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Study of supplementation of ORS with zinc and probiotic in treating children with acute watery diarrhea

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Abstract
The essential factors recommended by the World Health Organization for the control of acute gastroenteritis include the use of oral rehydration solution (ORS) with reduced osmolality and, if needed, intravenous fluids and zinc supplements. Many studies have suggested the consumption of probiotics as an adjunct method for the treatment of acute diarrhea.
Materials and Methods: The present study was done at our tertiary care centre to evaluate the efficacy of addition of Zinc and *Saccharomyces boulardii* (probiotic) to WHO-ORS and compare those effects with WHO-ORS alone.
Results and conclusion: In our study children receiving Probiotic were more likely to be diarrhea-free after the first 48 hours of intervention, with better outcomes at 72 and 96 hours along with improvement in consistency and reducing the duration of hospital stay.

Keywords: world health organization, ORS, zinc supplements

Introduction
Diarrhea, also spelled diarrhoea, is the condition of having at least three loose or liquid bowel movements each day [1]. It often lasts for a few days and can result in dehydration due to fluid loss. The essential factors recommended by the World Health Organization for the control of acute gastroenteritis include the use of oral rehydration solution (ORS) with reduced osmolality and, if needed, intravenous fluids and zinc supplements. The Indian Academy of Pediatrics, WHO, and UNICEF have already endorsed the use of zinc as a supplement to ORS in the management of diarrhea. A dosage of 20 mg of elemental zinc per day has been shown to be effective and safe in age group six months to five years. Administration of zinc is recommended through a primary healthcare.
Many studies have suggested the consumption of probiotics as an adjunct method for the treatment of acute diarrhea. From that time on, multiple definitions were proposed until in 1985 when Fuller gave a new definition for probiotics as a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance. The World Health Organization has referred to probiotics as the live microorganisms that will have benefits to the host's health when consumed in adequate amounts [2, 3].
The mechanism and effectiveness of probiotics usually depend on the interaction of probiotic microorganisms with one's specific normal flora and immune cells of the intestinal mucosa. From among the effects of probiotics, one can refer to such items as the stimulation of the immune system, reduced competition for the use of nutrients available in the intestine, connection to the intestinal membrane wall and mucus, and prevention of the connection of harmful factors, as well as the production of antimicrobial substances (H2S, bacitracin, and fatty acids). In addition probiotics lead to the elimination of harmful microorganisms in the digestive system due to the deconjugation of bile salts and pH reduction [4-6].
The present study was done at our tertiary care centre to evaluate the efficacy of addition of Zinc and *Saccharomyces boulardii* (probiotic) to WHO-ORS and compare those effects with WHO-ORS alone.

Material and Methods
The hospital based observational comparative study was undertaken to evaluate the efficacy of addition of Zinc and *Saccharomyces boulardii* (probiotic) to WHO-ORS and compare those effects with WHO-ORS alone in treating children with acute watery diarrhea.150 patients were divided into the following three groups of 50 patients:

- **ORS Group:** Patients received WHO-ORS only
- **ORS + Zinc Group:** Patients received WHO-ORS with Zinc
- **ORS + Probiotic Group:** Patents received WHO-ORS and *S.Boulardii*

Source of data
Paediatric patients attending Krishna Institute of medical sciences deemed university, Karad for treatment of acute diarrhea.

Study Duration: 2 Years

Study design
The hospital based observational comparative study

Sample size: 150 patients
150 (50 controls + 100 cases divided into group B and group C)
50 patients per group will be required to detect a significant difference and hence sample sizes of 150 patients were selected for the study.

Inclusion criteria

- All acute watery diarrhea cases between 6 months to 60 months (5 years) of age.
- Guardian willing to give informed consent.
- Patient with moderate and isonatremic dehydration.

Exclusion criteria

- Known HIV infected patients with diarrhea, and those with any associated infection along with diarrhea were excluded from the study.
- Children less than six month of age
- Patients with bacillary dysentery
- Already on anti-diarrheal and antibiotic
- Patients with mild and severe dehydration
- Patients with lactose intolerance

Method of Administration

- WHO - ORS sachet (1 sachet for 200ml water) –
  Empty one sachet (4.20g) in 200ml (1glass) of fresh drinking water and stir to dissolve.
  Reconstitute solution may be stored in fridge uptil 24 hours from preparation, otherwise unused should be discarded within one hour.
  Infant – give 30ml per hour of ORS
  Toddler – 60ml per hour of ORS / 200 ml after each loose stool
- ELEMENTAL - ZINC – 20mg/day per oral for 14 days
- *Saccharomyces boulardii* – 1sachet (250mg = 5billion CFU). 1 sachet dissolved in 4tsp of water, to be given twice daily for five days.

They were given the study drugs after screening the inclusion and exclusion criteria. They were observed for a period of 5 days. A detailed clinical history of all children particularly with respect to demographics was recorded. A thorough clinical examination was done for all children including weight, temperature, pulse rate, and respiratory rate. Status of vomiting, dehydration, stool frequency, stool consistency, and mean duration of diarrhea with mean duration of hospital stay was studied and compared in all the three groups. Those who were well hydrated, improved consistency and had well-formed stools were discharged accordingly and were not included in the study thereafter. Those children who complained of intractable vomiting and was not controlled by ORS were given oral Ondansetron (2mg) on 3rd day, as per their weight. Investigations like complete blood count, serum electrolytes and stool routine were done and recorded for all children during the study.

Statistical Analysis

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student-'t' test and Chi-Square test. 'p' value less than 0.05 is taken as significant**.**

Results

The age distribution in the groups were comparable and statistically not significant as per ANOVA ($p>0.05$). The gender distribution in the groups were comparable and statistically not significant as per Chi-Square test ($p>0.05$).

On Day 1, vomiting was present in 36% patients in ORS Group and in 30% and 28% patients of ORS + Zinc Group and ORS + Probiotic Group respectively. There was no vomiting present in all patients of ORS Group by Day 4 while vomiting was present in 2 patients of ORS + Zinc Group and 3 patients of ORS + Probiotic Group for which they were given antiemetic after which it resolved. There was no significant difference in controlling the vomiting between the three groups ($p>0.05$)

On Day 1, moderate dehydration was present in 80% patients in ORS Group and in 78% and 84% patients of ORS + Zinc Group and ORS + Probiotic Group respectively. There was no dehydration in all patients of ORS Group by Day 4 while all patients of ORS + Zinc Group and ORS + Probiotic Group were fully hydrated by Day 3. It was observed that patients were fully hydrated significantly faster in ORS + Probiotic Group and ORS + zinc group as compared to ORS Group ($p<0.0001$).

Except for Day 1 loose stool frequency was significantly controlled in ORS + Zinc Group and ORS + Probiotic Group as compared to ORS Group. It was observed that loose stool frequency stopped significantly faster in patients of Probiotic Group.

Table 1

Loose Stool Frequency	ORS Group			ORS + Zinc Group			ORS + Probiotic Group			ANOVA F-value	p Value
	N	Mean	SD	N	Mean	SD	N	Mean	SD		
Day 1	50	6.24	0.80	50	6.12	0.59	50	6.10	0.58	0.649	p= 0.524
Day 2	50	5.98	0.79	50	5.66	0.68	50	5.42	0.70	7.510	p= 0.001
Day 3	50	5.86	0.88	50	5.54	0.88	50	5.04	1.32	7.784	p<0.001
Day 4*	49	5.72	1.04	48	5.35	0.99	44	4.70	1.28	10.045	p<0.0001
Day 5*	47	4.90	1.29	45	4.78	1.56	38	4.02	1.63	4.160	p<0.05

On day 1, there was no significant difference in consistency of stools in between 3 groups. ($p=0.890$). On day 3, 2% from ORS group, 4% from ORS + Zinc group and 12% from ORS + Probiotic group developed well-formed stools which was statistically significant($p=0.004$). On day 5, probiotic group has maximum number of children 50% with well-formed stool when compared to others ($p<0.0001$)

Table 2

Stool Consistency		ORS Group		ORS + Zinc Group		ORS + Probiotic Group		Chi-Square	p Value
		N	%	N	%	N	%		
Day 1	Watery	43	86%	41	82%	43	86%	1.223	P =0.890
	Semisolid	5	10%	8	16%	6	12%		
	Soft	2	4%	1	2%	1	2%		
	Well-formed	0	-	0	-	0	-		
Day 2	Watery	33	66%	29	58%	11	22%	25.754	P = 0.0002
	Semisolid	14	28%	16	32%	27	54%		
	Soft	3	6%	5	10%	10	20%		
	Well-formed	0	-	0	-	2	4%		
Day 3	Watery	22	44%	15	30%	8	16%	18.552	P=0.004
	Semisolid	20	40%	21	42%	16	32%		
	Soft	7	14%	12	24%	20	40%		
	Well-formed	1	2%	2	4%	6	12%		
Day 4	Watery	10	20%	10	21%	4	9%	20.672	P=0.002
	Semisolid	26	52%	20	42%	13	29%		
	Soft	11	22%	15	31%	21	48%		
	Well-formed	2	4%	3	6%	6	14%		
Day 5	Watery	9	19%	5	11%	1	2%	21.556	P=0.0001
	Semisolid	16	34%	14	31%	1	2%		
	Soft	16	34%	17	38%	23	61%		
	Well-formed	6	13%	9	20%	13	35%		

It was observed the mean duration of diarrhea was least in patients of Probiotic Group.

Table 3

	ORS Group		ORS + Zinc Group		ORS + Probiotic Group		p value*
	Mean	SD	Mean	SD	Mean	SD	
Mean duration of diarrhea (days)	4.11	1.12	3.36	1.75	2.65	1.38	<0.05

It was observed the mean duration of hospital stay was least in patients of Probiotic Group.

Table 4

	ORS Group		ORS + Zinc Group		ORS + Probiotic Group		p value*
	Mean	SD	Mean	SD	Mean	SD	
Mean duration of hospital stay (days)	5.24	1.16	4.38	1.76	3.42	1.44	<0.05

On day 5, 50% of patients in ORS + Probiotic group, 28% from ORS + Zinc and 18% from ORS + Zinc were well hydrated with reduced frequency and improved consistency of stool, hence they were discharged. As the present study was planned for 5 days observation period, hence those cases which did not show all round improvement were observed and were under treatment in ward.

Table 5

Status of cases	Day	ORS	ORS + Zinc	ORS + Probiotic
Discharged	3	1	2	6
	4	2	3	6
	5	6	9	13
Under observation after 5th day		41	36	25

Discussion

The initial therapy recommended for acute watery diarrhea is treatment with oral fluids and use of ORS [10]. However ORS neither reduces the frequency of fluid loss or bowel movements nor decreases the time interval of diarrhea, therefore further adjunctive therapy options have been extensively studied [11].

Acute diarrhea of childhood have been treated with zinc, which has been supported by many studies, and contradictory results have been published concerning the geographical region and age. Zinc deficiency being a main factor of immunity and low weight in developing countries, and both are related with the duration of diarrhea [12-14]. Giving zinc decreases the time interval of the diarrhea as well as frequency and amount of the stool in randomized controlled trials and reviews [7-9].

The age distribution in the groups were comparable and statistically not noteworthy as per ANOVA (p>0.05). The distribution of gender in the groups were capable of being compared and statistically not significant as per Chi-Square test (p>0.05). Our study was similar to studies of Deepak R *et al*. [15], Heydarian *et al*. [16] and Naseer A *et al*. [17].

Deepak R *et al*. [15] observational, prospective, open label, comparative study evaluating the function of probiotics for remedy of mild and moderate pediatric diarrhea which was acute onset found male children group A were 18 (60%), group B22 (79.33%), group C 19 (63.33%)and female children in group A 12 (40%), group B 08 (26.67%), group C 11 (36.67%) with a mean Age (months) in group A 14±6.38, group B 11±5.19, group C 13±4.91 respectively.

Heydarian *et al*. [16] study reported the mean age of patient was 2.5 + 2.3 years. This difference in mean age of patient is mainly due the inclusion criteria adopted by different authors. Majority of the patients were male i.e. 62% in group A, and72% in group B. Male patients also

predominated the female patients i.e. 57% patients were male and 43% were female. In another study by Makbule E *et al*. [15], 65% were male and 35 % were female. These two studies were in contrast to our study showing male predominance.

Naseer A *et al.* [17] descriptive study comparing the mean time for diarrhea in between children taking yogurt and probiotics (lactobacillus) in acute watery diarrhea found mean age of the patients in group A was 22.140 ± 10.556 months (range 6 – 60 months). There were 14% patients of age range of 6 - 12 months, 16% patients of age range of 13 - 24 months, 28% patient of age range of 25 - 36 months, 22% patients of age3 7 - 48 months, and 20% patients of age range of 49 -60 months. Patient's mean age included in group B was21.091 ± 9.977 months [ranges from 6 – 60months]. There were 27% patients of age range of 6 - 12 months, 15% patients of age range of 13 - 24 months, 21% patient of age range of 25 - 36 months, 17% patients of age37 - 48 months, and 20% patients of age range of 49 - 60 months. There was no noteworthy distinction between two groups. There were 66% male patients in group A, while 35% patients were female. Female to male ratio was 1:1.63. In group B, there were 71% male patients, while 29% patients were female. Female to male ratio was1:2.45.

There was no significant difference in controlling the vomiting between the three groups (p>0.05) which can also be seen in the study of Patel A *et al*. [67].

Patel A *et al*. [9] in a systematic Review reported quantitative synthesis of these results observed after the patients were given zinc, the risk of vomiting increased significantly after giving zinc to an extent (19.2% in the zinc supplemented group and 9.2%in the zinc withheld group) summary Odds Ratio 2.13, 95% Confidence Interval 1.37–3.31). However, this zinc effect was significantly heterogeneously distributed across the trials (I2 81.2%,p,0.001). This study showed significant increase in vomiting after giving zinc which was not much significant when compared to our study.

It was noted that patients were fully hydrated significantly faster in ORS + Probiotic Group and ORS + zinc group as compared to ORS Group (p<0.0001). This is concordant to the study of Khanna V *et al*. [12].

Khanna V *et al*. [18] double-blind randomized controlled-trial on efficacy of tyndalized lactobacillus acidophilus in acute diarrhea among 98 children aged between 6 months to 12 years reported Lactobacillus or placebo was given to the children for 3 days with ORS and feeding. Out of the 98 children, 48 received lactobacillus and 50 received placebo. lactobacillus group showed improvement in acute diarrhea as compared with placebo. The results of the study were comparable and similar to our study.

In our study apart from Day 1 the rate of occurrence loose stool was controlled notably in ORS + Zinc Group and ORS + Probiotic Group in comparison with ORS Group. It was observed that loose stool frequency stopped significantly faster in patients of Probiotic Group. This is similar to the studies of Kiran M *et al*. [19], Makbule E *et al*. [20] and Stefano G *et al*. [21].

Kiran M *et al*. [19] Phase IV clinical trial assessing the safety and efficacy of *S.boulardii* on Indian children in the treatment of diarrhea reported on day 3 (Visit 2) after taking *Saccharomyces boulardii* there was a significant reduction in stool frequency to 5. 27 from 9.005 (Day1). On day 5 (Visit 3), it had notably lower frequency of 2.7 episodes. There was a significant reduction seen with the treatment of *Saccharomyces boulardii* from Day 1 to Day 5. The results of the study were comparable and similar to our study.

Makbule E *et al*. [20] who studied patients with infection from rotavirus showed reduction in diarrhea duration in the group taking yogurt (4.6 l ± 1.68) compared with *Saccharomyces boulardii* (5.47 ± 2.37) (P=0.74).

Stefano G *et al*. [21] study compared the placebo with lactobacillus. After enrollment, duration of diarrhea was 3.0 ± 1.14 days in placebo versus 2.42 ± 1.15 days in lactobacillus group (mean ± SD with P value = 0.03) and in rotavirus-positive children, duration of diarrhea lasted 3.19 ± l.73 days versus 2.34 ± 0.7 days respectively (P < 0.008). Diarrhea continued for more than 7 days in 10.7% of placebo group while it was 2.7% of lactobacillus group (P < 0.01).

On day 1, there was no significant difference in consistency of stools in between 3 groups. (p=0.890). On day 3, 2% from ORS group, 4% from ORS + Zinc group and 12% from ORS + Probiotic group developed well-formed stools which was statistically significant(p=0.004). On day 5, probiotic group has maximum number of children 32% with well-formed stool when compared to others (p=0.03). These findings were reliable with the studies of Deepak R *et al*. [15] and Yazar AS *et al*.

Deepak R *et al*. [15] observational, prospective, open label, comparative study evaluating the treatment of mild and moderate of diarrhea with the use of probiotics, where the participants were allocated to one of three study groups as follows; Group A: ORS & zinc Group, B: ORS, Zinc and lactic acid bacilli; Group C: ORS, Zinc and combination of lactic acid bacilli acidophilus, Bifidobacterium lactis and *Saccharomyces boulardii* and reported mean frequency of diarrhea on day 1 in Group A was 5.87±1.23, Group B; 6.5±1.15 and Group C, 6.63±1.42 respectively. There was no notable difference between the mean frequency of diarrhea on day 1 in the three groups (p>0.05). In group A, the mean frequency of diarrhea on day 1 was 5.87±1.23, day 2 was 2.93±0.82 and day 3; 1.33±0.47 respectively. In group B, the mean frequency of diarrhea on day 1 was 6.5±1.15, day 2 was 3.93±0.99 and day 3; 0.86±0.5 respectively. In group C, the mean frequency of diarrhea on day 1 was 6.63±1.42, day 2 was 2.73±0.79 and on day 3 was 0.53±0.5 respectively. Hence found combination of probiotics (group C) significantly reduced the mean frequency of diarrhea when compared to group A and B.

Yazar AS *et al*.[24] single-center, randomized controlled clinical trial to estimate the effect of a synbiotic, which contains probiotic and prebiotics both on the time interval of diarrhea in children contrast to a zinc suspension observed no effect on diarrhea at 24th hours of symbiotic intervention. The effects of synbiotics (diarrhoea-free percentage of children) started to be observed by 48 hours. At Day 3, 61.8% received combination of probiotics and prebiotics still had watery diarrhoea while 83.6% of the children who were controls had watery diarrhea (p=0.01). At 96 and 120 hours of intervention, the diarrhea-free percentage was less combination group when compared to control group (p<0.01 for both). The effects (diarrhoea-free percentage of children) of the zinc started to be observed at 48 hours of intervention. After 48 hours, 81.8% of the children receiving zinc still had watery diarrhea while it 98% in control group had loose stools which was watery (p=0.01). After 72, 96, and 120 hours, the number of children who were receiving zinc but still having watery

loose stools was less in relation with control group patients($p<0.01$ for all groups). The effect of synbiotics and zinc was similar at 24 and 48 hours of intervention ($p>0.05$). At 72 hours, 45.4% of children receiving zinc still had watery diarrhea, which was notably lower than in the group receiving combination of prebiotics and probiotics with 61.8%, ($p<0.05$). At 96 hours of intervention, the percentage of children with diarrhoea was lower in the zinc group while in combination (prebiotics and probiotics) group it was longer ($p<0.05$). This was in contrast to our study where ORS + probiotic was found to be more effective as compared to ORS + Zinc.

The mean time interval of loose stool in this study was substantially higher in ORS Group (4.11±1.12 days). Also the mean duration of diarrhea in ORS + Zinc Group (3.36±1.75 days) was appreciably higher in comparison to ORS + Probiotic Group (2.65±1.38 days) ($p<0.05$). It was observed the mean duration of diarrhea was least in patients of probiotic Group. Similar observations were noted in the studies of Deepak R *et al*. [15], Naseer A *et al*. [17], Yazar AS *et al*. [27], Van Niel CW *et al*. [22], Simakachorn N *et al*. [23] and Shornikova AV *et al*.

Deepak R *et al*. [15] observational, prospective, open label, comparative study to evaluate the efficacy of probiotics managing mild and moderate diarrhea reported mean time interval of loose stool in group A was found to be 4.5±0.76; group B, 3.47±0.5; and group C, 3.17±0.37 respectively. The reduction in mean duration of diarrhea in group B and C were found to be statistically significant when compared to group A ($p<0.05$), and the results were similar to our study

Naseer A *et al*. [17] descriptive study comparing the mean duration of diarrhea between children taking yogurt and probiotics (lactobacillus) in acute watery loose stool reported mean time interval of loose stool in group A was 1.98 ± 1.31days, while that in group B was 3.09 ± 1.64 days. This was in contrast to our study where ORS + Probiotic was found to be more effective in controlling the mean duration of diarrhea.

Yazar AS *et al*. [24] single-center, randomized, and controlled clinical trial to evaluate the efficacy of probiotics plus prebiotics (synbiotic) on the time interval of loose stool in children compared to a zinc, which showed that the duration of diarrohea was notably reduced (~24 hours) in the prebiotic plus probiotic group in while in the control group it was found not reduced. (91.0±28.9 hours vs. 114.3±30.9 hours, $p<0.001$, respectively). The time interval of diarrhea was reduced considerably (~28 hours) as in the patients allocated in zinc group while the patients in the control group had longer duration of diarrhea (86.4±30.8 hours vs. 114.3±30.9 hours, $p<0.001$, respectively). No statistical impact was noted between the prebiotic plus probiotic group and zinc groups (91.0±28.9 hours vs. 86.4±30.8 hours, $p>0.05$, respectively), but our study showed statistical difference in between ORS + Zinc and ORS + Probiotic groups.

Van Niel CW *et al*. [22] meta-analysis on randomized and double blinded studies on different strains of Lactobacilli in 122 children found that Lactobacilli decreased the duration of diarrhea by 0.7 days. It was also noticed that the frequency of stools was reduced to 1.6 on day 2. This was similar to our study.

Simakachorn N *et al*. [23] study on 53 children comparing the lactobacillus with yogurt and observed lesser duration of diarrhea with treatment with bacillus (1.81 ± 1.08) days and with placebo (2.38 ± 1.51). This was similar to our study.

Shornikova AV *et al*. [24] study on 46 children comparing outcome of yogurt with placebo reported 21 patients received treatment with yogurt and 25 were controls. They found that duration of diarrhea was shortened in patients who were treated with yogurt (1.5 ± 1.1) in relation to the controls (2.5 ± 1.5 days). This was similar to our study.

The mean duration of hospital stay in our study was notably higher in ORS Group (5.24±1.16 days) in comparison with other groups. Also the mean duration of hospital stay in ORS + Zinc Group (4.38±1.76 days) was more significantly when compared to ORS + Probiotic Group (3.42±1.44 days) ($p<0.05$) which was relatable in studies of Guandalini S *et al*. [25], Hussain I *et al*. [26] and Stefano G *et al*. [21].

Guandalini S *et al*. [25] randomized, double-blind, placebo-controlled trial among 287 children with acute onset of diarrhea. They were randomized into Group A with 140 children receiving ORS with placebo and group B with 147 children receiving ORS with lactobacillus acidophilus of 10^{10} CFU/250ml. The study concluded that administering ORS with lactobacillus to children with acute diarrhea is safe and results in shorter duration of diarrhea, less chance of a prolonged course, and early discharge from the hospital. This was similar to our study.

Hussain I *et al*. [26] trial of comparison of yogurt and probiotic *Saccharomyces boulardii* demonstrated that in both groups stool consistency normalized at the same time (3.07 ± 2.01 days versus 3.07 ± l.73 days ($P> 0.05$). Duration of hospitalization there was no difference among both groups (4.68 ± 2.37 versus 4.23 ± l.72 days; $P=0.45$).

Stefano G *et al*. [21] study compared the placebo with lactobacillus reported Hospital stay was significantly less in group B than in group A.

Conclusion

In children with acute non infectious watery diarrhea, Zinc or Probiotic (*Saccharomyces boulardii*) supplementation reduced the duration of diarrhea. In our study children receiving Probiotic were more likely to be diarrhea-free after the first 48 hours of intervention, with better outcomes at 72 and 96 hours along with improvement in consistency and reducing the duration of hospital stay.

S. boulardii was well accepted and tolerated by the children and there were no reports of any side effects.

Zinc is recommended by WHO and Probiotic (*Saccharomyces boulardii*) should be thought of adding in reducing the hospital stay, improving the consistency of stool and reducing the frequency of acute non infectious watery diarrhea.

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