ORIGINAL PROF-1558

THERAPEUTIC ROLE OF ZINC;
EVALUATION IN PATIENTS WITH DIARRHEAL ILLNESSES

DR. AISHA SAJID
MBBS, MCPS, FCPS (Pediatrics)
Department of Paediatrics
Madina Teaching Hospital
University Medical & Dental College
Sargodha Road, Faisalabad

DR. MAQBOOL AHMAD
MBBS, MCPS, FCPS (Paediatrics)
Department of Paediatrics
Madina Teaching Hospital
University Medical & Dental College
Sargodha Road, Faisalabad

DR. SURRIYA SAJID
MBBS, MCPS, FCPS (Pediatrics)
Department of Paedisatrics
Madina Teaching Hospital
University Medical & Dental College
Sargodha Road, Faisalabad

Article Citation:
Sajid A, Sajid S, Ahmad M. Therapeutic role of zinc; Evaluation of in patients with diarrheal illnesses. Professional Med J Sep 2010;17(3):472-478.

ABSTRACT... OBJECTIVES: To evaluate the efficacy of zinc supplementation in patients with diarrheal illnesses. **Study Design:** Quasi Experimental study. **Setting:** The study was conducted at the pediatrics department of Madina Teaching Hospital, Sargodha road, Faisalabad, **Period:** 6 months period from November 2008 to April 2009. **Material and Methods:** Two hundred children suffering from diarrhea with mild to moderate dehydration were included in the study and divided into two groups, A and B. Group A was given zinc supplementation along with ORS and adequate nutrition according to age. In group B 100 children were taken as control to whom only ORS and adequate nutrition for age was given. **Results:** Baseline clinical parameters were comparable in both groups at admission. The effect observed on stool consistency was more marked in 72 hours i.e. 71% patients were improved in group A versus 40% in group B, as compared to stool frequency in 72 hours i.e. 56% in group A versus 39% in group B. Although in 7 days, 99% patients showed improvement in stool consistency in group A,70% in group B(p value 0.037) and stool frequency showed improvement of 96% in group A as compared to 77% in group B(p value 0.037). Duration of hospital stay on the average was about 2 days less in case of zinc supplemented group as compared to control group. **Conclusion:** Zinc supplementation reduced the duration and severity of mild to moderate diarrheal illness and treatment was well tolerated with no significant side effects.

Key words: Diarrheal illnesses, zinc, Therapeutic effect

INTRODUCTION

Diarrhea is defined as the passage of three or more stools in a day of consistency softer than usual for the child or one watery stool per day[1]. There are three to four episodes of diarrhea per child per year in Pakistan and it causes an estimated 2.5 lac deaths in children under five years of age per year as compared to united states where approximately 125 deaths occur each year as a result of gastroenteritis[1]. It accounts for 40-50% of our hospital admission in summer[1].

Mortality due to diarrhea can be reduced by interventions like oral rehydration therapy, optimal breast feeding practices, improved nutrition, increased access to clear water and sanitation facilities, improved personal and domestic hygiene and appropriate drug therapy where necessary[2]. Antimotility agents (Loperamide) are generally contraindicated in dysentery and have no role in the management of acute watery diarrhea. Antiemetics

Article received on: 06/08/2009
Accepted for Publication: 12/10/2009
Received after proof reading: 04/08/2010
Correspondence Address:
Dr. Aisha Sajid
MBBS MCPS FCPS (Pediatrics)
15- Sadar Block, Lasani Town
Sargodha Road, Faisalabad
draisha_tanvir@hotmail.com

are also of little value and have serious side effects whereas antibiotics are used only in selective cases[3].

Among the different new treatment options for diarrhea, zinc supplementation is being studied world widely. Zinc is an essential micronutrient with catalytic role in over a hundred specific metabolic enzymes in human metabolism and also required for many aspects of immune system. Lack of zinc is associated with atrophy of thymus and dysfunction of T lymphocytes. The potential benefit of zinc on the immune system can be mediated by a variety of pathways including stabilization of epithelial barrier and function of neutrophils, natural killer cells, monocytes and macrophages[4]. The beneficial effects of zinc are not dependent upon the type of zinc salts[5].

Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhea and to increase survival in a number of randomized controlled trials[6]. Although long-term supplementation of large zinc quantities may not be healthy for serum copper status, the dose and duration of supplementation proposed, does not appear to have any negative effect on copper status. Two trials assessed copper status and found no difference in mean serum copper levels between zinc-supplemented and placebo-supplemented children after 14 days of supplementation[7,8]. Total zinc intake of 60 mg/day (50 mg supplemental and 10 mg dietary zinc) have been found to result in signs of copper deficiency. In order to prevent copper deficiency, the U.S. Food and Nutrition Board set the tolerable upper level of intake (UL) for adults at 40 mg/day, including dietary and supplemental zinc[9].
The possible mechanisms suggested by which zinc helps in diarrhea, are:

- To improve water and electrolyte absorption[10].
- To accelerate the regeneration of the gut epithelium and thus improving barrier dysfunction.
- To increase the activity of brush border enzymes[11]
- To enhance overall immune function[12]
- To inhibit the growth of pathogens

A study was performed by the department of microbiology in Indonesia to determine the inhibitory effect of zinc sulfate on enteric pathogens. All the enteric pathogens that were tested including Salmonella typhi, Salmonella groups A, B, C, D and E, Escherichia coli, Enterobacter, Shigella and Vibrio cholerae were inhibited by zinc sulfate showing that it may have antimicrobial effect over these pathogens[13].

MATERIAL AND METHODS

This hospital based study was conducted in the pediatric department of Madina Teaching Hospital, University medical and dental college, Sargodha road, Faisalabad, during period of 6 months starting from November 2008 to April 2009. Only indoor patients were included in the study.

Children with acute watery diarrhea, persistent diarrhea and dysentery of age between 6 months to 5 years of both sexes, with no or some dehydration and diarrhea with first and second degree malnutrition were included in the study. Children with severe dehydration and other serious illnesses like pneumonia, septicemia, meningitis, hemolytic uremic syndrome, acute renal failure, 3rd degree malnutrition, chronic diarrhea like cow's milk protein allergy, celiac disease, inflammatory bowel disease, lactose intolerance, severe dehydration and electrolyte imbalance were excluded from the study.

Study participants were divided into two groups with random allocation, Group A (odd no.) and Group B (even no.). Risks and benefits of zinc supplementation were explained to the parents. Informed written consent was taken. Data based on detailed history and examination was registered as per performa. Nutritional status was assessed from weight according to standard centile charts. Group A was supplemented with 20 mg zinc sulfate in the powder form dissolved in water in two divided doses[3] along with rehydration, nutritional support and appropriate antibiotics; Group B was given only rehydration therapy, with nutritional support and appropriate antibiotics. Performa was filled on the day of admission and then follow up was carried out at 24, 48 and 96 hours respectively. Those who did not improve or

worsen were subjected to serum electrolytes, stool culture, pH and reducing substances, and were treated accordingly, so excluding them from study. The outcome measures that showed the efficacy of treatment were consistency of stools, frequency of stools and shortened duration of hospital stay. The stool consistency was divided into two categories, loose and formed stools, for the purpose of analysis. All the children having watery loose or semisolid stools were included in the loose stool category. The longer follow up was done weekly for one month in only those cases who returned for the follow up.

Data was analyzed with the help of SPSS program (standard package of statistical studies). The following statistical analysis was done:

- Frequency and consistency of stools, duration of hospital stay were calculated.
- Mean + SD calculated for clinical parameters on admission like age, weight, frequency of stools and duration of diarrhea.

Quantitative data like frequency of stools, duration of hospital stay was measured by mean and standard deviation, and the test of significance was t-test.

RESULTS

The clinical parameters of both the groups i.e., group A (Zinc supplemented) and group B (non supplemented) including age, weight, duration of illness and frequency of stools were comparable at the time of admission and their distribution was not statistically different (table-I). Both Groups showed no significant improvement in 24 hours with p-value = 0.00, hence the drug is not effective in 24 hours (table-II).

In 48 hours also both groups showed no meaningful improvement (table-II). While in 72 hours there was a meaningful difference between two groups with Group A showing 71% of improved patients and B showing only 40% improvement (p-value = 0.037) (table-II, Figure-1). On 7th day follow up, 99% patients in group A had improvement and only 70% in group B. (p value =0.037) (table-II).

Table-I. Clinical parameters on admission.

Particular	Group A	Group B
No. of Patients	100	100
Age (Month)	18±112.09	17±11.41
Sex		
Male	64	57
Female	36	43
Dehydration		
No Dehydration	44	34
Some Dehydration	56	66
Duration of Diarrhea (days)	3±1.2	4±1.27
Frequency of Stools/day	6±1.86	6±1.33
Vomiting		
Yes	65	62
No	35	38
Fever		
Yes	56	53
NO	44	47
Weight (Kgs)	10±2.05	10±1.97

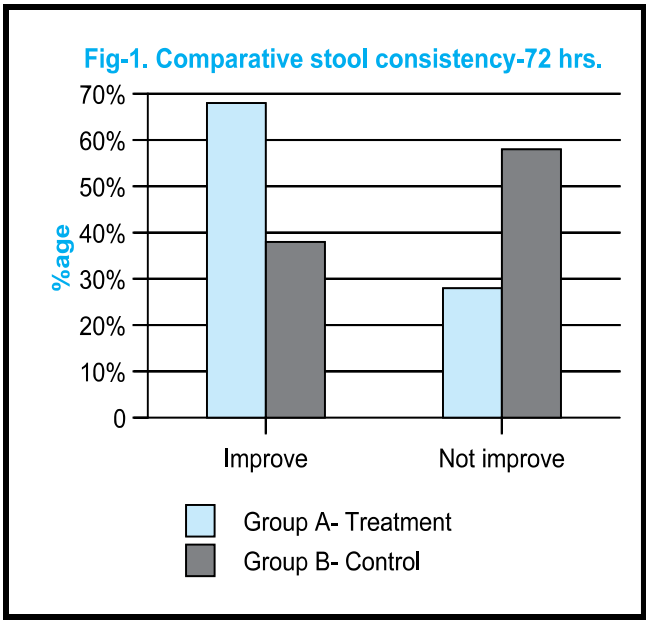


Table-II. Comparative stool consistency.					
Duration	**Group A**		**Group B**		**P-value**
	% Improved	**% Not improved**	**% Improved**	**% Not improved**	
24 hours	11	89	04	96	0.06
48 hours	41	59	19	81	<.001
72 hours	71	29	40	60	<0.001
7 days	99	01	70	30	< .001

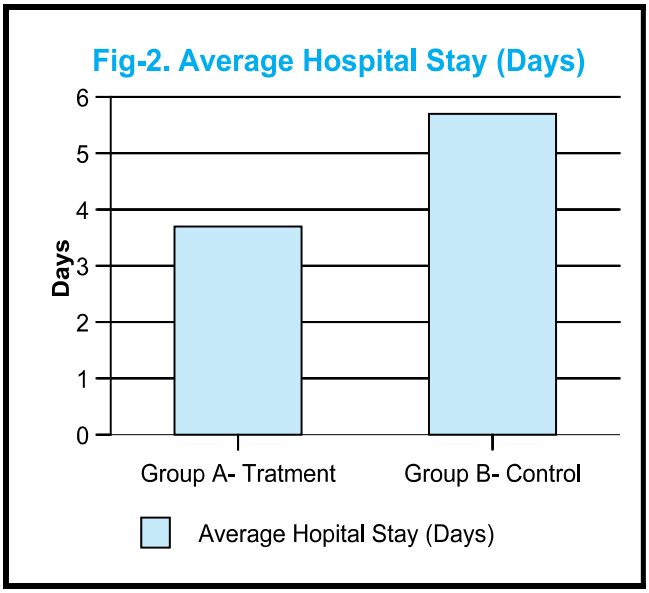
As far as stool frequency is concerned, both Groups showed no meaningful improvement in 24 hours with p-value = 0.00, as 100 percent patients showed no improvement in this case (table III).

In 48 hours also there is no significant improvement, while in 72 hours there is a meaningful difference and the research claim accepted, with Group A showing 56% improvement and B showing only 39% improvement (p-value = 0.037) (table III). On 7th day Group A had 96% improvement and B showed only 77% improvement (p=value 0.037) (table III). A substantial difference was observed between the average hospital stay of two groups with group A (Administered with drug) on average staying 2 days lesser than group B. There was much lesser standard deviation observed among Group A participant as compared to Group B (1.05 vs.1.19), showing a much stable response in terms of hospital stay for group A as compared to group B.(Figure II)

DISCUSSION

In our study we found considerable improvement in stool frequency and stool consistency starting from 48 hours and onwards. The effect observed on stool consistency was more marked in 72 hours i.e. 71% in group A versus 40% in group B, as compared to stool frequency in 72 hours i.e. 56% in group A versus 39% in group B. Although in 7 days the improvement in stool consistency and frequency was 99% and 96% in group A as compared to 70% and 77% in group B. As more patients showed subjective symptomatic improvement earlier in group A, discharge rate was better in this group and duration of hospital stay on the average was about 2 days less in case of zinc supplemented group as compared to control group, thus showing a considerable therapeutic effect of zinc on patients with diarrhea. The suffering of mothers and caretakers is reduced to a great extent even by a small improvement, so we recommended the use of zinc in the treatment of diarrhea in our children.

Table-III. Comparative stool frequency					
Duration	**Group A**		**Group B**		**P-value**
	% Improved	**% Not improved**	**% Improved**	**% Not improved**	
24 hours	0	100	0	100	-
48 hours	17	83	18	82	0.85
72 hours	56	44	39	61	<.001
7 days	96	04	77	23	<.001



Compliance in our study was fairly good because of meticulous follow up. As far as adverse effects of zinc are concerned, no serious systemic side effects were observed during our study. A few studies have reported vomiting as a side effect of zinc supplementation, but we could not evaluate that, as vomiting was also as a result of diarrhea itself. As other side effects like copper deficiency occur as a result of long term use, it would need a larger sample and longer duration of supplementation with zinc to reach a significant conclusion.

The long term follow up was not possible for all the patients as only a few patients returned for weekly follow up for next month after discharge from the hospital, that's why we could not analyze the effect of zinc on prevention of further episodes of diarrhea.

Other factors influencing the outcome measures like age, socioeconomic status, use of drugs and nutritional status of the patients were addressed by randomizing the subjects and thus reducing the chance of confounding by the above mentioned and other unknown factors.

Although we can not compare exactly our study with other international studies because of the difference in doses, population, study design and outcome measures, but we can interpret the results of these studies in relation to our study.

Regarding the hospital stay our study found that average duration of hospital stay was about 2 days less in the treatment group as compared to control group. Dutta et al also randomized 80 male children with acute diarrhea between the ages of 3 and 24months to receive zinc or placebo during hospitalization[14]. Zinc - supplemented children had a shorter duration of diarrhea than placebo-supplemented children (70.4 vs. 103.4; p=0.0001). Al-Sonboli et al randomized 71 children in Brazil to receive 22.5 or 45 mg zinc/day for the treatment of acute diarrhea[15]. Children receiving zinc had a shorter duration of diarrhea (1.2 vs. 2.5 days; p<0.001) compared to children not receiving the zinc supplement. Bhutta et al[16] also assessed the effect of zinc supplementation on the duration of diarrhea among children presenting with persistent diarrhea in 4 randomized trials conducted in Peru, Bangladesh, and Pakistan[17-20]. In these trials, zinc supplemented children had a 24% lower probability of continuing diarrhea.

Al-Sonboli et al found the mean number of stools per day to be less in the zinc supplemented children when compared to the placebo group (4.1 vs. 10.0; p<0.01)[21]. Roy et al found a 28% lower median total stool output when comparing zinc supplemented children to control children with acute diarrhea (p=0.06)[22]. Khatun et al also observed a lower mean daily stool output from day 2 to day 7 (p=0.034)[23]. The use of zinc is also associated with some additional benefits like increased use of ORS and decreased use of antibiotics, visit to pharmacies and village drug sellers[24].

CONCLUSION

On the basis of our experience in the study we conclude that the use of zinc in the treatment of diarrheal illnesses including acute watery diarrhea, persistent diarrhea and dysentery, improves frequency and consistency of stools thus reducing the duration of illness. As diarrhea is one of the leading causes of childhood mortality and morbidity particularly in the developing countries, this treatment modality may help us reduce the disease burden and removing the problems like drug resistance and opportunistic infections.

However like any good study, it has raised further questions on the issue, which should be addressed by larger trials including interaction with other drugs and possible adverse effect by using the therapeutic doses. Our study also could not address the role of zinc in prevention of diarrhea, but this is an area which definitely requires further research.

REFERENCES

1. Khan PA. **Infectious diseases.** Basis of pediatrics. 7th ed. Lahore, PA: Zahid Bashir Printers; 2008:201-82.
2. Khan SR, Acute diarrhea. **Handbook of clinical Pediatrics.** 2nd ed. Lahore: Ilmi kitab khana;1996:35-45.
3. Bhutta Z A. **Acute Gasteroenteritis in Children.** In: Kliegman, Behrman Jenson and Stanton. Nelson textbook of Pediatrics.18th ed. WB Saunders,2007:1605-20.
4. Fraker PJ, King LE, Laakko T, Vollmer TL. **The dynamic link between the integrity of immune system and zinc status.** Nutr 2000;130:1399s-406s.qa
5. Bhatnagar S, Natchu UM. **Zinc in child health and disease.** Indian J Pediatr 2004;71:991-995.
6. Bhutta ZA, Bird SM, Black RE, et al. **Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials.** Am J Clin Nutr. 2000;72(6):1516-1522.
7. Bhatnagar S, Bahl R, Sharma PK, Kumar GT, Saxena SK, Bhan MK. **Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial.** J Pediatr Gastroenterol Nutr 2004;38:34-40.
8. Strand TA, Chandyo RK, Bahl R, et al. **Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children.** Pediatrics 2002;109:898-903.
9. **Food and Nutrition Board, Institute of Medicine. Zinc. Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.** Washington D.C.: National Academy Press; 2001:442-501.
10. Ghishan FK. **Transport of electrolytes, water and glucose in zinc deficiency.** J Pediatr Gastroenterol Nutr; 19843(4):608-612.
11. Jones PE and TJ Peters. **Oral zinc supplements in non-responsive coeliac syndrome: effect on jejunal morphology, enterocyte production, and brush border disaccharidase activities.** Gut 1981;22(3): 194-198.
12. Ibs, K.H. and L. **Rink, Zinc-altered immune function.** J Nutr 2003;133(5 Suppl 1):1452S-6S.
13. Julius E. Surjawidjaja, H Adi ,L Murad. **Growth Inhibition of Enteric pathogen by Zinc Sulfate.** Medical Principles and Practice 2004;13:286-289.
14. Dutta P, Mitra U, Datta A, et al. **Impact of zinc supplementation in malnourished children with acute watery diarrhoea.** J Trop Pediatr 2000;46:259-63.
15. Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. **Zinc supplementation in Brazilian children with acute diarrhoea.** Ann Trop Paediatr 2003;23:3-8.
16. Zinc Investigators Collaborative Group: Bhutta ZA, Bird SM, Black RE et al. **Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries; pooled analysis of randomized controlled trials.** Am J Clin Nutr. 2000;72:1516-1522.
17. Bhutta ZA, Nizami SQ, Isani Z. **Zinc supplementation in malnourished children with persistent diarrhea in Pakistan.** Pediatrics 1999;103:e42.
18. Khatun UH, Malek MA, Black RE, et al. **A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh.** Acta Paediatr 2001;90:376-80.
19. Roy SK, Tomkins AM, Mahalanabis D, et al. **Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children.** Acta Paediatr 1998;87:1235-9.
20. Penny ME, Peerson JM, Marin RM, et al. **Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru.** J Pediatr 1999;135:208-17.
21. Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. **Zinc supplementation in Brazilian children with acute**

diarrhoea. Ann Trop Paediatr 2003;23:3-8.

22. Roy SK, Tomkins AM, Akramuzzaman SM, et al. **Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea.** Arch Dis Child 1997;77:196-200.

23. Khatun UH, Malek MA, Black RE, et al. **A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhea in Bangladesh.** Acta Paediatr 2001;90:376-80.

24. Baqui AH, Black RE, EL Arifeen S, et al. **Zinc Therapy of Diarrhea increased the use of Oral Rehydration Therapy and reduced the use of Antibiotics in Bangladeshi children.** J Health Popul Nutr 2004;22:440-2.