Original Research Article

IMPACT OF PROBIOTIC (SACCHAROMYCES BOULARDII) ADMINISTRATION IN PREVENTION AND MANAGEMENT OF CHRONIC DIARRHEA

ABSTRACT

BACKGROUND

Diarrheal disease is the second leading cause of death in children under five years old, and is responsible for killing around 525 000 children every year. Though many treatment modalities exist, chronic diarrheal conditions demand a safer alternative modality (with lesser side effects) and thus, role of probiotics in prevention and management of chronic diarrhea merits exploration.

OBJECTIVE

To study the impact of probiotic (Saccharomyces Boulardii) in prevention and management of chronic diarrhea.

METHODOLOGY

This experimental study comprised of a sample of 178 (chosen via non-probability, consecutive sampling) children aged 2 months to 12 years, presenting to the study setting with chronic diarrhea (from November 05, 2019 to May 04, 2020) to the Dept. of Pediatrics at Liaquat University Hospital, Hyderabad. After taking written consent, data was recorded onto a structured questionnaire containing inquiries about the socio-demographic details, diarrheal disease history, medication history and eventual treatment outcome. The study population was divided into 2 equal groups (S. Boulardii group & Control Group) of 89 each. The active treatment period was 5 days. All study participants were examined on day 0 (inclusion day), and followed up on day 3 and day 6 during active treatment phase and in the following month thereafter for observation. The data obtained was analyzed through SPSS version 20.

Comment [VO1]: Good to see number stratification by age groups

Comment [VO2]: What was the inclusion criteria for this parameter?

Comment [VO3]: Why this duration was chosen?

Comment [VO4]: What procedures were included into examination?

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RESULTS

The mean age of the sample stood at 6.5 (SD ± 1.5) years. 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 day 3 it reduced to 2.8 and 4.4 stools per day respectively and by day 6 it reduced to 1.4 (S. boulardii Group) and 3.7 (control group). The duration of diarrhea was 3.2 days in S. boulardii group whereas it was 5.2 day in control group (P = 0.001). In the following month, S. boulardii group had a significantly lower frequency of 0.46 episodes as compared to 1.28 episodes in control group. The drug was well accepted and tolerated. There were no reports of the side effects during treatment period.

CONCLUSION

Integrity of the uterine scar in pregnant women with previous cesarean delivery with scar tenderness was high. Thus excessive fear of rupture is unfounded and vaginal delivery trials may be commenced (under expert care) among patients with previous cesarean delivery with hope of positive outcome.

Comment [VO5]: Not sure if this type of age interpretation is correct as the spread of ages is really big – 2 months to 12 years. Taking into account that babies up to 3 years and kids microbiome behave differently it is not clear what it the purpose to calculate the mean age of stool samples.

Comment [VO6]: Same comment – obviously if the age distribution is so significant – data is analyzed separately within each age group.

Comment [VO7]: Not clear what was the mean frequency at the moment of inclusion

Comment [VO8]: What was the day after the treatment of the following month control? It's really surprising to see that after 5 days of treatment the effect Is to long – obviously probiotics can be found in stool about 7-14 days after the treatment, and in case of diarrhea it can be expected even less.

Comment [VO9]: How is it linked to the study?

KEYWORDS

Diarrhea, Probiotic, Normal Flora, Child Health and S. Boulardii.

INTRODUCTION

Diarrheal disease is the second leading cause of death in children under five years old, and is responsible for killing around 525 000 children every year. [1] In Pakistan, diarrheal diseases cause significant childhood morbidity and mortality, claiming over 45,000 lives of children every year. [2] According to other reports, 600 deaths per day in the country are brought about by diarrheal diseases. [3] In Pakistan, every child gets, on average, 5-6 episodes of diarrhea per year [4] and these repeated and chronic episodes of diarrhea lead to under-nutrition, contributing to debility poor health. [4]

Lately, great strides have been made towards better understanding of pathogenesis and management methods of diarrhea. Numerous modalities of interventions have been identified and put to the test around the world, in an attempt to curb this menace and decrease the mortality and morbidity. Among the interventions are oral rehydration salt (ORS), antibiotics, anti-diarrheal, antispasmodics and anti-emetics. However, continued use of most of the aforementioned modalities for persistent diarrhea is not free from side-effects. [5] The harmful effects include worsening and increased duration of diarrhea, negative effects on intestinal motility resulting in paralytic ileus and others. [6] Fresher alternatives with potent therapeutic efficacy but fewer side-effects are thus the need of the hour.

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Chronic gastrointestinal diseases often result in multitude of adverse consequences, chief among which is the disturbance of the gut's complex ecosystem. The belief that modulating bacterial activity and improving gut microbial function may yield positive results for the gastrointestinal health, has long existed but evidence on this matter is far from adequate. However, despite limited evidence, we have progressed from the use of yoghurt (as a source of various probiotic) in the treatment of diarrhea to using selective probiotics targeted to yield specific positive outcomes. It is, due to this very reason that, now greater recognition is being given to probiotics as a useful means of influencing the composition of gut flora and the gut ecosystem as a whole. Numerous probiotic agents have been studied for this purpose, including Lactobacillus GG, Lactobacillus reuteri, and Saccharomyces Boulardii (S. Boulardii). Amongst these, all are bacteria except S. Boulardii, which is yeast. [7]

Many other effective modalities exist to counter acute diarrhea and thus the use of S. Boulardii for acute diarrheal diseases remains limited. However, chronic diarrheal conditions demand a safer alternative modality (with lesser side effects) and thus, we hope to explore the impact of Saccharomyces Boulardii in prevention and management of chronic diarrhea.

METHODOLOGY

This experimental study comprised of a sample of 178 (chosen via non-probability, consecutive sampling) children aged 2 months to 12 years, presenting to the study setting with chronic diarrhea (from November 05, 2019 to May 04, 2020) to the Dept. of Pediatrics at Liaquat University Hospital, Hyderabad. After taking written consent, data was recorded onto a structured questionnaire containing inquiries about the socio-demographic details, diarrheal disease history, medication history and eventual treatment outcome. The study population was divided into 2 equal groups of 89 each. In S. Boulardii group, patients were managed by WHO-CDD protocol plus S. boulardii (250 mg B.I.D) administered orally diluted in water or other semi-solid food. In the control group patients were managed by WHO-CDD protocol only. The active treatment period was 5 days. Treatment of the subsequent episodes of diarrhea were left to the discretion of the treating physician. All study participants were examined on day 0 (inclusion day), and followed up on day 3 and day 6 during active treatment phase and in the following month thereafter for observation. The data obtained was analyzed through SPSS version 20.

Comment [VO10]: Pls see questions above

Comment [VO11]: What was the strain name? Need more details about S.Boulardi – what was the form of yeast (live or lyophilized or dried), what was the count of yeast per administration?

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Qualitative data (e.g. gender and diarrheal symptoms) was expressed as number and percentage (No & %). Quantitative data (age, weight, duration of diarrhea and Bristol stool scores) was expressed as mean & standard deviation (X ± SD). T-Test was used to compare the two groups for respective difference in disease duration. P value > 0.05 was considered statistically non-significant. P value ≤ 0.05 was considered statistically significant. Anonymity and confidentiality of the patients shall be protected by assigning codes to the data set, instead of names and keeping the data password protected. The data shall be discarded a set period of time after completion of the project.

ELIGIBILITY CRITERIA

Inclusion Criteria: Children of either gender, aged 2 months to 12 years, presenting to the study setting with chronic diarrhea were included into the study after taking written informed consent from the guardians (parents).

Comment [VO12]: Question remains on number of diarrhea episodes as an inclusion criteria.

Exclusion Criteria: Children presenting with severe inter-current illnesses, severe diarrhea and dehydration requiring hospitalization and intravenous therapy, and/or presenting with temperature above 38.5°C, who were have been treated by any other anti-diarrheal/antibiotics in last 24 h as well as severely malnourished children shall be excluded from the study sample. Also excluded were children taking systemic anti-mycotic treatment (in the past 6 weeks).

RESULTS

The mean age of the sample stood at 6.5 (SD ± 1.5) years. Baseline characteristics such as mean age, gender and the average frequency of stools were comparable in S. Boulardii and control group at the time of inclusion in the trial.

Comment [VO13]: Pls see comments above

Table 1. Experimental and control group

Variable		Experimental Group	Control group
Age		6.4 ± 1.6	6.6 ± 1.4
Gender	Male	56	61

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	Female	33	28
Weight (kg)		17.4	17.1
Frequency of Stool		8.8	9.2

Comment [VO14]: Also strange to calculate mean weight for 2 m.o. babie and 12 y.o. kids

Follow-up statistics (post treatment) were noted on day 3 and 6. The results are tabulated below:

Table 2. Post-treatment statistics

Variable	**Day 03**		**Day 06**	
	Experimental	**Control**	**Experimental**	**Control**
Stool Frequency	*2.8*	*4.4*	*1.4*	*3.7*

Comment [VO15]: Lacking the data at the moment of inclusion/baseline

The duration of diarrhea was 3.2 days in S. boulardii group whereas it was 5.2 day in control group (P = 0.001). In the following month, S. boulardii group had a significantly lower frequency of 0.46 episodes as compared to 1.28 episodes in control group. The drug was well accepted and tolerated. There were no reports of the side effects during treatment period.

DISCUSSION

Comment [VO16]: Disussion contain mostly literature review data rather than discussion of the results from the present study

S. Boulardii is a non-pathogenic yeast first isolated from lychee fruits in Indonesia and used first in France to treat diarrhea, in the beginning of the 1950s. [8] Preclinical and experimental studies of S. Boulardii have demonstrated an anti-inflammatory, antimicrobial, enzymatic, metabolic and antitoxin activity. [9] 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. [10] It is well tolerated by all, regardless of user's age or disease condition. [9]

From 1976 to 2015, 90 randomized controlled trials covering 15 different types of disease conditions have been conducted with S. Boulardii. [11] The most robust evidence-based efficacy is for the treatment of acute pediatric diarrhea and for the prevention of antibiotic-associated diarrhea. [12]

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A drop (from 23% to 7.9%) in incidence of diarrhea after administration of S. Boulardii was seen among children, as compared to controls in a study by Szajewska et al. [13] Strong evidence is also found for S. Boulardii efficacy for the treatment of acute adult diarrhea (75%) [14] and the treatment of inflammatory bowel disease (success rate 75%), [15] but these findings are supported with a fewer number of trials. Other disease indications (Clostridium difficile infections, [16] giardiasis, [17] traveler's diarrhea, [18] enteral nutrition-related diarrhea) [19] show promise, but need more studies. A recent meta-analysis shows the success rate of S. Boulardii to be 46.4% to 95% in acute pediatric diarrhea, 65% in antibiotic associated diarrhea and up to 100% in diarrhea caused by C. difficle infection and Giardia Lamblia. [20]

CONCLUSION

Comment [VO17]: Not clear how does conclusion link to the study

Integrity of the uterine scar in pregnant women with previous cesarean delivery with scar tenderness was high. Thus excessive fear of rupture is unfounded and vaginal delivery trials may be commenced (under expert care) among patients with previous cesarean delivery with hope of positive outcome.

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REFERENCES

1. *World Health Organization. Diarrhoeal disease [Internet]. 2017. Available from: http://www.who.int/mediacentre/factsheets/fs330/en/*

2. *Nazneen S, Haq NU, Shah A, Jahan S. Frequency of diarrhea and its risk factors among children under five years in three teaching hospitals of Peshawar, Pakistan. Int J Innov Res Dev. 2016 Oct 21;5(12).*

3. *Billoo AG, Memon MA, Khaskheli SA, Murtaza G, Iqbal K, Shekhani MS, et al. Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. World J Gastroenterol. 2006 Jul 28;12(28):4557.*

4. *Tanweer A, Zaman GP, Fatima W, Javed H. Report on malnutrition as an epidemic in Pakistan. Sci Int. 2015;27(3):2589-92.*

5. *Schiller LR. Antidiarrheal drug therapy. Curr Gastroenterol Rep. 2017 May 1;19(5):18.*

6. *Lääveri T, Sterne J, Rombo L, Kantele A. Systematic review of loperamide: No proof of antibiotics being superior to loperamide in treatment of mild/moderate travellers' diarrhoea. Travel Med Infect Dis. 2016 Jul 1;14(4):299-312.*

7. *Floch M, Ringel Y, Walker W. The microbiota in gastrointestinal pathophysiology. Elsevier Acad Press; 2017;2(3):145-156*

8. *McFarland LV. From yaks to yogurt: the history, development, and current use of probiotics. Clin Infect Dis. 2015 Apr 28;60(suppl_2):S85-90.*

9. *Sharma J, Upadhya S. Determination of antimicrobial potential of Saccharomyces boulardii and Bacillus clausii against some community acquired pathogens in vitro study. Int. J. Pharm. Sci. Res. 2015;6(7):1023-6.*

10. *Fakruddin M, Hossain MN, Ahmed MM. Antimicrobial and antioxidant activities of Saccharomyces cerevisiae IFST062013, a potential probiotic. BMC Complement Altern Med. 2017 Dec;17(1):64.*

11. *Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. J Pediatr Gastroenterol Nutr. 2016 Mar 1;62(3):495-506.*

12. *Cremonini FI, Di Caro SI, Nista EC, Bartolozzi F, Capelli GI, Gasbarrini G, Gasbarrini AN. Meta‐analysis: the effect of probiotic administration on antibiotic‐associated diarrhoea. Aliment Pharmacol Ther. 2002 Aug 1;16(8):1461-7.*

13. *Kotowska M, Albrecht P, Szajewska H. Saccharomyces boulardii in the prevention of antibiotic‐associated diarrhoea in children: a randomized double‐blind placebo‐controlled trial. Aliment Pharmacol Ther. 2005 Mar;21(5):583-90.*

14. *Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. Dig. Dis. Sc. 2002 Nov 1;47(11):2625-34.*

15. *Brun P, Scarpa M, Marchiori C, Sarasin G, Caputi V, Porzionato A, Giron MC, et al. Correction: Saccharomyces boulardii CNCM I-745 supplementation reduces gastrointestinal dysfunction in an animal model of IBS. PloS one. 2017 Nov 17;12(11):e0188563.*

16. *Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. Can Med Assoc J. 2005 Jul 19;173(2):167-70.*

17. *Vitetta L, Saltzman ET, Nikov T, Ibrahim I, Hall S. Modulating the gut micro-environment in the treatment of intestinal parasites. J Clin Med. 2016 Nov 16;5(11):102.*

18. *McFarland LV. Protecting elderly travelers from travelers' diarrhea. Do probiotics work?. Travel Med Infect Dis. 2015 Mar 1;13(2):119.*

19. *Osowska S, Alexander S, Kulik Z, Ławinski M, Pertkiewicz M. PP080-SUN: Impact of Saccharomyces Boulardii on Colonic Microbiota and Plasma Lactate in Short Bowel Syndrome Patients on Long-Term Parenteral Nutrition. Clin Nutr. 2014 Sep 1;33:S49.*

20. *McFarland LV. Common organisms and probiotics: Saccharomyces boulardii. InThe Microbiota in Gastrointestinal Pathophysiology 2017 Jan 1 (pp. 145-164). Academic Press.*

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