

## Zinc Therapy in Treatment of Acute Diarrhea in Children Less Than Two Years

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### Abstract

<b>Background</b>	Diarrhea is the leading cause of morbidity and mortality in children in developing countries, intervention trials showed that using zinc in acute diarrhea decrease morbidity and mortality.
<b>Objective</b>	To evaluate the role of zinc supplement in the recovery of hospitalized children with acute diarrhea.
<b>Method</b>	The study included one hundred patients presented with acute diarrhea (age 3 months -2 years), forty eight of them were males and fifty two were females, sixty of them were infants and forty were above twelve months. Fifty patients were treated with intravenous fluid only and the other fifty patients were treated with zinc in addition to intravenous fluid.
<b>Results</b>	The study showed that the percentage of improvement within the first three days in patients treated with zinc was 80% compared to 44% of control group with <i>P</i> value 0.001. Zn therapy reduce the severity of diarrhea, it is effective in infants but more effective in toddlers, it is similarly effective in both males and females, it is more effective in mixed fed babies than in those on breast or bottle feeding .Using low dose reduce the incidence of vomiting.
<b>Conclusion</b>	Zinc therapy is useful in decreasing the duration and severity of acute diarrhea in children.
<b>Keywords</b>	Zn (zinc), acute diarrhea.

### Introduction

Diarrhea is one of the most important causes of morbidity and mortality in children <sup>(1)</sup>. The World Health Organization (WHO) suspects that there are > 700 million episodes of diarrhea annually in children < 5 yr of age in developing countries. While global mortality may be declining, the overall incidence of diarrhea remains unchanged at about 3.2 episodes per child per year. The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of improved case management of diarrhea, as well as improved nutrition of infants and children <sup>(2)</sup>. Major risk factor includes environmental

contamination and increased exposure to enteropathogens. Additional risks include young age, immune deficiency, measles, malnutrition, and lack of exclusive or predominant breast-feeding. In children with vitamin A deficiency, the risk of dying from diarrhea, measles, and malaria is increased by 20-24% <sup>(3,4)</sup>. Zinc is the second most abundant trace mineral and is important in protein metabolism and synthesis, in nucleic acid metabolism, and in stabilization of cell membranes. Zinc function as a cofactor for more than 200 enzymes and is essential to numerous cellular metabolic function <sup>(5)</sup>. It also improves the absorption of water and electrolytes, improves regeneration of the

intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens<sup>(6)</sup>. Shellfish, beef, and other red meats are rich sources of zinc, nuts and legumes are relatively good plant sources of zinc<sup>(7)</sup>. Dietary Zn, which is ingested with food such as meat, grains, and fruits, is absorbed at a rate of 20-80% in the duodenum and proximal small intestine. Histidine and cysteine facilitate absorption, whereas phytate and fiber inhibit it. Excess dietary copper, iron or cadmium decrease Zn absorption by competing for cellular uptake and metallothion binding. After cellular uptake the metal is secreted into the portal circulation where it binds primarily to albumin. Zn absorbed from the intestine is taken up rapidly by the liver, kidney, pancreas, and spleen. Excretion occurs through fecal losses. In the presence of ongoing losses such as diarrhea requirement can dramatically increase<sup>(8)</sup>.

The objective of this study was to evaluate the role of zinc supplement in the recovery of hospitalized children with acute diarrhea.

### Method

This was a prospective clinical study in Al-Kadhimiya Teaching Hospital designed to evaluate the effectiveness of supplying daily zinc during acute diarrhea (without vomiting) episodes on the course and outcome of the illness. One hundred patients aged 3 months-2 years were, with a presenting symptom of acute diarrhea for less than 72 hours admitted between the 1<sup>st</sup> of June 2012 till 31 October 2012, they were divided into two groups, control

group include 50 children treated with intravenous fluid (IVF) only, and other 50 treated with IVF plus zinc therapy (zinc group). Zinc sulfate tablet available in forms of 20 mg given to the patient (according to WHO guideline) 10 mg for less than 6 months age and 20 mg for more than 6 months age for 14 days; if vomiting or regurgitation occurs within 1 hr after zinc administration another dose given by dividing dose regimen. The improvement of the patient was considered when there is decrease in frequency and volume of bowel motions with correction of dehydration within three days of treatment.

### Statistical analysis

Data were analyzed using SPSS version 16 and Microsoft Office Excel 2007. Nominal variables were expressed as number and percent. Chi-square test was used to study association between nominal variable, *P* value <0.05 was considered as statistically significant. Relative risk was calculated as number and 95% confidence interval.

### Results

One hundred cases presented with acute diarrhea were admitted to Al-Kadhimiya Teaching Hospital. Fifty of them were treated with Zn therapy and IVF while other fifty cases were treated with IVF only. Table (1) shows that the percentage of improvement after 72 hours in cases who were treated with Zn and IVF was 40 patients (80%) while for those treated with IVF only was 22 patients (44%), the relative risk was (1.81) and (*P* < 0.001) which statically significant value.

**Table 1. Effect of Zn on treatment of acute diarrhea**

Type of treatment	No. of improved children	No. of non-improved children	Total	% of improvement	P value	Relative risk (95%CI)
IVF+Zn	40	10	50	80	< 0.001	1.81 (1.29-2.56)
IVF only	22	28	50	44		
Total	62	38	100	62		

Regarding the age of patients, in infants (aged less or equal to 12 months) the improvement was more evident in patients who receive Zn therapy and IVF 23 (76.67%) patients while for those treated with IVF only was 14 patients (46.67%), the relative risk was 1.64 ( $P = 0.017$ ).

Children aged more than 12 months the improvement was more evident in patients who receive Zn therapy and IVF, 17 patients (85%) while for those treated with IVF only was 8 patients (40%), the relative risk was 2.12 ( $P = 0.003$ ) as shown in table 2.

**Table 2. Effect of Zn therapy in relation to age**

Age (Months)	Type of treatment	No. of improved children	No. of non-improved children	Total	% of improvement	P value	Relative risk (95%CI)
> 12 (n = 40)	IVF+Zn	17	3	20	85	0.003	2.12 (1.20-3.74)
	IVF only	8	12	20	40		
	Total	25	15	40	62.5		
≤ 12 (n = 60)	IVF+Zn	23	7	30	76.67	0.017	1.64 (1.06-2.52)
	IVF only	14	16	30	46.67		
	Total	37	23	60	61.67		

Regarding sex of patients, in males the improvement was more evident in patients who receive Zn therapy and IVF 21 patients, (84%) while for those treated with IVF only was 11 patients, (47.82%), the relative risk was 1.75 ( $P = 0.008$ ).

In females, the improvement was more evident in patients who receive Zn therapy and IVF 19 patients (76%) while for those treated with IVF only was 11 patients (40.74%), the relative risk was 1.86 ( $P = 0.01$ ) as shown in table 3.

**Table 3. Effect of Zn therapy in relation to gender**

Gender	Type of treatment	No. of improved children	No. of non-improved children	Total	% of improvement	P value	Relative risk (95%CI)
Males (n = 48)	IVF+Zn	21	4	25	84	0.008	1.75 (1.10-2.78)
	IVF only	11	12	23	47.82		
	Total	32	16	48	66.67		
Females (n = 52)	IVF+Zn	19	6	25	76	0.01	1.86 (1.12-3.09)
	IVF only	11	16	27	40.74		
	Total	30	22	52	57.69		

with IVF only was 8 (40%), the relative risk was 1.75 ( $P = 0.057$ ).

In mixed feeding, the improvement was more evident in patients who receive Zn therapy and IVF 13 (92.85%) patients while for those treated with IVF only was 6 patients (42.85%), the relative risk was 1.71 ( $P = 0.013$ ) as shown in table 4.

Regarding feeding pattern, in the breast fed babies, the improvement was more evident in patients who receive Zn therapy and IVF 14 (87.5 %) patients while for those treated with IVF only was 7 patients (43.75%), the relative risk was 2.00 ( $P = 0.009$ ).

In bottle fed babies, the improvement was more evident in patients who receive Zn therapy and IVF 14 (70%) patients while for those treated

**Table 4. Relationship between Zn therapy and type of feeding**

Feeding	Type of treatment	No. of improved children	No. of non-improved children	Total	% of improvement	P value	Relative risk (95%CI)
Breast (n = 32)	IVF+Zn	14	2	16	87.5	0.009	2.00 (1.11-3.59)
	IVF only	7	9	16	43.75		
	Total	21	11	32	65.62		
Bottle (n = 40)	IVF+Zn	14	6	20	70	0.057	1.75 (0.95-3.21)
	IVF only	8	12	20	40		
	Total	22	18	40	55		
Mixed (n = 28)	IVF+Zn	13	1	14	92.85	0.013	2.16 (1.16-4.04)
	IVF only	6	8	14	42.85		
	Total	19	9	28	67.85		

Vomiting occur in 5 (10 %) patients who were treated by Zn therapy and IVF and in 4 (8%) patients who were treated by IVF alone and the relative risk was 1.25% ( $P = 0.1000$ ) as shown in table 5.

**Table 5. Occurrence of vomiting in both groups (Zn and control group)**

Type of treatment	Occurrence of vomiting	No. of vomiting	Total	% of vomiting	P value	Relative risk (95%CI)
IVF+Zn	5	45	50	10	1.000	1.25 (0.35-4.38)
IVF only	4	46	50	8		
Total	9	91	100	9		

## Discussion

This study showed that zinc supplementation is effective in decreasing the frequency and volume of stool in acute diarrhea, which is similar to many other studies such as (65%, 39%) obtained in Nepal<sup>(9)</sup>, and (70%, 42%) in West Bengal<sup>(10)</sup>, and (66%, 38%) in New Delhi study<sup>(11)</sup>, other studies showed zinc has no effect on frequency or volume of stool but it decrease duration of diarrhea as obtained by Khan AM, Larson<sup>(12)</sup>. In this study, toddlers showed better response than infants to zinc therapy (85%, 76%, respectively). A similar difference was also found in a study performed in North India<sup>(13)</sup>.

This difference in improvement in relation to age may be explained by the following factors:

1. Milk contains small amount of Zn, and infants whose diet is mainly milk are expected to have Zn deficiency more readily than toddlers whose diet may include meat, nuts, and other

rich sources of Zn, also mothers of breast fed infants may have zinc deficiency<sup>(14)</sup>, both these facts cause serum level of zinc in infants at lower values than in toddlers, so they need longer duration of treatment to show improvement,

2. The calcium which is present in milk in high concentrations is known to decrease Zn absorption from intestine by competition<sup>(15)</sup>.

According to gender, males group treated with zinc and IVF showed much better improvement than those treated by IVF only. A study performed in Guatemala, showed similar improvement in males compared to females<sup>(16)</sup>. According to types of feeding, our study shows that there is a good response in breast-fed zinc group in comparison to breast-feed control group. There is better response for bottle fed zinc group in comparison to bottle feed control group.

In addition, there was a better response for mixed fed zinc group in comparison to mixed fed control group. The impact of adding Zn in the management of acute diarrhea was more impressive in mixed fed infants compared to both breast and bottle fed ones, this may be attributable to the fact that <sup>(15)</sup> this effect of breast milk on Zn absorption, may be also the cause beyond the occurrence of the manifestation of acrodermatitis enteropathica after weaning of breast to cow milk <sup>(11)</sup>. These results are supported by Al-Zubiady study <sup>(16)</sup>. In our study the percentage of vomiting was (10%) in Zn plus IVF group, and (8%) in IVF only group. These results were better than those obtained from Nepal study (14.2 % in Zn plus IVF group, and 8.1% in IVF only group), this difference is probably resulted from using small divided doses in our study, while in Nepal study higher dose of oral zinc were used 15 mg/day as a single dose for infant, and 30 mg/day as a single oral dose for toddlers which was associated with increased risk of vomiting <sup>(9)</sup>.

In conclusion, addition of zinc to the management of acute diarrhea is useful in decreasing severity of diarrhea in form of decreasing the volume and the frequency of stool.

- Zinc therapy is effective in both infant and older age group.
- Zinc therapy is more effective in mixed fed babies than in those on breast or bottle feeding.
- Zinc therapy is effective in both males and female.
- Using of divided dose regimen decreases the frequency of vomiting and regurgitation.

We recommend encouraging the use of zinc therapy in primary health care centers and educate the mothers about the importance of Zn in treatment of diarrhea.

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