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RESEARCH ARTICLE

SHORT COURSE OF ZINC PROPHYLAXIS IN INFANTS FOR REDUCTION OF DIARRHEAL EPISODES: A PROSPECTIVE STUDY

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ABSTRACT

Aim: Zinc deficiency is prevalent in children in developing countries and diarrhea is prevalent in worldwide. Supplemental zinc provides therapeutic benefits in diarrhea and prophylactic zinc supplementation reduces the diarrheal episodes and duration.

Method: In this prospective study, we enrolled infants aged 6 to 11 months from urban slum areas. Total 28 slum areas were selected and we enrolled total 946 infants, these were randomly assigned as cases and control. Cases (473) received 20 mg of zinc orally every day for 2 weeks and rest 473 infants were assigned as controls. The primary outcome was the incidence and episodes of diarrhea.

Results: In cases 382 (80%) infants had acute diarrhea and 452 (95%) in controls, whereas persistent diarrhea 35 (7%) in cases and 125 (26%) in controls. 48 (10%) infants of cases and 52 (11%) of controls had dysentery ($p=1.007$). Respiratory tract infection 122 (25%) in control and 48 (10%) in cases, whereas skin infection 34 (7%) in cases and 62 (13%) in controls. 15 (3%) infants of cases and 59 (12%) of controls had hospital admission.

Conclusion: Present study highlights, prophylactic zinc supplementation for 2 weeks in infants aged between 6 months to 11 months has significantly reduced the incidence and duration of diarrhea during follow-up of 5 months and also reduced incidence of acute respiratory tract infections and skin infection.

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INTRODUCTION

Diarrheal diseases pose a significant public health problem on a global scale and especially in developing countries. It is estimated that there are 1.5 billion episodes of diarrhea per year and that diarrheal disease accounted for 21% of all deaths in children who were younger than 5 years. This is equivalent to 2.5 million deaths in the same age group. (Black *et al.*, 2003; Kosek *et al.*, 2003) Recent data from the World Health Organization (WHO) showed that diarrheal disease accounts for 18% of the 10.6 million deaths in children who were younger than 5 years. (Bryce *et al.*, 2005) One of the major advances in the reduction of mortality from diarrhea was the introduction of WHO oral rehydration solution (ORS) (Claeson and Merson 1990); however, WHO ORS does not significantly decrease stool output and duration of diarrhea, and therefore other approaches to add to or to enhance the available ORS have been sought. One such approach is the supplementation of zinc. Zinc is required for multiple cellular tasks and the immune system depends on the sufficient availability of this essential trace element. (Beisel 1982) Zinc deficiency is common in several developing countries, including India. Randomized controlled trials have shown that zinc supplementation during acute diarrheal episodes reduces

the duration and severity, as well as the incidence of subsequent diarrheal episodes. (Baqui *et al.*, 2002; Walker and Black 2010; Sazawal *et al.*, 1995; Sazawal *et al.*, 1996; Sazawal *et al.*, 1997) However, recently published meta-analyses conclude that prophylactic zinc supplementation significantly reduces the incidence of diarrhea only in children 12 months of age. (Brown *et al.*, 2009; Bhutta *et al.*, 1999; Brown *et al.*, 2004) This study aimed at supplementation of prophylactic zinc therapy for children of slum areas aged at 6-11 months, as most of the diarrheal episodes are seen at around the period weaning.

MATERIAL AND METHODS

In this prospective study, we enrolled infants aged 6 to 11 months from urban slum areas of Chitradurga, Tumkur and Davangere district of Karnataka, India, between July 2013 to January 2014. Total 28 slum areas were selected and we enrolled total 946 infants, these were randomly assigned as cases and control. 473 infants received 20 mg of zinc orally every day for 2 weeks and rest 473 infants were assigned as controls. The primary outcome was the incidence and episodes of diarrhea. We hypothesized that zinc prophylaxis in infants for 2 weeks would reduce the incidence of diarrhea in subsequent months. Thus, we excluded any child receiving zinc supplement at the time of study or who had received it in the preceding 3 months, those who were severely malnourished,

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immune-deficient, currently on steroid therapy. A house-to-house survey was done at the beginning of the study was conducted to identify and select the eligible infants. The study purpose was explained to the family and an informed consent was obtained from parents of all infants before they were included in the trial. These infants were followed by subsequent 5 months.

Intervention: The field investigator administered the first dose of the intervention at the time of enrollment and advised the mother to give 5 mL of syrup daily to the infant for the remaining 13 days. Further, visits were made on the 7th and the 14th days to ensure compliance. We collected data for any possible side effects as reported by the caregivers during these visits.

Outcome: The primary outcome was the incidence of diarrhea. Diarrhea was defined as 3 or more loose, liquid, or watery stools or any change in consistency or frequency of stools or at least 1 loose stool containing blood in a 24-hour period. (www.who.int/mediacentre) Secondary outcomes included incidence dysentery, and persistent diarrhea; duration of diarrhea; and side effects. Acute diarrhea was defined as an episode of diarrhea lasting up to 14 days. If an episode lasted for 14 days, it was defined as persistent diarrhea. (www.who.int/mediacentre) The episode was classified as dysentery if the stool contained blood. (www.who.int/mediacentre).

A trained field investigator assessed all the outcomes. Follow-up for diarrhea began on the 15th day after intervention. The follow-up continued for 5 months after the completion of zinc supplementation. At each follow-up, the mother/caregiver was asked about the occurrence of diarrhea during the previous 15 days.

Statistical analysis

The Descriptive statistics was used to describe frequency, mean, median, standard deviation and confidence intervals for variables- number of infants (case and control), age, socioeconomical strata, feeding type, water used, total diarrheal episodes, hospital admission in SPSS software version 19. Comparisons of discrete variables were evaluated by using chi square analyses. $P < .05$ was considered significant.

RESULTS

The present study conducted in slum areas of Chitradurga, Tumkur and Davangere district. In total 946 infants were enrolled and these were allocated to cases and controls (N=473). Out of 946 infants 442 (46%) were males and 504 (54%) females. The mean age was 7.35 ± 1.23 . Whereas water usage was divided into bore well, tap and purified water, 151 (16%) were used bore well water 721 (76%) used tap water and 74 (8%) were purified water. Feeding type was mainly classified into exclusive, complementary and both. 312 (33%) infants were fed by exclusive breast-feed, 340 (36%) were fed by complementary feed and 294 (31%) were by both. Education of the parents, 833 (88%) were illiterate and 113 (12%) were literate. Baseline characteristics of cases and

controls given in Table 2. In cases 382 (80%) infants had acute diarrhea and 452 (95%) in controls ($p < 0.001$), whereas persistent diarrhea 35 (7%) in cases and 125 (26%) in controls ($p < 0.001$). Forty-eight (10%) infants of cases and 52 (11%) of controls had dysentery ($p = 1.007$). Respiratory tract infection 122 (25%) in control and 48 (10%) in cases ($p < 0.001$), whereas skin infection 34 (7%) in cases and 62 (13%) in controls ($p = 0.003$). 15 (3%) infants of cases and 59 (12%) of controls had hospital admission ($p < 0.001$).

Table 1. Baseline characteristics

Variables		N=946
Gender	Male	442
	Female	504
Age		7.35 ± 1.23
Water	Bore well	151
	Tap	721
	Purified	74
Feeding type	Exclusive breast feed	312
	Complementary feeding	340
	Both	294
Education	Illiterate	833
	Literate	113

247 infants in case group had single episode of diarrhea and in controls 155 infants, whereas more than one episode diarrhea was more common in controls. Total 91 infants in cases didn't had diarrhea whereas in controls only 21 infants didn't had diarrhea.

DISCUSSION

In the current study, we report that prophylactic zinc supplementation for 2 weeks in infants aged between 6months to 11months has significantly reduced the incidence and duration of diarrhea during follow-up of 5 months and we have also studied additional outcomes such as acute respiratory tract infections and skin infection.

Table 2. Incidence of diarrhea in cases and controls

Diseases	Cases	Controls	p-value
Acute diarrhea	382	452	<0.001
Persistent diarrhea	35	125	<0.001
Dysentery	48	52	1.007
Respiratory tract infection	48	122	<0.001
Skin infection	34	62	0.003
Hospital admission	15	59	<0.001

Table 3. Incidence of diarrheal episodes between cases and controls

Diarrheal episodes	Cases (N=473)	Controls (N=473)
0	91	21
1	247	155
2	90	130
3	21	68
4	8	54
5	6	27
6	3	6
7	5	3
8	2	9

Among the studies in which short course zinc prophylaxis of 2 weeks was used, only one study had shown significant reduction in the incidence of diarrhea in a children aged 12 to 35months. (Rahman *et al.*, 2001) Previous studies, which were

carried out in infants of 6 to 11 months, have shown similar results to the current trial but after continuous zinc supplementation. (Ruel *et al.*, 1997; Sur *et al.*, 2003; Brooks *et al.*, 2005; Long *et al.*, 2006) In a large study done in population of Delhi, zinc prophylaxis of 4 months was found to be effective only in children 12 months of age. (Bhandari *et al.*, 2002) Thus, unlike the previous studies, the current study showed that short-course zinc prophylaxis significantly reduced diarrheal incidence in an age group of 6 to 11 months. None of these trials included urban slum areas, as diarrheal episodes are common in these populations, but present study enrolled infants of slum areas. In 2 meta-analyses Zinc prophylaxis was shown to reduce the incidence of diarrhea in both continuous as well as short-course supplementation trials. (Brown *et al.*, 2009; Bhutta *et al.*, 1999) However, these studies were done in children 12 months of age. In this study we found that there were significant decrease in diarrheal episodes and duration in those who received zinc prophylaxis for 2 weeks. Whereas results of 2 previous trials have shown that no effect of continuous zinc prophylaxis on the duration of diarrhea. A significant reduction in incidence was seen when diarrhea was further classified into acute diarrhea, persistent diarrhea, and dysentery in the present study. In the past, only 1 study concluded that the incidence of acute diarrhea was reduced significantly by zinc supplementation, but in a wider age group (6–35 months). (Larson *et al.*, 2010) Regarding dysentery, only 1 study showed significant reduction in incidence of dysentery following zinc supplementation, that too in a wide age group of 6 to 35 months with continuous supplementation. (Penny *et al.*, 2004) Whereas in this study we found that there were no significant differences in incidence of dysentery between zinc and non-zinc group. In present trial we found that there were significant decrease in respiratory tract infection, skin infection, which is consistent with the studies from elsewhere. (Aggarwal *et al.*, 2007). The major limitation of this study is that serum zinc levels were not done to assess the deficiency and the subsequent effect on serum zinc levels after the administration.

Conclusion

The current study showed significant reduction in diarrhea morbidity in infants of 6 to 11 months, even 5 months after short-course zinc prophylaxis. Whereas previous trials and meta-analyses have shown the beneficial effect of zinc prophylaxis on diarrhea either by continuous supplementation for a long duration, ranging from 3 months to 1 year, or in age groups of 12 months. During immunization all infants should receive prophylactic zinc therapy; this will cover all target population and target population commonly slum areas as children of these area often suffers with recurrent episodes diarrhea. This in turn will reduce the overall incidence of diarrhea in the community compared with administration of zinc only to children who seek treatment for diarrhea. Prophylactic zinc therapy also reduces the respiratory tract infection such as pneumonia.

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