Effect of Probiotics on Rotavirus and Non-Rotavirus Diarrhea in Infants: Randomized Controlled Trial

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Abstract

Objective: In this trial, we have observed efficacy of two different probiotics in Rotavirus and non-Rotavirus diarrhea in infants of 6 months to 12 months.

Method: The study was done to observe efficacy of two different probiotic strains in Rotavirus and non-Rotavirus diarrhea in infants. The study included the infants suffering from acute severe diarrhea. 105 infants were selected and they were divided randomly into three groups. There were 35 infants in one group. The samples of stool were sent to microbiology lab for Rotavirus testing. The treatment plan was standard treatment of diarrhea for infants in group A. The treatment plan for infants of group B and group C included same standard management of diarrhea, in addition they also received probiotics Enterococcus faecium SF68 and Saccharomyces boulardii respectively.

Results: There was reduction in stool output and improvement in consistency of stool in infants of group B and C as compared to infants of group A. There was decrease in stool frequency in non-Rotavirus diarrhea in infants of group B and C while there was no significant difference between groups regarding Rotavirus diarrhea.

Conclusion: Probiotics helped to decrease the stool output in non-Rotavirus diarrhea. There was not any significant difference in groups regarding Rotavirus diarrhea.

Keywords: Rotavirus, Non-Rotavirus, Saccharomyces boulardii, Enterococcus faecium Sf68

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Introduction

Diarrhea is the major cause of death in children below five years of age worldwide. It is second important cause of death in infants in poor and developing nations. Infants and young children are mostly affected with childhood diarrhea which is responsible for 63% of the global burden of diarrhea. In developing continents like Asia and Africa, diarrhea is responsible for 1 in 8 deaths in infants annually.[1] Important pathogens responsible for diarrhea in infants include Shigella, Salmonella, Campylobacter, Rotavirus, Entamoeba histolytica and E coli. E coli and Rotavirus are the common causes of diarrhea in infants in developing nations.[2]

Dehydration due to diarrhea is the significant risk for the health of the child and it is the main reason for morbidity and mortality. Replacement of fluid to avoid dehydration is the main focus in the management of diarrhea. In mild and moderate dehydration oral route is preferred and for this purpose oral rehydrating salts are easily available all over the world. In severe dehy-

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dration or when children are unable to take orally, intravenous rehydration is recommended.[3] Antibiotic treatment is not mandatory in all children suffering from acute diarrhea except in some cases of infectious diarrhea. It should be given in severely ill children especially in those children who have risk factors.[4] Zinc supplementation has also an important role in decreasing the diarrheal duration as well as in improvement of consistency of stool in young children suffering from diarrhea.[5]

Probiotics help to decrease the diarrheal duration for the management of acute diarrhea in young children and infants. Probiotics increase efficacy of treatment and reduce days of hospital stay. Good quality RCTs are mandatory for verification of results of probiotics in severe diarrhea[6].

According to the trials, S. boulardii is proven to be effective for decreasing the severity and duration of diarrheal illness[7]. S. boulardii has shown an important role for the management of acute gastroenteritis in young children and infants[8]. E. faecium SF68 has shown efficacy for the management of acute gastroenteritis as well as for prevention of diarrhea associated with antibiotics. It has shown good safety profile.[9] Most of the studies suggested that S. boulardii is helpful for treatment of Rotavirus diarrhea as well as other types of diarrhea where etiology is not known.[10] Studies regarding use of probiotics in Rotavirus diarrhea are present but there are rare studies showing use of probiotics in non-Rotavirus diarrhea. The importance of this study is that effect of two different probiotics is observed in Rotavirus and Non-Rotavirus diarrhea in infants.

Materials and Methods

It was an experimental, single blind, randomized controlled trial. It was conducted in the Paediatrics Department at Children Hospital Lahore from June 2016 to October 2016. The trial was approved by Ethical Committee of Children Hospital Lahore. Infants of age six months to one year with acute diarrhea were included in the trial. Dehydration was severe in the infants (more than 10%). Hydration status was assessed according to WHO guidelines.[10] Infants having malnutrition, suffering from chronic disease, already taking probiotics or who are passing bloody diarrhea are excluded from the trial. The sample size was taken in accordance with the previous study. It was estimated by taken into account mean±SD of frequency of stools in a day having standard management versus standard management plus probiotics.[11] The size of sample was 32, so we have taken 35 infants in each group. Non-probability purposive sampling was done to select the infants. Parents of the infants gave proper consent before the enrollment of infants in the trial. 105 infants were enrolled in the study and divided randomly into three groups. Infants in group A obtained standard management of diarrhea i.e. IV fluids, supplementation with zinc and ORS salts. Antibiotic treatment was only given if needed. Infants in group B obtained standard management of diarrhea plus E. faecium SF68 twice daily for five days. Infants in group C obtained standard treatment of diarrhea plus S. boulardii twice daily for five days. The sequence of randomization of infants into groups was maintained and generated by the person not involved in the trial directly. Allocation concealment was properly done with the help of serially numbered opaque sealed envelopes.

After admission, history and physical examination was done. Routine lab investigations were taken. Stool sample of the infants were sent to microbiology for detection of Rotavirus. All the infants obtained IV fluids as there was severe dehydration. ORS and zinc supplements were given to infants of all the groups as soon as the infants were able to take oral feed. Respective probiotics were also given to the infants of intervention groups when the infants were able to tolerate oral feed. Frequency of diarrhea or no. of stools per day was the parameter of our study which was monitored for five days. Infant was said to be recovered from illness when eight hours had passed after passing of normal stool[11].

The data was processed with the help of Statistical Package for Social Sciences. The data was checked for normal distribution by Shaprio Wilk test and it was normally distributed. Quantitative variables were presented in mean and SD. We have applied ANOVA for analyzing significance between three groups. Post hoc Tukey's test was applied to pairwise compare between three groups.

Results

Total 105 sample of stool were sent to microbiology for detection Rotavirus antigen. 25 samples were positive for Rotavirus. 10 samples from group A (control group), 9 samples form group B (E. faecium SF68 group) and 6 samples of group C (S. boulardii grouop) were found to be positive for Rotavirus. The comparison of stool output per day in Rotavirus positive cases and non-Rotavirus cases was done.

Table 1 is showing mean ± SD of stool output per day

in infants having Rotavirus diarrhea. ANOVA showed no significant difference among three groups.

Table 2 is showing mean ± SD of stool output per day

Table 1: *Frequency of Stools in Infants of Rotavirus Diarrhea*

Number of stool	Group	N	Mean	Std. Deviation	p-value
Day1	Group A	10	10.40	2.41	0.284
	Group B	9	10.11	3.52	
	Group C	6	12.33	1.63	
Day2	Group A	10	9.00	1.89	0.150
	Group B	9	6.67	3.91	
	Group C	6	9.50	3.02	
Day3	Group A	10	7.70	3.23	0.173
	Group B	9	5.11	3.76	
	Group C	6	8.33	3.67	
Day4	Group A	10	6.00	2.94	0.354
	Group B	9	3.78	4.18	
	Group C	6	5.83	3.31	
Day5	Group A	10	3.90	2.18	0.857
	Group B	9	3.33	3.64	
	Group C	6	3.17	2.40	
	Total	25	3.52	2.74	

Group A (control) *Group B (SF68)* *Group C (S.boulardii)*

in infants having non-Rotavirus diarrhea. When means were compared by applying ANOVA, significant difference among three groups was shown. Table 3 is showing

Table 2: *Frequency of Stools in Infants in Non-Rotavirus Diarrhea*

Number of stool	Group	N	Mean	Std. Deviation	p-value
Day1	Group A	25	11.08	3.15	<0.001
	Group B	26	7.23	2.64	
	Group C	29	8.86	3.02	
Day2	Group A	25	9.24	3.28	<0.001
	Group B	26	4.46	2.60	
	Group C	29	6.14	2.95	
Day3	Group A	25	7.36	3.19	<0.001
	Group B	26	3.15	2.01	
	Group C	29	4.00	2.20	
Day4	Group A	25	6.36	3.08	<0.001
	Group B	26	2.54	1.65	
	Group C	29	3.34	2.32	
Day5	Group A	25	4.92	2.60	<0.001
	Group B	26	1.88	1.63	
	Group C	29	2.52	1.90	

Group A (control) *Group B (SF68)* *Group C (S.boulardii)*

post hoc Tukey's test for analyzing difference among group means in non-Rotavirus infants. Mean difference among group A and group B was significant from day 1 to day 5 having p value less than 0.001. There was also significant difference among group A and group C having p value 0.02 on day 1, 0.001 on day 2 and less than 0.001 from day 3 to day 5. No significant difference was shown among group B and group C.

Table 3: *Multiple Comparison of Frequency of Stools in Infants in Non-Rotavirus Diarrhea*

Stool for non-*Rotavirus*	Number of stool	I groups	J groups	Mean difference (I-J)	p-value
Infants	Day1	Group A	Group B	3.84923	<0.001
			Group C	2.21793	0.020
		Group B	Group C	-1.63	0.107
	Day2	Group A	Group B	4.77846	<0.001
			Group C	3.10207	0.001
		Group B	Group C	-1.68	0.096
	Day3	Group A	Group B	4.20615	<0.001
			Group C	3.36000	<0.001
		Group B	Group C	-0.85	0.426
	Day4	Group A	Group B	3.82154	<0.001
			Group C	3.01517	<0.001
		Group B	Group C	-0.81	0.434
	Day5	Group A	Group B	3.03538	<0.001
			Group C	2.40276	<0.001
		Group B	Group C	-0.63	0.498

Group A (control) *Group B (SF68)* *Group C (S.boulardii)*

Discussion

It was an experimental study, randomized controlled trial conducted at Paediatric Medicine Department of Children Hospital Lahore. The trial was conducted to observe the effect of two different strains of probiotics on acute Rotavirus and non-Rotavirus gastroenteritis.

Childhood diarrhea is the major health challenges in the developing nations. Effective interventions should be done to reduce the child mortality due to diarrhea[12]. In this study we have selected the infants among 6 months to 12 months of age. Infants and young children are more affected by diarrhea due to risk of dehydration.[13] There are several studies which proved efficacy of probiotics for mild and moderate gastroenteritis. On the other hand, a lack of trials is observed showing efficacy of probiotics in infants and children having severe diarrhea. Some studies showed lack of effective role of probiotics in severe diarrhea.[14] So in this trial, we

observed the effect of probiotics in severe gastroenteritis in infants. All the infants enrolled in the study were suffering from severe diarrhea having more than 10 stools per day. Infants in all the three groups had severe dehydration and they obtained IV fluids.

The most common pathogens causing gastroenteritis in young children infants were Rotavirus and Norovirus.[15] Studies suggested the use of probiotic S. boulardii in acute Rotavirus gastroenteritis.[10] S. boulardii is the probiotic obtained from yeast and it is used for management of disorders of gastrointestinal tract. Several pathways accounted for its probiotic activity including immune modulation, release of anti-microbial substances and improvement in the barrier function of gut.[16] S. boulardii reported good results in reducing severity of gastroenteritis in children where etiology is not known.[17] E. faecium has got special role because of its beneficial strain marketed as probiotics and it also play an important role in traditional fermented foods like cheese. E. faecium SF68 is a pharmaceutical probiotic having history of safe use.[18]

In this trial we have observed the effect of S. boulardii and E. faecium SF68 in infants suffering from acute Rotavirus and non-Rotavirus diarrhea. In non-Rotavirus diarrhea, etiology of gastroenteritis was not known. The infants were randomly divided among three groups. Infants of group A got standard treatment of diarrhea including IV fluids, ORS salts and Zinc syrup. Infants in group B and C also got standard management of diarrhea plus E. faecium SF68 and S. boluardii respectively. In group A, 10 cases were Rotavirus positive, 9 cases were Rotavirus positive in group B and 6 cases were Rotavirus positive in group C. No significant difference was shown among groups in this trial in case of Rotavirus diarrhea. Probiotics did not reduce the frequency of diarrhea in Rotavirus positive cases. On the other hand, there was significant difference among groups in non-Rotavirus diarrhea. Both probiotics helped to reduce the frequency of stool in non-Rotavirus diarrhea. The result of this trial in case of Rotavirus positive cases showed contradictory results to the previous studies because previous studies showed beneficial effect of S. boulardii in Rotavirus positive cases.[10,19,20] E. faecium SF68 even showed better results in improving severity of diarrhea than S. boulardii in non-Rotavirus cases although no significant difference was shown among both probiotic groups in this regard. There are not much studies regarding the effect of E. faecium SF68 in gastroenteritis in children. One animal study suggested beneficial effect of SF68 on the gastrointestinal tract.[21] It is the strength of our study that we evaluate the efficacy of E. faecium SF68 in Rotavirus and non-Rotavirus diarrhea in infants.

Importance of Study

The importance of this study is that it is the first study which shows comparison of two probiotics in Rotavirus and Non-Rotavirus diarrhea in infants.

Conclusion

S. boulardii and E. faecium SF68 helped to decrease the frequency of stools in non-Rotavirus diarrhea.

Conflict of Interest: *None*

Funding Source *None*

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Authors Contribution

FAK: Conceptualization of Project
ZI: Data Collection
MZK: Literature Search
NY: Statistical Analysis
MIP: Drafting, Revision
SZ: Writing of Manuscript