114.3 ± 30.9 hours, *p*<0.001 respectively)[12].

In 2018 Bhat *et al* compared efficacy of two probiotics in pediatric acute diarrhea at a tertiary care facility. Group I received World Health Organization treatment of diarrhea; group II received Bacillus clausii while group III received Saccharomyces boulardii. The duration of diarrhea and hospital stay was remarkably reduced (41.68 hrs) in group III compared to group I (57.65 hrs) and group II (53.33 hrs) (*p*<0.05). The frequency of stools reduced greatly on Day 4 and stool consistency improved on Day 3 in both Bacillus clausii & Saccharomyces boulardii groups (*p*<0.05)[21].

Dalgic *et al* in 2011 reported a prospective, randomized, single blinded controlled trial in children with acute diarrhea due to rotavirus in Turkey. In patients receiving Saccharomyces boulardii alone, there was no difference in the duration of nausea and vomiting or in the duration of hospital stay compared with the control group. However, this study showed that the combination of probiotics and zinc decreased the duration of diarrhea and hospital stay compared with the control group[22].

All above mentioned studies have shown the efficacy of Saccharomyces boulardii for reducing the duration of diarrhea among children. The same findings were obtained in our study validating the effective role of Saccharomyces boulardii in acute diarrhea in children.

ACKNOWLEDGMENT

We thank administration of CMH Tarbela for providing us all resources to carry out our study in the best possible manner. We thank Brig. Dr Nazir Ahmed Malik (R) (Associate Professor of Pediatrics at HITEC Institute of Medical Sciences, Taxilla); Dr Sohail Aslam, (Consultant Pediatrician at Combined Military Hospital, Kharian); Dr Muhammad Zahid (Consultant Pediatrician at CMH Sargodha); Dr Ehsan Qadir (Consultant Pediatrician at CMH Mangla) and Mr. Kashif Siddique (Biostatician at University of Lahore) for guidance.

CONCLUSION

Saccharomyces boulardii can be effectively used with Zinc to treat acute watery diarrhea in children less than five years of age as it significantly reduces mean duration of diarrhea.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Giannattasio A, Guarino A, Lo Vecchio A. Management of children with prolonged diarrhea. F1000 Research 2016; 5(F1000 Faculty Rev): 206.
2. Lazzerini M.Oral zinc provision in acute diarrhea.Curr Opin Clin Nutr Metab Car 2016; 19(3): 239-43.
3. Del Piano M, Coggiola F, Pane M, Amoruso A, Nicola S, Mogna L. Can probiotics reduce diarrhea and infant mortality in Africa? Clin Gastroenterol 2016; 50(2): 120-23.
4. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. JPGN 2016; 62(3): 495-506.
5. Stier H, Bischoff S. Influence of Saccharomyces boulardii CNCM I-745 on the gut-associated immune system. Clin Exp Gastroenterol 2016; 9(1): 269-79.
6. Liu JJ, Kong II, Zhang GC, Jayakody LN, Kim H, Xia PF, et al. Metabolic engineering of probiotic Saccharomyces boulardii. Appl Environ Microbiol 2016; 82(8): 2280-87.
7. Riaz M, Alam S, Malik A, Ali SM. Efficacy and safety of Saccharomyces boulardii in acute childhood diarrhea: a double blind randomised controlled trial. Indian J Pediatr 2012; 79(4): 478-82.
8. Dinleyici EC. Latest advances in the use of probiotics/synbiotics for acute infectious diarrhea in children.Biotascope 2016; 3(1): 6-12.
9. Anteneh ZA, Andargie K, Tarekegn M. Prevalence and determinants of acute diarrhea among children younger than five years old in Jabithennan District, Northwest Ethiopia, 2014. Bio Med Centeral Public Health 2017; 17(1): 99.
10. Bruzzese E, Giannattasio A, Guarino A. Antibiotic treatment of acute gastroenteritis in children. F1000 Research 2018; 7: 193.
11. Das S, Gupta PK, Das RR. Efficacy and safety of saccharomyces boulardii in acute rotavirus diarrhea: double blind randomized controlled trial from a developing country. J Trop Pediatr 2016; 62(6): 464-70.
12. Yazar AS, Guven S, Dinleyici EC. Effects of zinc or synbiotic on the duration of diarrhea in children with acute infectious diarrhea.Turk J Gastroenterol 2016; 27(1): 537-40.
13. Islam S. Clinical Uses of Probiotics. MD J 2016; 95(5): 1-5.
14. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients - a systematic review and meta-analysis. Antibiotics (Basel) 2017; 6(4): 21.
15. Szajewska H. What are the indications for using probiotics in children?. Arch Dis Child 2016; 101(4): 398–403.
16. Mandal A, Sahi P. Probiotics for diarrhea in children. JMRI 2017; 1(2): AV5-AV12.
17. Appel-da-Silva MC, Narvaez GA, Perez LRR, Drehmer L, Lewgoyc J. Saccharomyces cerevisiae var. boulardii fungemia following probiotic treatment. Med Mycol Case Rep 2017; 18(1): 15-17.
18. Niamah AK. Physicochemical and microbial characteristics of yogurt with added saccharomyces boulardii. Curr Res Nutr Food Sci Jour 2017; 5(3): 300-07.
19. Eren M, Dinleyici EC, Vandenplas Y. Clinical efficacy comparison of Saccharomyces boulardii and yogurt fluid in acute non-bloody diarrhea in children: a randomized, controlled, open label study. Am J Trop Med Hyg 2010; 82(3): 488-91.
20. Farhat A, Shaukat A, Sadiq N. Comparison of clinical efficacy of combined versus monotherapy of oral zinc and probiotic in pediatric acute diarrhoea at benazir bhutto shaheed teaching hospital, Abbottabad. J Bahria Uni Med Dental Coll 2018; 8(4): 210-13.
21. Shreekrishna BS, Savio CD. Efficacy of probiotics in acute diarrhoea in children. Int J Contemp Pediatr 2018; 5(4): 1646-50.
22. Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose-free formula in children with rotavirus diarrhea: are they effective? Pediatr Int 2011; 53(5): 677-82.