

# To Compare Prophylactic Zinc Supplementation Versus Placebo in Terms of Frequency of Diarrhea in Infants of 6-11 Months

Prophylactic Zinc  
Supplementation Vs  
Placebo for  
Diarrhea in Infants

Sobia Noor<sup>1</sup>, Sohail Ashraf<sup>1</sup>, Sommaya Siddiqua<sup>2</sup>, Saba Mushtaq<sup>1</sup> and Munazza Saleem<sup>1</sup>

## ABSTRACT

**Objective:** To compare prophylactic zinc supplementation versus placebo in terms of frequency of diarrhea in infants of 6-11 months.

**Study Design:** Randomized control trial study

**Place and Duration of Study:** This study was conducted at the Outpatient Department of Pediatrics, POF Hospital, Wah Cantt from March 2016 to September 2016.

**Materials and Methods:** Non Probability Consecutive sampling was used to enroll children and was divided into two groups by lottery method as control group receiving placebo and case group receiving the supplemental zinc. The case group was then given 5ml of syrup containing 20 mg of elemental zinc daily for 2 weeks followed by 6 months of follow-up. The control group was given placebo. At each follow-up, the mother/caregiver was asked about the occurrence of diarrheal episodes and duration of diarrhea during the previous month.

**Results:** Total of 120 children were included in the study and divided into two equal groups. In group A (control group) mean age 8.23 months and SD  $\pm 1.37$ . In group B(case group) mean age 8.02 months and SD  $\pm 1.17$ . In group A minimum diarrhea episode was nil, maximum diarrhea episodes were 15 with mean diarrhea episodes 8.53 and SD  $\pm 3.15$ . In group B minimum diarrhea episode was nil, maximum were 9 with mean diarrhea episodes 5.13 and SD  $\pm 2.73$ .

**Conclusion:** Diarrhea is a common disease in developing countries with significant morbidity and mortality. Results of the current study show significant reduction in diarrheal morbidity in infants even 6 months after short-course of zinc prophylaxis.

**Key Words:** Diarrhea, Placebo, Zinc

**Citation of articles:** Noor S, Ashraf S, Siddiqua S, Khan S, Mushtaq S, Saleem M. To Compare Prophylactic Zinc Supplementation Versus Placebo in Terms of Frequency of Diarrhea in Infants of 6-11 Months. Med Forum 2018;29(11):55-59.

## INTRODUCTION

Zinc has a pivotal role in multiple cellular tasks and the immune system depends on the sufficient availability of this micronutrient<sup>1</sup>. Regular dietary zinc consumption is needed because zinc can neither be produced nor stored<sup>2</sup>. Inadequate dietary consumption and diarrheal diseases associated with negative zinc balance may contribute to deficiency of zinc which can lead to growth retardation and immune dysfunction<sup>3,4</sup>. Zinc deficiency is prevalent in developing countries, including Pakistan<sup>4,5</sup>.

This is because the staple foods commonly consumed in these countries are deficient in zinc and rich in phytates which further impede zinc absorption and utilization<sup>1,5</sup>. Diarrheal diseases are a significant health problem in developing countries<sup>6</sup>. There are 1.5 billion episodes of diarrhea per year and 21% of all deaths in children younger than 5 years are caused by diarrheal diseases<sup>7</sup>. Diarrhea is a major cause of death in children under 5 years of age in Pakistan, contributing 20-30% of these deaths. In a study from Egypt, Pakistan, Bangladesh, and Ethiopia report that 43% to 78% of deaths from diarrhea among children occur in the first year of life<sup>8</sup>. There was 23% reduction in mortality due to diarrhea and 19% reduction in incidence of recurrent diarrhea after zinc supplementation when given in suspension form<sup>9</sup> or dispersible form<sup>10</sup> during acute stage.

Similarly prophylactic zinc also results in significant reduction in the incidence of diarrheal diseases among infants<sup>3</sup>. Another study shows a 13% reduction in the incidence of diarrhea with preventive zinc supplementation<sup>4</sup>. Malik et al studied the effect of preventive zinc supplementation on diarrheal morbidity in infants 6-11 months and reported a 39% reduction in episodes of diarrhea, 39% in the total number of days

<sup>1</sup>. Department of Pediatrics, Wah Med. College, Wah Cantt.

<sup>2</sup>. Department of Pediatrics, HITEC institute of Medical Sciences, Taxila.

Correspondence: Dr. Sobia Noor, Senior Registrar, Pediatrics Department, Wah Medical College, Wah Cantt.

Contact No: 0332-4525142

Email: sohailaa2000@yahoo.com

Received by: March, 2018

Accepted by: August, 2018

Printed by: November 2018

that a child suffered from diarrhea, and reduction of 36% in duration per episode of diarrhea <sup>1</sup>.

To date, there is no published literature in Pakistan regarding the role of prophylactic zinc supplementation among infants in reducing the incidence as well as severity of diarrheal diseases. Because the incidence of diarrhea is higher in children 6-12 months of age<sup>1</sup>, the purpose of this study was to evaluate the role of zinc in reducing diarrheal morbidity by short course prophylactic supplementation to infants aged 6-11 months. The results of this study will help to consider the prophylactic zinc supplementation to infants in a diarrhea prevalent country like Pakistan.

## MATERIALS AND METHODS

This Randomized control trial was done at Outpatient Department of Pediatrics, POF Hospital, Wah Cantt from 1<sup>st</sup> March 2016 till 30<sup>th</sup> September 2016 and Non Probability Consecutive sampling technique was used. Sample size was calculated by using WHO formula 2.2a with following values:

Level of significance = 5%

Power of test = 80%

Anticipated population proportion<sub>1</sub>, P<sub>1</sub>=80%<sup>2</sup>

Anticipated population proportion<sub>2</sub>, P<sub>2</sub>=95%<sup>2</sup>

Required sample size is 60 infants in each group.

### a) Inclusion criteria:

- Infants with age ranging from 6 to 11 months visiting outpatient pediatric department of POF hospital for vaccination or healthy siblings.
- Either gender.

### b) Exclusion criteria:

- Any infant receiving zinc supplement at the time of study
- Any infant who had received zinc supplement in the preceding 3 months
- Those who were severely malnourished, immune-deficient or currently on steroid therapy
- Those who are severely ill requiring hospitalization,
- Families likely to migrate from the study area

### Operational Definitions:

**Diarrhea:** Diarrhea was defined as 3 or more watery stools in a 24 hour period within 6 months of zinc supplementation.

**Short Course Zinc Supplementation:** Oral zinc preparation containing 20 mg elemental zinc/5ml given in a dose of 5ml once daily for 14 days

**Data collection Procedure:** Permission from the hospital ethics committee was sought before the commencement of the study. Informed consent was obtained from parents/guardians for inclusion in the study. All children 6-11 months of age fulfilling the above mentioned inclusion criteria were enrolled in the study by first year postgraduate residents. The enrolled

children were divided into groups by lottery method as control group receiving placebo and case group receiving the supplemental zinc. Demographic features such as age and gender were asked and noted on a specially designed performa.

A baseline assessment was done at the time of recruitment, which included weight and length measurements. The case group was then given 5ml of syrup containing 20 mg of elemental zinc daily for 2 weeks followed by 6 months of follow-up. The control group was given placebo. Follow-up for diarrhea began on the 15th day after intervention. Each child was followed-up monthly by phone calls and the follow-up was continued for 6 months after the completion of zinc supplementation. To ensure that the child did not receive additional doses of zinc, mothers were provided identity cards indicating the study title. These cards were to be produced whenever the child is taken to any medical practitioner. At each follow-up, the mother/caregiver was asked about the occurrence of diarrheal episodes during the previous month.

**Data Analysis Procedure:** The data was entered and analyzed using SPSS version 16. For continuous variables such as age and diarrheal episodes; mean  $\pm$  SD was calculated. Frequencies and percentages were measured for categorical variables such as gender and frequency of episodes of diarrhea. To compare frequency of diarrhea between two groups chi-square test was applied. p-value  $\leq$  0.05 was considered as significant.

## RESULTS

Total of 120 children were divided into two equal groups. In group A minimum age of patients was 6 months, maximum age was 11 months with mean age 8.23 months and SD  $\pm$ 1.37. In group B minimum age of patients was 6 months, maximum age was 11 months with mean age 8.02 months and SD  $\pm$ 1.17. There was predominance of female patients in the study (Table 1). In group A maximum diarrheal episodes were 15 with mean diarrheal episodes 8.53 and SD  $\pm$ 3.10. In group B maximum were 9 with mean diarrheal episodes 5.13 and SD  $\pm$ 2.73.

**Table No.1: Demographic Data**

Characteristics	Group A (control) (n=60)	Group B (case) (n=60)	Total (N=120)
<b>SEX:</b>			
• Male	26 (43%)	25 (42%)	51 (26.2%)
• Female	34 (57%)	35 (58%)	69 (34.2%)
<b>AGE CATEGORY:</b>			
• 6-7 months	19 (31.6%)	20 (33.3%)	39 (32.5%)
• 8-9 months	32 (53.3%)	34 (56.6%)	66 (55%)
• 10-11 months	9 (15%)	6 (10%)	15 (12.5%)

In group A there were 56(93%) patients with diarrheal episodes and in group B there were 49(82%) patients with diarrheal episodes (p-value 0.0001). Zinc supplementation had significant effect on patients between 8-9 months of age (p-value- 0.016). (Table 2).

**Table No.2: Effect of Zinc and Placebo**

(1) Gender:		Presence of Diarrheal Episodes		p-Value
		Yes	No	
Male	Group A (n-26)	25 (96.1%)	1 (3.8%)	0.087
	Group B (n-25)	20 (80%)	5 (20%)	
Female	Group A (n-34)	31 (91.1%)	3 (8.8%)	0.253
	Group B (n-35)	29 (82.8%)	6 (17.1%)	
(2) Age category:				
6-7 months	Group A (n-19)	17 (89.4%)	02 (10.5%)	0.957
	Group B (n-20)	18 (90%)	02 (10%)	
8-9 months	Group A (n-32)	31 (96.8%)	01 (3.1%)	0.016
	Group B (n-34)	26 (76.4%)	08 (23.5%)	
10-11 months	Group A (n-9)	08 (88.8%)	01 (11.1%)	0.756
	Group B (n-6)	05 (83.3%)	01 (16.6%)	

## DISCUSSION

Zinc deficiency is associated with growth retardation and impairment of immune function, changes that are reversed when zinc is provided. In clinical conditions with severe zinc deficiency, or in animal experiments with zinc depletion, diarrhea is consistently found and responds quickly to zinc supplementation<sup>11</sup>.

A clinical trial in an urban slum of Karachi, studied the effect of the daily use of micronutrients for two months on diarrhea in 6-11 months infants compared to placebo<sup>12</sup> and found decreased prevalence of diarrhea in children receiving zinc whereas in our study, this effect was seen after 2 weeks of supplementation. In another study in which zinc was supplemented for 7 months 23 % reduction of zinc morbidity was found with more effect in children less than 5 years of age<sup>13</sup>.

The response to zinc was equal in males and females in our study as also seen by Larson et al<sup>5</sup> although Garenne et al<sup>14</sup> had found zinc to be more effective in males. This effect has been attributed to difference in immune function between sexes.

In a similar trial of infants aged 6 to 11 months there was a 39% reduction in episodes of diarrhea, 39% in the total number of days that a child had diarrhea, and reduction of 36% in duration per episode of diarrhea

during the 5 months of follow-up<sup>1</sup>. Similarly zinc has also been seen to reduce the number of stools per day<sup>15</sup>. The current study is limited to the frequency and number of episodes of diarrhea. The effect on the duration of each episode and types of diarrhea still needs to be studied.

In a community-based study, a birth cohort of 100 Low birth weight infants was randomly allocated into either an intervention group receiving zinc in vitamin B complex-based syrup or a placebo group receiving vitamin-based syrup from birth up to 1 completed year of age. The group which received zinc had diarrheal incidence of 1.36 episodes per child per year, whereas it was 1.93 episodes per child per year among the placebo group. Significant differences were present in linear growth and weight between the supplemented and placebo groups at the end of 1 year<sup>16</sup>. Another meta-analysis showed increase in length of 0.37 (±0.25) cm after zinc was supplemented for 24 weeks<sup>17</sup>. The current study has not studied the effects of zinc on linear growth and weight. However, this can be studied in future trials.

In a study in which children of 6 to 30 months were randomized to receive daily zinc gluconate during the 4 months of follow-up, a lower incidence of diarrhea was seen in the group who received zinc as compared with the placebo group<sup>18</sup>. In our study in the placebo group there were 56(93%) patients with diarrheal episodes while in zinc group there were 49(82%) patients with diarrheal episodes.

In another trial in which various children were given multivitamins, median percentage of days of diarrhea was less in children taking Vitamin A and zinc as compared to other children<sup>19</sup>. In a Tanzanian study, daily zinc supplementation of infants beginning at 6 weeks of age lowered the burden of diarrhea but provision of multivitamins did not confer additional benefit<sup>20</sup>.

The major limitation of this study is that serum zinc levels were not measured to assess the deficiency and the subsequent effect on serum zinc levels after zinc supplementation. Studies in populations of Delhi have shown high prevalence of zinc deficiency<sup>21</sup>. Becquey et al<sup>22</sup> in their study had found more increase in serum zinc level and reduced diarrhea incidence in the children receiving prophylactic zinc as compared to the children who took it only as therapeutic agent.

Moreover, the current study was done in a population that had not received zinc supplementation for the preceding 3 months and was apparently healthy. This coupled with the fact that the maximum burden of diarrhea is seen in the age group of 6 to 11 months<sup>23</sup> may have been responsible for such significant results in the current study. The intervention evaluated in the current trial is simple and inexpensive and can be incorporated into existing diarrheal disease control efforts.

## CONCLUSION

Diarrhea is a common disease in developing countries with significant morbidity and mortality. The benefit of zinc given as a community-based prophylactic intervention is that it will decrease the incidence of diarrhea in the community compared with zinc supplementation during acute diarrheal episodes. Moreover, many children may not come to a health facility, especially in the slum populations, and thus keep suffering from repeated episodes of diarrhea. More studies need to be done to study the efficacy of zinc supplementation in diet so that more detailed observations can be done.

### Author's Contribution:

Concept & Design of Study: Sobia Noor  
 Drafting: Sohail Ashraf, Sommaya Siddiqua  
 Data Analysis: Saba Mushtaq, Munazza Saleem  
 Revisiting Critically: Sobia Noor  
 Final Approval of version: Sobia Noor

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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