

Original Research Article

Serum zinc levels and effect of zinc and vitamin A supplementation in children with diarrhea: a randomized control study

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ABSTRACT

Background: Zinc deficiency affects about two billion people in the developing world and is associated with many diseases. Zinc is crucial for normal development and function of cells mediating nonspecific immunity such as neutrophils and natural killer cells. Zinc supplementation has been shown to be effective for preventing diarrhea in children. Vitamin A helps to regulate the immune system, which helps to prevent or fight off infections by making white blood cells that destroy harmful bacteria and viruses.

Methods: In this randomized control study 82 children aged 6 months to 5 years were randomized 52 in the group of acute diarrhoea and 30 in the control group. Blood samples were drawn for estimation of serum zinc levels. Children in the acute diarrhoea group 23 received zinc alone and 23 received zinc and vitamin A and followed up for 6 months.

Results: The serum zinc levels were significantly lower in children with acute diarrhea (66.7 µg/dl) as compared to that of the children in the control group (80.5433 µg/dl) ($p < 0.001$). The children with malnourishment had a mean zinc level that was significantly lesser ($p < 0.01$). In the acute diarrhea group, children receiving zinc supplementation alone, 10 of the children had at least 1 episode of diarrhea over the next 6 months. Children receiving zinc and vitamin A supplementation, there were only 5 such children with at least 1 episode of acute diarrhea.

Conclusions: Combination of zinc and vitamin A supplementation in acute diarrhea decreases the chances of recurrence of diarrhoea and reduces the hospital stay significantly.

Keywords: Acute diarrhoea, Vitamin A, Zinc

INTRODUCTION

Zinc is an essential mineral of exceptional biologic and public health importance.¹ Zinc deficiency affects about two billion people in the developing world and is associated with many diseases.² The global prevalence of zinc deficiency was estimated at 31%, ranging from 4-73% across sub regions and zinc deficiency was estimated to cause 176000 diarrhea deaths.³ Zinc is crucial for normal development and function of cells mediating nonspecific immunity such as neutrophils and natural killer cells. Zinc also functions as an antioxidant

and can stabilize membranes.⁴ Zinc supplementation has been shown to be effective for preventing diarrhea in children.^{5,6} When used as a therapy for acute or persistent diarrhoea, zinc reduces the duration of the episode as well as its severity and complications.^{7,8} Worldwide inadequate treatment of gastroenteritis kills 5 to 8 million people per year and is a leading cause of death among infants and children under 510.

Vitamin A helps to regulate the immune system, which helps to prevent or fight off infections by making white blood cells that destroy harmful bacteria and viruses.¹¹

Vitamin A also helps the skin and mucous membranes function as a barrier to bacteria and viruses.¹² Vitamin A deficiency is common in developing countries and is commonly associated with severe zinc deficiency. In countries where such deficiency is common and immunization programs are limited, millions of children die each year from complications of infectious diseases such as measles.¹³ There are numerous studies on the beneficial effects of zinc supplementation in children with gastroenteritis but limited and inconclusive studies on the combined effects of zinc and vitamin A in these children.

METHODS

This randomized control study was conducted at a tertiary care hospital over a period of 2 years. 82 children were included in the age group of 6 months to 5 years. 52 were in the group of acute diarrhea and 30 children were in the control group. Blood samples were drawn from all the children as part of routine investigation purposes and also for estimation of serum zinc levels at enrolment after obtaining the informed consent from the parents. All enrolled children were treated according to the standard protocol for treatment of infants and children with acute diarrhea.

The 52 children in the acute diarrhea group were divided into 2 random groups of 26 children each. The first group of 26 children received zinc supplementation while the second group received zinc and vitamin A supplementation. Zinc supplementation was in the form of oral zinc acetate syrup (5 ml=20 mg). Children less than 1 year received 10 mg of zinc acetate once daily while children above 1 year received 20 mg of zinc acetate once daily which was continued for 14 days. Vitamin A was in the form of oral supplementation of 1 lakh IU for children of less than 1 year of age and 2 lakh IU for children above 1 year of age as a stat dose at the time of admission.

Measurement of the serum zinc concentrations was carried out by using an Atomic Absorption Spectrophotometer with air-acetylene as the oxidant. Diarrhea was considered when 3 episodes of loose or unformed stools are present in a single day. In children with acute diarrhea, frequency and volume of stools, number of days in the hospital as well as daily weight monitoring, urine output and signs of dehydration were also noted. The children in the control group included children who were asymptomatic without acute diarrhea. Out of this, 6 blood samples in the acute gastroenteritis group (3 each in the 2 sub-groups) were found to be hemolysed. The zinc values obtained from these samples were discarded. Thus 46 children in the acute diarrhea group were included for the study. 23 were in the zinc alone group and 23 were in the zinc and vitamin A group. Both these medications were given under direct supervision by a paediatrician. Subsequent doses of oral zinc were given under supervision by the duty

paediatrician and nurse during hospital stay. Most of the children were discharged before 1 week and in these children oral zinc supplementation was given for the full course of 2 weeks at the time of discharge. Regular follow up of these children was done via monthly visits to the OPD or if symptomatic. During the follow up period, 10 children in the acute diarrhea group were lost to follow up.

RESULTS

In this study, the selected children were in the age group of 6 months to 5 years with a mean age of 2.19 and 2.26 years in the acute diarrhea and control groups respectively. It was observed that majority of children in the acute diarrhea group and control group were boys about 63% and 60% respectively. The serum zinc levels were significantly lower in children with acute diarrhea (66.7µg/dl) as compared to that of the children in the control group (80.5433 µg/dl) which was statistically significant ($p<0.001$) (Table 1).

Table 1: Serum zinc levels in the acute diarrhea group and control group.

Group	N	Mean	Std. deviation	F	P
Acute diarrhea	46	66.7000	14.13415	10.987	<0.001
Control group	30	80.5433	14.80891		

More than half of the children in the control group who were otherwise asymptomatic also showed a low plasma zinc level. In addition, out of the 46 children in the diarrhea group, 14 children had grade 1 malnutrition. When compared with the other 32 children in the group, the children with malnourishment had a mean zinc level that was significantly lesser ($p<0.01$) (Table.2).

Table 2: Comparison between malnourished and adequately nourished children in the acute diarrhea group with respect to mean zinc levels and resolution of symptoms.

Acute diarrhea group	Mean Zn level	P	Symptoms resolution (days)	P
Malnourished	61.19	<0.01	4.14	=0.42
Normally nourished	67.15		3.9	

During the course of the treatment, it was found that in the diarrhea group, the children who were supplemented with zinc and vitamin A had a mild reduction in mean duration of hospital stay (3.87 days) when compared to that of the zinc supplemented children alone (4.22 days) but on statistical analysis this was not found to be significant ($P=0.226$). All the children in the zinc and vitamin A supplemented group showed a decrease in the

frequency of stool passage after supplementation during the hospital stay when compared to the supplementation of zinc alone group but this was not statistically significant. The malnourished children in the diarrhea group had an average resolution of symptoms that was slightly more than that of the adequately nourished children. But this was not statistically significant. Out of the 14 malnourished children with acute diarrhea, 7 received treatment with zinc supplementation alone and 7 received treatment with zinc and vitamin A supplementation. The children with zinc and vitamin A supplementation had faster resolution of symptoms but this was not statistically significant (Table 2).

In addition, children with acute diarrhea and dehydration with or without malnutrition were also found to have a much lower level of plasma zinc values but the number of such cases in this study was too small to be statistically significant. During the follow up period, 10 children in the acute diarrhea group were lost to follow up. A total of 36 children in the acute diarrhea group (19 in the zinc alone group and 17 in the zinc and vitamin A group) were followed up over a period of 6 months. In the acute diarrhea group, out of a total of 19 children receiving zinc supplementation alone, 10 of the children had at least 1 episode of diarrhea characterized by a minimum of at least 3 episodes of loose or unformed stools over the next 6 months but none of them needed hospitalization for the same. Out of a total of 17 children receiving zinc and vitamin A supplementation, there were only 5 such children with at least 1 episode of acute diarrhea, none of which needed hospitalization. But this was not statistically significant (Table 3).

Table 3: Comparison of recurrence of acute diarrhea in children in the zinc alone and zinc and vitamin A groups during the follow up period.

Group	Number (N)	Recurrences	P
Zinc/vitamin A	17	05	0.116
Zinc (alone)	19	10	

DISCUSSION

There have been a number of studies on the beneficial effects of zinc and vitamin A on the morbidity associated with gastroenteritis. Most of the studies and reports of the past are universally of the opinion that zinc has a beneficial effect in gastroenteritis.^{14,15} The beneficial effects of zinc and vitamin A administration as combination too have been emphasized by some of the studies.^{16,17} However, the effects of vitamin A alone in this condition is controversial with some studies stressing its importance and some studies showing that vitamin A actually increases symptoms.^{18,19}

A number of studies have shown that there is no difference in supplementation with zinc or vitamin A in combination or alone. In the present study, children with

gastroenteritis were found to have a reduced level of zinc when compared to asymptomatic children. This is comparable with Black R.E who have reported the prevalence of micronutrient deficiencies including zinc and vitamin A in children with gastroenteritis.²⁰ Study done by Olmez et al showed that the baseline characteristics in the mean zinc levels in both the groups of children were of the same with no statistical difference.²¹

The low zinc level in the asymptomatic children too suggests an underlying zinc deficiency in children in that part of the district. This is possible as in southern Asia, macronutrient malnutrition and micronutrient deficiencies, especially deficiencies of iron, zinc, and vitamin A are common in young children. This problem was attributed to dietary insufficiency, limited nutrient bioavailability from local diets, and excretion of nutrients during recurrent episodes of infection. This was comparable with some of the studies done previously. Baqui A.H et al in their study noticed that serum zinc was low in 44% of healthy children at the time of drawing of first blood.²² Olmez et al in their prospective study observed zinc levels below the average for that age in 39% of asymptomatic children.²¹ During the course of treatment, it was found that zinc and vitamin A supplementation decreased the mean hospital stay in acute diarrhea children clinically. All the other previous studies have shown a beneficial effect of combined therapy in reducing symptoms. Wang Y et al conducted a study showed that short term zinc and zinc+ vitamin A supplementation can improve treatment outcomes to varying degrees.^{23,24}

Supplementation with concurrent vitamin A+ zinc supplementation is one of the best options to shorten the duration of persistent diarrhoea and improve the nutritional status of the children. In a study by Rahman M.M observed the incidence and prevalence of diarrhea were lower in zinc and vitamin A groups than in the placebo group.¹⁶ Combined zinc and vitamin A synergistically reduced the prevalence of persistent diarrhoea and dysentery in the same study.

Sazawal et. Al reported a significant reduction in the incidence and prevalence of acute and persistent diarrhoea with zinc and multivitamin supplementation in Indian children.¹⁷ M K Bhan et.al zinc supplementation had no effect in children of 6-11 months old.²⁵ In children >11 months, there was significantly less diarrhoea in the zinc group. Zinc supplementation resulted in a 17% lower diarrhoeal incidence in children with plasma zinc concentrations <9.18µmol/L at enrollment and a 33% lower incidence in children with concentration <50µmol/L.

Patel et al in their meta-analysis found that zinc supplementation has a modest beneficial association (9% reduction) with incidence of diarrhea, a stronger beneficial association (19% reduction) with prevalence of

diarrhoea and occurrence of multiple diarrheal episodes (28% reduction).²⁶ Zinc supplementation did not show statistically significant benefit in reducing the incidence of persistent diarrhea, dysentery or mortality. In the present study, even though the mean hospital stay was reduced, it was not statistically significant, maybe because of the small sample size in this study. This is in comparable with study done by Rahman M.M et al in 800 Bangladeshi children which showed that a zinc supplementation reduced diarrhoeal episodes, but it conversely increased incidence of respiratory illness.¹⁶ The study also showed that the combined supplementation of zinc and vitamin A together helped to reduce the adverse effects of zinc and thus reduces the incidence of respiratory illness.

All the children in the zinc and vitamin A supplemented group showed a decrease in the frequency of stool passage after supplementation during the hospital stay when compared to the zinc alone group but this was not statistically significant. This is comparable with all other studies done and is probably due to the synergistic effects of combined zinc and vitamin A supplementation in children with acute gastroenteritis.^{16,23} Even though clinical significance but not statistical significance was obtained in the present study, it was probably due to relative small sample size. It was noticed that children with malnourishment had a mean zinc level that was significantly lesser. These children also had an average resolution of symptoms that was slightly more than that of the adequately nourished children. But this was again clinically but not statistically significant. The children with zinc and vitamin A supplementation had faster resolution of symptoms clinically but this was not statistically significant. The time taken for average resolution of symptoms in these children was also significantly more than the adequately nourished children.

In the malnourished children, the children receiving both zinc and vitamin A supplementation had a faster recovery than the children receiving zinc supplementation alone that was statistically not significant. In addition, children with acute gastroenteritis and dehydration with or without malnutrition were also found to have a much lower level of plasma zinc values but the number of such cases in this study was too small to be statistically significant. In this study children receiving zinc supplementation alone 10 children had at least 1 episode of acute diarrhea in the subsequent 6 months. Children receiving both zinc and vitamin A supplementation, there were only 5 such children with at least 1 episode of acute diarrhea in the follow-up period of 6 months, none of which needed hospitalization. But this was not statistically significant.

Similar findings were obtained in the study done by Valery C.P study showed that there was no statistical significance among the four groups with respect to final outcome. Some of the other studies have shown that zinc and vitamin A supplementation has significantly reduced

the recurrence of gastroenteritis in these children.²⁷ In a study by Rahman M.M the incidence and prevalence of diarrhoea were lower in the zinc and vitamin A groups than in the placebo group and combined zinc and vitamin A synergistically reduced the prevalence of persistent diarrhoea and dysentery.¹⁶

This is in contrast to the study done by Long K.Z Vitamin A supplementation was associated with a 27% increase in diarrhoea, whereas zinc had no effect.

CONCLUSION

Children with acute diarrhea have a reduced zinc level and even half of the asymptomatic children had reduced levels of zinc when compared to the reference range. Combination of Zinc and vitamin A supplementation in acute diarrhea decreases the chances of recurrence of diarrhea and reduces the hospital stay significantly.

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