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A Randomized, Controlled, Prospective Study To Compare The Efficacy And Safety of Zinc And Probiotics As Adjunct Therapy In Acute Diarrheal Disease of Children.

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Abstract: *Aim: To compare the safety of zinc and probiotics as adjunct therapy in acute diarrheal disease in children of 6 to 24 months of age.*
Methods: Children of age 6 to 24 months with acute diarrheal disease admitted in the pediatric ward were randomized into 3 groups. Along with the usual fluid replacement therapy, first group received 20mg of zinc sulphate tablet once daily, the second group received probiotics saccharomyces 2.5 billion spores & lactic acid bacillus 100 million spores. The control group received only fluid replacement .Stool frequency and consistencies, mean duration of diarrhea, episodes of vomiting and amount of fluids utilized were monitored in the three groups.
Results: Stool frequency and stool consistency improved faster in the zinc than the other groups and the probiotics group improved faster than the control. The mean duration of diarrhea was much shorter in the zinc group. The amount of ORS and IV fluids utilized was also much lower in the zinc group, but episodes of vomiting were more.
Conclusion: This study supports the fact that zinc supplementation is effective and safe in the treatment of ADD as an adjunct to fluid replacement. Probiotics also play a role in reducing the severity of illness but only next to zinc.

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Aim: To compare the safety of zinc and probiotics as adjunct therapy in acute diarrheal illness in children of 6 to 24 months of age.
Methods: Children of age 6 months to 24 months, either sex with acute diarrheal disease admitted in the pediatric ward were randomized into 3 groups. Along with the usual fluid replacement therapy, one group of children received
Aim of the study: To compare the safety of zinc and probiotics as adjunct therapy in acute diarrheal illness in children of 6 to 24 months of age.
Study design: randomized, controlled, comparative, open label, single centre, prospective, parallel group study.
Study centre: Department of Pediatrics, Tirunelveli medical college hospital, Tirunelveli.
This study was approved by Institutional Ethics Committee of Tirunelveli medical college. Written informed consent was obtained from the parents of children who participated in the study in local vernacular language.
Inclusion criteria:

1. Children with symptoms of acute diarrheal disease (ADD)
2. History of duration of diarrhea should be less than 3 days.
3. Children of either sex.
4. Age from 6 months to 24 months.

Exclusion criteria:

1. Children with history of chronic diarrhea.
2. Children with symptoms of dysentery.
3. Children with acute renal failure.
4. Children with shock.
5. Children with electrolyte imbalances.
6. Children with other co morbidities.
7. Children with known HIV status.

Screening
General examination:
Weight, state of dehydration, pulse, Blood pressure, presence of other co morbidities was recorded.
Laboratory investigations:
Urine analysis, stool examination, Serum electrolytes, Blood urea, Serum creatinine
Treatment protocol & follow up:

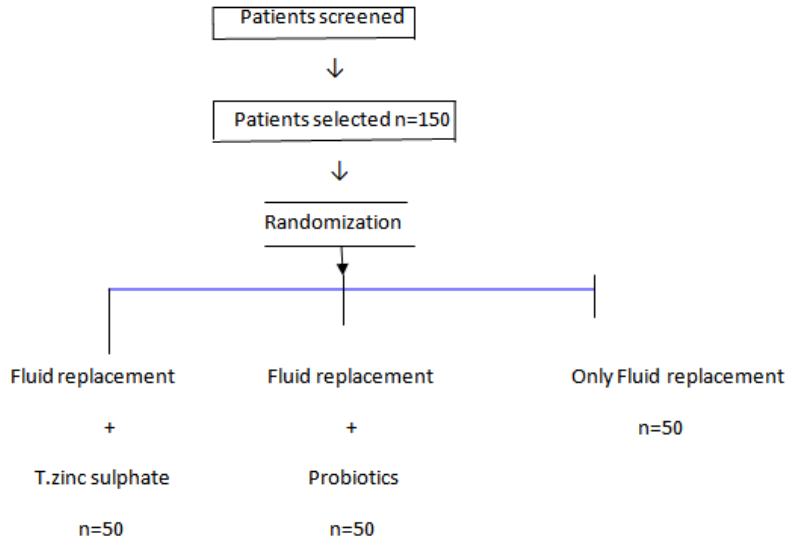
Children who fulfilled the inclusion criteria were enrolled for study and admitted in the pediatric ward. After randomization the children in all the groups were treated with ORS and IV fluids accordingly to correct the initial dehydration, to maintain the hydration ant for replacement of fluids in stools or vomitus.The Zinc group was given 20mg Zinc sulphate tablet once daily along with the usual fluid replacement .The tablet was powdered and dissolved in 10ml of water and given to the child. The children of probiotics group were given a probiotic consisting of Saccharomyces 2.5 billion spores and Lactic acid bacillus 100 million spores in a sachet. The powder in the sachet was dissolved in 20ml of lukewarm water and given to the child. Parents of the children were instructed to note down the frequency and consistency of stools and number of episodes of vomiting in a printed format. Every 24 hrs the investigator checked and collected the details noted by the parents. Patients were under the supervision of the pediatrician who treated them.

Parameters assessed:

1. Stool frequency every 24 hrs.
2. Change in stool consistency every 24 hrs.
3. Number of episodes of vomiting every 24 hrs.
4. Duration of diarrhea after intervention is noted in hours. (time duration from admission up to the time of last unformed stool)
5. Amount of IV fluids and ORS administered.

Statistical analysis:

The continuous variables in the treatment groups were compared by ANOVA (Analysis of variance) and the difference between the groups were compared for their significance by Bonferroni post hoc test. The nominal scale variables were compared by X 2 test for understanding the relationship between the three groups. The above statistical procedures were performed by the statistical package IBM SPSS statistics 20. The P values less than 0.05 was defined as significant in two tailed.
Patient disposition:



I. Results

Results and observation:
The clinical trials were matched according to their basal characteristics for making comparison between them. The basal characteristics were age, gender, duration of diarrhea before enrolment, and the presence of bottle feeding.

Table-1
Matching of the basal characteristics among the three groups

variables	zinc		probiotics		control		'F'	'df'	significance
	mean	SD	mean	SD	mean	SD			
Age (months)	9.5	3.4	9.7	3.6	10.4	5.0	0.721	2,147	P>0.05
Weight (Kg)	6.6	1.7	6.8	1.7	6.7	6.7	0.249	2,147	P>0.05
Duration of diarrhea (days)	2.1	1.0	2.6	1.4	2.2	1.1	2.580	2,147	P>0.05

Table-1 shows the basal characteristics such as age, weight, duration of diarrhea before enrolment. There is no significant difference among the three groups. (P>0.05).

Table: 2

Sex distribution

Groups	Genders			χ^2	df	significance
	Male	Female	Total			
Zinc	22	28	50	1.932	2	P>0.05
Probiotics	22	28	50			
Control	28	22	50			
Total	72	78	150			

Table: 2 show the sex distribution among the three groups.
There is no significant difference among groups in sex distribution. P>0.05.

Table-3 : Matching of bottle feeding among the three groups.

Groups	Bottle feeding			χ^2	df	significance
	absent	present	Total			
Zinc	8	42	50	3.918	2	P>0.05
Probiotics	6	44	50			
Control	2	48	50			
Total	16	134	150			

Table3 shows the history of bottle feeding practice was matched among the three groups.
The three groups were not significantly different with respect to the history of bottle feeding practice.
The overall percentage of children having the history of bottle feeding practice was 89.3%.

Figure: 1 Comparison of bottle feeding practice among three groups

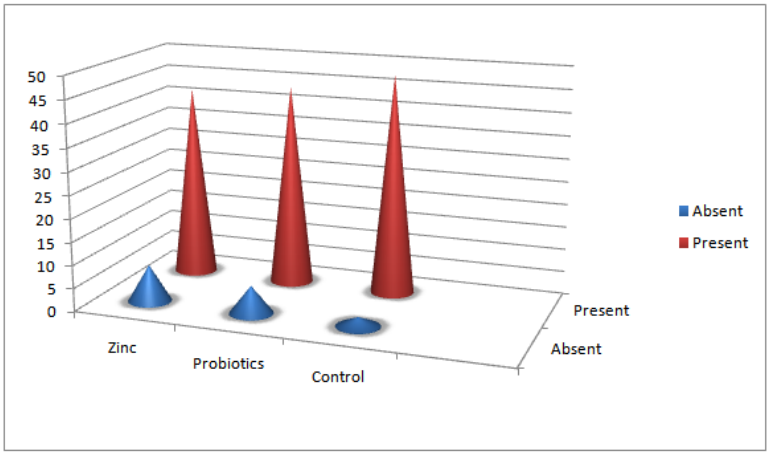


Table: 4 Comparison of stool frequency among groups through day 1 to day 4

day	zinc		probiotics		control		'F'	'df'	Significance	Comparison Of significance
	mean	SD	mean	SD	mean	SD				
1	7.1	2.4	7.6	2.7	7.3	2.3	0.500	2,147	P>0.05	1≈2≈3
2	4.1	2.4	4.4	2.5	5.9	2.1	8.609	2,147	P>0.05	1≈2,1<3,2<3
3	1.9	1.7	3.0	2.3	4.7	1.9	24.687	2,147	P>0.05	1<2,1<3,2<3
4	0.6	0.8	1.3	1.4	3.5	1.3	82.989	2,147	P>0.05	1<2,1<3,2<3

Table-4. Shows the comparison of stool frequency among groups through day1 to 4.

The stool frequency from the first day to the fourth day was compared among the groups.
On the first day the three groups were more or less equal.
On the second day , groups 1 and 2 were more or less equal .Frequency in the groups 1 and 2 was significantly lesser than in group 3.On the third day group 1 showed lesser frequency than the groups 2&3 with a significant P value (P<0.001). Frequency in group2 was also significantly lesser than group3.
On the fourth day also all the three groups were significantly different (1<2,1<3,2<3 and P<0.001).

Figure: 2 Stool frequency among groups through day1 to day4

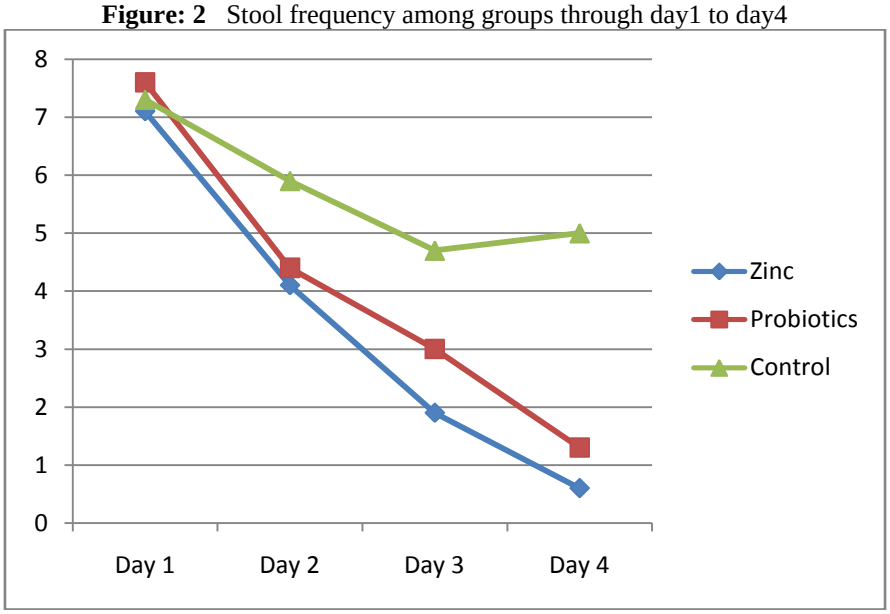


Figure 6: is a pictorial representation of comparison of stool frequency among groups through day1 to 4.

Table-5 Stool consistency among groups on the second day.

Consistency	Zinc group	Probiotics Group	Control	Total	X2	df	significance
normal	1	1	0	2			
Semi liquid	27	11	1	39			
liquid	22	38	49	109			
total	50	50	50	150	37.608	4	P<0.001

Table-7 shows the comparison of stool consistency among groups on the second day.
On the first day the stool consistency was liquid in all children enrolled.
On the second day the improvement from liquid to semi liquid in group1 was 54% and the same in second group was 22%. But in third group the improvement was only 2%. The improvements among the groups were statistically significant (P>0.001).

Figure3

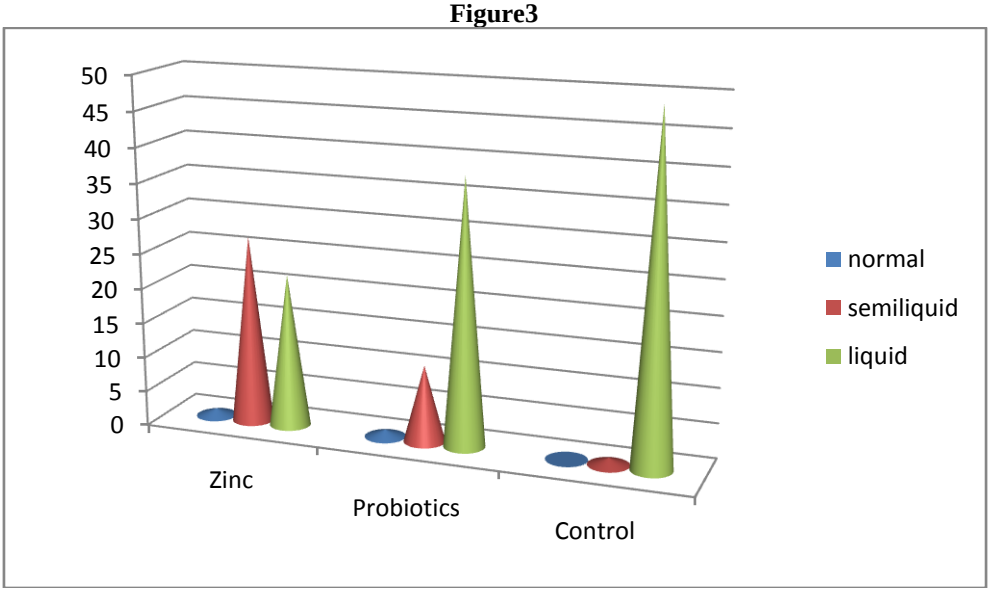


Figure 3: This is a pictorial representation of stool consistency among the three groups on the second day.

Table-6: Stool consistency among groups on the third day

Consistency	Zinc group	Probiotics Group	Control	Total	X2	df	significance
normal	22	11	10	34			
Semi liquid	21	25	1	47			
liquid	5	13	48	66			
total	50	50	50	150			
					37.608	4	P<0.001

The improvement from semi liquid to normal in group 1 was 45.8% and the same in second group was 23.4%.But in the third group the improvement was only 2%. The above improvements among the groups were statistically significant (P>0.001).

Figure 4 Stool consistency on the third day

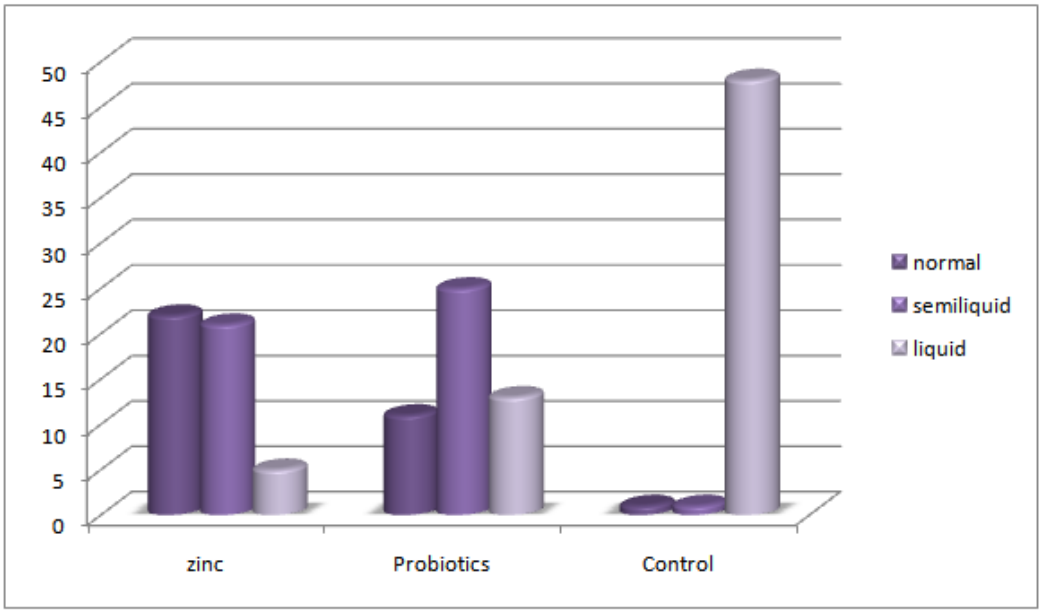


Table-7: stool consistency among groups on the fourth day.

Consistency	Zinc group	Probiotics Group	Control	Total	X2	df	significance
normal	22	26	1	49			
Semi liquid	4	9	10	23			
liquid	1	3	38	42			
total	27	38	49	114			
					73.490	4	P<0.001

Table-7 shows the comparison of stool consistency among groups on the fourth day.
The improvement to normal in group 1 was 81.5% and the same in second group was 68.4%. But in third group the improvements between the groups were statistically significant (P>0.001).

Figure5: stool consistency on the fourth day

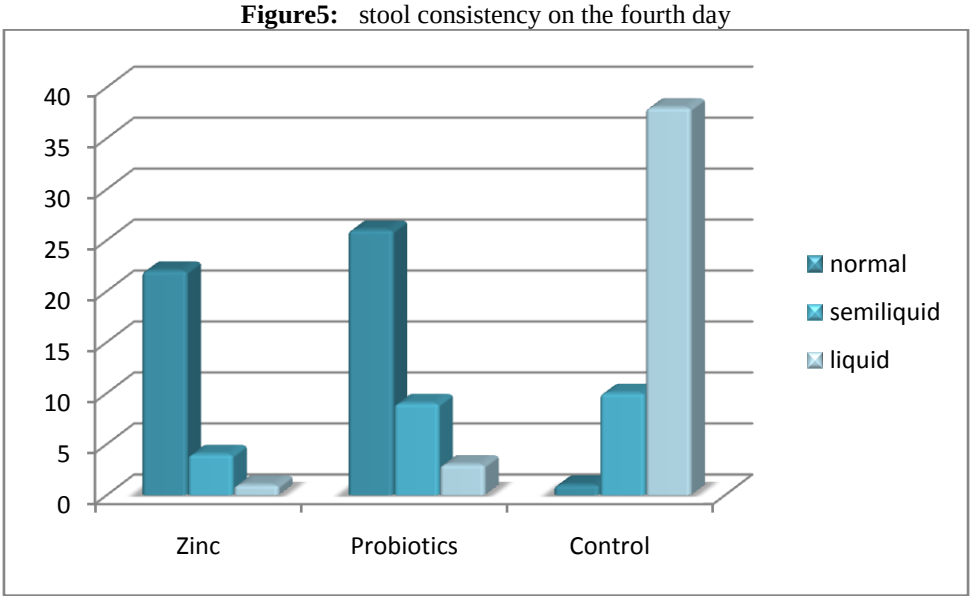


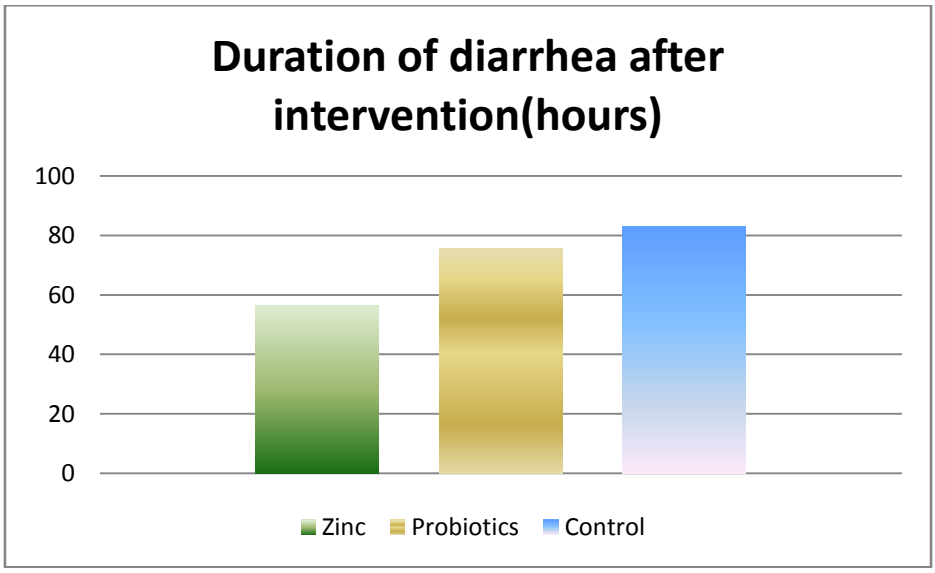
Figure5 : shows the comparison of stool consistency among the three groups on the fourth day.

Table8: Duration of diarrhea after intervention

S.no	Groups	Duration (hours)		F	df	Significance	Comparison of significance
		mean	SD				
1	Zinc	56.5	15.9				
2	Probiotics	75.6	15.6				
3	Control	82.9	14.4	39.231	2,147	P<0.001	1<2&3.2≈3

Table:8 : shows the comparison of mean duration of diarrhea after intervention among the three groups.

- The duration of diarrhea after intervention among the three groups were compared. The mean duration of diarrhea after intervention in group 1 (56.5±15.9 hrs) was significantly (P<0.001)lesser than the mean duration of groups 2&3 (75.6±15.6≈82.9±14.4)
- The mean duration of diarrhea after intervention in groups 2&3 was more or less equal (75.6±15.6≈82.9±14.4 and P>0.05).



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- **Table9:** Vomiting episodes among the groups on the second day

No of times of vomiting	Zinc		Probiotics		Control		Total	
	No	%	No	%	No	%	No	%
0	35	70	47	94	45	90	127	84.6
1	12	24	3	6	4	8	19	12.7
2	3	6	0	0	0	0	3	2.0
4	0	0	0	0	1	2	1	0.7
Total	5o	100	50	100	50	100	150	100

Significance -X2=17.637, df=6 and P<0.05

Table9: The vomiting episodes on the second day among the three groups were compared in the table.

- 94% subjects in the Probiotics group and 90% subjects in the control did not have vomiting on the second day. This was significantly earlier than the Zinc group (P<0.05).
- In the Zinc group only 70% of the subjects were free from vomiting.

Table10: Comparison of total quantity of fluids required

S.no	Groups	Total fluids IV &ORS (ml)		F	df	Significance	Comparison of significance
		mean	SD				
1	Zinc	1352.0	533.6				
2	Probiotics	1612.0	529.0				
3	Control	1872.0	483.2	12.706	2,147	P<0.001	1<2&3,2<3

Table 10 shows the comparison of mean quantity of fluids (IV and ORS) required for children among the three groups for correction and maintenance of dehydration.

-The mea n quantity of fluids required in the Zinc group was significantly lesser than the Probiotics and control groups.

-The mean quantity of fluids required in the Probiotics group was significantly lesser than the control group.

II. Discussion

Acute is a leading cause of under -5 mortality in India. It accounts for about 13% deaths in under-5 age group.2 The broad principles of management of acute gastroenteritis in children include oral rehydration therapy, enteral feeding, and diet selection, zinc supplementation, and additional therapies such as probioticcs.3 This study was aimed to compare the efficacy and safety of zinc and probiotics in treatment of acute diarrhea in children.

The basal characteristics age, weight, gender were comparable in all the three groups with no significant difference among the three groups. The mean group of children presented with ADD ranged from nine to ten months. This correlates with the literature showing highest incidence of diarrheal episodes in 6-11 months.

There was no significant difference in the mean duration of diarrhea before enrolment among the three groups. So, regarding the severity all the three groups were more or less similar. The percentage of children with history of bottle feeding was 89.3%. This shows the fact that bottle fed infants are more prone for ADD and bottle feeding is still practiced by majority in our population. The history of bottle feeding practice also did not show any significant difference among the study groups.

The stool frequency was similar in all the subjects on the first day. This shows that the severity of illness was same in all the children enrolled. On the 2nd, 3rd and 4th day after intervention, the children in the 1st group showed much reduced stool frequency than the 3rd group. This result coincides with the study of Trivedi et al.95 On the 3rd and 4th day zinc group showed a significant decrease in frequency than the probiotics group. This is probably due to the effect of zinc that inhibits the Camp induced, chloride-dependent fluid secretion and also improving the levels of brush border enzymes.84, 85, 86

The stool consistency was same in all the groups on the first day. On the 2nd, 3rd and 4th day the zinc group showed a more significant improvement towards normal than the other two groups. This correlates with the studies by Dutta et al 97 showing less liquid stools in zinc therapy. This is due to the role of zinc in regeneration of epithelial cells lining the GIT and better absorption of water and electrolytes.86

Regarding probiotics, the stool frequency on the 3rd and 4th day showed a significant improvement than the control group. The improvement in stool consistency was also better with probiotics when compared with the control. This correlates with the study of Roberto et al 101. This is due to the effect of probiotics acting as a barrier preventing adherence of pathogens 83 and also that the multiplication of nonpathogenic organisms compete with the pathogens thus depleting their nutrition.93

Mean duration of diarrhea after intervention was significantly reduced in the zinc group than the control group. This correlates with the studies of Sazawal et al 94 and Gregerio et al.96 The duration of diarrhea in children treated with zinc was about 19 hrs shorter than the probiotics group. This difference was significant and correlate with the study of Dalgic et al.106 .This may be due to the effect of zinc that improves the regeneration of intestinal epithelium, and enhances the immune response allowing for a better clearance of pathogens.86

On the 2nd day 90-95% of subjects in probiotics and control group had no vomiting but only 70% of the zinc group was free from vomiting. This shows a slight increase in the episodes of vomiting in the zinc group. This can be explained by the fact that zinc forms corrosive zinc chloride which produces adverse gastrointestinal effects.88

The subjects in the zinc group required less amount of ORS and other fluids than the other two groups. This result correlates with the study of Dutta et al. 97 As the consumption of ORS and IV fluids coincide with the severity of diarrhea and dehydration, this shows that zinc supplementation decreases the severity of illness compared to the other two groups.

III. Conclusion

This study supports the fact that zinc supplementation is effective and safe in the treatment of ADD as an adjunct to fluid replacement. Probiotics also play a role in reducing the severity of illness but only next to zinc.

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